Current Opinion in Rheumatology

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Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal’s Section Editors for this issue.

Section Editors

Dafna D. Gladman, MD

Dr Gladman is Professor of Medicine at the University of Toronto, and Senior Scientist at the Toronto Western Research Institute. She is Deputy Director of the Centre for Prognosis Studies in The Rheumatic Diseases and Director, Psoriatic Arthritis Program, University Health Network. Dr Gladman has researched both psoriatic arthritis and systemic lupus erythematosus with emphasis on database development, prognosis studies, genetic markers for disease expression, assessment instruments, and quality of life measures.

Dr Gladman has 236 peer-reviewed publications, 85 invited publications, and 288 published abstracts. Important contributions to psoriatic arthritis include the recognition that the disease was more severe than previously noted. Dr Gladman and colleagues demonstrated that psoriatic arthritis progressed over time, and was associated with increased mortality. Moreover, her group identified predictors for disease progression and mortality. On the other hand, they also identified patients who achieved remission.

Dr Gladman is a member of the steering committee of the newly formed Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

J.S. Hill-Gaston, MA, PhD, FRCP, FMedSci

Professor Hill-Gaston, was appointed foundation Professor of Rheumatology at the University of Cambridge in 1995. He qualified in medicine from Oxford University, and obtained a Ph.D. in the immunology of EBV infection at Bristol University. He spent two years in postdoctoral training at Stanford University, followed by ten years at the University of Birmingham where he was an MRC research fellow and a Wellcome Trust senior clinical fellow. Next he was appointed Senior Lecturer, and later Reader and Professor, in Experimental Rheumatology.

His research interests are in immunological mechanisms in rheumatic diseases, particularly the spondyloarthropathies, and the interactions between bacteria and the immune system. This research is currently focussed on immune responses to Chlamydia trachomatis, T cell interactions with HLA-B27, and the influence of T cells recognizing heat shock proteins in inflammatory arthritis.

Steven Goldring, MD

Dr Goldring is a Professor of Medicine at Harvard Medical School and Chief of Rheumatology at New England Baptist Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. His research interests focus on the cellular and molecular mechanisms involved in the regulation of physiological and pathological bone remodeling. His work has helped to define the role of cytokines and other inflammatory mediators in bone and cartilage loss in rheumatoid arthritis and other inflammatory disorders. He presently serves as the Director of Research of the New England Baptist Bone and Joint Institute Laboratory at the Harvard Institutes of Medicine. He is the President-elect of the American Society of Bone and Mineral Research and has been
the Chairman of the Gordon Research Conference on the Molecular Biology of Bones and Teeth, Co-Chairman of the Keystone Conference on the Pathogenesis of Rheumatoid Arthritis, and Vice-Chairman of the National Institutes of Health, Consensus Development Panel on Osteoporosis.

Dr Goldring is a co-recipient of the Carol Nachman Prize in Rheumatology and has received the Arthritis Foundation’s James H. Fairclough, Jr. Award and the Paget’s Disease Foundation Research Award. He is a member of the American College of Rheumatology, the American Society of Bone and Mineral Research, International Bone and Mineral Society and the Orthopaedic Research Society. Professor Goldring is an Associate Editor of Arthritis Research and a member of the editorial boards of Bone and the Journal of Bone and Mineral Research.
The spondyloarthropathies have been considered rare among the rheumatic diseases. Until the recent advent of biologic therapies rheumatology, there has been limited interest in this group of patients. Recent evidence suggests, however, that they are not rare, and indeed not as mild as previously thought. As a group, these conditions likely occur in more than 1% of the population. Studies have demonstrated that ankylosing spondylitis and psoriatic arthritis are disabling diseases. Traditional management of these conditions has been difficult because disease modifying antirheumatic drugs have not been very effective [1].

This issue of Current Opinion in Rheumatology provides an update on these conditions, concentrating on psoriatic arthritis and ankylosing spondylitis. The concept of psoriatic arthritis was introduced through the work of Wright [2] in the late 1950s. However, the identity of psoriatic arthritis as separate from the spondyloarthritides remains controversial [3]. Psoriatic arthritis is associated with psoriasis but is similar to the spondyloarthropathy in certain features [1]. It differs in the degree of inflammatory arthritis that affects most patients. Even the spondylitis of psoriatic arthritis is less severe and the association with HLA-B*27 is weaker than in ankylosing spondylitis [4]. Healey and Helliwell provide a review of the controversy and the importance of achieving a resolution. This may be achieved through efforts into a better understanding of the pathogenesis and therapeutic responses of the conditions included among the spondyloarthropathy group.

One way to try and resolve the issue of whether psoriatic arthritis should be considered a separate entity from spondylitis is to understand whether the pathogenesis of the conditions is identical. Inman et al. tackle the review of the pathogenesis of ankylosing spondylitis whereas Ritchlin reviews the relevant literatures on psoriatic arthritis. Although some of the mechanisms may be similar, such as cytokine production there are clearly differences. These differences are related to genetic factors. In ankylosing spondylitis there is a central role for HLA-B*27, but this allele is present in less than half the patients with psoriatic arthritis. As highlighted by Ritchlin, these may be related to the presence of psoriasis, but this is part of the disease entity, which contributes to the uniqueness of the condition. Although the pathogenetic mechanisms are still not fully clarified, a story is emerging that may provide additional therapeutic targets in the future. Similar pathogenetic mechanisms are relevant to the remainder of the spondyloarthritis group of conditions.

Until recently, both ankylosing spondylitis and psoriatic arthritis were difficult to study in therapeutic trials because of lack of standardized, widely accepted, and validated instruments to assess disease and clinical response. This has changed during the past few years [5]. Several instruments to assess spinal disease in ankylosing spondylitis have been developed and validated. These include the Bath Ankylosing Spondylitis Disease Activity Index [6], the Bath Ankylosing Spondylitis Functional Index [7], the Bath Ankylosing Spondylitis Metrology Index [8], and the Bath Ankylosing Spondylitis Radiology Index [9]. The Assessments in Ankylosing Spondylitis working group developed response criteria for trials in ankylosing spondylitis [10]. Whether the same instruments will work in patients with psoriatic spondylitis is not clear, because the Bath Ankylosing Spondylitis Disease Activity Index did not function well in two studies [11,12]. Instruments are currently being validated for psoriatic arthritis [13].

Currently, the main outcome measure in ankylosing spondylitis is based on patient-derived assessment. Imaging techniques, however, are in the process of development and validation to be able to study more objectively the effect of new therapies on these conditions. Van der Heijde and Landewe review new development in this field, particularly with reference to the assessment of spondylitis. Based on the clinical and radiologic modalities, the evaluation of therapeutic intervention in spondylitis has been facilitated. Zochling and Braun review the advances in therapies for spondylitis, whereas Mease reviews the advances in therapy for psoriatic arthritis. Although none of the therapies has been remitting, they have certainly improved the lot for patients with ankylosing spondylitis and psoriatic arthritis.
References

Classification of the spondyloarthropathies
Paul J. Healy and Philip S. Helliwell

Purpose of review
The spondyloarthropathies are a group of conditions which share similar clinical features. Classification criteria permit separation of the conditions, allow better targeting of therapies, better measurement of outcomes, and better prognostic information. Early diagnosis remains problematic, but validated criteria for established disease are now emerging.

Recent findings
Histopathology and histochemistry are providing a better understanding of the underlying process of inflammatory arthritis in spondyloarthropathy and other inflammatory arthritides. Early disease, however, continues to challenge current criteria. Sophisticated imaging with magnetic resonance imaging is being increasingly used and is proving useful for early diagnosis as well as helping to understand the pathophysiology of disease. Juvenile idiopathic arthritis continues to provide problems and criteria have recently been modified to allow a greater clinical utility and inclusion of more patients. Poststreptococcal reactive arthritis appears to be a heterogenous clinical entity, with a group looking more like rheumatic fever and a group with spondyloarthropathy traits. It may be that the association is not streptococcal, but is a throat infection. Currently available criteria for psoriatic arthritis have been evaluated in a large cohort. Four of the criteria performed well with high specificity and sensitivity whereas the other two had moderate specificity and low sensitivity. It was shown that rheumatoid factor positivity does not exclude a diagnosis of psoriatic arthritis—the single most important clinical feature of this condition being the presence of psoriasis.

Summary
The spondyloarthropathy classification criteria continue to be an area of development. This is most apparent in juvenile arthritis and psoriatic arthritis. The latter is currently undergoing intense scrutiny to develop classification criteria and outcome measures.

Keywords
classification, histopathology, imaging, psoriasis, spondyloarthropathy

Abbreviations
AS ankylosing spondylitis
CASPAR Classification of Psoriatic Arthritis
CCP cyclic citrullinated peptide
ESSG European Spondyloarthropathy Study Group
HLA human leukocyte antigen
MRI magnetic resonance imaging
PsA psoriatic arthritis
RA rheumatoid arthritis
ReA reactive arthritis
RF rheumatoid factor
SpA spondyloarthropathy

Introduction
The spondyloarthropathies (SpAs) as a group have seronegative, inflammatory arthritis characterised by involvement of the spine, peripheral arthritis, and enthesitis. As a group they have a similar prevalence to rheumatoid arthritis (RA). With new effective therapies becoming available, there is increasing interest in classification criteria and outcome tools.

The SpAs represent a variety of diagnoses, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic and undifferentiated SpA. Although each of these clinical groups has a characteristic set of signs and symptoms, there is a wide overlap between groups and with other inflammatory arthritides. As a result, proposed diagnostic criteria often overlap, as do outcome tools. There has been the suggestion that the SpAs could be regarded as a generic group with characteristic disease features (e.g., axial disease, peripheral arthritis, enthesitis; and dactylitis; skin involvement; eye inflammation; and inflammatory bowel disease), but a recent review argued that the consideration of individual disease entities is likely to be of greatest benefit [1].

This article addresses the current knowledge in classifying the individual diseases and problems moving to a firm diagnosis.

Synovial histopathology
Histopathologic classification of inflammatory arthritis may be possible if a synovial biopsy is obtained. Baeten et al. [2] studied 154 consecutive patients referred for evaluation of inflammatory arthritis who had at least a knee joint involved. All patients underwent a synovial biopsy. Initial clinical classification found 32 with RA (American College of Rheumatology criteria [3]), 22 with SpA.
Spondyloarthropathies

(Adapted from Baeten et al. [2].

Table 1. Performance of histopathological variables according to final diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Anticitrulline staining</td>
<td>43.8</td>
<td>100</td>
<td>100</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>mAb 12A staining</td>
<td>40.8</td>
<td>100</td>
<td>100</td>
<td>n/a</td>
</tr>
<tr>
<td>SpA</td>
<td>Microscopic vascularity &gt;2</td>
<td>54.5</td>
<td>91.1</td>
<td>75</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Microscopic vascularity &gt;1</td>
<td>90.9</td>
<td>62.2</td>
<td>n/a</td>
<td>93.3</td>
</tr>
<tr>
<td>Other</td>
<td>Crystal deposits</td>
<td>30.8</td>
<td>100</td>
<td>100</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Cohort 1 consists of patients who could be classified at the initial visit. Cohort 2 consists of patients who could only be classified at 6 months.

Anticyclic citrullinated peptide (anti-CCP) antibodies are antibodies against synthetic citrullinated peptides and are regarded as specific markers for RA. They belong to a broader group of anticitrullinated peptide/protein antibodies. Despite the high specificity for RA (90 to 98%), various groups have noted their presence in PsA so that the utility of CCP in PsA is still under review.

Two recent studies have looked at CCP in PsA. The first looked at 102 consecutive patients with PsA seen in an outpatient setting [7*]. CCP was present in 16 (15%). In 6 of 16 there was clear-cut PsA whereas the remaining could have had RA and psoriasis. CCP positivity in PsA seemed to be associated with a greater risk of aggressive, erosive disease and higher joint counts. This higher joint count results in greater symmetry [8] and leads to questions of RA-like disease. They noted that CCP had a stronger association with erosive disease than rheumatoid factor (RF) and was independent of RF.

The second study took patients with skin or nail psoriasis who also had spondylitis or peripheral arthritis and form whom the laboratory had a serum sample (n = 192) [9]. The clinical and radiologic characteristics were obtained from retrospective chart and radiologic review respectively. Anti-CCP antibodies were found in 15 (7.8%). Analysis of the clinical and radiologic features of these 15 showed that at least 10 appeared to be genuine cases of PsA having features commonly seen in this condition.

The role of CCP in PsA therefore remains uncertain, but it does not appear to be a useful test to distinguish PsA from, for example, RA in cases of symmetric polyarthritis and psoriasis.

Imaging

Sacroilitis is the hallmark feature of AS and is important in the classification of other SpAs. Classification criteria currently require evidence of sacroilitis on plain radiography. However the development of radiologic disease is a function of disease duration and is of little help in early
disease. Furthermore, the relation between clinical findings and plain radiology has previously been shown to be poor [10]. A recent editorial has highlighted the difficulties inherent in the diagnosis of axial disease in SpA and in the difficulties with subgroup classification in PsA, concluding that there is a strong argument for abandoning subgroups altogether, using combinations of specific features for the purpose of classification [11].

The use of magnetic resonance imaging (MRI) has allowed a better assessment of the sacroiliac joint, but there is no well-established method of evaluating MRI findings of the sacroiliac joint. Both computed tomography and MRI have recently been compared. Both modalities were found to be equally good in detecting joint erosion and sclerosis, but MRI also visualized inflammatory changes. A graded scoring system was used for each of the following features: erosions, sclerosis, fat accumulation in bone marrow, joint space width, bone marrow oedema, and contrast enhancement [12]. In a further study, Puhakka et al. [13] used the recently developed set of MRI criteria for evaluating the sacroiliac joint and compared it with clinical findings and B27 status. The patients were referred to a tertiary clinic with a history satisfying ESSG criteria and inflammatory back pain with a median duration of 19 months. There was evidence of sacroiliac joint changes on MRI in 35 of 41 cases. Correlation with clinical features was poor, but B27 positivity predicted both acute and chronic changes.

Braun et al. [14] have also used a scoring system based on MRI and have shown MRI to be superior to conventional plain radiography for assessing the thoracic spine. This may have implications for classification when evidence is required for definite axial involvement, although the cost and availability of MRI continues to be a barrier to including this in classification criteria.

Psoriatic arthritis
PsA was first considered a distinct entity by Wright [15] in 1959. Although PsA has well-recognized clinical, radiologic, and familial characteristics, there is still controversy regarding which patients to include in this group. This is further exacerbated by the presence of several disease subtypes, particularly the polyarticular group.

There have been several criteria suggested for classification. However, only those by Fournie et al. [16] have been developed on patient-derived data. These criteria still have to be tested in other populations. A previous review has discussed the difficulties in application of criteria to different populations and the variability of criteria interpretation by clinicians [17].

A recent study examined the performance of a variety of classification criteria when tested against patient data from notes and radiology review [18**]. Data from 499 patients from Bradford and Milan with either RA (n = 156) or PsA (n = 343) were gathered by retrospective chart review. The Fournie criteria could not be applied to 24% of cases because of lack of human leukocyte antigen (HLA) data and therefore were not included in the analysis. The most sensitive criteria were by Vasey and Espinoza [19], McGonagle et al. [20], Gladman et al. [21], and Moll and Wright [22] (99%, 99%, 97%, and 94% respectively) and these criteria sets also had a similar specificity (99%, 96%, 99%, and 99% respectively). The Bennett [23] and ESSG [4] criteria were the least sensitive (69% and 56% respectively). The easiest criteria to use were those by Moll and Wright [22], and Vasey and Espinoza [19]. Further analysis found that a positive RF should not necessarily exclude PsA in the presence of other characteristic features of PsA, in particular nail disease or psoriasis. In the absence of either of these, RF is strongly associated with RA. The presence of psoriasis was a strong distinguishing variable. This study also attempted to derive data-driven criteria for classification. None of these, however, was more accurate than the criteria already proposed. It was possible to derive models with good accuracy even without RF or psoriasis. It is important to note that the comparator group was RA and this may contribute to the high specificity. In addition, the data were derived from only two centers and were based on rheumatologist-diagnosed patients.

Helliwell and Taylor [24*] commented on diagnosis and classification, in particular some of the distinguishing characteristics of PsA, including the significance of negative RF, joint symmetry, spinal involvement, and psoriatic skin disease. There is a brief review of time line and concept changes in the development of the available classification criteria. They state, again, that there are no universally agreed-on or properly validated case definitions, and establishing these is a fundamental issue. There is a brief mention of the Classification of Psoriatic Arthritis (CASPAR) group, that will produce data-defined criteria [24*].

Although the CASPAR group used consultant diagnosis as the ‘gold standard,’ the validity of the concept of ‘consultant diagnosis’ has recently been examined by Symmons et al. [25]. They developed a questionnaire through three phases to examine heterogeneity of diagnosis among a group of physicians with a declared interest in psoriatic arthritis. For patients with clear-cut PsA or not PsA, the physicians showed good agreement on the diagnosis. However, in those patients in whom there was uncertainty, the results were less convincing and the physicians appeared to split between high ‘diagnosters’ (those likely to give a diagnosis of PsA) and low ‘diagnosters’ (those unlikely to give a diagnosis). This suggests there is likely to be some disagreement between physicians on a derived ‘gold standard,’ that may have implications for the CASPAR study.
However, given the broad range of centers (n = 32) in the CASPAR group, this is unlikely to make a significant impact on the results of this study.

Reactive arthritis

ReA is defined as a sterile joint inflammation triggered by a distant infection. It is not limited to the joint, often being associated with eye disease, skin disease, enthesitis, dactylitis, and a variety of urogenital problems. When a trigger can be found, the microbes generally infect mucosal surfaces, the most frequent infections being sexually acquired and dysenteric. The diagnosis of ReA generally allows a more positive prognosis to be given to an individual.

Poststreptococcal reactive arthritis is still subject to debate. Mackie and Keat [26*] have recently published a review of 188 cases. Although noting that case reports may produce a reporting bias and that numbers are small, the authors still thought it was possible to draw some conclusions from their review. Age of onset appeared to have a bimodal distribution, with peaks at 8 to 14 years and 21 to 37 years. There was a subset of patients who were HLA B27 positive (6 of 36 HLA typed) who may be more likely to develop sacroilitis. The infection was almost always documented by self-reporting of a sore throat, but there were 69 of 188 patients in whom streptococcal infection was documented, usually from a throat swab. The arthritis was typically nonmigratory and involved large joints, usually in the lower limb, and was not exclusively oligoarthritis. Carditis was uncommon (4 of 188), but patient follow-up was often short. Overall it was felt that poststreptococcal reactive arthritis is a heterogenous set of clinical entities that can share features with acute rheumatic fever in some cases or the SpAs in others. The association with streptococci was not established and the authors questioned whether the association should be with throat infections rather than ‘streptococcal throat.’

Juvenile idiopathic arthritis

The classification criteria for juvenile arthritis continue to evolve. The criteria for juvenile idiopathic arthritis [27] have recently been further revised [28]. The revisions changed several of the exclusion criteria to allow greater clinical utility. As in adult disease, the main area of confusion is in the SpA group. There is a clear division for psoriatic arthritis. This excludes, however, those who may have enthesitis or inflammatory back pain as one of their symptoms and those who are RF positive.

Duffy et al. [29] comment on the nomenclature and classification debate in the light of the development of these criteria. They note the enthesitis-related arthritis group includes those with diagnosed AS, that may be unhelpful for prognosis and outcome evaluation. They make the valid point, however, that the enthesitis group may prove to be useful for classification of early-onset SpA where enthesitis may be the sole clinical problem rather than axial disease (as seen in adults).

The criteria were evaluated in a Spanish cohort who had previously been classified using the revised Durban criteria. They found the Edmonton revision easier to use and allocated more patients to distinct groups. In particular this resulted in a more precise definition of the exclusion criteria for RF-negative polyarthritis and decreased the numbers that were not classifiable [30].

Somewhat against the trend, a recent paper evaluated existing ‘standalone’ classification criteria for juvenile SpA using a control group established by applying the Durban criteria (having already excluded from this group those patients who were classified as having enthesitis-related arthritis and psoriatic arthritis) [31]. They found that the ESSG and Amor criteria were good for distinguishing juvenile SpA from other forms of juvenile idiopathic arthritis, but was relatively poor at dividing the undifferentiated SpAs from the broad group. This is unsurprising given the similar problems in adult populations.

Conclusion

Classification criteria for the SpAs remain an area of development and controversy. The advent of new treatments is limited by our ability first to classify and second to measure outcomes. This is especially so in PsA. Histopathology is providing a better understanding of the underlying process of inflammatory arthritis as a whole. This will no doubt help us develop a better aetipathologic model of disease. The concept of early disease also remains problematic, and sophisticated imaging modalities are increasingly used to aid this process. MRI is proving useful as a research tool and will no doubt provide a better understanding of disease development. Cost considerations, however, may limit applicability at this stage. The evolution of classification criteria in juvenile disease will allow better classification of a larger group of children, thus leading to advances in treatment and prognosis. PsA is undergoing intense scrutiny to develop appropriate classification criteria and outcome measures, supported by a new international collaboration (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, or GRAPPA [32]).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest


The authors used data derived from disease-classified patients to diagnose unclassified patients with good success. They suggest there are distinct histopathologic patterns to SpA and RA.


This paper provides histopathologic confirmation of the clinical impression that PsA fits better in the SpA group than in the RA group.


This prospective study shows CCP is present in a significant number of PsA patients, including patients with distinctive features of psoriatic arthritis. CCP positivity is associated with a worse prognosis, with more erosions and higher joint counts.


This is the largest study to assess the validity and usefulness of the available classification criteria for PsA. It also evaluates the importance of a positive RF and a history of psoriasis.


This article reviews the distinguishing characteristics of PsA and how the currently available criteria assess them.


This is a review of all available case reports of poststreptococcal arthritis. This was an attempt to identify a cohesive group of clinical features that may be linked to streptococcal throat infections.


Pathogenesis of ankylosing spondylitis and reactive arthritis
Tae-Hwan Kim, Wan-Sik Uhm and Robert D. Inman

Purpose of review
The hallmark of ankylosing spondylitis is acute and chronic spinal inflammation initiating in the sacroiliac joints, often coupled with enthesitis, presenting as chronic inflammation at the sites of ligamentous and tendinous insertions into bone. Peripheral joint synovitis can be a prominent feature as well. Reactive arthritis is a sterile synovitis arising after an extra-articular infection of enteric or urogenital tracts. HLA-B27 has been known for about the past 30 years to be associated with ankylosing spondylitis and reactive arthritis, but the pathogenesis of ankylosing spondylitis and reactive arthritis is still not well defined. Although the clinical manifestations of ankylosing spondylitis and reactive arthritis may differ, this update discusses the two diseases together and focuses on recent evidence in both.

Recent findings
With respect to HLA-B27 several recent studies address arthritogenic peptides, molecular mimicry, and aberrant forms of B27. Several candidate genes in addition to B27 have been implicated in recent genetic studies. With respect to bacterial infection, recent findings in bacterial antigenicity, host response through interactions of antigen-presenting cells, T cells, and cytokines are providing new understanding of host–pathogen interactions and the pathogenesis of arthritis. Endogenous host factors such as proteoglycans may play a role as autoantigens and contribute to chronic inflammation on that basis.

Summary
Recent advances provide additional new insights into distinct pathogenetic mechanisms in AS and ReA that arise from a complex interplay between genetic factors including HLA-B27 and environmental factors.

Keywords
bacterial infection, HLA-B27, T cells

Introduction
The term spondyloarthropathy (SpA) was introduced to describe a family of arthritides sharing certain clinical features and having a strong association with HLA-B27. The recognition that HLA-B27 was associated with ankylosing spondylitis (AS) dates back 30 years, and many studies have focused on the biochemistry and immunology of HLA-B27, including genetic polymorphisms, infections, T-cell responses, and cytokines in the pathogenesis of SpA. The pathogenesis of SpA is as yet unexplained, however.

Spondyloarthopathy includes AS, reactive arthritis (ReA), psoriatic arthritis, arthritis related to inflammatory bowel diseases, as well as undifferentiated SpA. AS is a progressive disease in which chronic inflammation can lead to extensive new bone formation throughout the spine. In AS more than 90% of patients are HLA-B27 positive. ReA is thought to be triggered by urogenital and gastrointestinal infections and it shares with AS a strong association with HLA-B27. In this review, we provide a brief overview of pathogenesis of AS and ReA focusing on recent advances.

HLA-B27
HLA-B27 consists of a heavy chain having three α-domains, which noncovalently binds short peptides and β2-microglobulin (β2m) [1,2]. There are 24 HLA-B27 subtypes currently recognized. The structural patterns are consistent with B2705 being the ancestral allele and the other types being generated by small mutations [1]. B2705 is the dominant subtype and is associated with AS across broad ethnic and geographic boundaries. Of the subtypes studied to date, it appears that B2706 and B2709 do not confer susceptibility to AS. Although the HLA-B27 has remained a center of extensive research, the mechanism whereby HLA-B27 confers susceptibility to AS is not well defined. Current hypotheses regarding the pathogenesis of AS and ReA have sought to incorporate HLA B27 into mechanistic models.

Several different hypotheses have been proposed. In the arthritogenic peptide theory, HLA-B27 binds unique peptides of microbial or self-origin and presents them to CD8+ T cells [1]. These peptides usually have an anchor arginine residue at their second position and the side chain of arginine is bound in the B pocket of HLA-B27 [2]. It was recently reported that CD4+ T cells may be involved in class I–restricted immune recognition [3*]. Consequently AS could involve an HLA-B27-restricted CD8+ T-cell or CD4+ T-cell response to microbial or
self-peptides [4–6]. The principle of molecular mimicry is still proposed as a possible mechanism in B27-related pathogenesis. This postulates that the antibodies directed against foreign antigens arising during a bacterial infection are cross-reactive with HLA-B27. Recent reports have addressed molecular mimicry in AS. Fiorillo et al. [7*] recently showed allele-dependent similarity between a viral and a self-peptide derived from vasoactive intestinal peptide receptor (VIPR) 1 presented by HLA-B27 subtypes carrying the B*2709 or B*2705 alleles. The crystallographic study by Hulsmeyer et al. [8*] sheds light on the possible structural basis of differential susceptibility to AS conferred by different B27 subtypes. HLA-*B2705, an AS-associated subtype, has the capacity to bind a candidate autoantigen in two different conformations, in a way that is not shared by HLA-*B2709, which is a non-AS-associated subtype. Peptides from HLA-B27 have sequence homology with ligands for paired immunoglobulinlike receptors [17]. There has been considerable interest in aberrant processing or folding of the heavy chain of HLA-B27. Under normal circumstances cell surface HLA-B27 consists of a heavy chain bound to β2m and peptide. This complex is formed in the endoplasmic reticulum [13]. Heavy chain folding of HLA-B27 appears to be slower compared with other HLA alleles, however, possibly because of specific amino acid residues in the B pocket [14]. This misfolded heavy chain is usually removed in endoplasmic reticulum, but in the event of insufficient or unavailable chaperone, peptide, or β2m, misfolded heavy chains are homologed. This may increase expression of the protein BiP and generate an unfolded protein response in the endoplasmic reticulum, leading to activation of nuclear factor-κB [15]. In studies of transgenic rats, disulfide-linked intracellular heavy chain complexes are more prone to form and bind BiP in disease-prone wild-type B27 rats than in disease-resistant HLA-B7 rats [16*]. The data support the notion that accumulation of misfolded B27 may contribute to the pathogenesis of B27-associated disease. It should be noted that this slow folding may not be limited to HLA-B27 and viral infection can influence misfolding. The latter is not thought to contribute to the pathogenesis of AS or ReA, however, and further studies will be needed to resolve this issue [1]. In addition to misfolding within the endoplasmic reticulum assembly process, there is evidence that HLA-B27 is distinctive in its propensity to form heavy chain homodimers on the cell surface. Whether these homodimers could function as peptide-presenting structures has not been resolved, but these homodimers appear to be ligands for paired immunoglobulinlike receptors [17*].

Abnormal forms of HLA-B27 may react with CD4+ T cells or natural killer cells, rather than CD8+ T cells. The HLA-B27 molecule appropriately loaded with peptide usually interacts with CD8+ T cells. HLA-B27-restricted CD8+ T cells are unlikely to serve as effector cells in the transgenic rat model of HLA-B27-associated disease, however, because it was shown that CD4+ T cells were capable of inducing arthritis [18]. Adoptive transfer studies showed CD4+ T cells to be more important than CD8+ T cells for arthritis [19]. Recently Roddis et al. [20**] has found that CD4+ as well as CD8+ T-cell responses are induced in B27-transgenic mice and HLA-B27-restricted alloreactive CD4+ T cells were demonstrated with human cells and cell lines [3*,21]. HLA class I molecules are ligands for members of the killer immunoglobulin receptor and immunoglobulinlike transcript families (KIR3DL1, ILT4, and LIR6), which are expressed on natural killer cells, T cells, or monocytes [22]. As mentioned previously, HLA-B27, which exists on the cell surface as a classical heterodimer with β2m, or as a less conventional heavy chain homodimer, acts as a ligand for these immune receptors although the affinities with HLA-B27 differ [17**,22,23], but evidence is lacking to define the pathogenetic significance of this interaction.

A recent hypothesis is that of autodisplay [24*]. In this construct, β2m-free, peptide-free heavy chains support a helix-coil transition from α2 domain of HLA-B27 to α3 domain, facilitating rotation of backbone angles around residues 167 / 168, thereby occupying the molecule’s own peptide binding cleft. This autodisplay of HLA-B27, occurring either within B27 molecules or between B27 molecules, might be the grounds for self-perpetuating inflammatory and immune stimulation.

Finally, there is a theory invoking β2m deposition [25]. Cells bearing AS-associated HLA-B27 subtypes exhibit a higher rate of β2m dissociation from surface HLA-B27 complex than non-AS-associated HLA-B27 subtypes. It is postulated that release of β2m from a subpopulation of cell surface–expressed HLA-B27 molecules leads to β2m deposition within the synovium and to the initiation of chronic inflammation on that basis.

The quest for the critical arthritogenic peptides continues to attract researchers in AS and ReA. Although there is evidence of HLA-B27-bound peptides, derived either from self or microbes, their arthritogenic capacity has proved difficult to define.

Genes other than HLA-B27
Several recent studies have been reported on genes other than HLA-B27 in AS [26*]. HLA-B60 was reported to be an important contributor to AS susceptibility and may act as an independent factor in B27-positive and B27-negative AS patients [27,28]. There was a report that HLA-DR1 is associated with AS [29]. Large multifunctional proteases and transporters associated with antigen presentation act
as chaperones for peptide transport and have been studied in the context of AS susceptibility, but with varying conclusions [30,31]. CARD15, which is thought to function as an intracytosolic toll-like receptor, has been associated with Crohn disease and psoriatic arthritis, but this appears not to be associated with AS [32,33]. Tumor necrosis factor-α (TNF-α), ank, matrix metalloproteinase-3, transforming growth factor-β, interleukin-1, and interleukin-1RN polymorphisms have been examined as possible candidate genes for susceptibility to AS, and there have been informative studies reporting both positive and negative results with these candidate genes [34–38,39,40]. Evidence is compelling for genetic susceptibility to AS beyond HLA-B27 and the identity of these additional genes remains an active area of research. Well-controlled large studies are needed to pursue some of these promising leads.

Infection
Although ReA, another B27-related SpA, has a clear relation to antecedent infection, this is less clear for AS. B27-transgenic rats raised in a germ-free environment do not develop inflammatory pathology in the gut or the joints, and induction of arthritis following reintroduction of commensal gut flora supports the notion that such organisms play an important role in the pathogenesis of B27-associated gut and joint inflammation [41]. The following considers the role of infection with respect to bacteria and host immune response.

Bacteria
Evidence of previous infection can be defined in approximately 60% of ReA cases. The commonest triggering agents are *Chlamydia* organisms in the case of urogenital tract infections and gram-negative bacteria (e.g., *Shigella, Salmonella, Yersinia*, and *Campylobacter*) in the case of gastrointestinal infections [42*] but important regional difference may occur [43]. *Chlamydia* is the commonest causative agent in ReA. *Chlamydia* DNA, mRNA, rRNA, and intact *Chlamydia*-like cells have been found in synovial tissues and peripheral blood [44–46]. The mechanisms accounting for persistence of *Chlamydia* infection, whereby avoidance of host immune clearance, have been proposed as follows [47,48]. In the chronic persistent state there is altered regulation of specific *Chlamydia* genes with reduced expression of major outer membrane protein and increased expression of heat shock protein 60 (HSP) and lipopolysaccharide. *Chlamydia* has the capacity to downregulate surface major histocompatibility complex (MHC) expression in infected cells [47]. Recent investigations have reported that interferon-γ reduces tryptophan, which plays an important role in chlamydial growth by enzyme reduction [47]. *Chlamydia* also inhibits of apoptosis of host cell by cytochrome c reduction and can induce T-cell apoptosis by local production of TNF-α [47,49,50]. Several factors likely affect the persistence of *Chlamydia* including direct stimulation of *Chlamydia*-upregulated proinflammatory soluble mediators. New techniques such as HLA-B27 tetramers with greater sensitivity have been applied to the detection of low-frequency antigen-specific T cells in *Chlamydia*-induced arthritis [51].

In enteric forms of ReA, the monocyte may serve as a reservoir or as a transporter of bacteria to synovial tissue [42*]. New analytical techniques have been applied to probing synovial fluids and tissue for evidence of prior or current microbes [52,53]. Invasion by *Salmonella*, however, did not alter the B27 peptide presentation profile [54]. Quantitative analysis of invasion of gram-negative bacteria into human synoviocytes did not correlate with the B27 status of the target cells, in contrast to prior studies using B27-transfected cells as targets [55]. Serologic studies have previously implicated certain gram-negative bacteria, notably *Klebsiella pneumoniae*, in the pathogenesis of AS. One recent analysis, which addressed both humoral and cellular host immune responses to candidate pathogens, found no evidence to support the notion that *K. pneumoniae* has a distinct pathogenic role in AS [56*].

Lipopolysaccharide in synovial tissue is a potent macrophage stimulator and can induce a range of inflammatory cytokines, largely via the nuclear factor-κB pathway [42*]. Lipopolysaccharide also induces monocyte chemotactic protein [57], enhances secretion of the neutrophil chemotactic and activating cytokine interleukin-8 from chondrocytes [58], and decreases C5aR expression on monocytes [59]. This sets the stage for persistence of activated macrophages within the synovium and the ensuing chronic inflammation. One unresolved issue is how an antecedent infection might induce inflammation and erosions in a joint such as the sacroiliac joint in the absence of viable organisms. Synovial fibroblast might play an intermediary role in this sequence of events, in light of the recent observation that synovial fibroblasts infected with *Salmonella typhimurium* mediate osteoclast differentiation and activation [60*].

Host factors
As described previously, the HLA-B27 is detected with five to 10 times greater frequency in ReA than in the general population [42*]. One important unresolved issue is whether HLA-B27 confers a selective host advantage or disadvantage in host responses to pathogens. In this regard it is of interest that HLA-B27 may confer a relative protective role against HIV infection [61]. Whether this experience in viral infections can be translated to bacterial infections is not yet resolved. It has been observed that there is enhanced intracellular replication of *Salmonella* in HLA-B27-expressing monocytic cells [62*]. HLA-B27 may also decrease the costimulatory function of antigen-presenting cells, as reported in the B27-transgenic rat model [63*]. This latter may lead to loss of tolerance toward microbial flora. *Salmonella* has been shown to promote expression
of the transcription factor activating protein 1 and to modulate signal transduction in HeLa cells with HLA-B27 [64]. Consequently, HLA-B27 affects the cell’s ability to resist the bacteria and to mount a successful host defense.

### Cytokines

Among host cytokines active in host defense against intracellular pathogens, three have received the most attention recently by investigators. TNF-α and interferon-γ are potent antibacterial Th1 cytokines, whereas interleukin-10 is a Th2 cytokine [65]. A significant reduction in the expression of Th1 cytokines was detected in HLA-B27 AS patients [66]. At onset of ReA, low production of TNF-α was observed in peripheral blood. Impaired Th1 cytokine production may delay elimination of bacteria, leading to persistence of the pathogen. Tumor necrosis factor receptor (TNFR) p55 knockout mice develop more severe arthritis after *Yersinia* infection [67]. Butrimiene et al. [68] showed that in chronic ReA TNF-α production was higher and TNF-α-positive and interferon-γ-positive CD3+ cells were significantly higher, suggesting that the Th1 response in chronic ReAs is more dominant than that in acute ReA. In ReA, both CD8+ and CD4+ cells exhibit a Th1 profile with higher production of TNF-α and interferon-γ, suggesting that T cells contribute to pathogenesis by inducing a Th1 cytokine [69]. These studies need to be interpreted in the light of the fact that anti-TNF-α therapy may be an effective treatment of chronic ReA.

### Other host factors

The extracellular matrix of articular cartilage is primarily composed of type II collagen and proteoglycan. Aggrecan is an important protein in fibrocartilaginous regions of tendons, which are target sites for inflammation in AS and ReA. Proteoglycans may prove to be important contributors to inflammation in AS. Aggrecan has three globular domains that bind chondroitin sulfate and keratan sulfate. Versican is an important proteoglycan and exhibits considerable homology with human aggrecan [70]. In a murine model of AS using cartilage proteoglycan immunization, Shi et al. [71] demonstrated that animals with peripheral and axial inflammation manifested immunity to aggrecan, whereas spinal inflammation and sacroiliitis without appendicular involvement were associated with immunity to versican. Kuon et al. [72] analyzed CD8+ T cells in response to aggrecan and identified new HLA-B27-restricted nonamer peptides. The structural aspects of this interaction have recently been studied and have observed that the residue Cys67 plays an important role in T-cell recognition of aggrecan peptides. These studies provide supportive evidence that HLA-B27-restricted epitopes derived from human aggrecan or versican may be involved in the induction of inflammation.

Baeten et al. [73] showed that in SpA synovial tissues there are increased numbers of CD163+ macrophages and local production of soluble CD163+ when compared with rheumatoid arthritis patients, and these findings are associated with the degree of inflammation. This finding suggests that these CD163+ cells play a functional role in early inflammation of AS and ReA.

### Conclusion

HLA-B27 stands as the earliest and most robust genetic marker associated with a rheumatic disease. Although the association with AS dates back three decades and there have been marked advances in the research tools of immunology and biochemistry, the pathogenesis of AS and ReA and role of HLA-B27 have not been definitively solved. The pursuit of this goal has implications not only for the SpA but also for resolving pathogenic mechanisms for new genetic markers of susceptibility in arthritis in general.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- • of outstanding interest

The disulfide-linked intracellular heavy chain complexes are more prone to form and bind BiP in disease-prone wild-type B27 rats than in disease-resistant HLA-B7 rats. The accumulation of misfolded B27 may contribute to the pathogenesis of B27-associated disease.


Wei JC, Tsai WC, Lin HS, et al. HLA-B60 and B61 are strongly associated with ankylosing spondylitis in HLA-B27-negative Taiwan Chinese patients. Rheumatology 2004; 43:830—842.


This review paper focuses on HLA-B27-associated ReA and describes bacterial antigens and host factors.


This study showed that an arthritogenic organism could contribute to osteoclast differentiation and activation through regulation of the receptor activator of nuclear factor-κB ligand in synovial fibroblasts.


Cells expressing wild-type HLA-B27 were more permissive of intracellular replication of Salmonella enteritidis compared with mock-transfected or A2-transfected controls, not reduced elimination of Salmonella.


The antigen-presenting cells are important to lead inflammation. In the HLA-B27-transgenic rat, defective stimulation of T cells by antigen-presenting cells was observed.


This study showed analysis of cytokine production in patients with acute and chronic ReA. Anti-TNF-α treatment may be effective in chronic ReA because of high production of TNF-α and interferon-γ.


This study showed that HLA-B27-restricted epitopes derived from human aggrecan are involved in the induction of experimental spondylitis and that this proteoglycan may be important in the pathogenesis of SpA.


The synovium in Spa is different from rheumatoid arthritis and is characterized by abundant CD163+ macrophages.

Ankylosing spondylitis and reactive arthritis Kim et al. 405
Pathogenesis of psoriatic arthritis
Christopher T. Ritchlin

Purpose of review
Heterogeneity in clinical presentation and disease course has hindered understanding of disease mechanisms in psoriatic arthritis, but recent studies have provided insights into pathogenesis. This review examines relevant animal models and genetic factors implicated in disease susceptibility. Also, recent reports on mechanisms related to synovial and entheseal inflammation are discussed.

Recent findings
Two transgenic mouse models (amphiregulin, STAT-3) were reported that have features of psoriatic arthritis and psoriasis respectively. Genetic studies did not find associations between psoriatic arthritis and several class I major histocompatibility complex alleles, the caspase-activating recruitment domain 15 domain, or the major histocompatibility complex class I chain-related gene A9 allele, in sharp contrast to previous reports. The striking association of psoriatic arthritis with mutations in the killer immunoglobulin receptors on natural killer cells is particularly exciting but needs further study. Psoriatic arthritis has histopathologic features that are more characteristic of other forms of spondyloarthritis than rheumatoid arthritis. Moreover, several of these features correlate with clinical disease activity. Matrix metalloproteinases are strongly expressed in psoriatic arthritis synovium, and serum matrix metalloproteinases-3 may be a reliable biomarker for monitoring disease response. Finally, the concept of an ‘enthesis organ’ may explain the magnetic resonance imaging findings and clinical signs of psoriatic enthesitis and dactylitis.

Summary
Recent findings highlight the importance of innate immune mechanisms in disease pathogenesis. Moreover, psoriatic arthritis and rheumatoid arthritis synovium have divergent histopathologic features that indicate distinct disease mechanisms. The generation of appropriate animal models coupled with reliable biomarkers will result in a deeper understanding of disease pathogenesis and will facilitate the identification of new therapeutic targets.

Keywords
animal models, enthesitis, pathogenesis, psoriatic arthritis, synovitis

Abbreviations
Ang angiopoietin
CARD caspase-activating recruitment domain
DC dendritic cell
IL interleukin
KIR killer immunoglobulin-like receptor
MHC major histocompatibility complex
MICA MHC class I chain-related gene A
MMP matrix metalloproteinase
NK natural killer
PsA psoriatic arthritis
RA rheumatoid arthritis
SpA spondyloarthritis
STAT signal transducer and activator of inflammation
TIMP tissue inhibitor of metalloproteinase
TNF tumor necrosis factor
VEGF vascular endothelial growth factor

Introduction
The remarkable success of biologic agents in the treatment of psoriasis and psoriatic arthritis (PsA) has fostered a great deal of hope and optimism among patients who suffer from these potentially disabling and disfiguring disorders. These therapeutic breakthroughs have been accompanied by scientific advances that have shed new light on the mechanisms that underlie the skin and joint disease of PsA. In particular, during the last year, new animal models have been developed that provide insight into the molecular events that drive the inflammatory phenotypes in the skin and joint. In addition, genetic studies have unveiled new alleles and polymorphisms that are associated with PsA. At the level of the end organ, analyses of synovial tissue have demonstrated features in the PsA joint that, although similar to those observed in other forms of spondyloarthritis, differ from the histopathology found in rheumatoid synovial tissue. Finally, a more complete understanding of the anatomy of entheses throughout the body provides a fresh perspective on the potential role of this important structure in disease pathogenesis. This review focuses on scientific findings during the last year that add to our understanding of disease pathogenesis in PsA. The bulk of the recent literature that relates to PsA falls into four broad categories: animal models, genetic factors, synovial histopathology, and entheseal structure and function.

Animal models
Although no animal model to date recapitulates the extensive joint and skin inflammation observed in PsA, several transgenic and knockout models manifest individual features of the disorder (Table 1 [1–6]). In three of these models, altered expression, either increased or decreased, of major histocompatibility complex (MHC) alleles resulted in joint pathology. Interestingly, studies of baboons revealed that about 30% spontaneously develop radiographic changes
that resemble those observed in PsA [4]. Inflammatory skin lesions have been observed in baboons, but a definitive diagnosis of psoriasis has not been reported in this species [4].

A subset of male DBA/1 mice, caged together for 12 weeks, spontaneously developed paw dactylitis [5]. The number of joints involved gradually increased over time. Histologic analysis showed diffuse neutrophil accumulation along with ankylosing enthesitis, onychoperiostitis with progressive destruction of the nailbed and underlying distal phalanx resorption. Moreover, areas of enthesitis were not contiguous to regions of synovitis or dactylitis, which does not support the view that inflammation begins at the enthesis and then spreads out to involve adjacent structures [7]. These mice did not have any skin lesions.

Mice overexpressing amphiregulin, an epidermal growth factor-related polypeptide growth factor, developed skin and joint pathology [8]. Amphiregulin is an autocrine growth factor for keratinocytes that produces a psoriasis-like skin pathology and mild knee synovitis when the transgene is expressed in the suprabasal epidermis under a keratin promoter. Histologic exam of the joints showed tortuous dilated blood vessels, and a mixed infiltrate comprised of lymphocytes, plasma cells, and neutrophils. No mention was made, however, regarding the presence or absence of synovial hyperplasia, bone resorption, cartilage erosion, or enthesal inflammation. Evaluation of these mice was limited by their short 3-week lifespan.

The model that exhibits the most characteristic cutaneous characteristics of psoriasis is the signal transducer and activator of inflammation (STAT)-3 transgenic mouse [9]. STATs are a family of latent cytoplasmic proteins that transmit signals to the nucleus, which controls cell migration, proliferation, and survival [10]. STAT-3 is essential for wound healing in keratinocytes, and mice with overexpression of this growth factor developed inflammatory plaques with histologic features observed in psoriasis (hyperkeratosis, parakeratosis, dermal infiltrates with CD4+ cells, dilated blood vessels, and Munro abscesses). Grafting of skin from the transgensics to athymic nude mice did not yield psoriatic plaques until activated T lymphocytes were also delivered to the dermis. These experiments indicated that the psoriatic phenotype is triggered by interplay between the epidermal keratinocytes and T lymphocytes. The cutaneous inflammation was inhibited with a decoy molecule that competes with binding to STAT-3 and interferes with transcriptional activity. Of note, STAT-3 is overexpressed in the epidermis of both involved and uninvolved skin of psoriasis patients, but not in the epidermis of other cutaneous inflammatory disorders, highlighting the potential significance of this molecule in human disease. It is not known, however, whether these mice develop joint pathology [11].

<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Genetic alteration</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammer et al. [1]</td>
<td>Rat</td>
<td>HLAB27/β2 transgene</td>
<td>Psoriasiform skin lesions, peripheral arthritis, gut and nail lesion</td>
</tr>
<tr>
<td>Khare et al. [2]</td>
<td>Mouse</td>
<td>β2 microglobulin knockout</td>
<td>Paw swelling, joint ankylosis, nail changes</td>
</tr>
<tr>
<td>Bardos et al. [3]</td>
<td>Mouse</td>
<td>Lack endogenous MHC class II molecules</td>
<td>Psoriasiform skin lesions, resorption of distal phalanges, nail changes</td>
</tr>
<tr>
<td>Rothchild and</td>
<td>Baboon</td>
<td>None</td>
<td>30% of baboons exhibit radiographic changes</td>
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<tr>
<td>woods [4]</td>
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<td>similar to PsA</td>
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<tr>
<td>Lories et al. [5]</td>
<td>Mouse, DBA/1 strain Mouse, FVB/NCrI BR strain</td>
<td>None Amphiregulin expression under control of INV-AR</td>
<td>Ankylosing enthesitis, dactylitis, onychoperiostitis Psoriasiform skin lesions, mild knee synovitis</td>
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**Genetic factors**

A variety of genetic factors have been associated with PsA [12]. These include alleles in the MHC locus (human leukocyte antigen [HLA] B13, 17, 57, Cw6, MHC class I chain-related gene A (MICA)-9), the caspase-activating recruitment domain (CARD) 15 domain on chromosome 16q, and polymorphisms in the tumor necrosis factor (TNF) gene. Studies performed during the last year analyzed the association of several of the loci outlined here with PsA, and the findings did not concur with previous reports. In a northern Swedish population with a homogeneous ethnic background, six different susceptibility regions were investigated in 120 PsA patients and 94 control subjects [13]. These authors found an association with one of the markers in the TNFB locus (P value corrected for number of alleles (p_c) = 0.024) in the HLA region, but they did not uncover any associations with any of the HLA-B or HLA-C alleles previously shown to be associated with PsA. A significant linkage was found between TNFB loci and HLA-B antigens (P = 0.0001). Also, they did not find the association of PsA with the CARD15 domain on chromosome 16q that was recently published [14].

A study of 193 Italian PsA patients and 150 control subjects also failed to show an association between CARD15 polymorphisms and PsA [15]. In a Spanish study of 120 PsA patients, 50 psoriasis patients and 175 healthy control subjects, Cw6 was associated with psoriasis but not PsA. They did not find any association between HLA-DR alleles and PsA, but the presence of HLA-DR8 was associated with polyarthritis in subgroup analysis [16].

**Table 1. Animal models with features of psoriatic arthritis**
a Croatian population of 58 PsA patients and 157 healthy control subjects, development of PsA was associated with the MICA-A4 (p_c = 0.017), but not the previously identified MICA-A9 triplet [17]. The frequencies of MHC B39 and 57 were also increased in the PsA population. In a German population of 57 PsA patients, 239 psoriasis patients, and 135 control subjects, the promotor polymorphism at the TNF locus, TNFA-238 was associated with psoriasis whereas the TNFA-309 polymorphism was decreased in this population. The TNFA-309 polymorphism was also decreased in PsA patients compared with control subjects, but it was a marker of more severe joint disease. The finding that the TNFA-309 polymorphism is associated with more erosive disease is in agreement with previous results [18]. Interestingly, the TNF-308 allele is associated with high levels of TNF production, and this may provide a mechanism to explain the more severe joint disease found in patients with this polymorphism.

Taken together, it is quite challenging to construct a coherent model that incorporates genetic factors in PsA based on the highly discordant data derived from different populations. Several caveats must be considered, however, when analyzing the genetics of PsA [19]. First, the data are consistent with a multifactorial pattern of inheritance [20]. Second, PsA is a heterogeneous disease with multiple subsets (erosive polyarthritis, axial disease, oligoarthritis, distal joint arthritis with or without spondylitis) and contributing genetic factors may differ in the subgroups. Third, the HLA region is highly diverse and many loci are in strong linkage disequilibrium. Fourth, PsA almost always occurs in the setting of psoriasis so that factors related to the skin disease may mask or confound those related to arthritis. Thus, major genetic determinants in PsA will likely be identified in the future with strategies that combine linkage and association studies performed on large data sets with well-characterized patients [20].

Natural killer (NK) cells are lymphocytes activated during the early phase of the innate immune response. They eliminate pathogens or malignant cells via a direct cytotoxic assault or by the release of cytokines and chemokines [21•]. NK cells possess both inhibitory and activating immunoglobulin-like receptors (KIR), and cell activation or inhibition is determined by an integration of these receptor signals. The inhibitory KIR2DL bind HLA-Cw ligands and genes encoding these receptors are present in almost all individuals whereas the activating receptor genes, KIR2DS1 and KIR2DS2, are present in only 35 to 56% of European Americans. The ligands for the activating KIRs have not been elucidated.

Perhaps the most impressive and somewhat unexpected genetic association recently described is the strong link between the presence of certain activating KIR on NK cells and PsA [22]. These investigators reported that subjects were most susceptible to PsA if they had certain activating KIRs combined with the absence of HLA ligands for corresponding homologous inhibitory KIRs. Activating KIRs have also been associated with an increased risk of psoriasis [23]. Nelson et al. [24•] revised their original model based on the concept that susceptibility to PsA is determined by the overall balance of activating KIR and inhibitory KIR-HLA genotypes. The presence of the two activating receptors KIR2DS1 and KIR2DS2 increases the risk for PsA, and this risk is enhanced if the inhibitory HLA class I ligands for the inhibitory KIR2DL are missing (Fig. 1). Both NK cells and T lymphocytes express the KIRs [25]. NK T cells have been isolated from the epidermis of acute and chronic psoriatic lesions and they cluster around the inner margin of the plaque, suggesting involvement in the latter phases of inflammation [26,27]. NK T cells become activated in a CD1d-restricted manner. CD1d is a non-polymorphic molecule that is overexpressed by psoriatic keratinocytes [28]. Moreover, NK T cells cocultured with CD-1d-positive keratinocytes produce large quantities of interferon-γ. Thus, NK T cells tipped toward activation

Figure 1. Killer immunoglobulin-like receptors (KIRs) and susceptibility to psoriatic arthritis

(a) Putative protective phenotype. Both inhibitory KIRs bind to their HLA-Cw ligands and no excitatory KIR is expressed. (b) Putative susceptible phenotype. The activating ligand binds to a KIR receptor and the inhibitory KIR does not have a corresponding ligand. (Source: Nelson GW, Martin MP, Gladman D, et al. Cutting edge: heterozygote advantage in autoimmune disease: hierarchy of protection/susceptibility conferred by HLA and killer Ig-like receptor combinations in psoriatic arthritis. J Immunol 2004; 173:4273–4276. Modified, with permission.)
by the presence of activating KIRs and the absence of inhibitory ligands have the potential to promote a Th1 response. In a related study, Spadaro et al. [29] reported that NK T cells were significantly reduced in the synovial fluid but not the blood of PsA and rheumatoid arthritis (RA) patients compared with healthy control subjects. The investigators did not analyze synovial tissues or skin biopsies so they could not exclude the possibility that the NK T cells were selectively homing to the synovial membrane and/or the psoriatic plaque.

**Synovial histopathology**

Analysis of PsA and RA synovial tissues using histologic and immunohistochemical techniques with disease-specific markers indicated the presence of important histopathologic features that differentiate the two arthropides. Notably, PsA synovial membranes share more common characteristics with other forms of spondyloarthritis (SpA) than with RA [30].

A study of synovial biopsies obtained by needle arthroscopy and analyzed by two blinded observers demonstrated that 99 SpA (33 PsA) tissues had significantly less lining layer thickness and greater vascularity than 86 RA samples [31*]. Increased vascularity at the macroscopic and microscopic level in PsA membranes has been reported by other investigators [32, 33]. In one open-label trial of infliximab in nine PsA patients, tissue expression of vascular endothelial growth factor (VEGF), VEGF receptor-1, VEGF receptor-2, stromal-derived factor-1 proteins, and the CD31 vascular area declined significantly after three infusions [34]. In contrast, T-lymphocyte subsets, B lymphocytes, and plasma cell populations were unchanged, but angiopoietin (Ang)-2 protein expression increased. These data show that TNF antagonism modulates several molecules involved in angiogenesis and provide further support for the concept that TNF-α is required for the maintenance of the abnormal vascular pathology in the psoriatic joint. The increased Ang-2 expression after treatment was somewhat surprising given its putative role in psoriatic neoangiogenesis [35]. Recently studies have shown, however, that Ang-2 is required for vascular regression when VEGF is inhibited [36].

Immunohistochemical analysis of the 99 SpA and 65 RA samples mentioned earlier revealed a significant reduction of infiltrating CD68+ sublining macrophages in SpA tissues but a greater percentage of these macrophages expressed CD163 [31*]. The transmembrane protein CD163 is a member of the scavenger receptor, cysteine-rich superfamily. Macrophages expressing this receptor release greater quantities of interleukin (IL)-1 and TNF in vitro after lipopolysaccharide (LPS) stimulation than CD163-macrophages [37]. Of particular relevance is a report that identified CD163+ macrophages in the colon of patients with Crohn disease and in SpA patients but not healthy control subjects [38]. The presence of these cells in the colon and the joint provides a common mechanism linking inflammation at these two sites. RA tissues had significantly more lymphoid aggregates, and a greater percentage of cells stained positively for CD1a – a marker of monocytedendritic cells. Staining for citrulline and the shared epitope MHC-HC gp39 complexes was detected in 27 of 59 and 28 of 58 RA tissues respectively, whereas only 1 of 82 SpA samples expressed the shared epitope and none of the 82 tissues reacted with the anticitrulline antibody. In a separate analysis, lining cell hyperplasia, infiltration of neutrophils, and CD163+ macrophages along with lining layer hyperplasia correlated with disease activity independent of SpA subtype. In contrast, global disease activity in RA correlated with the extent of CD3 cell infiltration and the presence of T-cell antigens (citrullinated proteins and MHC-HC-gp39 complexes).

One interpretation of the studies outlined here is that a persistently altered innate immune response is the driving force behind the pathologic changes observed in PsA synovium. The finding of increased levels of the innate cytokine IL-18 in PsA serum and synovial tissue also fits with this interpretation [39]. IL-18 is a member of the IL-1 superfamily with a diverse range of biologic functions. IL-18 promotes Th1 differentiation, synergizes with other cytokines, stimulates angiogenesis, upregulates CXC chemokine expression on synovial fibroblasts, participates in articular destruction, and increases mononuclear cell recruitment. Most IL-18 is produced by CD68+ macrophages, and both IL-1 and TNF induce expression of this cytokine [40]. Dendritic cells (DCs) also participate in the innate immune response, and large numbers of monocytedendritic cells have been identified in psoriatic plaques [41]. Lande et al. [42] found a higher frequency of synovial fluid immature plasmacytoid DC in PsA and RA compared with osteoarthritis. Plasmacytoid DCs are a rare population of DCs that home to target tissues and are likely involved in chronic inflammation [43]. Although the cells isolated from the fluid were of an immature phenotype, stimulation with a CpG oligonucleotide or infection with virus in vitro resulted in maturation and release of type I interferon. These experiments show that the plasmacytoid DCs do not have a functional maturation defect; however, they may have maturation arrest because of inhibitory factors in the joint fluid. Further studies are required to understand better the role of plasmacytoid DCs in disease pathogenesis.

Somatic mutations of the p53 gene have been demonstrated in fibroblastoid cells in RA synovium, and microdissection studies suggest that these mutations are induced by oxidative stress [44, 45]. Synovial tissues removed arthroscopically from 27 PsA and 18 RA patients were immunostained with a mouse anti-53 monoclonal antibody, and the extent of cellular infiltration was analyzed
with monoclonal antibodies to T cells, B cells, and macrophages [46]. The p53 protein was detected in 16 of 18 RA patients and 9 of 16 tissues, and the mean score of p53 expression was significantly higher in RA synovium despite a similar degree of mononuclear cell infiltration. Also, the mean score of p53 expression was associated with the baseline erosion score in RA but not PsA. Differential expression of p53 implies distinct disease mechanisms, although these results must be interpreted with some caution because the investigators did not control for extent of synovial proliferation. Synovial hyperplasia, generally higher in RA compared with PsA tissues, could lead to increased oxidative stress and subsequent elevation of p53 expression.

Cartilage degradation and tissue remodeling are mediated in part by matrix metalloproteinases (MMPs), and their importance in RA joint damage has been extensively investigated [47]. The role of MMPs in SpA was examined by staining 41 SpA (19 PsA) and 20 RA tissues with antibodies to MMP-1, MMP-2, MMP-3, MMP-9, TIMP-1, and TIMP-2 [48*]. Serum and synovial fluid samples were also collected for MMP analysis by enzyme-linked immunosorbent assay. MMPs and TIMPs were equally expressed in SpA and RA synovium, and these results concur with those recently reported by Gianelli et al. [49]. Intriguingly, serum levels of MMP-3 correlated with peripheral joint disease activity and not global inflammation. Specifically, ankylosing spondylitis (AS) patients without peripheral arthritis had lower MMP-3 levels that did not correlate with disease activity in the spine. After infliximab treatment, a rapid and sustained decline of serum MMP-3 (but not the other MMPs) was noted. One potential stimulus to MMP-1 and MMP-3 release aside from IL-1 and TNF is serum amyloid A—an acute-phase protein that induces MMP-1 and MMP-3 release, and fibrocartilage; and zone 4, bone [52]. The presence of diffuse magnetic resonance imaging changes in bone and soft tissue adjacent to entheses coupled with pain and tenderness extending beyond the insertion site suggest that enthesal structure and function may be more complex than initially proposed [6]. McGonagle et al. [53] developed the concept of an ‘enthesis organ’ (Fig. 2) that varies in structure at different locations, but in general consists of the enthesis and adjacent fibrocartilage, periosteum, and synovial and/or bursal membranes. These structures come in close contact, particularly during flexion, and this may have implications for understanding the origins of concomitant synovial and enthesal inflammation in PsA.

Pathologic studies of entheses associated with the medial and lateral epicondyles from cadavers revealed several interesting findings [54]. First, the entheses from both epicondyles fused with the collateral ligaments, which fanned out over a large area. This wide insertional area conceivably serves to dissipate stress from a small focal insertion point. Second, fibrocartilage was a consistent component of all entheses and did not represent a pathologic degeneration that is consistent with a chronic functional adaptation response to stress. Third, entheses from elderly subjects had extensive microscopic damage possibly reflecting normal degeneration that is consistent with a chronic functional adaptation response to stress.

In a separate study, these same authors examined entheses from 28 sites in limbs of formalin-fixed cadavers [55*]. Articular entheses organs were identified at 14 entheses, including attachments of the lateral collateral and cruciate ligaments of the knee, the digital extensor tendons, the popliteal tendon, and the tibialis anterior. Extraarticular entheses organs were found at the biceps brachii and patellar tendon insertions. These findings demonstrate that enthesis organs are not limited to the Achilles tendon and may help to explain the clinical pattern of widespread enthesal pain observed in many PsA patients.

**Conclusion**

A coherent model for understanding PsA pathogenesis is emerging based on data derived from animal models, genetic studies, skin and synovial histopathology, and clinical
trials. Animal models demonstrate the significance of MHC molecules in PsA in that manipulation of class I or class II MHC molecules generates aspects of the psoriatic phenotype in both the joint and skin. The strong association of PsA with activating KIRs suggests a role for NK cells and NK T cells, in part through their binding to class I MHC ligands expressed on target cells. Histopathologic studies highlight the importance of the innate immune response with the demonstration that monocytes, particularly the presence of the CD163+ subset, correlate with disease severity and treatment response. Lastly, the marked reduction in vascularity and macrophage infiltration following anti-TNF therapy underscores the pivotal importance of this innate cytokine in maintaining joint inflammation. Future studies that incorporate new technologies of genetic analyses performed on large well-characterized populations will yield valuable information regarding etiology and susceptibility. In addition, clinical trials directed at new targets on T cells, B cells, osteoclasts, and possibly osteoblasts will allow investigators to define more effectively disease mechanisms in psoriatic skin and joints.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as **of special interest** and *of outstanding interest*


7. Expression of amphiregulin under a keratin promoter generated a murine model with both psoriasisform skin disease and synovitis of the knees; however, the mice only lived 3 weeks and the arthritis was mild and nondestructive.


9. Elegant study that demonstrated overexpression of STAT-3 in the keratinocytes of human psoriatic plaques. Subsequent overexpression of the transgene STAT-3 in mice resulted in a psoriatic phenotype that exhibited many of the clinical and histopathologic features of the human disease.


This cadaveric analysis supports the concept that ‘enthesis organs’ are widespread throughout the body and not just limited to the Achilles tendon and the proximal interphalangeal joints.
Imaging in spondylitis
Désirée van der Heijde and Robert Landewe

Purpose of review
The purpose of this review is to describe and evaluate recent findings with respect to imaging in ankylosing spondylitis. The review includes articles from the literature that were published in 2004.

Recent findings
Three types of articles are described: methodological studies aimed at validating scoring methods for detecting inflammation and structural damage by plain radiography and magnetic resonance imaging, descriptive reviews on imaging in ankylosing spondylitis and two studies evaluating miscellaneous aspects of imaging. Methodological studies showed promising psychometric properties of scoring methods for assessing structural damage of the spine by plain radiography, and for assessing inflammation of the spine by magnetic resonance imaging. Based on methodological qualifications, a method of preference (the modified Stoke ankylosing spondylitis spine score) could be identified for assessing 2-year change in structural damage. A number of reviews outlined the particular potential of magnetic resonance imaging in evaluating characteristics of inflammation and structural changes in ankylosing spondylitis. Two unrelated studies showed the potential yields of multidetector computed tomography in detecting spinal fractures in ankylosing spondylitis, and of magnetic resonance imaging in detecting shoulder problems in ankylosing spondylitis.

Summary
MRI inflammation may become an important outcome measure in clinical trials in ankylosing spondylitis patients, and plain radiography may be used to assess 2-year progression of structural damage of the spine in ankylosing spondylitis. The descriptive reviews may serve as an introduction in the field of imaging in ankylosing spondylitis, and the studies on multidetector computed tomography and magnetic resonance imaging in detecting shoulder problems may have direct impact for the treatment of patients with ankylosing spondylitis in the clinical context.

Keywords
ankylosing spondylitis, imaging, magnetic resonance imaging, plain radiographs, scoring methods

Abbreviations
AS
ankylosing spondylitis
ASspiMRI-c
ankylosing spondylitis spine MRI chronicity
BASRI
Bath ankylosing spondylitis radiology index
CT
computed tomography
DISH
diffuse idiopathic skeletal hyperostosis
MDCT
multidetector CT
MRI
magnetic resonance imaging
mSASSS
modified Stoke ankylosing spondylitis spine score
SASSS
Stoke ankylosing spondylitis spine score
SI
sacroiliac
VU
vertebral unit

Introduction
Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the sacroiliac (SI)-joints and the spine. The research in the field of AS has recently been boosted by the introduction of biologic agents, which have demonstrated superb clinical efficacy. One of the major fields in AS research is the imaging of the spine and SI-joints. There are several reasons. Magnetic resonance imaging (MRI) in the field of AS provides an image of the inflammation of the spine and SI-joints before conventional radiography shows any abnormality. This may facilitate earlier diagnosis of AS, which is more important now that effective drugs are available. This is analogous to a therapy for rheumatoid arthritis in which the demonstration of drug effects on radiographic progression has become of pivotal importance to the claim that such drugs are effective in preserving structural integrity. Now that biologic agents have shown to be effective in mitigating inflammatory symptoms of AS, efforts will be put into proving that these drugs may retard the progression of structural spinal changes that are so characteristic for this disease. Much of the recent research has been dedicated to scoring methods of the spine, both for plain radiography and for MRI.

In this review, recent work that has been published with regard to validating abnormalities found on plain radiographs and MRI will be discussed. The focus is on the methodology rather than on the imaging technique. A number of reviews that have been written recently will be covered as well, with a focus on the potential of different imaging techniques in AS rather than on the methodological aspects. These reviews, which include many informative X-ray and MRI images, serve as an introduction to relatively uninvolved readers. Finally, a few miscellaneous studies on different topics related to imaging in AS will be briefly reviewed.
Plain radiographs
Abnormalities depicted on plain radiographs of the spine in AS patients showed very slow progression and so were difficult to use as an outcome measure. With the availability of more sophisticated scoring methods, these insights are changing. Many pathologic features can be seen in patients with AS on spinal plain radiographs. These features include erosions, squaring, sclerosis, syndesmophytes, bridging syndesmophytes, spondylodiscitis, and fractures. Three methods have been described in the literature to score abnormalities in the spine. The first is the bath ankylosing spondylitis radiology index (BASRI) [1]. This method is a global grading of the lateral cervical spine, the anterior and lateral lumbar spine combined, and the SI joints. Each site is scored from 0 (normal) to 4 (fusion involving at least three vertebral units). The maximum score is 72. The modified score is 2 if assessed by mSASSS, compared with only 5% by the mSASSS. As the BASRI also needs an anteroposterior (AP) view of the lumbar spine, more radiation is involved. Time needed to score the radiographs is comparable. Taking all these results together, the authors conclude that the mSASSS is the preferred method for clinical trials. Based on the preference of the rheumatologist, both the mSASSS and BASRI could be used in clinical practice.

Magnetic resonance imaging
The next sections describe the use of magnetic resonance imaging in both the spine and SI joints in patients with AS.

Spine
Braun et al. investigated the comparative validity of MRI and conventional radiography with respect to detecting structural (‘chronic’) changes in the spine of 39 randomly selected AS patients [6]. Mean age was 40 years, and mean disease duration was 15 years, ranging from 2–34 years, thus providing an appropriately broad spectrum of patients.

T1-weighted MRI was performed in all patients, and scored according to the ankylosing spondylitis spine MRI chronicity (ASspiMRI-c) score, which quantifies structural damage (erosions, sclerosis, squaring, syndesmophytes, bridging and fusion) on a semiquantitative scale (from 0 = normal, to 6 = complete fusion) in 23 vertebral units (VU) covering the entire spine from C2 to S1. A vertebral unit is defined as the lower part of the vertebral body of the upper vertebra, the adjacent intervertebral disc and the upper part of the vertebral body of the lower vertebra.
Conventional radiography of the entire spine was also performed in all patients, and scored according to three existing methods: the BASRI, the modified SASSS and the Berlin score. The Berlin score is a newly proposed and yet unvalidated method, based on the same features and VUs as included in the ASspiMRI-c. Two readers performed all scorings, and average reader scores were used in the analyses.

Scores obtained by conventional radiography (three methods) and MRI (one method) correlated moderately well (correlation coefficients ranging form 0.51–0.66), with an exception for the comparison between modified SASSS and ASspiMRI-c (correlation coefficient 0.15). A possible explanation for this lack of correlation is that the thoracic spine dominates the ASspiMRI-c, while it is omitted in the modified SASSS for technical reasons (overprojection of the lungs). Structural changes were detected by conventional radiography (Berlin score) in 34%, 37% and 31% of the patients in the cervical, the thoracic and the lumbar spine, respectively. MRI detected such changes in 28%, 58% and 26% of the patients, respectively. There were differences between conventional radiography and MRI with respect to dominant sites of involvement: While conventional radiography detected lesions predominantly in the vertebrae of the cervical spine, MRI did so in VUs of the thoracic spine.

Important shortcomings of ASspiMRI-c for MRI in comparison with scoring methods for conventional radiography of the spine is the lower interreader reliability, as was also investigated in the same patient group. In 38 patients with active disease, documented by a mean Bath ankylosing spondylitis disease activity index (BASDAI) of 6.4 on a scale from 0–10, and a mean C-reactive protein of 22.2 mg/dl, two MRI sequences were performed: T1-weighted fat-saturated spin echo after gadolineum diethylenetriamine pentaacetic acid (T1/Gd), and short-tau inversion recovery (STIR). Both sequences were scored using the ASspiMRI-a score, which quantifies signs of inflammation (bone marrow oedema with or without vertebral erosion) on a semiquantitative scale ranging from 0 (normal) to 6 (large erosion in combination with bone marrow oedema) in 23 VUs.

Between-reader comparison revealed a very good agreement with regard to total scores (sum of all VU scores) (intraclass correlation coefficient: 0.91 for T1/Gd, and 0.86 for STIR). Method comparison between STIR and T1/Gd revealed 84% concordance with respect to affected VUs. 10% of the VUs that were found normal on T1/Gd were found abnormal on STIR. Vice versa, 6% of the VUs that were found normal on STIR were found abnormal on T1/Gd, thus accounting for a discordance rate of 16%. Abnormalities were detected in 31% of the VUs with STIR, and in 27% of the VUs with T1/Gd, and this difference in sensitivity was found similarly across all three sites of the spine.

In a third article on this group of patients, Baraliakos et al. described the distribution pattern of inflammatory lesions in the spine [8]. VU T7-T8 most frequently showed inflammatory lesions, both by STIR and T1/Gd, followed by VU T6-T7 and VU T11-T12. Lower lumbar VUs and mid cervical VUs were least frequently affected with regard to inflammation. Looking at the patient level, 24% of the patients showed definite inflammation in the cervical spine, 74% of the patients in the thoracic spine and 18% of the patients in the lumbar spine.

Sacroiliac joints

Jee et al. described MRI abnormalities of SI-joints, and investigated the association between MRI abnormalities and disease activity in 19 patients [9]. They claim that all patients have documented AS according to the New York criteria, but 3/19 patients appeared to have normal pelvic radiographs. They found abnormalities in 84% (68% bilateral, 16% unilateral) of the patients by plain radiography, in 94% (84% bilateral, 10% unilateral) of the patients by MRI (STIR and T1/Gd) and in 64% of the patients by bone scintigraphy. Abnormalities that were associated with disease activity (erythocyte sedimentation rate and C-reactive protein) included bone marrow oedema and synovial enhancement. Bone scintigraphy correlated well with synovial enhancement (MRI) but not with ESR and/or CRP.

The authors conclude that MRI may be advantageous in diagnosing AS early, which sounds sensible, but the low number of patients and the poor definition of the patient group seriously hamper this study.

Reviews

Bennett et al. review clinical and epidemiological aspects of AS (and psoriatic arthritis) for a radiologic readership, and focus on imaging modalities [10]. They claim that plain radiography of the SI-joints remains the sine qua non for a diagnosis of AS (which is technically wrong because diagnostic criteria for AS are lacking), and they see a promising future for MRI in detecting inflammation of SI-joints before radiographic abnormalities have occurred. The main reason that it is valuable to detect AS earlier is that currently effective therapies (tumor necrosis factor blocking drugs) are available. They also review imaging of the spine by describing characteristic radiographic abnormalities and typical abnormalities found on MRI. They conclude by stating that MRI is a promising technique in the imaging of AS and/or spondylarthropathies.
Levine et al. reviewed for a radiologic readership the lesions that could commonly be found by MRI in patients with AS in a far more comprehensive way [11]. They provide a number of helpful images, and they describe the appearance of common and less common lesions such as facet- and costovertebral lesions, osteitis, syndesmophytes, atlantoaxial lesions, ligamentous and disc calcifications, and others. They refer to complications of fractures in patients with AS—these patients are indeed vulnerable to fractures due to rigidity and osteoporosis—and claim that MRI has advantages over CT and plain radiography in detecting these complications such as prevertebral hematoma, disruption of longitudinal ligaments and of the intervertebral disc. This comprehensive review is interesting for rheumatologists who want to learn about MRI abnormalities in AS, but does not provide new information.

Hermann and Bollow also review the value of MRI in patients with inflammatory arthritides, among which is AS [12]. This review solely focuses on MRI, and contains descriptive information and numerous useful MRI examples. Spine and SI-joints are covered, as well as inflammatory and structural lesions. Importantly, Bollow dedicates a paragraph to differential diagnosis of AS, such as diffuse idiopathic skeletal hyperostosis (DISH) and infectious spondylitis. MRI can be particularly helpful in distinguishing these conditions.

In her review on the importance of quantification of damage in inflammatory arthritis, including AS, van der Heijde is strongly in favor of using validated scoring methods when quantifying lesions. With respect to AS, three different methods are available, which all have been validated by their designers. As already stated above, a direct comparison of BASRI, SASSS and modified SASSS provided evidence that modified SASSS outweighs the other two methods on various aspects.

Miscellaneous
Two interesting articles on the different aspects of imaging in AS are reviewed below. The first is on the preferred imaging modality for assessing cervical spine fractures; the second is on the use of MRI in shoulder problems.

Imaging of cervical spine fractures
Patients with AS are at increased risk for spinal fractures, which are frequently located at the lower cervical spine and cervicothoracic junction. This can occur after only minor trauma, and establishing a diagnosis of a spinal fracture is important as patients with AS may have a higher risk of neurologic complications. Plain radiographs have a limited ability to diagnose spinal fractures in AS patients accurately. Conventional helical computed tomography (CT) is considered an accurate and reliable imaging modality for screening cervical spine trauma in high-risk patients. However, multidetector CT (MDCT) is faster than conventional helical CT resulting in shorter scanning time, with fewer motion artefacts, reduced partial volume effects, decreased image noise, high-quality multiplanar reformation, and isotropic viewing. All these factors substantially increase the diagnostic power of this imaging modality. Koivikko et al. evaluated the use of MDCT in patients with advanced AS with suspected cervical spine fractures and compared the MDCT findings with plain radiography and MRI [13**]. It is a retrospective study in a hospital serving 1.4 million people. All patients received CT if a cervical spine fracture was suspected. Plain radiography was not routinely performed in these patients. All patients with AS with trauma and whose cervical spines were initially examined with MDCT were included in the study. To obtain consensus, MDCT and plain radiographs (if available) were viewed by two radiologists. A third radiologist reviewed the MRI scans (if available), blinded for the MDCT information. Eighteen patients with AS met the inclusion criteria. A simple fall was present in 13 patients, a bicycle accident in 2, a fall from approximately 2 meters in 2, and a fall from a horse in 1. Nine patients showed neurologic symptoms upon arrival in the hospital. Primary MDCT detected cervical spine injury in 17 of the 18 cases. Altogether, MDCT revealed 31 fractures and 1 facet joint subluxation. Seven patients had multiple fractures. Plain radiographs were available for 12 cases, but 11 lateral cervical spine films were inadequate because of failure to visualise the entire spine. Plain radiography detected only 12 of the 25 fractures in these patients with available films. Eleven patients underwent cervical spine MRI. Twelve of the 20 fractures detected by MDCT in these patients were also detected by MRI. As expected, MRI was superior to MDCT in the assessment of soft tissue and spinal cord injury. Every patient suffering from advanced AS should be considered a high-risk patient; even a minor trauma can result in unstable cervical spine fracture. Fractures in advanced AS often show an abnormal orientation and are frequently associated with spinal cord injuries. MDCT is recommended as the primary screening tool in AS patients with trauma suspecting a cervical spinal injury.

MRI of the shoulder
Involvement of the shoulder is a frequent clinical problem in patients with AS. However, data on the prevalence are scarce. This was studied by Lambert et al. by a retrospective chart review of 400 patients with AS with a mean disease duration of 18.4 years [14**]. Not a single patient was recorded as having specific shoulder joint pathology, but shoulder pain was recorded in 3.5% of the patients. The main purpose of this study was to assess shoulder problems by clinical examination and MRI in patients with AS, and compare this with controls. One hundred of the 400 AS patients included in the chart review were randomly selected for systematic clinical evaluation. Those patients with current shoulder pain of at least one-month
duration and pain within the shoulder-specific area of a manikin were further evaluated by MRI. Several control cohorts were defined and there was also a validation in a prospective cohort of AS patients. In the patients that underwent clinical examination 24.7% of the AS patients had clinically evident shoulder involvement vs. 14.2% in the control cohort. Rotator cuff tendonitis was significantly more prevalent in patients (15.1%) than in controls (3.5%). Shoulder lesions in AS are characterised on MRI by intense bone oedema localised to the supraspinatus/greater tuberosity and deltoid/acromial entheses. Intense acromial bone oedema at the deltoid origin was not described before and is a highly specific feature of AS (41.2% of AS patients, 0% in controls). The authors state that enthesopathy of the rotator cuff is underrecognized in AS. In the prospective cohort of AS patients, 22.4% had rotator cuff enthesopathy.

Conclusions
Apart from a number of descriptive reviews, useful to serve as an introduction in the field, a few studies have been published in 2004 that aimed at the validation of scoring methods of plain radiography and MRI of the spine in AS. These studies showed that scoring progression of structural damage on plain radiographs is feasible and reliable if a time period of 2 years is taken into account, and if the modified SASSS is used as a scoring method.

Other studies aimed at validating scoring methods for the assessment of inflammatory activity and structural damage by MRI. Interreader reliability of these scoring methods (ASspiMRI-a and ASspiMRI-c) appeared to be promising, although MRI was not clearly more sensitive than plain radiography in detecting structural changes in the spine. Undoubtedly, MRI will be of great advantage in detecting and monitoring inflammation of the spine in AS. Whether MRI will be useful in the early detection of sacroiliitis remains to be seen. The only study that addressed this issue in 2004 was of poor methodological standard, but high-quality efforts in this field are underway.

Two unrelated studies showed evidence for the role of multidetector CT in detecting spinal fractures in AS, and for the role of MRI in detecting shoulder problems in AS.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


This paper compares the validity of three widely used scoring systems for assessing radiographic damage in the spine.


This paper compares two sequences for assessing inflammation in the spine on MRI by a novel scoring method.


Comparison of various imaging techniques for assessment of cervical spine fractures.
Management and treatment of ankylosing spondylitis

Jane Zochling and Jürgen Braun

Purpose of review
Our purpose is to review the developments in the treatment of ankylosing spondylitis in 2004.

Recent findings
Tumor necrosis factor blockers have been shown to have rapid and persistent efficacy with limited additional toxicity up to 4 years with continuing therapy, but cessation of therapy results in relapse in most patients. Therapy is cost-effective. There are some differences between the different tumor necrosis factor blockers currently available. Other biologic therapies are not as promising. Algorithms have been developed to aid in early diagnosis. This may be relevant for future therapeutic strategies.

Summary
Tumor necrosis factor blockers are effective and safe in active spinal disease, but simple measures such as exercise and nonsteroidal anti-inflammatory drug therapy are still considered the basis of standard therapy. Early disease diagnosis is becoming easier, and is likely to be important for optimal therapeutic responses. Future research will include the effect of tumor necrosis factor blockade on structural disease progression.

Keywords
ankylosing spondylitis, spondyloarthritis, therapy, tumor necrosis factor blockers

Introduction
Spinal inflammation is one of the key features of the group of disorders known as the spondyloarthritides (SpA), including ankylosing spondylitis (AS), psoriatic SpA (PsSpA), reactive SpA (ReSpA), SpA associated with inflammatory bowel disease (SpAIBD) and undifferentiated SpA (uSpA). These disorders are common [1], associated with significant pain and functional disability [2] and impact greatly on patients’ quality of life [3]. Inflammatory back pain reflecting spinal inflammation is an important feature of any of the SpAs. Ankylosing spondylitis, the ‘prototype’ of the SpA, has by definition the most severe spinal involvement in comparison to the other SpA subtypes [4], mainly due to new bone formation leading to syndesmophytes and ankylosis, and AS with additional psoriasis or inflammatory bowel disease may have even more severe disease [5].

In a group of diseases that have shown little therapeutic progress over the previous decades, the last 5 years have seen exceptional achievements in terms of patient care—as comprehensively reviewed in 2004 [6]. This present review looks at the significant developments made in the field of therapy of AS over the last 12 months.

Assessment of therapies in ankylosing spondylitis
To assess the effect of any therapy on a disease state, it is important to predefine those measurable disease factors that reflect change in a disease state. One of the ongoing projects of the Assessments in Ankylosing Spondylitis (ASAS) International Working Group is the definition, validation and standardization of outcome measurement in AS. This has led to the introduction of new evidence-based tools for the assessment of efficacy in therapeutic trials, such as the ASAS 20% response criteria (ASAS20). Table 1 summarizes those assessment instruments and response criteria recently used in AS research to define treatment response [7–11].

Baseline therapy
The use of nonsteroidal anti-inflammatory drugs (NSAIDs) [12–14] and structured exercise [15–17] have comprised the standard treatments for spinal symptoms in AS for decades. The most significant development in this area has been recent evidence that continuous NSAID therapy reduces spinal radiographic progression [18]. This study, by Wanders et al, is the first to address the important issue of structural modification with NSAIDS in AS, and warrants further investigation. We stress that physical therapy...
and NSAIDs still form the basis of patient care, referred to here as ‘baseline therapy’. Whether and to which extent physical therapy and exercise are beneficial in every stage of the disease is not known. Disease activity, especially the degree of spinal inflammation, function and damage are very likely to influence the outcome of physical therapy and regular exercise.

### Disease-modifying anti-rheumatic drugs

The use of disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of axial disease in the SpA has been rather disappointing. Therapies which are effective in suppressing disease activity and slowing disease progression in rheumatoid arthritis have notably failed to impress in the spondyloarthritides, particularly for spinal disease.

**Table 1. Outcome measures in ankylosing spondylitis**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>Bath Ankylosing Spondylitis Disease Activity Index [7]</td>
<td>BASDAI</td>
<td>A composite index made up of six questions, each measured on a 0–100 mm visual analogue scale (VAS):</td>
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<td>– Fatigue</td>
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<td>– Neck, back or hip pain</td>
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<td>– Pain/swelling in other joints (not neck, back or hip)</td>
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<td>– Overall discomfort from tender areas</td>
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<td></td>
<td>– Overall level of morning stiffness (intensity)</td>
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<td></td>
<td></td>
<td>– Duration of morning stiffness</td>
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<tr>
<td>Bath Ankylosing Spondylitis Functional Index [8]</td>
<td>BASFI</td>
<td>A composite index made up of 10 questions, covering basic daily functions such as bending and standing, each measured on a 0–100 mm VAS</td>
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<tr>
<td>Bath Ankylosing Spondylitis Metrology Index [9]</td>
<td>BASMI</td>
<td>A composite index made up of 5 clinical measurements:</td>
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<td>– Cervical rotation</td>
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<td>– Tragus to wall distance</td>
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<td>– Lumbar side flexion</td>
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<td>– Modified Schober’s test</td>
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**Response Criteria**

| ASAS improvement criteria [10] | ASAS-IC | Four domains, based on the discrimination between NSAID treatment and placebo: |
| | | – Physical function, measured by the BASFI |
| | | – Spinal pain, measured on a 0–100 mm VAS |
| | | – Patient global assessment in the last week, on a 0–100 mm VAS |
| | | – Inflammation, measured as the mean of the last 2 BASDAI questions (intensity and duration of morning stiffness) |
| ASAS 20% response criteria [10] | ASAS20 | Treatment response is defined as: |
| | | – ≥20% and ≥10 mm VAS on a 0–100 scale in at least three of the four ASAS-IC domains, and |
| | | – No worsening of ≥20% and ≥10 mm VAS on a 0–100 scale in the remaining fourth domain |
| ASAS 40% response criteria [11] | ASAS40 | Treatment response is defined as: |
| | | – ≥40% and ≥20 mm VAS on a 0–100 scale in at least three of the four ASAS-IC domains, and |
| | | – No worsening of ≥40% and ≥20 mm VAS on a 0–100 scale in the remaining fourth domain |
| ASAS 5 out of 6 response criteria [11] | ASAS 5/6 | Developed for use in trials of anti-TNF therapy, six domains were included: |
| | | – Pain |
| | | – Patient global assessment |
| | | – Function |
| | | – Inflammation |
| | | – Spinal mobility |
| | | – C Reactive protein (acute phase reactant) |
| | | Treatment response is defined as improvement in five of six domains without deterioration in sixth domain, using predefined % improvements. |

**Sulfasalazine**

Sulfasalazine has been shown to improve SpA-associated peripheral arthritis [19,20], but not spinal pain [21,22]. There are differences between the trials related to disease duration and the proportion of patients with peripheral arthritis.

In contrast, a recent multicentre randomized controlled trial of sulfasalazine in uSpA and early AS suggests an effect on spinal pain [23*]. Two hundred and forty two patients were enrolled from 12 centres, with entry criteria being inflammatory back pain and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) above 3 (indicating high disease activity). In total, 112 patients received active drug (1g twice a day), and 118 received placebo for up to 6 months. Half of the group was male,
and 67% were HLA-B27 positive. Fifty percent had enthesitis at entry, 47% peripheral arthritis and 14% dactylitis. Those patients with inflammatory back pain but no peripheral arthritis were seen to have a significantly larger improvement in BASDAI with treatment than the placebo group, but other patient subgroups were not significantly different from placebo (all groups improved). Patients receiving sulfasalazine also used on average less NSAIDs to control their symptoms than did the control group, which might have influenced the lower level of pain seen in the intervention group. It is difficult to draw further conclusions, as it may be the higher NSAID dose in the placebo group that has masked any real benefit attributable to the sulfasalazine. Nevertheless, it is possible that in early disease or uSpA, symptoms attributable to chronic structural spinal changes are less pronounced and may be more amenable to modification by sulfasalazine. There are no direct studies of sulfasalazine comparing efficacy between different subgroups of SpA to answer this question.

**Methotrexate**

Methotrexate is commonly used in rheumatoid arthritis with good result, improving symptoms and slowing the progression of radiologic erosive disease. It has not enjoyed such success in AS, underscoring the different theoretical mechanisms of the two diseases. Chen et al. [24•] systematically reviewed the use of methotrexate in AS, concluding there was no effect on inflammatory back pain and inconclusive evidence of efficacy for peripheral joint disease. The only randomized controlled trial of methotrexate in AS to be published subsequently [25] has also failed to show any significant effect on patients using 7.5 mg oral methotrexate weekly for spondylitis compared with placebo. There may have been some improvement of peripheral arthritis as reported in that study. Many rheumatologists use methotrexate for that indication. Historically, that has mainly been due to a lack of other options.

**Leflunomide**

Leflunomide is effective in treating the symptoms and slowing radiographic change in rheumatoid arthritis [26]. Recent studies in spondylitis suggest that it is not effective for the axial manifestations of AS [27], and does not give a significant ASAS20 response in AS patients [28]. Patients with peripheral arthritis may have had some benefit with this agent.

The story is somewhat different in psoriatic arthritis. Kaltwasser et al. [29] have recently published results from the Treatment of Psoriatic Arthritis Study (TOPAS), a multinational, double-blind, placebo-controlled study of the efficacy and safety of leflunomide in psoriasis and psoriatic arthritis. The study group included patients with all subgroups of psoriatic arthritis, including ankylosing spondylitis-like disease, but results were not analyzed separately for each disease subtype, and the effect of leflunomide on spondylitis or inflammatory back pain was not reported. Leflunomide was seen to have a significant effect on peripheral joint involvement, physician’s and patient’s global self-assessment, and there were significantly more PsARC (Psoriatic Arthritis Response Criteria [30]) responders in the active treatment group than placebo (59% vs. 30%, respectively). It would be interesting to assess the effect of therapy on spinal disease in PsSpA, given its apparent lack of efficacy in AS; this has important implications on the ultimate choice of therapy in those PsSpA patients with significant spondylitic involvement.

**Tumor necrosis factor blockers**

The introduction of TNF blockers has been the most substantial development in the treatment of spondylitis in the last few years. Large randomized controlled trials of both infliximab [31] and etanercept [32–34] in AS have shown impressive short-term improvements in spinal pain, function and inflammatory markers with therapy as compared with placebo. As experience with these therapies grows out to 2- and 3-year trials, efficacy has been seen to persist with ongoing treatment.

**Infliximab**

The largest trial to date of infliximab in ankylosing spondylitis has just been published, showing significant improvements in pain, function and disease activity in 279 patients with active disease compared with placebo [35•]. After 24 weeks, 61% of the treatment group had achieved an ASAS20 response, compared with 19% in the placebo arm ($P < 0.001$). All outcomes measured, including the BASDAI, the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Metrology Index (BASMI), and the physical component summary of the SF-36 (a measure of health-related quality of life), showed significant improvements with therapy. Improvements were seen within 2 weeks of commencement of therapy, and sustained over the entire study period. Side effects were seen in up to 80% of patients receiving active drug; they were mild and did not require cessation of therapy.

A number of early pivotal trials of infliximab therapy for SpA have now published data on open-label extension studies. Braun et al. [36•] report the results of infliximab treatment in 52 AS patients over 2 years, showing early and sustained improvement in BASDAI and BASFI throughout treatment. There was no significant difference between the percentage of responders at 1 year and at 2 years, defined as a reduction of at least 50% of the BASDAI score (63% vs. 58%). Response to therapy, whether defined by the ASAS20, the ASAS40 or the ASAS 5 out of six criteria, was also maintained and no increase in toxicity was seen. Results after 3 years of follow-up [37•] showed continued efficacy, without development of tolerance or safety issues. A larger study of 107 SpA patients
treated with infliximab showed similar persistence of efficacy, up to 4 years with continuing therapy [38]. Although two recent studies of infliximab therapy in PsSpA have shown promising results with improvement in peripheral joint symptoms, PsARC response and skin disease, spondylitis has not been assessed as a distinct outcome [39,40]. This is likely influenced by the fact that once a patient has significant spinal disease, he or she is diagnosed as having AS (i.e. fulfilling the modified New York criteria for AS, [41]) despite having concomitant psoriasis or inflammatory bowel disease; these patients are selectively excluded from the PsSpA or SpAIBD groups, leaving a low incidence of spondylitis in these subgroups. The recent ASSERT [35] trial included patients with concomitant psoriasis or IBD, there being no reason to believe that these patients behave differently with infliximab therapy.

Alongside the demonstrated long-term efficacy and safety of infliximab in spondylitis, it is important to note the rapid loss of response after cessation of therapy [42]. Forty-three patients stopped infliximab after 3 years of successful therapy, and after a mean follow-up time of 13.4 weeks, over 60% of patients relapsed, requiring reinfusion. At the time of publication, all 27 patients requiring repeat therapy continued to show a good clinical response to reinfusion. It will be particularly interesting to see if reinfusion is associated with a higher incidence of autoantibody formation to infliximab; as yet, these data are not available.

Therapy with infliximab has been shown to have an effect on active spinal inflammation detected on magnetic resonance imaging (MRI) [43], but its value as a disease modifier has not been clarified. Baraliakos et al. [44] looked at lateral lumbar and cervical spine X-rays in 40 patients who underwent infliximab therapy over 2 years for AS, and found there was no significant radiologic progression of disease as assessed by the modified SASSS (Stoke Ankylosing Spondylitis Spine Score, validated this year for use in scoring radiographs in AS [45]). This is the first report of an influence of TNF blockade on disease progression, and more studies with larger patient numbers are required to confirm these preliminary findings. In a disease with significant long-term functional disability due to the development of syndesmophytes and spinal ankylosis [46], any therapy which is proven not only to suppress clinical and radiologic disease activity but also to retard disease progression will be of great importance for patient care.

Cost-effectiveness is always an issue when expensive therapies such as the TNF blockers are discussed. Despite the relative expense of infliximab compared with more traditional therapies for musculoskeletal disease, Kobelt et al. [47] have recently demonstrated that the significant clinical benefits and improvement to quality of life with infliximab result in lower disease-associated costs than standard care, resulting in an approximate short-term cost of approximately £35 000 per quality-adjusted life year (QALY) gained. When modeling for long-term therapy, using annual disease progression of 0.07 on BASFI in the sensitivity analysis, the cost per QALY gained is reduced to £9600. Until long-term data on disease progression with infliximab therapy in AS is available, these conclusions remain hypothetical, but it would seem that costs for infliximab therapy fall well inside what is considered to be ‘cost-effective’ in economic analyses.

**Etanercept**

The efficacy of etanercept in AS has been well established [32–34] and recently reconfirmed in a large multicentre randomized placebo-controlled trial [48]. Eighty-four patients with active spinal inflammation (at least 30 mm on a 100 mm visual analogue scale for pain (VAS)) were randomized to receive 25 mg subcutaneous etanercept twice weekly or placebo. Primary outcome measures were the ASAS response criteria, including spinal inflammation, back pain, patient global assessment and physical impairment, measured at 12 weeks. The active therapy group had a significantly higher percentage of responders (ASAS20) than the placebo group, 60% vs. 23%, P < 0.001, and response was seen as early as 2 weeks into therapy, the first time-point at which response was assessed. All items measured improved significantly with etanercept compared with controls, and inflammatory markers decreased by 70–80% in the active therapy group. As with infliximab therapy [35], the rapid onset of symptom control with etanercept is particularly exciting, and is likely to have an important impact on patient compliance and satisfaction.

As with infliximab, studies of etanercept use over longer periods in SpA are now emerging. Patients from the original 6-month randomized controlled study of etanercept in AS [32] were enrolled in an open extension trial, after several months without therapy [49,50]. Patients who had a recrudescence of disease activity after the 6-month trial was completed were eligible for the open trial, and to date have been followed for 2 years. This study design allowed two important conclusions to be made: the beneficial effect of therapy with etanercept does not persist after cessation of active drug (26 of the original 30 patients developed high disease activity once the drug was ceased); and response to therapy on reintroduction of etanercept shows a similar efficacy and safety profile as in treatment-naive patients.

The first study of etanercept in uSpA has now been published [51], an open-label trial describing the effect of therapy in 10 patients with severe active disease of at least 6 months duration. The authors concluded that etanercept therapy (25 mg s/c twice weekly) gave similar results after 12 weeks as previously seen in AS [32,33]. Patients fulfilled the European Spondyloarthritis Study Group (ESSG [52]) criteria for spondyloarthritis, but none of the
Spondyloarthropathies

patients (13 completers) over 24 weeks found no significant changes in either BASFI or BASDAI at all [60]. In particular, no improvement was seen in MRI findings in the 10 patients with both pre- and post-therapy films. A small number of patients achieved an ASAS40 response with therapy which persisted at least 3 months after the cessation of therapy, suggesting that anakinra may be effective in selected patients, although numbers were too small to further define which patients are likely to benefit from therapy. Anakinra has not been investigated in other spondyloarthritides. There is to date insufficient evidence to support its use in spondylitis.

Bisphosphonates and thalidomide

Both of these therapies have looked promising for spinal symptoms in AS [61–63] but there have been no new developments since these trials were published. An ongoing British trial of oral alendronate in AS is nearing completion; the results are awaited with interest.

Antibiotic therapy

Treatment of reactive arthritis (ReSpA) with long-term antibiotics has been disappointing in the past [64], and the most recent addition to the literature failed to show any short-term effect of 3 months therapy with azithromycin on any of the clinical features measured compared with placebo [65]. It may however have an effect on long-term prognosis in ReSpA, as shown in a follow-up study of patients treated acutely for 3 months with ciprofloxacin [66]. Four to seven years after therapy, 40% of patients who received placebo had developed a chronic form of SpA, compared with only 8% of the patients who received antibiotic therapy at the time of acute ReSpA. Martinez et al. [67] have recently described a temporal association between enteric and urinary tract infections and the development of active AS and uSpA, suggesting that an infectious trigger may be important also in these subtypes of SpA. There has been one recent trial comparing doxycycline with rifampicin plus doxycycline in uSpA [68], which failed to show a significant improvement in inflammatory spinal pain in either group over 9 months of therapy, although there may have been some effect on peripheral joint involvement in the combination therapy arm. Nevertheless, in the absence of good efficacy of antibiotic therapy in ReA, it is unlikely that similar therapy in other SpA groups would be of clinical benefit.

Who to treat

Few studies have been designed to differentiate therapeutic effects according to patient characteristics. Rudwaleit et al. [69**] recently reviewed the results of two randomized trials of biologic therapy in AS according to patient factors, and found that response to therapy was better in patients with shorter disease duration and less functional disability. Both studies were carried out in patients with high disease activity at baseline, so it is not possible...
to generalize these conclusions in a wider population of spondylitis patients.

ASAS published a consensus statement for the use of anti-TNF agents in AS in 2003 [70], giving a comprehensive overview of issues that need to be considered when considering the commencement of TNF blockers in clinical practice. The major indicators for needing biologic therapy were identified as the persistence of active disease, the threat of severe disease or damage, and the likelihood of response to treatment. The cited study [69**] allows us to better identify patients who might fulfil the latter indication. The working group agreed that elevation of acute phase reactants such as the C-reactive protein (CRP), and rapid radiologic progression are useful for determining the severity of disease and possible therapeutic response. MRI is also likely to play an important role in assessing these indicators, as it is the best imaging technique for assessing early inflammation of the spine and sacroiliac joints and its progression. Due to the limited accessibility and cost of MRI, it cannot be recommended for routine practice, but it has been recognized as a valid imaging method for the assessment of the three ASAS group indicators for therapy with TNF blockers.

The major problem with the management and treatment of SpA lies in the long delay between onset of symptoms and diagnosis [71,72], particularly in light of improved responses when therapy is commenced early. In the absence of established radiographic spondylitis or sacroiliitis, a high level of clinical suspicion is required to diagnose axial SpA. Two studies have recently outlined strategies to help with early diagnosis. Rudwaleit et al. [73**] have described a clinical algorithm based on the presence of inflammatory back pain, assigning likelihood ratios for diagnosis to different clinical features. The presence of inflammatory back pain and two-to-three other SpA features (including enthesitis, alternating buttock pain, peripheral arthritis, dactylitis, anterior uveitis, psoriasis, family history and response to NSAIDs) gave a positive test probability of over 90% for the diagnosis of early SpA. Recommendations for screening for AS in a primary care setting simplify this further [74*], suggesting inflammatory back pain and a positive HLA-B27 test together should be used to identify those patients requiring referral to a specialist, as they give a high likelihood of having AS or early AS and might improve early referral rates.

**How long to treat**

There is no doubt that TNF blockers are effective in AS. The new therapeutic dilemma lies in how long to continue therapy. Ongoing therapy at least for a few years brings persistent clinically important responses. Do we continue this therapy indefinitely in a disease process that can go on for 50 years? We now have data that show a large relapse rate on discontinuation of infliximab therapy [42**, but there are still some patients who maintain their disease improvement without continuing TNF blocker treatment, at least in the short-term. Are we able to differentiate between patients who can stop anti-TNF therapy, and those who will require ongoing disease? Is there a discrete time-period over which TNF blockers should be used, and then effectively switched to other DMARDs which might not have been previously effective? Or is there a place for intermittent anti-TNF therapy, perhaps for 3 months in every 12, to reduce costs without compromising patient care? There are still many questions to be answered on the optimal therapeutic strategies for TNF blockers in AS, and it is only with ongoing studies of this relatively new class of AS therapies that the answers will begin to emerge.

**Conclusions**

Spinal inflammation and AS are no longer the impossible clinical problem that it was a decade ago, as rapid developments in therapy are giving rapid, persistent control of clinical symptoms and improvement in daily function. Exercise and NSAID therapy remain important in every patient; they should not be neglected despite the availability of exciting new therapeutic options. Tumor necrosis factor blockers should be considered in patients with active disease who do not achieve optimal disease control with simple measures. It remains to be seen whether the new therapeutic strategies available will have a significant effect on structural disease progression. Early diagnosis may be critical to maximize the effects of therapy.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


This is the first study to look at the effect of TNF-blockade on uSpA.

The newer TNF-blocker adalimumab has been shown to be effective in AS in this open clinical study.

This is an interesting study looking at which AS patients will achieve the most benefit from treatment with TNF blockers, and has important implications for daily clinical practice and the selection of patients for these costly therapies.

This presents a useful approach to early diagnosis for the primary care physician.
Psoriatic arthritis therapy advances
Philip J. Mease

Purpose of review
This paper will review the data published in 2004 on the treatment of psoriatic arthritis, which arthritis affects 6 to 39% of all patients with psoriasis.

Recent findings
New data from placebo-controlled trials of anti–tumor necrosis factor agents, etanercept, infliximab, and adalimumab continue to show sustained effectiveness of these therapies in their ability to control the symptoms and signs of both arthritis and psoriasis, improve quality of life and function, and inhibit disease progression as measured by radiologic changes. Medications that inhibit T cells have been approved for the treatment of psoriasis and have been studied in psoriatic arthritis. The effectiveness of one of these agents, efalizumab, did not achieve statistical significance in the treatment of psoriatic arthritis. The results of a trial with a second agent, alefacept are pending public review.

Summary
There has been a persistent increased focus on the diagnosis and treatment of psoriatic arthritis as newer and more effective drugs than traditional disease-modifying agents have become available.

Keywords
biologics, psoriatic arthritis, psoriasis, therapy

Introduction
Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, which occurs in 6 to 39% of patients with psoriasis, depending on the population studies and the method of diagnosis ascertainment [1–4]. Psoriasis occurs in approximately 2% of the population of North America and Europe [5]. A higher prevalence is documented when the disease is assessed in psoriasis-specific populations, especially those with more severe disease, whereas lower prevalence is documented in large population surveys, which include patients with psoriasis of low severity [1–4]. A difficulty with accurate determination of prevalence from large population cohorts is that the diagnosis may be overestimated, for example, if a psoriasis patient with concomitant osteoarthritis or rheumatoid arthritis is mistakenly categorized as having PsA. Conversely, the disease may be underestimated if a psoriasis patient with PsA receives instead a diagnosis of osteoarthritis – a disease better known to primary care physicians.

Psoriatic arthritis is an immunologic inflammatory disease, akin to but distinct from rheumatoid arthritis (RA) and other inflammatory arthritides [6]. Understanding of the immunologic pathophysiology of PsA, which has important similarities and differences with RA, and between skin lesions of psoriasis and joint inflammation of PsA, has led us to targeted therapy. A review of this area is beyond the scope of this article and has been well reviewed in this journal and elsewhere [7•,8•,9•–11•,12]. A fellow paper in this issue is related to PsA pathogenesis and clinical. Increased understanding of the pathophysiology of PsA demonstrates the central role of inflammatory cytokines such as tumor necrosis factor (TNF)α and activated T cells, which are targets of current targeted therapies. Several other cellular, cytokine, and chemokine targets have been identified, and there are numerous drug development programs in RA, PsA, and psoriasis aiming at these additional targets, which will affect future options for PsA therapeutics.

Several important therapeutic studies in PsA described in a review article in this journal last year, while in abstract form, have been published in 2004, and will be further detailed here [13]. Additionally, several drug development programs in PsA as well as psoriasis have matured, thus providing further data to review. As a result of findings from these studies, rheumatologists, now quite familiar with the use of biologics for the treatment of rheumatoid arthritis (RA), are actively using these agents in PsA patients with progressive disease who have not adequately responded to nonsteroidal anti-inflammatory drug (NSAID).
or traditional disease-modifying antirheumatic drug (DMARD) therapy alone. In parallel, the approval of bio-
lógics for the treatment of moderate to severe psoriasis has
resulted in rapid uptake of these agents by many derma-
tologists. It is likely that this dual discipline use will
increase the effective treatment of previously undiag-
nosed and un- or undertreated PsA patients who are pri-
marily treated in dermatology and primary care offices.
Whether this trend will affect the natural history of PsA
or even prevent its emergence, which usually first mani-
fests years after psoriasis begins, is unknown. Overall
awareness about PsA has risen through the educational
efforts of patient service organizations globally, such as
the National Psoriasis Foundation in the United States
and country-specific organizations in Europe and other
parts of the world. These are supported both by interna-
tional consortia of psoriasis and PsA researchers such as
the Group for Research and Assessment of Psoriasis and
Psoriatic Arthritis (GRAPPA) as well as the biopharma-
caceutical industry. A multiarticle supplement of the Annals
of the Rheumatic Diseases, with state-of-the-art reviews on
psoriasis and PsA by GRAPPA members, will be published
in March 2005.

Biologic therapy
There has been a significant increase of acceptance of tar-
geted biologic therapy as its potential for therapeutic ef-
cicacy has been increasingly recognized by rheumatologists,
dermatologists, patients, third-party payers, and govern-
ment and as its safety issues are increasingly understood
and monitored. Several helpful reviews in this arena were
published in 2004, as well as an international consensus
statement on biologic therapies in psoriasis [14*,15,16*,
17,18,19**.20].

Tumor necrosis factor-α inhibition
The TNFα blockers continue to be the most durably ef-
cective agents for the treatment of PsA. Because of their
relatively high cost, practically speaking they are reserved
for patients with progressive moderate to severe disease
not adequately controlled with DMARD agents such as
methotrexate, sulfasalazine, leflunomide, or cyclosporine.
Patients with mild disease may be treated with NSAIDs
and/or DMARDs; however, some patients with milder dis-
ease may benefit from biologic therapy if they cannot tol-
erate DMARD therapy and have inadequate response to
NSAIDs.

Etanercept
Etanercept, a fully human soluble TNF receptor-IgG fu-
sion protein, was approved by the FDA for the treatment
of PsA early in 2002, on the basis of the results of a then-
published phase II trial in PsA and data from a phase III
trial, now published [21,22**]. It also has been approved in
Europe for PsA and in the United States and Europe for
psoriasis (without PsA), the latter on the basis of an exten-
sive phase II and III development program [21,22**].

The phase III study with etanercept in PsA used a dosage
of 25 mg given subcutaneously twice weekly in 205 patients,
41% of whom were receiving background methotrexate,
divided equally between treatment groups. The primary
endpoint was the American College of Rheumatology
(ACR) 20 response at 12 weeks, although the study re-
mained placebo-controlled through 24 weeks. At 12 weeks,
59% of etanercept-treated patients achieved an ACR 20
response, whereas 15% in the placebo group did so (P <
0.0001). A secondary joint response, the Psoriatic Arthritis
Response Criteria (PsARC), was achieved by 72% in the
treatment group and 31% of the placebo patients [21,23].
The mean improvement according to the Psoriasis Area
and Severity Index (PASI) was 42% in the 66 evaluable
(≥3% body surface area involvement) etanercept patients
and –8.1% in the 62 evaluable placebo patients [24]. A
PASI 75 response was achieved by 23% of the etanercept
patients but not in any of the placebo patients. Measures
of function and quality of life also showed significant im-
provement in the treated group and not in placebo patients.
The Health Assessment Questionnaire (HAQ), a measure
of functional outcome validated in RA, changed from 1.1
to 0.6 in the treated group, greater than a value of 0.3 con-
sidered to be the minimal clinically important difference
of HAQ for PsA [25*]. These results were sustained for as
long as 2 years in a follow-on open label study [26]. The
ACR 20 response was 64%, the PsARC was 80%, and the
PASI 50 score was 62%. No new safety concerns distinct
from those observed in RA clinical trials or post-marketing
surveillance have been seen in PsA trials.

A critically important observation from this trial and its
long-term extension was the ability of etanercept to inhib-
it disease progression as measured radiographically. After
6 months of placebo control, patients remained blinded
to study drug assignment, and placebo patients were not
allowed to receive etanercept until the last patient had
completed the 6-month phase. Thus, patients in the pla-
celeo arm received between 2 and 6 months of etanercept
therapy when evaluated radiographically at 1 year. This
group progressed a total of one point of Total Sharp Score,
whereas the patients originally treated with etanercept
showed no progression (P = 0.0001) [22**]. At 2 years,
the original etanercept group continued to show no progres-
sion of radiographic damage, as was true of the group origi-
nally treated with placebo [26]. This demonstration of
absence of radiologic deterioration is consistent with the ex-
perience with anti-TNF agents in RA and has not been
equalled by other disease-modifying drugs in RA or in a sin-
gle retrospective trial with methotrexate in PsA [27]. The
method of radiologic assessment in RA, PsA, and ankylosing
spondylitis has been recently reviewed [28**].
The rapidity and degree of skin response in PsA may not entirely correlate with the joint response. In the original phase II trial in PsA, it was noted that the full degree of joint response occurred sooner than the full skin response and that improvement was still occurring in the skin well into the open-label aspect of the trial [21,29]. In the phase II and III trials in psoriasis, more complete response in the skin was observed at 6 months than at 3 months [30,31]. Additionally, a dose–response effect was seen, with more complete and rapid skin responses seen with a dosage of 50 mg twice a week. This response was sustainable when etanercept was stepped down to 25 mg twice a week at 3 months. It should be noted that many patients express therapeutic satisfaction with a PASI 50 response.

The practical clinical aspects regarding etanercept administration in PsA and psoriasis have been well reviewed [14-32].

**Infliximab**

Infliximab is a chimeric monoclonal antibody that neutralizes both soluble and membrane-bound TNFα and is approved for the treatment of RA and Crohn disease in the United States and Europe. Studies through phase II supporting its approval for PsA have been previously reviewed [13]. In the phase II trial (IMPACT) 104 patients were studied, infliximab 5 mg/kg in comparison with placebo was used, and most patients were receiving background DMARD therapy (64%, with 46% receiving methotrexate) [35–37]. At week 16, 69% achieved an ACR 20 response compared with 8% in the placebo group (P < 0.001). ACR 50 and 70 responses were 49% and 29%, respectively, and none in the placebo group. Of patients with baseline PASI ≥2.5, median response was 81% and PASI 75 response was seen in 67% of the treatment group and none in the placebo group. Measures of enthesitis and dactylitis also showed improvement.

Radiographs of the hands and feet were obtained at baseline and 50 weeks. No progression of joint damage was seen in either the originally infliximab-treated or the placebo-treated patients. One reason for this lack of difference may have been that 36 weeks of treatment with infliximab before final radiographic evaluation in the originally placebo-treated group yielded enough benefit to ablate measurable difference from the 50 week treated group [38].

The phase III trial (IMPACT II) was a multinational study, which assessed 200 patients [39]. At week 14, an ACR 20 response was observed in 58% of the infliximab-treated group compared with 11% of the placebo-treated group (P < 0.001). Infliximab has been shown to have a significant impact on skin lesions of psoriasis [40,41]. An analysis was performed of skin response in patients who did achieve an ACR 20 response in comparison with those who did not. In those who had at least an ACR 20 response, and who could be evaluated by PASI score, the median PASI improvement was 87% [34]. In those who did not achieve an ACR 20 response, the median PASI change was 74%, suggesting that the drug can have a significant impact on the skin lesions of psoriasis even when the impact on joints is not significant. Radiographic data will be reported in 2005. No new side effect issues emerged.

An open-label trial in 16 patients showed significant efficacy in the skin, modest response in joint disease, and some adverse effects related to infection and liver function abnormalities in patients both with and without methotrexate background treatment. [40].

Several translational studies have elucidated the histologic and immunohistochemical changes occurring in skin and synovium after infliximab administration [42-44,45-47].

**Adalimumab**

Two studies were presented on adalimumab in PsA during 2004. Adalimumab is a fully human anti-TNF monoclonal antibody approved for the treatment of RA, given at a dosage of 40 mg every other week subcutaneously. A proportion of patients may experience increased benefit with weekly dosing.

Ritchlin et al. [46] used adalimumab, 40 mg every other week, in an open trial of 15 patients with PsA. Significant improvement in articular and cutaneous disease was noted as well as improvement in function and quality-of-life measures. A positive response in both skin and joints was also noted in two additional patients [47].

A large placebo-controlled trial (ADEPT) of adalimumab 40 mg every other week in 313 PsA patients was reported [48]. As in other trials of anti-TNF agents in PsA, methotrexate was allowed but not required, and it was used by 50% of patients in each arm of the study. At 6 months, 57% of the adalimumab patients achieved an ACR 20 response, whereas 15% in the placebo group did so (P < 0.001). ACR 50 and 70 responses were seen in 39% and 23% of the adalimumab patients and in 6% and 1% of the placebo patients (P < 0.001). PASI 75 responses in the skin were seen in 59% of treated and 1% of placebo patients (P < 0.001). Responses in both the joints and skin were seen as early as 2 weeks. Functional improvement was shown, with HAQ change of 0.4, exceeding what has been suggested as the minimal clinically important difference of 0.3 [25]. No new adverse effects different from those seen in RA trials were reported.

**Onercept**

Onercept is a recombinant human p55 TNF-binding protein currently in development. A phase II study of 126
patients with PsA has been reported [49]. Two dosages, 50 and 100 mg administered subcutaneously weekly, were used in comparison with placebo. An ACR 20 response was experienced by 67% in the 100-mg group and 31% in the placebo group. Further studies in PsA and psoriasis are planned.

Special considerations
What about patients who either have not responded initially to an anti-TNF medication, experience loss of efficacy over time, or for another reason have had to discontinue such medication? Is lack of efficacy a sign that it would be worthless to use another medication in the same class, or is there potential value in switching within the class? Small studies in RA patients have shown that there may be potential utility in switching from one anti-TNF agent to another. As many as 60% of patients switching from etanercept to infliximab and vice versa may experience an ACR 20 response, and similar data have been shown with a switch from either of these medications to adalimumab [50–52]. A successful switch from infliximab to etanercept in a patient with PsA, who had experienced loss of effectiveness from infliximab, has been reported [53].

What about the patient with PsA who also has hepatitis C virus infection, currently the most common chronic viral infection in the population? Methotrexate might be avoided in such patients because of the potential for additive hepatotoxicity. Etanercept has been used successfully in patients with PsA and hepatitis C without causing elevations in liver function tests or assays of viral load [54,55]. It also has been successfully used in three patients with PsA and hepatitis C without causing elevations in liver function tests or assays of viral load [56].

Two patients, one each receiving etanercept and infliximab, experienced aggressive cutaneous T cell lymphomas with rapid onset and fulminant course. The authors thought that the lymphoma was related to TNF blockade on the basis of the clinical course and suggested several possible mechanisms [41].

Costimulatory blockade agents
As stated by Krueger [8], psoriasis is one of the most T lymphocyte–driven diseases. Thus, there has been focused interest in the development of drugs that might interfere with the activation of pathologic T lymphocytes. Although the interaction of the major histocompatibility complex and the T cell receptor as the ‘first signal’ of T cell activation is of great importance, it is also true that activation depends in part on a second or costimulatory signal via the interaction of several ligand–receptor pairs. These include leucocyte function-associated antigen (LFA)-3 and CD2, intercellular adhesion molecule (ICAM)-1 and LFA-1, and CD80/CD86 and CD28/CTLA4. Drugs that block each of these interactions have been developed, have shown efficacy in psoriasis, and have been or will be tested in PsA.

Alefazept
Alefazept is a human LFA-3/IgG1 fusion protein that has been approved for psoriasis [57]. It binds to CD2 receptors on T cells to block the interaction of this receptor with LFA-3 on antigen-presenting cells, thus limiting activation of the T lymphocyte. In addition, the IgG1 portion binds to FcγRII IgG receptors on natural killer cells that induce apoptosis of the T cell. Via the latter mechanism, there is a predictable drop in CD4 cell number as a result of this therapy, which is recommended to be monitored. An open-label study in 11 patients, treated with 12.5 mg per week for 12 weeks, showed an ACR 20 response in 7 patients and a decrease in CD4, CD8 and CD68 (macrophages) cells in the synovial lining. The results of a larger placebo-controlled study will be reported in 2005.

Efalizumab
Efalizumab is a humanized monoclonal IgG1 antibody that binds to LFA-1 (CD11a) and prevents the interaction between LFA-1 on the T cell surface and ICAM-1 on the antigen-presenting cell, thus decreasing T cell activation. Additionally, given that ICAM-1 is an adhesion molecule expressed by endothelial cells, this blockade decreases the migration of T cells to sites of inflammation from the bloodstream. It has been approved as a weekly subcutaneous injection for the treatment of psoriasis [58]. A 12-week placebo-controlled trial in 107 patients with PsA did not show a statistically significant difference between treated and placebo patients, although there was a favorable trend [59]. It is not known whether a longer duration of use or other factors of trial design would have shown a more clear distinction.

Abatacept
Abatacept is a soluble receptor composed of CTLA-4 and an IgG Fc fragment that blocks the interaction of two ligands expressed on antigen-presenting cells, CD80 (B7-1) and CD86 (B7-2), and their receptor on the T lymphocyte, CD28. Studies supporting the approval of this drug for the treatment of RA, in monthly intravenous form, have shown significant benefit [60]. The ability to inhibit radiographic progression of RA seems not to be as great as has been seen with the anti-TNF agents, however [60]. An open-label study in psoriasis also showed benefit [61]. It is expected to be available for RA later in 2005. Studies in PsA are anticipated.

Emerging biologic approaches
Other emerging biologics being used or tested in RA are currently or likely to be tested in PsA. The interleukin (IL)-1 inhibitor approved for RA treatment, anakinra, administered daily subcutaneously, is currently being studied
in PsA in Dublin (Fitzgerald, personal communication). There are plans to test a weekly subcutaneous IL-1 antagonist, IL-1 TRAP. An IL-15 inhibitor has been shown to have efficacy in a small open trial performed in Glasgow [62*]. An anti–IL-6 compound is being studied in RA and will likely be tested in PsA. Several drugs that ablate or moderate B lymphocytes, such as rituximab, which is approved for the treatment of lymphoma, are being studied in RA and will be assessed in PsA and psoriasis. Several ‘small molecule’ biologic strategies are being developed in RA, including mitogen-activated protein kinase inhibitors and an inhibitor of TNFα-converting enzyme that may be beneficial in PsA. A novel gene therapy approach in which the gene encoding the etanercept molecule is injected intra-articularly into inflamed joints, using an adeno-associated virus vector, is undergoing safety trials in patients with RA, PsA, and ankylosing spondylitis (Mease, personal communication).

Drugs in development for psoriasis, such as anti–IL-12, will be assessed for their effects on the joint disease of patients with PsA, either in a pilot fashion within psoriasis studies or in specific PsA studies.

A single case report of successful treatment of severe psoriatic arthritis with autologous stem cell transplantation was published, in a 34-year-old man unresponsive to conventional therapies and not yet able to receive biologics [63]. Polyarthritis symptoms recurred in a mild form 16 months after treatment but now can be controlled with modest doses of methotrexate.

There are undoubtedly numerous potential agents not touched on here that target specific aspects of the inflammatory cascade and may ultimately prove useful in PsA.

**Disease-modifying pharmaceuticals**

Leflunomide, an inhibitor of pyrimidine synthesis, which blocks the proliferation of stimulated T lymphocytes and is approved for RA, showed efficacy in PsA [64*]. On the basis of this study not conducted in the United States, it has been approved for the treatment of PsA in Europe. In this 24-week placebo-controlled trial in 95 PsA patients, leflunomide 20 mg per day yielded a PsARC response in 59% of treated patients and 30% of placebo patients ($P < 0.0001$). An ACR 20 response was seen in 29 of treated patients and 16 of placebo patients ($P < 0.0138$), and the mean PASI response was 22.4 and 2.2, respectively ($P = 0.0030$). The drug was generally well tolerated. Liver function test abnormalities were noted in 13% of patients but led to study discontinuation in only 2 leflunomide-treated patients.

In this study, 72 patients with an incomplete response to methotrexate in standard dose were randomized to receive either cyclosporine or placebo for 12 months [65]. Improvement in most domains studied occurred in both groups but achieved statistical significance in the cyclosporine arm in swollen joint count, C-reactive protein, PASI score, and ultrasound assessed synovitis but not in tender joint count, pain scores, or HAQ. The improvement in PASI score was from 2 to 0.8 ($P < 0.001$), underscoring the effectiveness of cyclosporine in psoriasis. More than a third of the patients discontinued the study prematurely, more so in the cyclosporine group, although changes in blood pressure and creatinine were fairly minimal.

A brief report of an open trial of sulfasalazine in 20 patients with PsA and enthesitis did not show significant improvement of enthesis over 6 months of therapy [66].

**Conclusions**

Further advances in the treatment of PsA and psoriasis, reflected in publications in 2004, are reviewed here. It is clear that we have seen a significant advance in our ability to affect disease signs and symptoms in both the joints and the skin, improve function and quality of life, and, with the anti-TNF medications, inhibit disease progression as measured radiographically. More effective use of all medications, in addition to increased disease awareness and understanding through patient, physician, and public education, has improved our ability to care for patients with PsA and psoriasis.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

4. Salonen S. The EUROSPO psoriasis patient study: treatment history and satisfaction reported by 17,900 members of European psoriasis patients associations (poster). In Spring Symposium of the European Academy of Dermatology and Venereology; Malta, 2003.

This general review of TNF pathophysiology in psoriasis and PsA and cellular and immunohistochemical impact of TNF inhibition has an excellent bibliography of primary references in the field.

This is a general review from a dermatologic perspective of the pathophysiologic role of TNF in the skin and joints and the role of TNF inhibition.
Psoriatic arthritis therapy Mease 431


43 This is a translational study of the histologic and immunohistochemical impact of anti-TNF therapy on skin and synovial tissue.


47 This is a thorough review of the histologic and immunohistochemical effects of anti-TNF therapy in spondyloarthropathies, including PsA, from translational group in Ghent.


51 This is an abstract regarding the phase III trial of infliximab in PsA.


Early arthritis and infection
Marjatta Leirisalo-Repo

Purpose of review
To summarize the recent literature on the association of infection with early arthritis, and to discuss the possible role of such infections with respect to the development of chronic rheumatic complications.

Recent findings
Viral infections are frequently associated with arthritis. Alphaviruses belong to mosquito-borne viruses, one form of which (Sindbis virus) can in Scandinavia and Karelia cause acute arthritis with typical rash. The role of this infection leading to chronic erosive arthritis needs further prospective studies. Patients infected with HIV can have various forms of arthritis. The role of HIV virus as an arthritogenic agent is still debated. On the basis of population studies, Campylobacter infections seem to be increasing as causative infections in reactive arthritis. There is no role for prolonged antibiotic therapy to shorten the duration of acute reactive arthritis, but the possibility that such a treatment might reduce the development of chronic sequelae needs to be examined in a larger study. The role of preceding infection initiating the process of rheumatoid arthritis is still an option, the association being observed in about 20% of patients studied in the early phase of arthritis.

Summary
Viral and microbial infections play a role in acute arthritis. The role of these infections in the development of chronic arthritis needs further prospective controlled studies.

Keywords
early arthritis, infection, microbe, virus

Introduction
In a patient with acute arthritis, infectious causes are often suspected and searched for. Septic arthritis, though uncommon, is important to diagnose, and early treatment is required. Only high suspicion and prompt treatment can lead to restoration of normal function [1]. In addition to acute septic arthritis, infection is often suspected in the case of a patient with recent monoarthritis, oligoarthritis, or polyarthritis. I shall review here the literature on the infectious causes of early arthritis, especially from the viewpoint of epidemiologic surveys.

Viral causes of arthritis
Parvovirus B19 infection is a common viral infection affecting predominantly children. In children, it is frequently associated with anemia and erythema infectiosum, a typical rash, and can be easily diagnosed. In adults, its manifestations are more protean (Table 1), including symptoms such as aplastic anemia, thrombocytopenia, and pancytopenia. Arthritis or arthralgia occurs in approximately 8% of juvenile and 60% of adult patients [2]. The patients can produce rheumatoid factor transiently, as well as positive antineutrophil cytoplasmic antibodies, which can make the differential diagnosis very complicated [3]. The role of parvovirus in propagating chronic arthritis has been discussed for years. In an extensive review, Meyer [2] discussed the topic and concluded that progression of parvovirus arthritis to chronic rheumatoid arthritis (RA) is extremely rare. Similar conclusions were also made previously by Harrison et al. [4], who based their opinion on the results of the Norfolk early arthritis register; however, the conclusion was contradicted by a recent report demonstrating that parvoviral B19 DNA was present in synovial fluid samples of 3 of 20 patients with early synovitis [5]. Also, 8 of 31 patients with chronic RA had parvoviral DNA in similar samples. Evidently, the discussion is still continuing.

Interestingly, approximately 50% of both juvenile and adult patients with various rheumatic diseases and positive antiphospholipid antibodies have evidence of persisting parvovirus B19 infection [6]. The same group recently reported that the use of intravenous gamma globulin therapy resulted in a loss of parvovirus B19 viremia and good clinical response in two of four juvenile arthritis patients with evidence of parvovirus persistence who were resistant to all previous medications [7].

The clinical pictures of systemic lupus erythematosus (SLE) and parvovirus infection can be very similar; furthermore, parvovirus antibodies can be produced by a patient with established SLE. On the basis of a literature
survey, however, Meyer [2] concluded that the association between parvovirus infection and the development or flare-up of SLE rarely exists.

Epstein–Barr virus (EBV) has been one of the infectious candidates implicated in RA for several years. In 2004, Balandraud et al. [8••] summarized the present knowledge of the poor control of EBV infection in patients with chronic RA. The patients have higher levels of anti-EBV antibodies than do healthy control individuals. In addition, EBV-specific cytotoxic T cell function, which is needed for the control of the chronic infection, is defective in patients with RA; this probably causes the increased viral load observed in the patients. There is no good evidence in favor of the primary infection as a trigger of subsequent RA [9]. The authors concluded, however, that on the basis of the above-mentioned immune aberrations, EBV would be a good candidate to trigger chronic immune complex disease. In fact, in a cohort of 45 patients with recent-onset RA, the patients produced increased quantities of immunoglobulins when their peripheral blood lymphocytes were stimulated by EBV in vitro [10]. The enhanced response to EBV predicted the development of joint destruction (erosions) in the patients during the subsequent 2-year follow-up [10]. This is indirect evidence of an abnormal response to EBV, and in the case of EBV infection in a patient during the incubation phase of RA, this would be an indicator of a more persistent and destructive form of arthritis.

Cytomegalovirus, EBV, and parvovirus B19 have been observed to persist in a latent form in the synovial fluid and synovial tissue of patients with RA and psoriatic arthritis, but less frequently in those with reactive arthritis (ReA) [11•,12]. The authors interpreted this as further evidence of a primary role of these viruses in autoimmune arthritis. Another explanation for the persistence of viral antigens in the inflamed synovium was suggested by Stahl et al. [13], who presented evidence of the presence of single or multiple viruses (cytomegalovirus, EBV, herpes simplex virus, parvovirus B19) in the synovial fluid or synovial tissue of patients with various forms of early arthritides, irrespective of the diagnosis. In the few trauma patients who were examined, no viruses were detected (Table 2) [14]. Thus, a very logical explanation might be that the circulating inflammatory cells harboring the viral DNA of persisting viruses migrate as innocent bystanders into the inflamed synovium.

Other herpesvirus infections have previously been associated with acute arthritis. Varicella zoster virus has been demonstrated in the joint fluid in a patient with acute arthritis associated with chicken pox, and cytomegalovirus in the synovial fluid of a patient with acute shoulder arthritis after kidney transplantation [14,15].

Patients infected with HIV have an increased frequency of musculoskeletal symptoms [16]. Joint complications occur usually late in the disease, but they can even be a presenting feature of HIV infection. ReA or Reiter syndrome is observed in 5 to 10% of patients, psoriatic arthritis in 1 to 6%, and undifferentiated spondyloarthritis in 3 to 11%. There have been great difficulties in explaining the differences in clinical features in the phenotypes of the arthritides seen in African patients with AIDS and in Western patients, those in the West having more typically ReA. In

<table>
<thead>
<tr>
<th>Virus</th>
<th>Type of arthritis</th>
<th>Other autoimmune features</th>
<th>Other manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Acute</td>
<td>Vasculitis, antiphospholipid syndrome, SLE (?)</td>
<td>Rash, hematologic changes, hepatitis, myocarditis, myositis, CNS symptoms</td>
</tr>
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<td></td>
<td>Chronic</td>
<td></td>
<td>Mononucleosis, hepatitis, CNS infection, dilated cardiomyopathy, lymphoma, nasopharyngeal carcinoma</td>
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<tr>
<td>Epstein-Barr virus</td>
<td>Acute</td>
<td>Vasculitis, polyarthritis, SLE (?)</td>
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<td>Chronic</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Acute</td>
<td>Vasculitis, polyarthritis, SLE (?)</td>
<td>Thrombotic thrombocytopenic purpura, colitis, CNS infections, myocarditis, dilated cardiomyopathy</td>
</tr>
<tr>
<td>Alphaviruses*</td>
<td>Acute</td>
<td>Arthralgia, myalgia</td>
<td>Rash, hemorrhagic symptoms, paresthesias, glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
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aData from Laine et al. [22••]. SLE, systemic lupus erythematosus; CNS, central nervous system.

<table>
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<tr>
<th>Virus</th>
<th>Undifferentiated arthritis</th>
<th>Spondyloarthritis</th>
<th>Rheumatoid arthritis</th>
<th>Osteoarthritis</th>
<th>Crystal-induced arthritis</th>
<th>Trauma</th>
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<tr>
<td>Parvovirus B19</td>
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<td>Epstein-Barr virus</td>
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<tr>
<td>Herpes simplex</td>
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<tr>
<td>Cytomegalovirus</td>
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Modified from Stahl et al. [13].
the pathogenesis of arthritides, direct spreading of the HIV to the joints, the immune response of the host to the infection, and infection of the host with pathogens known to be capable of triggering ReA, especially in HLA-B27 positive subjects (Chlamydia, Salmonella, Yersinia, Shigella, Campylobacter) have been discussed [16]. Interestingly, in a recent report from Congo, infective joint complications were frequently observed in AIDS patients. In addition, AIDS was the leading cause of aseptic arthritis (60% of cases). In a series of 83 patients with stage IV AIDS, 80% had aseptic polyarthritis, and the rest had oligoarthritis. The arthritis was symmetric and nonerosive, with a predilection for tic polyarthritis, and the rest had oligoarthritis. The arthritis was symmetric and nonerosive, with a predilection for large joints in the lower extremities. Most of the patients responded to nonsteroidal antiinflammatory drugs [17**].

In these patients, the disease did not meet the classification criteria for spondyloarthritis.

The availability of highly active antiretroviral therapy has made a great change in the well-being and prognosis of patients infected with HIV. With respect to the occurrence and spectrum of musculoskeletal symptoms, Marquez et al. [18*] presented interesting data on 75 patients with HIV with a mean disease duration of 13 years. Musculoskeletal symptoms were very common, but there was a great shift in the diagnoses compared with historical data. Infectious complications occurred in 41% and fibromyalgia in 17%. In addition, malignant complications (non-Hodgkin lymphoma and Kaposi sarcoma) were frequently observed (11%). Only a few patients had seronegative symmetric polyarthritis, oligoarthritis, or psoriatic arthropathy. Risk factors for the increased rate of septic infections included low CD4 count and the use of intravenous drugs. An exceptional infection of the ankle caused by Mycobacterium avium intracellulare was also reported [19].

Two recent reviews on imaging findings in various musculoskeletal complications in AIDS were also reported, with an emphasis on the radiologic possibilities of visualizing several infective, inflammatory, and malignant complications [20,21]. Thus, whereas the patients have good benefit from modern antiretroviral drugs and consequently live longer, there is a shift in the spectrum of musculoskeletal complications to more distinctly infective forms. These results must, however, be confirmed by other centers, both in the West and in the developing world.

Alpha viruses belong to a group of arboviruses and share the common feature of transmission by arthropod vectors. They have a potential to induce arthritis, fever, fatigue, and rash. The most severe form is induced by Chikungunya virus. In northern Europe, milder forms of disease induced by Sindbis viruses have been described in several countries. In Finland, this mosquito-borne viral disease is called Pogosta disease, in Sweden it is called Ockelbo disease, and in Russian Karelia it is called Karelia fever. An excellent review on the Sindbis virus and the clinical picture of Pogosta disease has been recently published [22**].

The arthritis in Pogosta disease is often oligoarticular (ankle, knee, wrist, fingers, especially metacarpophalangeal joints) and manifests itself usually in the summer and early autumn. Other features are maculopapular rash, often itchy, present in most patients. The arthritis is usually transient, but in about half of the patients the recovery can take more than 1 month. One patient experienced chronic erosive arthritis (seronegative for rheumatoid factor). Another group from Finland recently reported the isolation of the Sindbis virus from the blood and skin lesions of the infected patients [23*]. No isolations from the synovial fluid or tissue have been reported. Thus, in addition to Borrelia-induced arthritis, virus arthritis can also be endemic during the summer season. The diagnosis of Pogosta disease is based on the clinical picture (rash and arthritis) and confirmed by serology.

**Streptococcal infection and reactive arthritis: does the link exist?**

Streptococcal sore throat can be complicated by the development of acute rheumatic fever, of which one of the five major manifestations is migratory polyarthritis. For the diagnosis of rheumatic fever, the updated Jones criteria are still valid [24]. According to these criteria, a patient with streptococcal infection followed by arthritis as the only major manifestation should have at least two other minor manifestations for the diagnosis. A workshop 10 years later still asserted the validity of these criteria but left discussion about the presence of a definite poststreptococcal ReA open [25]. A recent review, trying to address this question, came to the conclusion that among the case reports in the literature, poststreptococcal ReA is not an entity but a very heterogeneous group of disease manifestations from acute rheumatic fever to an arthritis more like HLA-B27–associated ReA without other features of acute rheumatic fever [25**]. The previously reported associations between the HLA-DRB1 locus and poststreptococcal ReA (increased frequency of HLA-DRB1*01) and acute rheumatic fever (increased frequency of HLA-DRB1*16) was not confirmed by a recent Italian report [27,28*]. The small number of patients in each study, together with possible racial, methodologic, and classification differences can easily explain the variation in the findings.

**Bacterial infections and musculoskeletal symptoms**

It is well established that gram-negative microbes causing enteric infections are associated with a risk of ReA in approximately 1 to 15% of the patients. The classic microbes having this association include Yersinia, Salmonella, Shigella, Campylobacter, and also (though less frequently) Clostridium difficile. Chlamydia trachomatis is by far the most common cause of urethritis and of ReA after urethritis. Of the other microbes causing urethritis, there is no consensus about whether Neisseria gonorrhoea can trigger ReA, although the infection is well known to cause septic and sterile arthritis. Infection with Mycoplasma genitalium is associated with
urethritis, but its role as an independent trigger (in the absence of Chlamydia infection) is still discussed, as is also the case with Ureaplasma urealyticum [20••,30•].

In addition to infection, the development of ReA is related to genetic susceptibility: approximately 60 to 80% of the patients have HLA-B27, and its presence predicts a more severe and prolonged disease. In addition to genetic factors, patients with Chlamydia-induced arthritis seem to have a more severe and chronic course [31]. An imbalance in the production of pro-inflammatory cytokines by peripheral blood mononuclear cells during acute arthritis (low tumor necrosis factor-α production) has been observed [32]. This has been confirmed recently by Butrimiene et al. [33]. The recent evidence of elevated levels of interleukin-10–secreting and transforming growth factor-β–secreting cells in the synovial membrane of patients with Chlamydia-induced ReA compared with RA patients also speaks in favor of ineffective elimination of the microbes from the joint, thus permitting the prolongation of arthritis [34].

The clinical picture, diagnosis, and pathogenesis of ReA were well covered by two reviews in 2004 [30••,35•]. The first review also excellently covered the diagnostic methods applied in the detection of the microbial causes of urethritis.

**Epidemiologic studies on reactive arthritis and spondyloarthropathies**

Epidemiologic studies can be reliably performed in patients with enteric infections and in countries with good collaboration between rheumatologists and nationwide laboratory registers of pathogenic microbial isolations. When these facilities were applied in Finland, Campylobacter-induced ReA proved to be frequent, with an annual incidence of 4.3 per 100,000. The disease is usually mild, oligoarticular, or polyarticular, and at population level there is no increased frequency of HLA-B27 [36]. Similar results were also reported during a single outbreak of Campylobacter jejuni infection in Finland [37•]. In both studies, the patients were identified and the clinical diagnosis was confirmed by a detailed questionnaire, often supplemented with clinical examination. Another approach was applied by Lake et al. [38•] in New Zealand, where a marked increase in the number of notified cases of infectious intestinal diseases, especially campylobacteriosis, was observed from 1988 to 2002. The authors reasoned that possible fluctuations in the frequency of enteric infections would be reflected in the numbers of patients with a hospital discharge diagnoses of Reiter disease, postdysenteric arthropathy, unspecified infective arthritis, or other inflammatory spondyloarthropathies. During the years 1988 to 2002, there was a slight increase or no increase in the reported infections due to Salmonella and Shigella and a greater than fourfold increase in the number of reported Campylobacter infections. At the same time, the annual number of patients discharged from the hospitals with the diagnosis of Reiter disease or with postdysenteric arthropathy was constantly at a very low level, in contrast to the patients with unspecified infective arthritis (a rise from 16 to 384) and other inflammatory spondyloarthropathies (from near 0 to 11–16). The authors were very careful not to draw any conclusions about the association between the two findings. This might be wise in consideration of the various biases and uncertainties in the study, which was based on only two separate registers with no identification of the cases, no detailed information about the character of the arthritis, and the identification of only those arthritis patients needing hospital treatment. Given that the numbers of patients with Reiter syndrome and postdysenteric arthropathy remained at a very low and unchanged level, however, the exceptionally rapid increasing incidence of the other disease groups suggests that further studies of the relation between Campylobacter infections and various forms of arthritis are required.

Shigellosis is a rare disease in Finland and in the vast majority of cases, is imported. We recently published the results of nationwide screening of patients with ReA in association with Shigella infection. ReA occurred in 7% of the patients, with an annual incidence of 1.3 per 100,000 [39•]. The frequency of HLA-B27 was slightly higher (36%) than in the normal Finnish population (14%). In contrast to previous reports, besides the classic Shigella flexneri, S. sonnei, and S. dysenteriae were also shown to be associated with acute ReA. These results highlight the importance of population-based studies, in which a selection bias can be avoided. Otherwise, only patients with severe symptoms contact a doctor, and of them, only those with more severe cases are referred to rheumatologists for treatment.

Two 2004 case reports of ReA in association with gut infection are worth noting. The spectrum of Salmonella species associated with ReA is constantly expanding. A case report of an HLA-B27–positive patient infected with Salmonella blockley in whom a chronic and progressive arthritis developed is interesting [40]. The serovar is common in Southeast Asia but is expanding to the Western world; the patient was infected in Cyprus while eating a chicken meal. The other report described two children with Clostridium difficile–induced ReA, a rare event in children [41]. One of the patients was positive for HLA-B27 and had a severe prolonged course but recovered without sequelae.

The list potential triggering infections in ReA is gradually growing (Table 3).

**Effect of antibiotics on acute arthritis**

The effect of short-term and long-term antibiotic therapy to treat ReA has been a focus of research during the past 10 years. Some evidence has addressed the effect of antibiotics during the infectious phase, before the arthritis has
had time to develop [42,43]. If the arthritis has already developed when antibiotics are introduced, however, the therapy does not modify the course of the disease. The latest such negative results came from a large European placebo-controlled study of early inflammatory arthritis, for which the treatment was azithromycin or placebo for 3 months [44,45]. Soon after that, Yli-Kerttula et al. [46] performed on hospital-based patients, often with established RA, a focus on only one or a few potential candidate microbes. Söderlin et al. [50] did a population-based systematic survey of the infectious background of patients with early synovitis (duration of symptoms <12 months, untreated with antirheumatic drugs and glucocorticoids) and patients with established RA visiting a university clinic, IgG class anti-Proteus antibodies were elevated in comparison with control individuals [49,*]. A similar analysis of antibodies to Serratia or E. coli did not show differences between patients and control individuals [49,*].

Most of the studies addressing this question have been performed on hospital-based patients, often with established RA, with a focus on only one or a few potential candidate microbes. Söderlin et al. [50] did a population-based systematic survey of the infectious background of patients with early synovitis (duration of symptoms <3 months). Among such patients, 45% had evidence of recent infection. Of the patients with early synovitis, 15 (21%) experienced RA, and 2 (13%) had serologic evidence of recent infection (one of parvovirus B19, the other of Chlamydia pneumoniae).

Thus, approximately 10–20% of patients with early RA have serologic evidence of recent infective agents as triggers of RA. There is not one single putative microbial trigger, but several microbes may be able induce joint disease in a susceptible patient.

### Conclusion

Arthritis is frequently associated with viral infections, but evidence of their role in propagating chronic arthritis, especially in inducing chronic RA, is much weaker. Parvovirus B19, though occasionally persisting in the joints, probably has a minor role. Half of the patients with early arthritis have clinical or laboratory evidence of preceding infection, mostly related to the clinical picture of RA but occasionally associated with early RA. On the basis of population studies, Campylobacter infections seem to have an increasing role in the triggering of RA. There is no role for prolonged antibiotic therapy to shorten the duration...
of acute ReA, but the possibility that such treatment might reduce the development of chronic sequelae needs to be examined in larger studies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
** of outstanding interest


In this important study authors show that during infection with parvovirus B19 or EBV, approximately 10% of patients have positive antineutrophil cytoplasmic antibodies.


This study add confirmatory data on the association of parvovirus B19 with early arthritis, both in early RA and in SLE, and also shows the presence of parvovirus in the synovial fluid in established RA.


In this interesting study the authors show that persisting infection with parvovirus B19 may lead to chronic juvenile polyarthritis. Of four such patients, two re- responded to intravenous treatment with commercially available immunoglobulin known to have high titers against parvoviral capsid proteins. Intravenous gamma globulin therapy is a candidate therapy for other such patients.


In this excellent review on the interaction of EBV virus and the RA host, the authors summarize the information about defective EBV-specific cytotoxic T cell activity in RA and link the finding especially to the association between HLA-DRB1*1004 and low frequencies of T cells specific for EBV gp110, which is critical for the control of EBV infection. Thus, patients with a genetic defect in mounting the nor- mal immune response needed to control EBV may be more prone to the develop- ment of RA.


The authors show by RNA and DNA in situ hybridization that EBV and/or cytomegalovirus was found in synovial tissue in a considerable number of patients with RA or psoriatic arthritis, but less frequently in patients with ReA. This suggests that the persistence of the two viruses may have a primary role in the development of chronic arthritis.


The authors describe the clinical features of nonseptic arthritis in HIV-positive pa- tients admitted to a teaching hospital in Brazzaville, Congo. All the patients had AIDS. Most of the patients had polyarthritis and responded well to nonsteroidal anti-inflammatory drugs. Only one patient fulfilled the European Spondyloarthropathy Study Group and Amor criteria for spondyloarthropathy. This is an interesting di- fference from the observations in Western countries.


The authors present a spectrum of musculoskeletal diseases in HIV-positive pa- tients who have been treated in a United States center for several years with highly active antiretroviral therapy. Joint symptoms were common, and in comparison with previous publications, the spectrum has changed: in the study described here, joint infection was common, and also lymphoproliferative diseases were ob- served in approximately 12% of the patients. The results are unexpected when the use of antiretroviral drugs might have been less than optimal, which would have contrib- uted to an increased risk of infections. The results have to be confirmed by other centers, and confounding factors should be analyzed.


This is a very good review on the epidemiology and clinical features of arthritis and infections with Sindbis and other alphaviruses.


This is a report of the isolation of Sindbis virus from blood and skin lesions in five patients with Pogosta disease.


In this excellent discussion of the pros and cons of arthritis in association with throat infection and streptococcal sore throat, the conclusion is that poststrepto- coccal arthritis is not a single entity but a spectrum of various diseases.


The authors describe the HLA-DRB1 genotypes of 33 children with poststrepto- coccal ReA, 25 children with acute rheumatic fever, and respective healthy control participants. There were no statistically significant differences in the frequencies of HLA-DRB1*01 and HLA-DRB1*11 between the three groups, and a previously reported result was therefore not confirmed.


This is an excellent review on the contribution of Mycoplasma genitalium in urethritis.


In this good review of the causes and complications of nongonococcal urethritis, the authors discuss the serologic and isolation methods in the diagnosis of Chla- mydia trachomatis. C. trachomatis is the most common cause of nongonococcal urethritis, whereas Ureaplasma urealyticum and Mycoplasma genitalium are re- sponsible forles.

Butrimiene I, Jarmalaite S, Ranceva J, Appel H, Neure L, Kuhne M, a questionnaire followed up by clinical examination of most patients with musculoskeletal infection in Finland (all stool culture positive and almost all imported from abroad). Using This important study is based on epidemiologic screening of patients with add to
etiology, hypotheses on pathogenesis, clinical picture, and treatment. In this extensive review of the current knowledge of ReA, the authors sum up the etiology, hypotheses on pathogenesis, clinical picture, and treatment.


Hannu T, Kauppi M, Tuimala M, et al. Reactive arthritis following an outbreak of Campylobacter jejuni infection. J Rheumatol 2004; 31:928—530. This is a recent report of a clinical study of patients recruited from an area in Finland with an outbreak of acute gastroenteritis due to Campylobacter infection. Patients with acute-onset musculoskeletal symptoms visiting the primary health care center within 2 months from the outbreak were referred for examination by a rheumatologist within 3 months from the outbreak of epidemic. The frequency of ReA was only 2.8%. This figure is only approximate, because of the 15 patients with ReA, 10 had not had stool cultured for Campylobacter; and 3 of these 10 patients had serologic evidence of recent Campylobacter infection.


This was an interesting approach to link two databases available in New Zealand from 1998 to 2002: the number of notified cases of infectious intestinal disease (salmonellosis, shigellosis, and campylobacteriosis) and the number of patients with various forms of postinfectious and reactive arthritis and inflammatory spondyloarthritides treated at the hospitals (based on hospital discharge registers). A fivefold increase in the frequency of Campylobacter infections reported was annually (from 2796 to 14,471) during that period; at the same time, the number of patients treated at hospitals with a diagnosis of unspecified infective arthritis increased from 16 to 384, and other inflammatory arthropathies from 3 to 16. There are several pitfalls in the study, but the similar trends raise interest. Further detailed analysis and identification of the cases would be needed to confirm the association.

Hannu T, Mattila L, Sitonen A, Leirisalo-Repo M. Reactive arthritis attributable to Shigella infection: a clinical and epidemiological nation-wide study. Ann Rheum Dis 2004; 63:594—598. This important study is based on epidemiologic screening of patients with Shigella infection in Finland (all stool culture positive and almost all imported from abroad). Using a questionnaire followed up by clinical examination of most patients with musculoskeletal symptoms, the authors show that the incidence of ReA due to Shigella is 7%. Additional musculoskeletal symptoms occurred in 2% of patients. Most interestingly, in addition to S. flexneri, S. dysenteriae and S. sonnei were also associated with ReA.


Carly SM, Snowden N, Silman AJ. Should infection still be considered as the most likely triggering factor for rheumatoid arthritis? Ann Rheum Dis 2004; 63 (Suppl 2):i46—i49.

This in updated summary of the evidence in favor of and against the role of infections as a possible triggering factor in RA, the authors have not found a definitely positive answer to the question they pose.


Infections have long been suspected to be one of several environmental factors in RA, although definite evidence is still lacking. This group has previously presented evidence of positive/enhanced anti-proteus antibodies in patients with RA. This paper provides further evidence in favor of this hypothesis, because Finnish patients with early RA have elevated anti-proteus antibodies compared with control individuals, and patients with chronic RA (one group from Finland, two groups from Japan) also had such antibodies. The role of these antibodies in the pathogenesis of RA is hard to understand. They can be only indirect evidence of antimicrobial antibodies that cross-react with host HLA structures, as shown in the paper.

Human immunodeficiencies that predispose to intracellular bacterial infections
Rainer Doffinger, Smita Patel, and Dinakantha S. Kumararatne

Purpose of review
Patients treated with anti–tumour necrosis factor agents have an increased risk of active tuberculosis. Mycobacteria are bacterial pathogens capable of surviving and multiplying within macrophages; these infections are characterised by granulomatous inflammation. This review addresses the effects of inherited and acquired immunodeficiencies on the susceptibility to the development of intracellular bacterial infections.

Recent findings
Primary and secondary immunodeficiencies that result in severely impaired T cell function or macrophage activation result in an increased risk of mycobacterial and Salmonella infection. Conversely, inherited or acquired antibody or complement deficiency does not lead to increased susceptibility to these pathogens. Inherited defects in the interleukin-12/interleukin-23–dependent interferon-γ pathway due to mutations in genes encoding the p40 chain common to interleukin-12 and interleukin-23, the β1 chain shared by interleukin-12 and interleukin-23 receptors, interferon-γ receptor chains 1 or 2, or signal transducer and activator of transcription, predispose to severe infections caused by poorly pathogenic mycobacteria and Salmonella species. Acquired defects of cytokine function causing increased susceptibility to these pathogens include anti–tumor necrosis factor therapy and the generation of interferon-γ–neutralising autoantibodies. Defective nuclear factor κB activation caused by hypomorphic mutations of the nuclear factor κB essential modulator gene, which compromises the function of Toll receptors, interleukin-1L receptors, and tumor necrosis factor–α receptors, also increases susceptibility to severe mycobacterial infections. Patients with inherited defects in the phagocyte nicotine-adenine dinucleotide phosphate oxidase system are highly susceptible to Salmonella infections but only exhibit slightly increased susceptibility to mycobacteria.

Summary
Collectively, these observations highlight immune mechanisms that are essential for protection against intracellular bacteria. This information provides clinicians with a framework for investigating patients with potentially life-threatening intracellular bacterial infections.

Keywords
human immunodeficiency, intracellular bacterial infection

Introduction
Some bacterial pathogens, most notably mycobacterial and Salmonella species, have the capacity to survive and multiply within mononuclear phagocytes and also to survive in the extracellular milieu. These bacteria have evolved specific pathogenic mechanisms that enable persistence within their hosts, resulting in chronic infections. The outcome of the encounter between these microbial pathogens and the human host depends on an interplay between microbial factors (e.g., virulence, infecting dose) and the innate and acquired immune responses of the host. It is therefore axiomatic that impaired immunity in the host may result in increased susceptibility to these intracellular bacterial pathogens. The increased incidence of tuberculosis reported in HIV-infected individuals or after the use of tumor necrosis factor–α (TNF-α) antagonists is a striking example of this phenomenon [1,2]. This review primarily addresses the nature of immunodeficiencies that increase susceptibility to mycobacterial disease and, to a lesser extent, Salmonella infections.

The genus Mycobacterium consists of more than 85 species that are potential human pathogens. Of these, Mycobacterium tuberculosis is the most virulent pathogen; it currently infects almost 30% of the global population. In individuals infected with M. tuberculosis, the lifetime risk for the development of clinical tuberculosis is approximately 10%. Hence, the vast majority of infected individuals are capable of containing the infection through the action of their immune response. Epidemiologic studies provide strong
evidence that human anti-tuberculous immunity is not sterilizing but bacteriostatic in nature. *M. tuberculosis* is well adapted to the human host, and viable organisms may persist in a dormant state within an infected individual for many years and retain the potential to cause progressive disease [3].

The poorly pathogenic nontuberculous mycobacteria (NTM) are ubiquitous in our environment, and virtually all individuals are exposed to these organisms within a few years of birth. These organisms are acquired from the environment, and person-to-person spread is not a mode of transmission. NTM do not usually cause infection in individuals without an underlying predisposing factor like chronic lung disease or immunodeficiency. Bacille Calmette-Guerin (BCG) is an attenuated strain of *M. bovis* that is used as a vaccine against tuberculosis. This organism, again, does not cause progressive infection in immunocompetent individuals.

Immunodeficiency may be primary, due to an inherited defect of a component of the immune system [4•]. Alternatively, immunodeficiency may be secondarily caused by another pathologic condition that may impair immune function (e.g., lymphoid malignancy or HIV infection) or be iatrogenic, due to therapeutic agents or irradiation. The chief consequence of both primary and secondary immunodeficiency is increased susceptibility to infection, giving rise to a spectrum of infection, the nature of which is determined by the component of immunity that is deficient.

### Immunodeficiencies that increase susceptibility to mycobacterial infection

Table 1 summarises the influence of different types of immunodeficiency on susceptibility to mycobacterial infections. The main conclusion from this table is that cell-mediated immunity, which depends on the interaction between T cells and macrophages and cytokines that are produced by these cells, is critically important for the normal expression of antimycobacterial immunity. Individuals who are deficient in components of cell-mediated immunity because of inherited or acquired disorders, therefore, show increased susceptibility to mycobacterial infections. The relevant defects of cell-mediated immunity can be classified into three categories: (1) primary or secondary immunodeficiency resulting in severely impaired T cell function, (2) mendelian defects resulting in impaired function of the Type 1 cytokine axis, or (3) acquired type 1 cytokine deficiency. By contrast, defects in antibody production, function of the classic and alternative complement pathway, mannan binding lectin, and neutropenia do not result in increased susceptibility to mycobacterial infection.

### Immunodeficiency states resulting in severely impaired T cell function

Severe combined immunodeficiency comprises a group of diseases characterised by severe failure in T cell development and in some cases by the absence of B cells and natural killer cells [5]. Patients with severe combined immunodeficiency are extremely vulnerable to infection from birth and succumb to opportunistic infections unless they are rescued with bone marrow transplantation. In babies with severe combined immunodeficiency who have been BCG vaccinated, fatal disseminated BCG infections develop [6]. Reports of NTM or tuberculosis in this condition are scanty, probably because the patients do not survive long enough to acquire these infections.

Infection with HIV increases susceptibility to tuberculosis even before CD4 counts are reduced [1]. NTM infections are seen in patients with low CD4 cell counts, and the risk greatly diminishes as T cell counts rise after highly active antiretroviral therapy. High-dose corticosteroids (greater than mg/kg or for >3 months) and other drugs that suppress T cell function (e.g., cyclosporin, tacrolimus) also increase the likelihood of reactivation of latent tuberculous infection [7,8].

### Inherited defects of neutrophil function

Chronic granulomatous disease (CGD) comprises a group of disorders caused by mutations in genes encoding for components of the nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase system [9]. Post-phagocytic activation of the phagocyte oxidase system results in the influx of a high concentration of reactive oxygen species into the phagosome. The consequent increased negative electrostatic charge within the phagosome is compensated by an influx of K+, resulting in a net rise in the ionic concentration within this structure. This results in the release and activation of cationic lysosomal proteases, including elastase and cathepsin G, which kill and digest bacteria within the phagosome [10,11]. Patients with CGD are highly susceptible to disseminated infections caused by *Salmonella* species. BCG and NTM infections, however, are only rarely reported in CGD [12]. Because NTM are ubiquitously distributed in the environment, most CGD patients will be exposed to these bacteria. Hence, the paucity of mycobacterial infection in CGD indicates that the mechanisms activated by the NADPH oxidase pathway are not critically important in antimycobacterial immunity.

### Defects in the type 1 cytokine pathway

Disseminated infection caused by poorly pathogenic mycobacteria (NTM or BCG) in the absence of recognised primary or secondary immunodeficiency states has been documented in a series of patients (see database: Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/Database/index.html; MIM 209950).
Infectious arthritis and immune dysfunction

Physiology of the interleukin-12—dependent high-output interferon-γ pathway

After infection with intercellular pathogens like mycobacteria, antigen-presenting cells (APC) (e.g., dendritic cells and macrophages) secrete the heterodimeric cytokine IL-12, which is composed of two disulphide linked subunits, p40 and p35, which together form the biologically active IL-12 molecule (Fig. 1). The stimulus for the production of IL-12 by subsets of APC is the activation of cell surface Toll-like receptors by bacterial ligands like mycobacterial lipoarabinomannan. The receptor for IL-12 (IL-12R) is expressed by natural killer cells and activated T cells. IL-12R is made up of two chains called IL-12Rβ1 and IL-12Rβ2, respectively. Binding of IL-12 to its receptor expressed by activated CD4 cells partitions them to develop and differentiate along the so-called Th1 pathway, which is critically important for effective cell-mediated immunity against intracellular pathogens. IL-12 induces a high level of production of the cytokine IFN-γ by responding T cells and natural killer cells. The recently identified cytokine IL-23 is a heterodimer composed of the same p40 subunit as in IL-12, coupled to a unique second chain, p19. The receptor for IL-23 consists of the IL-12Rβ1 subunit coupled to an additional receptor chain, IL-23Rβ3. IL-23 has an action similar to that of IL-12 on T cells, inducing IFN-γ production. Two additional cytokines with actions similar to those of IL-12 are IL-21 and IL-22. Some of these cases were familial, and others were sporadic. The common feature of most of these patients who have been investigated was their inability to produce or respond to interferon-γ (IFN-γ) in vitro. Genetic analysis of the affected kindreds have to date defined mutations in five different genes participating in the interleukin-12 (IL-12)–dependent high-output IFN-γ pathway (see below).

Table 1. The association of mycobacterial and salmonella infections with immunodeficiencies

<table>
<thead>
<tr>
<th>Immunodeficiency</th>
<th>Abnormality</th>
<th>Effect on mycobacterial infections</th>
<th>Effect on Salmonella infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral immunodeficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary and secondary antibody deficiency</td>
<td>Reduced circulating antibodies</td>
<td>No increase</td>
<td>Self-limiting intestinal disease or chronic carriage</td>
</tr>
<tr>
<td>X-linked hyper IgM syndrome</td>
<td>CD40L deficiency</td>
<td>Slightly increased risk</td>
<td>Self-limiting intestinal disease or chronic carriage</td>
</tr>
<tr>
<td>Complement</td>
<td>Inherited or acquired complement deficiency</td>
<td>No increase</td>
<td>No increase</td>
</tr>
<tr>
<td></td>
<td>Inherited mannose-binding lectin deficiency</td>
<td>No increase</td>
<td>No increase</td>
</tr>
<tr>
<td>Phagocyte deficiency</td>
<td>Reduced circulating phagocytes</td>
<td>No increase</td>
<td>Salmonella bacteremia reported</td>
</tr>
<tr>
<td>Primary and secondary neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte adhesin deficiency</td>
<td>CD18/11a,b,c deficiency</td>
<td>No increase</td>
<td>No infections reported</td>
</tr>
<tr>
<td>Chronic Granulomatous disease</td>
<td>Defect in phagocyte NADPH oxidase</td>
<td>Slightly increased risk of BCG and NTM infection</td>
<td>Greatly increased risk of Salmonella septicemia/metastatic disease</td>
</tr>
<tr>
<td>Deficiency of cell-mediated immunity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary T cell deficiency</td>
<td>Severe combined immunodeficiency; all genetic variants HIV</td>
<td>Increased risk of disseminated BCG infection</td>
<td>Probable increased risk</td>
</tr>
<tr>
<td>Secondary T cell deficiency</td>
<td>Immunosuppressive therapy</td>
<td>Increased risk of TB, NTM, BCG infection</td>
<td>Salmonella septicemia/metastatic disease</td>
</tr>
<tr>
<td>Cytokine receptor deficiency</td>
<td>IFNγR1 or R2 deficiency</td>
<td>Greatly increased risk of disseminated NTM/BCG infection</td>
<td>Salmonella septicemia/metastatic disease</td>
</tr>
<tr>
<td></td>
<td>IL12Rβ1 deficiency</td>
<td>Increased risk of disseminated NTM/BCG infection</td>
<td>Greatly increased risk of Salmonella septicemia/metastatic disease</td>
</tr>
<tr>
<td>Inherited cytokine deficiency</td>
<td>IL12p40 deficiency</td>
<td>Increased risk of disseminated NTM/BCG infection</td>
<td>Few cases of Salmonella septicemia/metastatic disease reported</td>
</tr>
<tr>
<td>Acquired cytokine deficiency</td>
<td>TNF antagonants</td>
<td>Increased risk of disseminated NTM/BCG infection</td>
<td>Few cases of Salmonella septicemia/metastatic disease reported</td>
</tr>
<tr>
<td>Signaling defects</td>
<td>Neutralizing autoantibodies to IFNγ</td>
<td>Increased risk of disseminated NTM/TB infection</td>
<td>Probable increased risk</td>
</tr>
<tr>
<td></td>
<td>STAT1 defect</td>
<td>Increased risk of disseminated NTM/BCG infection</td>
<td>On case of Salmonella septicemia reported</td>
</tr>
<tr>
<td></td>
<td>NFκB defect</td>
<td>Fatal NTM infections reported</td>
<td></td>
</tr>
</tbody>
</table>

IFN, interferon; IL, interleukin; BCG, bacille Calmette-Guérin; NTM, nontuberculous mycobacteria; TB, tuberculosis; TNF, tumour necrosis factor; NFκB, nuclear factor κB.
parasites capable of intramacrophage survival. Biologically active IFN-γ is a homodimer, which has a range of pleiotropic effects on a large range of cell types [15]. It is one of the principal macrophage activity cytokines, and mice with disrupted IFN-γ or IFN-γ receptor genes show increased susceptibility to intracellular pathogens, including mycobacteria. Specific receptors for IFN-γ are widely expressed on most nucleated cells and comprise two trans-membrane proteins: IFN-γ receptor 1 (IFN-γR1), which is the ligand binding chain, and IFN-γR2, which is required for signal transduction. The structure of the IFN-γ receptor and the activation of signal transduction by IFN-γ using the JAK-STAT signalling pathway are summarised in Figure 2.

Currently defined defects of the type 1 cytokine cascade

These defects include mutations in two genes controlling the production of IFN-γ: *IL-12B* (encoding IL-12 p40) and *IL-12RB1* (encoding the IL-12 receptor chain, IL-12Rβ1). Other defects impair the activation of the effector pathways induced by IFN-γ. These are mutations in *IFN-GR1* (encoding the ligand binding chain of the IFN-γ receptor), *IFN-GR2* (encoding the signalling chain of the IFN-γ receptor), and *STAT1*, (encoding the signal transducer and activator of transcription 1). Mutations of these genes result in the production of nonfunctional or partially functional proteins (Fig. 1) [16**,17**].

Broadly speaking, the severity of the phenotype and the spectrum of infections seen were found to correlate with the precise genetic defect. Patients with complete IFN-γR1 or R2 deficiencies experience disseminated mycobacterial infections caused by BCG or NTM, which occur in early childhood and have a high mortality [18**]. The lesions in this patient cohort are characteristically multibacillary and are associated with impaired granuloma formation. By contrast, partial IFN-γR1 and IFN-γR2 deficiency, complete IL-12B deficiency (resulting in IL-12 and IL-23 deficiency), and IL-12/IL-23 receptor deficiency predisposed to curable mycobacterial infections occurring at a later age [19–22]. The lesions in such patients are typically associated with a ‘tuberculoid’ granulomatous response and are often paucibacillary [23].
Patients with partial or complete mutations of \textit{STAT1}, with consequently impaired biologic response to IFN-\(\gamma\), are also associated with poorly pathogenic mycobacterial infections [24,25]. The dominant form of partial \textit{STAT1} deficiency seems to primarily affect antimycobacterial defences, leaving antiviral immunity intact. By contrast, recessive complete \textit{STAT1} deficiency leads to disseminated mycobacterial infections and to fatal viral infections that occur in infancy. Complete \textit{STAT1} deficiency results in an inability to respond to IFN-\(\alpha\), which predisposed to the lethal viral infection seen in the two patients discovered to date.

In addition to this, extra-intestinal, or septicemic, relapsing infections caused by nontyphoid \textit{Salmonella} species predominate in patients with defects in the IL-12/IL-23 system [26]. Mycobacterial infections also occur in these patients but are less common. The situation is reversed in patients with defects in the IFN-\(\gamma\) receptors or \textit{STAT1}. Mycobacterial infections predominate in these patients, whereas \textit{Salmonella} infection is far less common. Such observations suggest that host defense against \textit{Salmonella} species might also include an IL-12/23–dependent but IFN-\(\gamma\)–independent mechanism.

The lethality of mycobacterial infection in patients with complete defects in IFN-\(\gamma\)R1 or R2 indicates that IFN-\(\gamma\) activates effector mechanisms that are essential for protection from this genus. It is also noteworthy that patients with type 1 cytokine deficiency are resistant to a wide range of ubiquitous bacteria, fungi, viruses, and parasites.

**Defects in the nuclear factor–\(\kappa B\) signalling pathway and intracellular bacterial infection**

Hypomorphic mutations of the nuclear factor–\(\kappa B\) (NF-\(\kappa B\)) essential modulator gene (NEMO) causes X-linked immunodeficiency with or occasionally without anhydrotic ectodermal dysplasia [27,28]. The NEMO protein is a regulatory component of the inhibitor of NF-\(\kappa B\) kinase complex. Activation of NF-\(\kappa B\) is essential for signal transduction by a whole battery of receptors required for the normal expression of innate immunity and Ig class-switching. Thus, the immunodeficiency in patients with NEMO mutations typically includes hypogammaglobulinaemia and impaired innate immunity, including defective function of Toll receptors, IL-1 receptors, and TNF-\(\alpha\) receptors. This complex immunodeficiency results in increased susceptibility to infections caused by a broad range of pathogens, including gram-positive and gram-negative bacteria, fungi, and cytomegalovirus. In addition, severe NTM infections are also commonly reported in these patients [29,30]. \textit{Salmonella} sepsis has been reported in one patient to date. It is interesting to note that three patients with the NF-\(\kappa B\) inhibitory protein \(\kappa B\)\(\alpha\) and four patients with IRAK4 deficiency, which impairs Toll receptor function upstream of NEMO, have not shown susceptibility to mycobacterial infections [31–34]. The number of patients affected in each case is very small, however, and we cannot yet draw firm conclusions about the relevance of these pathways to antimycobacterial immunity.

**Acquired cytokine deficiency and intracellular bacterial infection: infections associated with tumor necrosis factor antagonists**

Tumor necrosis factor-\(\alpha\) plays a critical role in protective immunity to \textit{M. tuberculosis} infection as well as in the induction of immunopathology and tissue damage [2]. TNF-\(\alpha\) is produced primarily by activated mononuclear phagocytes in response to a range of stimuli, including lipopolysaccharides, viral infection, and infection with gram-negative and gram-positive bacteria. Response to TNF-\(\alpha\) is mediated by TNF-R1 and TNF-R2 receptors. Soluble TNF-\(\alpha\) mainly binds to TNF-R1, whereas the membrane-associated form of TNF-\(\alpha\) is a main agonist of TNF-R2 receptors. Observations in immunologically deprived or gene-disrupted mice indicate that TNF-\(\alpha\) acting through its TNF-R1 receptor plays a major role in coordinating a granulomatous response to, and the subsequent containment of, mycobacterial infections [3]. Through these mechanisms, TNF-\(\alpha\) helps to control bacterial growth, dissemination, and secondary damage to host tissue; however, excessive production of TNF-\(\alpha\) and increased tissue sensitivity to this cytokine have been shown to contribute to the immunopathology of tuberculosis. The precise mechanism by which TNF-\(\alpha\) contributes to antimycobacterial immunity is likely to be complex and is not fully understood. These observations explain the association of the increased risk of mycobacterial disease in patients treated with TNF antagonists.

Three TNF antagonists have been used for the treatment of chronic inflammatory conditions, like rheumatoid arthritis and Crohn disease. Of these, infliximab and adalimumab are monoclonal antibodies with inhibitory activity against TNF-\(\alpha\). The third, etanercept, is a chimeric soluble TNF receptor, which blocks TNF function. The clinical use of anti-TNF agents has been associated with an increased incidence of tuberculosis. In a keynote paper, Wallis et al. [35••] reviewed the incidence of granulomatous infection in patients who had received etanercept, between January 1998 and September 2002, by analyzing data collected through the adverse event reporting system of the United States Food and Drug Administration. The rate of granulomatous infection was 239 per 10,000 patients who received infliximab and 74 per 10,000 patients who received etanercept. There was a significantly higher incidence of granulomatous infection in those who received infliximab than in those who received etanercept \((P < 0.001)\). Tuberculosis was the most frequently reported infection and occurred in 54 and 28 per 10,000 patients who
received infliximab and those who received etanercept, respectively (P < 0.001) [36]. Concomitant corticosteroid usage was reported in 41% of patients receiving infliximab and in 66% of patients who received etanercept and subsequently experienced granulomatous infection. The concomitant methotrexate use in these groups was 43% and 41%, respectively. Among patients who received infliximab, more than half of the cases of tuberculosis were extrapulmonary, and 25% of the total patients had disseminated tuberculosis. This atypical presentation could result in delayed diagnosis. Epidemiologic studies also indicated that three quarters of the cases of active tuberculosis occurred within the first 3 months of infliximab treatment, whereas more than 95% occurred within the first year. This observation suggests that these cases of tuberculosis after infliximab therapy are most likely to be due to reactivation of latent infection [36]. In contrast to patients receiving infliximab therapy, in recipients of etanercept, active tuberculosis typically presents after a longer duration of treatment. In this case, a median time from first dose to diagnosis of tuberculosis was 5 months (range 1–20).

Other intracellular pathogens that were associated with anti-TNF therapy included *Histoplasma, Listeria, NTM,* and *Salmonella* causing sepsis in a few cases [2,36]. These infections, too, were more common amongst infliximab-treated patients, compared with those treated with etanercept.

Although the groups of patients who receive infliximab may not be exactly comparable with those receiving etanercept, the general consensus is that infliximab is associated with a higher risk of tuberculosis and other granulomatous infections. Infliximab binds with higher affinity to soluble and transmembrane forms of TNF-α when compared with etanercept. These biologic differences as well as differences in the in-vivo kinetics of these two agents may explain the differential risk of granulomatous infection with them. A detailed discussion of this matter is outside the scope of this article (but see [2]).

Comprehensive data are not yet available for adalimumab, but it may behave in a similar way to infliximab. Relevant algorithms for the management of the risk of tuberculosis reactivation and other opportunistic infections in patients treated with anti-TNF agents are discussed in detail elsewhere [2].

**Acquired interferon-γ deficiency**

A few patients have been recently described with acquired IFN-γ deficiency, caused by serum auto-antibodies that specifically neutralised the biologic activity of IFN-γ [37,38]. These patients experienced disseminated tuberculosis as well as fatal NTM infections.

**Conclusions**

Experiments of nature exemplified by immunodeficient humans indicates those components of immunity which are essential and conversely redundant for the expression of normal immunity to intracellular bacteria. Primary and secondary complement and antibody deficiencies do not cause increased susceptibility to mycobacterial infection. Antibody deficiency causes an increase in susceptibility to persistent enteric infection by *Salmonella* species. Congenital and acquired neutropenia is not associated with mycobacterial disease. The optimal operation of cell-mediated immunity is essential for protection of the human host from mycobacteria and *Salmonella* species. Patients with NADPH oxidase defect are highly susceptible to *Salmonella* infections but show only a slightly increased susceptibility to mycobacteria.

Novel data accruing in the past decade have highlighted the importance of the IL-12/23–dependent high-output INF-γ pathway in protection against mycobacteria and *Salmonella* infections. The lethality of mycobacterial infection in patients with complete defects in IFN-γR1 or R2 indicates that IFN-γ activates effector mechanisms that are essential for protection from this genus. It is also noteworthy that patients with type 1 cytokine deficiency are resistant to a wide range of ubiquitous bacteria, fungi, viruses, and parasites, indicating that this pathway plays a minor or redundant role against these organisms. TNF-α seems to be critical for the normal expression of antituberculous immunity. Taken together, these observations indicate candidate genetic mechanisms that may be relevant for providing protection from these pathogens in the normal human host.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

This seminal publication summarises the clinical consequences of IFN-γ receptor 1 deficiency in a child with tuberculoid bacille Calmette-Guerin infection. Lancet 1995; 346:581.


Extrahepatic manifestations in patients with chronic hepatitis C virus infection
Manuel Ramos-Casals and Josep Font

Purpose of review
Chronic hepatitis C virus infection often has autoimmune clinical and analytic features. This review analyzes recent data on the close association of chronic hepatitis C virus infection with autoimmune and lymphoproliferative processes.

Recent findings
Hepatitis C virus infection has been associated with both organ-specific (thyroiditis, diabetes) and systemic autoimmune diseases. Experimental, virologic, and clinical evidence has demonstrated a close association between hepatitis C virus infection and Sjögren syndrome, with hepatitis C virus–associated Sjögren syndrome being indistinguishable in most cases from the primary form. With respect to rheumatoid arthritis, patients with hepatitis C virus–related polyarthritis and positive rheumatoid factor may fulfill the classification criteria for rheumatoid arthritis. Hepatitis C virus has also been associated with an atypical presentation of antiphospholipid syndrome, as well as with the development of sarcoidosis. A higher prevalence of hematologic processes in patients with hepatitis C virus infection has recently been reported, including cytopenias and lymphoproliferative disorders. Recent data are available on the use of new immunosuppressive and biologic agents (mainly mycophenolate mofetil, anti–tumor necrosis factor agents, and rituximab) in patients with hepatitis C virus infection and autoimmune or lymphoproliferative manifestations.

Summary
There is increasing evidence of a close association of hepatitis C virus infection with autoimmune and hematologic processes. The sialotropism of hepatitis C virus may explain the close association with Sjögren syndrome, and its lymphotropism links the virus to cryoglobulinemia, autoimmune cytopenias, and lymphoma. The substantial overlap between cryoglobulinemic features and the classification criteria for some systemic autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, and polyarteritis nodosa) make the differentiation between mimicking and coexistence difficult.

Keywords
antiphospholipid syndrome, cryoglobulinemia, extrahepatic manifestations, hepatitis C virus, lymphoma, rheumatoid arthritis, sarcoidosis, Sjögren syndrome

Introduction
The hepatitis C virus (HCV), a linear, single-stranded RNA virus identified in 1989, is recognized as one of the viruses most often associated with autoimmune features [1]. A decade ago, various authors described the association of HCV infection with a heterogeneous group of extrahepatic conditions, such as pulmonary fibrosis, cutaneous vasculitis, glomerulonephritis, Mooren ulcers, porphyria cutanea tarda, or lichen planus, although it is currently accepted that a weak degree of association exists in some of them [2,3]. More recently, there has been growing interest in the association of chronic HCV infection with circulating autoantibodies, lymphoproliferative processes, and autoimmune (both systemic and organ-specific) diseases.

Autoantibodies and hepatitis C virus
Circulating autoantibodies are often detected in patients with chronic HCV infection. Antinuclear antibodies (ANA), rheumatoid factor (RF), and anti–smooth muscle antibodies are the most frequently found, and other autoantibodies (such as anti–dsDNA, anti–extractable nuclear antigens [anti–ENA], antimitochondrial antibodies [AMA], or anti–liver-kidney microsomes [anti–LKM-1]) are infrequent (Table 1) [4–17,18,19]. ANA have been detected in 589 (18.6%) of 3169 unselected HCV patients included in 16 studies (Table 1), although the geographic prevalence varied significantly [19]. Yee et al. [19] reported

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**Abbreviations**
- ANA: antinuclear antibodies
- APS: antiphospholipid syndrome
- CCP: cyclic citrullinated peptide
- ELISA: enzyme-linked immunosorbent assay
- HCV: hepatitis C virus
- MALT: mucosa-associated lymphoid tissue
- MC: mixed cryoglobulinemia
- MMF: mycophenolate mofetil
- NHL: non-Hodgkin lymphoma
- RA: rheumatoid arthritis
- RF: rheumatoid factor
- SAD: systemic autoimmune disease
- SS: Sjögren syndrome
- TNF: tumor necrosis factor

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**Keywords**
- antiphospholipid syndrome
- cryoglobulinemia
- extrahepatic manifestations
- hepatitis C virus
- lymphoma
- rheumatoid arthritis
- sarcoidosis
- Sjögren syndrome

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Table 1. Meta-analysis of the main studies analysing prevalence of autoantibodies in unselected series of patients with chronic HCV infection

<table>
<thead>
<tr>
<th>Study</th>
<th>HCV patients (n)</th>
<th>ANA</th>
<th>SMA</th>
<th>LKM</th>
<th>DNA</th>
<th>ENA</th>
<th>AMA</th>
<th>Cryog</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried et al. [4]</td>
<td>62</td>
<td>13</td>
<td>34</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Abuaf et al. [5]</td>
<td>272</td>
<td>50</td>
<td>69</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Borotto et al. [6]</td>
<td>97</td>
<td>20</td>
<td>18</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rolachon et al. [7]</td>
<td>93</td>
<td>14</td>
<td>14</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pawlotsky et al. [8]</td>
<td>61</td>
<td>13</td>
<td>13</td>
<td>3</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td>McFarlane et al. [9]</td>
<td>101</td>
<td>0</td>
<td>18</td>
<td>6</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Richardet et al. [10]</td>
<td>156</td>
<td>18</td>
<td>8</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Czaja et al. [12]</td>
<td>75</td>
<td>24</td>
<td>8/74</td>
<td>1/74</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>21/72</td>
<td></td>
</tr>
<tr>
<td>Cassani et al. [13]</td>
<td>290</td>
<td>26</td>
<td>59</td>
<td>18</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buskila et al. [14]</td>
<td>90</td>
<td>31</td>
<td>—</td>
<td>4</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rivera et al. [15]</td>
<td>189</td>
<td>43</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>64</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Drygiannakis et al. [17]</td>
<td>142</td>
<td>72</td>
<td>33</td>
<td>1</td>
<td>4</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stroffolini et al. [18]</td>
<td>502</td>
<td>79</td>
<td>137</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yee et al. [19]</td>
<td>645</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total number</td>
<td>3188</td>
<td>589/3169</td>
<td>481/2203</td>
<td>75/2193</td>
<td>16/606</td>
<td>11/444</td>
<td>4/1201</td>
<td>204/514</td>
<td>281/738</td>
</tr>
</tbody>
</table>

| %                      |                   | 18.6 | 21.8 | 18.6 | 21.8 | 3.4 | 2.8 | 2.5 | 0.3 | 39.7 | 38.1 |

HCV, hepatitis C virus; ANA, antinuclear antibodies; SMA, anti-smooth muscle antibodies; LKM, anti-liver-kidney microsomes antibodies; ENA, anti-extractable nuclear antigens (anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm); AMA, antimitochondrial antibodies; cryog, cryoglobulins; RF, rheumatoid factor.

With respect to other immunologic markers, Watt et al. [20] found a correlation between serum immunoglobulin levels in HCV patients (IgA, IgG, and total Ig) and histologic progression to liver fibrosis. These results are consistent with our findings in 321 patients with HCV-related cryoglobulinemia, in whom hypergammaglobulinemia was observed more frequently in cirrhotic than in noncirrhotic patients [21].

Organ-specific autoimmune diseases and hepatitis C virus

Recent studies have analyzed the association of HCV with some organ-specific autoimmune diseases such as thyroiditis or diabetes mellitus. Bini and Mehandru [22••] described the development of thyroid disease (overt or subclinical) in 11% of 225 male HCV-infected patients treated with combined antiviral therapy, although the thyroid disease responded well to specific treatment and was reversible in most cases. Antonelli et al. [23••,24] reported a higher frequency of hypothyroidism (13%) and antithyroid antibodies (21%) in 630 treatment-naïve HCV patients compared with normal control individuals. They also found similar results in a subset of these HCV patients with associated mixed cryoglobulinemia (MC); however, other studies performed in the same geographic area did not find this close association [25].

Antonelli et al. [26•] have also reported that the prevalence of type 2 diabetes is higher in patients with MC-HCV than in control individuals, with diabetic MC-HCV+ patients having a more pronounced autoimmune reactivity than non-HCV patients with classic type 2 diabetes. Metabolic disorders in HCV patients may be related to the development of steatosis, whose clinical significance in HCV patients has recently been emphasized [27•].

Systemic autoimmune diseases and hepatitis C virus

The association between HCV and systemic autoimmune disease (SAD) has generated growing interest in recent years. The extrahepatic manifestations often observed in patients with chronic HCV infection (both clinical and immunologic) may lead to the fulfillment of the current classification criteria for some SAD (Table 2). Recent research has focused on Sjögren syndrome (SS), rheumatoid arthritis (RA), antiphospholipid syndrome (APS), cryoglobulinemic vasculitis, and sarcoidosis.

Sjögren syndrome

Recent experimental, virologic, and clinical evidence has revealed a close association between HCV and SS [28–34]. In 2002, we formed the SS-HCV Study Group, a multicenter international collaboration that so far has recruited 137 SS-HCV patients [35]. We have found that HCV-associated SS is indistinguishable in most cases from the primary...
form according to the most recent set of classification criteria, and we have proposed the term ‘SS secondary to HCV’ in HCV patients who fulfill the 2002 classification criteria [36]. Chronic HCV infection should be considered an exclusion criterion for the classification of primary SS, not because it mimics primary SS but because the virus may be implicated in the development of SS in a specific subset of patients [36,37].

The main differential aspect between primary and HCV-related SS is the immunologic pattern, with a predominance of cryoglobulinemic-related markers (mixed cryoglobulins, RF, hypocomplementemia) over SS-related markers (anti-Ro/SS-A and anti-La/SS-B autoantibodies) in HCV-related SS [35]. We have found a threelfold higher prevalence of hypocomplementemia in SS-HCV patients than in patients with primary SS [38]. Cryoglobulinemia seems to be the key immunologic marker of SS associated with HCV, having a close association with RF activity and complement activation.

**Rheumatoid arthritis**

It is understandable that HCV patients with polyarthritis and positive RF may be clinically classified as having RA. Of the 1988 revised American College of Rheumatology criteria, there are four (arthritis of three or more joint areas, arthritis of hand joints, symmetric arthritis, and RF) that some HCV patients may experience. Rosner et al. [39•] reviewed the prevalence and clinical characteristics of the HCV-related arthritis exhaustively and also analyzed the significant overlap with RA. The most frequent clinical presentation of HCV-related arthritis is chronic inflammatory polyarthritis, which may lead to the fulfillment of the American College of Rheumatology classification criteria for RA in more than 50% of cases. The existence of morning stiffness, rheumatoid nodules, and erosive arthritis (rarely described in the setting of HCV infection) and the presence of antibodies to cyclic citrullinated peptide (CCP) may be useful to diagnose a true coexistence of RA and HCV [40,41]. Wener et al. [42] found no anti-CCP antibodies in HCV patients, although some false-positive results were observed in patients with MC, whereas Bombardieri et al. [43•] found anti-CCP antibodies in 76% of patients with RA and in 60% of those with coexisting RA and HCV, but not in HCV patients, irrespective of their articular involvement. This suggests that anti-CCP antibodies may be useful in discriminating HCV patients with true RA from those with HCV-associated arthropathy.

**Antiphospholipid syndrome**

The association between HCV and APS is controversial [44]. We have recently analyzed the clinical features in 45 APS-HCV patients [45]. In comparison with unselected APS patients, APS-HCV patients had a lower frequency of typical APS features such as peripheral thrombosis or neurologic features but a higher prevalence of some atypical or infrequent features such as myocardial infarction or intra-abdominal thrombotic events. In addition, a higher frequency of positive immunologic markers was observed in patients with APS-HCV, including ANA, cryoglobulins, hypocomplementemia, and RF. Infectious agents may play a diverse etiopathogenic role in the clinical expression of APS, with bacterial infections probably acting as acute triggering agents of a devastating multi-organic form of APS (catastrophic APS), whereas chronic viral infections (such as HCV and HIV infections) may trigger a heterogeneous, atypical presentation of APS [45–47].

**Cryoglobulinemic vasculitis**

Two studies have analyzed the clinical characteristics of HCV-related cryoglobulinemia in large series of patients. Sene et al. [48•] studied 125 patients with MC retrospectively and found that cryoglobulinemic vasculitis was associated with advanced age, longer duration of HCV infection, type II MC, and a higher MC serum level. Ferri

---

**Table 2. Different degrees of association between HCV and systemic autoimmune diseases**

<table>
<thead>
<tr>
<th>Degree of association</th>
<th>Extrahepatic HCV features overlapping with classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Xerostomia, xerophthalmia, ocular tests (+), salivary biopsy (+), ANA, RF</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, RF</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Articular involvement, renal involvement, ANA, aPL, cytopenias</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Weakness, peripheral neuropathy, elevated creatinine, positive HBV markers</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Positive aPL, atypical thrombotic events</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Weakness, elevated GOT, GPT</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Inflammatory myopathies</td>
<td>Renal involvement</td>
</tr>
<tr>
<td>Low</td>
<td>Age &gt;60 years</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td></td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td></td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td></td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus; ANA, antinuclear antibodies; RF, rheumatoid factor; aPL, antiphospholipid antibodies; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase.
et al. [49*] analyzed the demographic, clinical, and serologic features and survival in 231 patients with MC; 168 patients were tested for HCV infection, with 155 (92%) being positive. Malignancies were observed in 15% of patients, mainly non-Hodgkin lymphoma (NHL) and hepatocellular carcinoma, and the main causes of death were related to MC (64%), NHL (13%), and liver involvement (13%).

Sarcoidosis
Since the first case reported in 1993, the number of cases of sarcoidosis associated with HCV reported annually has increased significantly, related or not related to antiviral therapy [50–53]. We reviewed the clinical characteristics of 59 patients with sarcoidosis associated with HCV infection and found that sarcoidosis was triggered by antiviral therapy (mainly by interferon) in 75% of cases [54]. Clinicians should be aware of the possibility that sarcoidosis may initially manifest or reactivate during or shortly after treatment with antiviral therapy in patients with chronic HCV infection.

Other systemic autoimmune diseases
Herrera et al. [55*] reported a patient with relapsing polychondritis, HCV, and mixed cryoglobulinemia, in whom treatment with anti-HCV therapy improved the symptoms of relapsing polychondritis. We described two patients with coexisting polyarteritis nodosa, HCV, and NHL [56]. All patients has associated cryoglobulinemia. Isolated cases of HCV patients with Takayasu arteritis or systemic sclerosis have been reported [57,58].

Hematologic diseases and hepatitis C virus
The specific tropism of HCV for many extrahepatic cell types (Table 3), especially for circulating blood cells, has recently been demonstrated by several studies, providing a clear link between HCV and the development of autoimmune and neoplastic hematologic processes [30,31,60–68,69*]. The susceptibility of blood cells to HCV infection might be enhanced by coexisting additional chronic viral infections. Laskus et al. [70*] reported that HIV facilitates the infection and replication of HCV in circulating blood cells, a fact that might be related to the development of severe cytopenias in some HCV-HIV patients [71].

Autoimmune cytopenias
Although HCV-related cytopenias are not uncommon, they are usually considered as mild laboratory abnormalities with no clinical significance, especially in patients with hypersplenism. The most frequent is thrombocytopenia, which has a chronic clinical course, with severe bleeding being uncommon. De Almeida et al. [61] found no association between HCV genotypes and thrombocytopenia, although HCV-RNA was detected more frequently in the platelets of thrombocytopenic patients than in those with a normal platelet count. Wang et al. [72*] described a tenfold higher frequency of thrombocytopenia in HCV patients than in HCV-negative control individuals. Thrombocytopenia correlated with the severity of HCV-related liver disease.

Severe cytopenias are observed in some HCV patients, related or not related to antiviral therapy. Thrombocytopenia may be severe (<30 × 109/L) in treatment-naive HCV patients, and in some patients it is associated with concomitant autoimmune diseases, cryoglobulinemia, and HIV coinfection [71]. Two cases of severe Coombs-positive autoimmune hemolytic anemia have recently been reported in patients not treated with interferon [73,74]. Previously, 17 cases of HCV-related autoimmune hemolytic anemia had been reported, frequently associated with autoimmune diseases, with cryoglobulinemia being the most frequent immunologic marker [71]. Finally, isolated cases of pure red blood cell aplasia have also been described in HCV patients [71,75].

Lymphoproliferative diseases
Recent studies have found a higher prevalence of lymphoproliferative disorders in HCV patients [76–78,79*]. Matsuo et al. [79**] performed an elegant meta-analysis of 23 epidemiologic studies on the association between HCV and NHL, including 4049 NHL patients. The summary odds ratio for NHL in HCV patients was 5.70, being 5.04 for B-cell and 2.51 for T-cell NHL [79**]. The prevalence of HCV infection in NHL patients may be higher, given that Paydas et al. [80*] have described false negative results in the enzyme-linked immunosorbent assay (ELISA) detection of anti-HCV antibodies in 8 (72%) of 11 patients with NHL, in whom the presence of HCV-RNA was confirmed in paraffin-embedded lymphomatous tissues. This occult HCV infection has also been described in some patients with an altered liver profile of unknown origin, in whom the virus was isolated from liver tissue and circulating mononuclear cells, and was not

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**Table 3. Extrahepatic localizations of the hepatitis C virus infection**

<table>
<thead>
<tr>
<th>Study</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieni et al. [59], Crovatto et al. [60], Ducoulombier et al. [69]</td>
<td>Circulating blood cells</td>
</tr>
<tr>
<td>Crovatto et al. [60]</td>
<td>B lymphocytes</td>
</tr>
<tr>
<td>Crovatto et al. [60]</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td>Crovatto et al. [60]</td>
<td>Monocytes</td>
</tr>
<tr>
<td>de Almeida et al. [61]</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Anrieta et al. [30], Toussirot et al. [31]</td>
<td>Platelets</td>
</tr>
<tr>
<td>De Vita et al. [62]</td>
<td>Extrahaepatic tissues</td>
</tr>
<tr>
<td>Authier et al. [63], Di Muzio et al. [64]</td>
<td>Salivary glands</td>
</tr>
<tr>
<td>Authier et al. [63], Bonetti et al. [65]</td>
<td>Gastric mucosa</td>
</tr>
<tr>
<td>Radkowski et al. [66]</td>
<td>Striated muscle</td>
</tr>
<tr>
<td>Okabe et al. [67]</td>
<td>Peripheral nerve</td>
</tr>
<tr>
<td>Agenello &amp; Abel [68]</td>
<td>Central nervous system</td>
</tr>
<tr>
<td></td>
<td>Myocardium</td>
</tr>
<tr>
<td></td>
<td>Cutaneous lesions</td>
</tr>
</tbody>
</table>
detectable by ELISA and polymerase chain reaction techniques in serum [81**].

Lymphomagenesis in HCV patients might be initiated by the chronic stimulation of polyclonal B cells by the virus, with the posterior development of specific B-cell clonal expansions and pro-carcinogenic mutations [82**,83*,84**,85**,86]. Vallat et al. [84**] suggested that B-cell clonality in the blood and liver may be a marker of lymphoma development in some HCV patients. Machida et al. [85**] reported that both acute and chronic HCV infection caused a fivefold to tenfold increase in mutation frequency in the Ig heavy chain, BCL-6, p53, and β-catenin genes, whereas Libra et al. [86] detected bcl-2 rearrangement in mucosa-associated lymphoid tissue (MALT) lymphomas from HCV patients.

The close relation between autoimmunity, viruses, and cancer is demonstrated by the description of patients with HCV infection, SAD, and B-cell lymphoma, who had a high prevalence of cryoglobulinemia, a high frequency of primary extranodal NHL involvement, and a poor prognosis [56]. The clearest example is the development of NHL in patients with SS-HCV (Fig. 1) [87]. Recently, Ambrosetti et al. [88*] have reported that most cases of primary salivary MALT lymphoma are associated with either SS or HCV infection. The close relation between HCV and NHL might have therapeutic implications [89,90]. Tursi et al. [91*] have reported the disappearance of gastric MALT lymphoma in 13 of 18 HCV patients after 6 months of antiviral therapy. We recommend a careful evaluation of patients with B-cell NHL to detect silent autoimmune or chronic viral diseases.

**Therapeutic management of extrahepatic features**

The therapeutic management of HCV-related autoimmune features has become a clinical challenge in HCV patients, in whom chronic liver disease associated with severe autoimmune features contributes to a very poor prognosis [92]. Both antiviral and immunosuppressive therapies, either alone or in combination, seem likely to have an important role, although these treatments should be individualized according to cost, follow-up, relapses, organ involvement, risk of exacerbation of autoimmune disease, and the possible consequences of immunosuppression in the setting of chronic HCV infection [93*,94,95]. Recent data are available for the use of immunosuppressive and biologic agents in HCV patients with autoimmune or lymphoproliferative manifestations (Table 4).

**Mycophenolate mofetil**

Recent reports have suggested a promising role for mycophenolate mofetil (MMF) in the treatment of HCV-related autoimmune processes, especially severe cytopenias and cryoglobulinemic vasculitis [96–98]. In addition, Medina et al. [99] have reported preliminary results on the successful use of MMF to treat diffuse proliferative glomerulonephritis in five patients with HCV-related systemic lupus erythematosus. The favorable response to MMF in these patients, with no major side effects and no signs of worsening of HCV infection, suggests that MMF may
be used as monotherapy or in association with other drugs in patients with SAD associated with chronic HCV infection.

Rituximab

In 2003, some studies demonstrated the efficacy of using rituximab in cryoglobulinemic vasculitis [100–102]. Recent reports have described the successful use of rituximab in HCV patients with cryoglobulinemic glomerulonephritis, although the nephritis relapsed and required a second course of rituximab in some patients [103]. The successful use of rituximab to treat hematologic processes associated with HCV, such as severe cytopenias or NHL, has also been reported. Etienne et al. [74] have successfully treated an HCV patient with severe autoimmune hemolytic anemia, and we have used rituximab to treat indolent B-cell lymphoma in patients with SS and HCV [104]. In comparison with standard chemotherapy regimens, monotherapy with rituximab is generally well tolerated, and serious adverse effects are uncommon.

Anti-tumor necrosis factor agents

Finally, anti-tumor necrosis factor (TNF) agents have recently been used in some HCV patients with coexisting systemic and rheumatic diseases. The use of anti-TNF agents (infliximab or etanercept) in patients with coexisting RA and HCV infection has been reported, although few details on the clinical response of the articular in-

Table 4. Use of the new immunosuppressive and biological agents in patients with autoimmune or lymphoproliferative diseases associated with chronic HCV infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed et al. [97], Caponnetto et al. [98]</td>
<td>Autoimmune and rheumatologic disease</td>
</tr>
<tr>
<td>Chandresis et al. [108]</td>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Lamprecht et al. [100], Zaja et al. [101], Sansonno et al. [102], Roccatello et al. [103]</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Caponnetto et al. [98], Medina et al. [99]</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Parke et al. [105], Oniankitan et al. [107]</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Magliocco et al. [109]</td>
<td>IFN-induced sarcoidosis</td>
</tr>
<tr>
<td>Menon et al. [51]</td>
<td>Myasthenia gravis</td>
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<td>Caponnetto et al. [98]</td>
<td>Autoimmune cytopenias</td>
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<td>Lerardi et al. [96]</td>
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<td>Lerardi et al. [96]</td>
<td>Coombs-positive hemolytic anemia</td>
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<td>Etienne et al. [74]</td>
<td>Rituximab</td>
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<td>Ramos-Casals et al. [104]</td>
<td>SS-HCV-NHL</td>
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HCV, hepatitis C virus; IFN, interferon; NHL, non-Hodgkin lymphoma; MMF, mycophenolate mofetil; anti-TNF, anti-tumor necrosis factor agents; SS, Sjögren syndrome.

Conclusion

Evidence for a close association of HCV with autoimmune and hematologic processes is increasingly demonstrated. The extrahepatic tropism of HCV shows a close etiopathogenic link with some of these processes. The sialotropism of HCV may explain the close association with SS, and its lymphotropism links the virus with cryoglobulinemia, autoimmune cytopenias, and lymphoma. It should be noted that cryoglobulinemic features overlap considerably with several classification criteria for some SAD like systemic lupus erythematosus, RA, and polyarteritis nodosa, making it difficult to differentiate between mimicking and coexistence situations. Antiviral therapies, however, are also associated with the development of autoimmune manifestations such as sarcoidosis or cytopenia. The therapeutic management of the HCV-related autoimmune features is very difficult, and recent studies have evaluated the role of new immunosuppressive and biologic agents, although the role of new antiviral therapies such as HCV serine protease inhibitors should be evaluated in future studies [111].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
•Of special interest
••Of outstanding interest

19 This multicenter study involving 502 Italian HCV patients shows the lack of correlation between non-organ-specific antibodies and the main biochemical and histologic features, on one hand, and the response to antiviral therapy, on the other.
21 The authors analyzed the ANA in 645 HCV patients from Sweden, the United Kingdom, and Italy and found important geographic differences in the prevalence of ANA.
25 This study included 225 HCV-infected patients treated with antiviral therapy, with thyroid disease being observed in 11%; however, only male HCV patients were analysed.
27 The authors describe a frequency of type 2 diabetes mellitus two times higher in patients with HCV-related cryoglobulinemia in comparison with the control group, underlining the importance of analyzing the coexistence of metabolic disturbances in HCV patients.
29 This very interesting article about the significance of the steatosis in HCV patients centers on the possible influence of HCV in the host insulin and lipid metabolism, thereby opening new lines of therapeutic interventions.
33 This study included 225 HCV-infected patients treated with antiviral therapy, with thyroid disease being observed in 11%; however, only male HCV patients were analysed.
34 The authors analyzed the ANA in 645 HCV patients from Sweden, the United Kingdom, and Italy and found important geographic differences in the prevalence of ANA.
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39 The authors analyzed the ANA in 645 HCV patients from Sweden, the United Kingdom, and Italy and found important geographic differences in the prevalence of ANA.
44 The authors suggest that anti-CCP antibodies may be useful in differentiating a true RA coexisting with HCV from a RA mimicked by HCV-related arthritis.

This retrospective study describes the progress in 125 HCV patients with sarcoïdosis after a 24-month minimum interval of follow-up.


This exhaustive description of a large series of patients with MC (most associated with HCV infection) has an interesting description of the main causes of morbidity and mortality.


The authors present a rare case of association between relapsing polychondritis, HCV, and cryoglobulinemia that responded successfully to antiviral therapy, and the authors investigated the molecular mechanisms of interaction between HCV and HIV in mononuclear cells from co-infected individuals, offering possible molecular explanations for the frequent detection of autoimmune and lymphoproliferative processes in patients with HCV/HIV co-infection.


The authors performed an elegant meta-analysis of 23 studies including more than 4000 NHL patients, demonstrating a summary odds ratio for NHL of 5.7 in HCV patients compared with seronegative control individuals.


The authors describe a close association between the occurrence of B cell clonal expansions and extrahepatic manifestations of chronic HCV infection. Eur J Immunol 2004; 34:126–136.

The authors describe a close association between the occurrence of B cell clonal expansion and extrahepatic manifestations in HCV patients.
Extrahepatic manifestations in chronic hepatitis C infection

Ramos-Casals and Font


85 Machida K, Cheng KT, Sung VM, et al. Hepatitis C virus induces a mutator phenotype: enhanced mutations of immunoglobulin and protooncogenes. Proc Natl Acad Sci USA 2004; 101:4262–4267. The authors provide molecular evidence of the close association between HCV and cancer. They investigated the enhanced frequency of mutations in immunoglobulin genes and proto-oncogenes in HCV-infected cells. These two different oncogenic mechanisms may explain the Janus-like neoplastic expression observed in HCV patients with hepatocarcinoma and B cell lymphoma, the most frequently detected neoplasm in these patients.


88 Ambrosetti A, Zanotti R, Pattaro C, et al. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjögren syndrome or hepatitis C virus infection. Br J Haematol 2004; 126:43–49. This is a meticulous description of 33 patients with MALT lymphoma in the salivary glands, of which 73% were observed in patients with SS or HCV infection, underlining the sialotropism of the lymphomas occurring in patients with SS or HCV infection.


105 Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum 2004; 51:800–804. The authors present the results of the use of anti-TNF agents in 5 patients with coexisting RA and HCV infection, centered on their safety with respect to liver and virologic parameters but with few data on the clinical response of RA.


110 Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. Ann Rheum Dis 2004; 63(Suppl 2):ii18–ii24. This is a good review (more etiopathogenic than clinical) of the use of anti-TNF agents in patients with chronic viral diseases, with two key messages: that there are very limited clinical data and that there is not yet adequate follow-up evaluating the possible long-term sequelae induced by the immunosuppression of anti-TNF blockade in these patients.

Introduction

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1]. These fragility fractures, found at areas typified by large amounts of trabecular bone, have devastating health consequences through their association with increased mortality and morbidity and are consequently a considerable burden to the health care system. Previous prospective studies indicate that the risk of osteoporotic fracture increases continuously as bone mineral density (BMD) declines, with a 1.5-fold to threefold increase in risk of fracture for each standard deviation fall in BMD [2]. In the Rotterdam Study, a prospective population-based cohort study of 7806 men and women aged 55 years or older, the age-adjusted hazard ratio per standard deviation decrease in femoral neck BMD was 1.5 for women and 1.4 for men [3**]. This article reviews recent research findings regarding the epidemiology and diagnosis of this disabling condition.

Absolute risks of fracture in individuals

Although most American women under the age of 50 have normal BMD, 27% are osteopenic and 70% are osteoporotic at the hip, lumbar spine, or forearm by the age of 80 years. Epidemiologic studies from North America have estimated the remaining lifetime risk of common fragility fractures to be 17.5% for hip fracture, 15.6% for clinically diagnosed vertebral fracture, and 16% for distal forearm fracture among white women aged 50 years. The corresponding risks among men are 6%, 5%, and 2.5%, respectively. A British study using the General Practice Research Database estimated the lifetime risk of any fracture to be 53.2% at age 50 years among women and 20.7% at the same age among men (Table 1) [4]. Our knowledge of the epidemiology of childhood fractures in the United Kingdom has recently been expanded by interrogation of the same database; at their childhood peak, the incidence of fractures (boys 3%, girls 1.5%) is surpassed only at 85 years of age among women and never among men (Fig. 1) [5**].

Health impact of osteoporotic fracture

All osteoporotic fractures are associated with significant morbidity, but both hip and vertebral fractures are also associated with excess mortality. Although this may represent complications of the fracture and subsequent surgery for hip fractures, it is likely to reflect coexisting comorbidity in persons experiencing vertebral fracture. By 2 years after hip fracture, mortality rates decline back to
baseline except in elderly patients and among men. The four main predictors for higher mortality seem to be male sex, increasing age, coexisting illness, and poor functional status before fracture.

Excess mortality after vertebral fracture seems to increase progressively after diagnosis of the fracture (Table 2) [6]. This has been observed in studies based on clinically diagnosed vertebral deformities and in those using radiologic morphometric approaches to classify vertebral deformity [7]. The 5-year survival seems to be worse for men (72% 5-year survival) than for women (84% 5-year survival). In women, an excess risk of death from cardiovascular and pulmonary disease that rises with increasing number of vertebral fractures has been observed [8].

In the United States, approximately 7% of survivors of all types of fragility fractures have some degree of permanent disability, and 8% require long-term nursing home care.

The impact of a single vertebral fracture may be low, but multiple fractures cause progressive loss of height and kyphosis and severe back pain in the acute stages. The resultant loss of mobility can further exacerbate underlying osteoporosis, leading to increased risk of further fractures [9]. Participants in the European Prospective Osteoporosis Study with radiologically identified vertebral fracture at baseline had repeat radiographs performed 3 years later. Women who experienced a further fracture during follow-up experienced substantial levels of disability with impairment in key physical functions of independent living [10]. The psychologic impact of functional loss can cause depression and social isolation as well as loss of self-esteem. Although good functional recovery after distal forearm fracture may be poor, reflecting complications such as reflex sympathetic dystrophy, neuropathies, and post-traumatic arthritis, mortality after Colles fracture does not deviate from the expected rate.

Geographic variation
Several studies have suggested a wide geographic variation in hip fractures between as well as within countries. In general, people who live in latitudes farther from the equator seem to have a higher incidence of fracture [11]. The highest rates of hip fracture are seen in Caucasians living in northern Europe, especially in Scandinavian countries, where the age-adjusted 1-year cumulative incidence was 903/100,000 for women and 384/100,000 for men in Norway 1989 [12]. The rates are intermediate in the populations of Asia, China, and Kuwait and lowest in black populations [13–16]. Whereas studies in central Norway suggest stabilisation in fracture rates in recent years, a Californian study reported a doubling of hip fracture rates in Hispanic patients, and no significant change occurred among black or Asian men or women [17,18]. An Australian study concluded that although the increase in hip fracture rates during most of the past century may have ended, the number of admissions for hip fracture is still rising because of an aging population [19]. Many of the lower incidence rates in the developing countries can be partially explained by lower life expectancy; in Latin America only 5.7% of the population is over 65 [20]. Reduced longevity was also the explanation given for the low fracture rates observed in Morocco [21]. Other papers have highlighted the poor appreciation of the role played by osteoporosis in fragility fracture; in one Lebanese study, fewer than 10% of hip fracture patients received any therapy for osteoporosis [22].

The epidemiology of fracture
Fracture incidence in the community is bimodal, with a peak in the young and elderly (Fig. 2). The geographic

Table 1. Estimated risks of fractures at various ages

<table>
<thead>
<tr>
<th>Lifetime risk</th>
<th>Current age (yr)</th>
<th>Any fractures (%)</th>
<th>Radius/ulna (%)</th>
<th>Femur/hip (%)</th>
<th>Vertebral (%)</th>
</tr>
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<tbody>
<tr>
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<td>53.2</td>
<td>16.6</td>
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<td></td>
<td>80</td>
<td>28.6</td>
<td>6.9</td>
<td>12.3</td>
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<tr>
<td>Men</td>
<td>50</td>
<td>20.7</td>
<td>2.9</td>
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<td>80</td>
<td>9.6</td>
<td>1.1</td>
<td>3.7</td>
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10-Year risk

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<tr>
<td>Men</td>
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Reproduced with permission [4].
variations in fracture rates demonstrated even within countries suggest that environmental factors are also important in the pathogenesis of hip fracture. Social deprivation may be one such factor, as well as dietary factors such as adequate protein intake [23,24]. Other studies have highlighted the importance of adequate serum 25(OH)D levels; a population-based study set in southeast Australia demonstrated that a fall in 25(OH)D level in winter was accompanied by a rise in parathyroid hormone 1 month later and increased bone resorption markers 1 month after that. The seasonal periodicity in fracture rate peaked 1.5 to 3 months after this trough in 25(OH)D [25].

In Western populations, among individuals above 50 years of age, there is a female preponderance of hip fracture, with a female-to-male incidence ratio of approximately 2/1. The advent of the description of morphometric and semiquantitative visual techniques has now enabled several studies to report the prevalence of vertebral fracture. Only about a third of all vertebral deformities noted on radiographs come to medical attention, and fewer than 10% necessitate admission to hospital [26]. Recent data from the Epidemiology of Osteoporosis Study (EPIDOS) study have yielded estimates of prevalence of vertebral fractures of 19% among women aged 75 to 79 years, to 21.9% among those aged 80 to 84 years, to 41.4% among those aged 85 years and older; these data are broadly in accord with estimates from other populations [27]. Only a quarter of vertebral fractures result from falls, and most are precipitated by routine daily activities such as bending or lifting light objects, reflecting the compressive load of such acts. By contrast, distal forearm fracture almost always results as a consequence of a fall onto an outstretched hand. A much stronger sex ratio exists for this fracture than for most others, and this has been estimated to be 4:1 in favor of women. Recent data from Dorset in the United Kingdom showed that among women, the incidence of distal radius fracture rose from a premenopausal baseline of 10 per 10,000 population per year to a peak of 120 per 10,000 population per year over 85 years [28]. Although geographic variation exists, a partial explanation may be methodologic considerations of case ascertainment, given that fewer than 20% of patients with forearm fracture are hospitalised. A winter peak is again demonstrated, but this probably is due to falls outside on icy surfaces. The plateau with age in women may

| Table 2. Observed and expected survival following fracture among men and women aged >65 years |
|---------------------------------|---------------------------------|---------------------------------|
|                                  | Radius/ulna (%)                 | Femur/hip (%)                   | Vertebral (%)                   |
|                                  | Observed | Expected | Observed | Expected | Observed | Expected |
| Women                            |          |          |          |          |          |          |
| At 3 months                      | 98.2  | 98.6     | 85.6    | 97.7     | 94.3     | 98.4     |
| At 12 months                     | 94.0   | 94.4     | 74.9    | 91.1     | 86.5     | 93.6     |
| At 5 years                       | 75.5   | 73.8     | 41.7    | 60.9     | 56.5     | 69.6     |
| Men                              |          |          |          |          |          |          |
| At 3 months                      | 97.3   | 98.0     | 77.7    | 97.3     | 87.8     | 97.9     |
| At 12 months                     | 89.6   | 92.4     | 63.3    | 90.0     | 74.3     | 91.8     |
| At 5 years                       | 62.8   | 66.4     | 32.2    | 58.2     | 42.1     | 64.4     |

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be due to mode of falls; later in life a woman is more likely to fall onto a hip than onto an outstretched hand as her neuromuscular coordination deteriorates.

The incidence rates of proximal humeral, pelvic, and proximal tibial fractures also rise steeply with age and are greater in women than men. These are often termed frailty fractures because they typically occur in women who are losing weight involuntarily [29]. Furthermore, there is some direct evidence that these fractures are associated with low BMD [30]. Three quarters of all proximal humerus fractures are due to moderate trauma, typically a fall from standing height or less, and tend to be more common in women with poor neuromuscular function [31].

Diagnosis

Only 44% of all nonvertebral fractures occurred in women with a T score below –2.5 in the Rotterdam study; among men, the figure was even lower [3**]. Hence, there is a clear need for the development of more sensitive risk assessment tools, using not just BMD. Potential clinical risk factors were identified in the Study of Osteoporotic Fractures; older age, previous self-reported fracture after age 50, maternal history of hip fracture after age 50, greater height at age 25, impaired cognition, slower walking speed, nulliparity, type II diabetes, Parkinson disease, and depth perception problems each independently predicted a 1.17- to 1.83-fold increase in hip fracture risk, whereas each standard deviation of decrease in hip BMD was independently associated with a 1.84 increase in risk. Lower body mass index also increases fracture risk, but this effect seems to be mediated through BMD change [32*]. A study of 149,524 white postmenopausal women (mean age 64.5 years) used peripheral BMD at the heel, finger, or forearm and questionnaire data to derive an algorithm that included previous fracture, T score, or forearm and questionnaire data to derive an (mean age 64.5 years) used peripheral BMD at the heel, or less, self-rated poor health status, and poor mobility whereas each standard deviation of decrease in hip BMD was independently associated with a 1.84 increase in risk. Lower body mass index also increases fracture risk, but this effect seems to be mediated through BMD change [32*]. A study of 149,524 white postmenopausal women (mean age 64.5 years) used peripheral BMD at the heel, finger, or forearm and questionnaire data to derive an algorithm that included previous fracture, T score –1.8 or less, self-rated poor health status, and poor mobility to correctly classify 74% of the women who experienced a fracture [33*]. There has been considerable interest in the use of other diagnostic techniques, particularly calcaneal quantitative ultrasound, in recent years. In one United Kingdom study of 14,824 men and women aged 42 to 82 years from the Norfolk cohort of the European Prospective Investigation into Cancer, a fall of one SD in broadband ultrasound attenuation was associated with a relative risk of fracture of 1.95 (95% CI 1.50–2.52), independently of age, sex, weight, height, cigarette smoking, and past fracture [34*]. A Spanish cross-sectional study of 5195 women aged 65 years or older cited age-adjusted odds ratios for fracture corresponding to each decrease of one standard deviation of the different quantitative ultrasound parameters ranging from 1.47 to 1.55 [35]. Research tools being developed at present include an assessment of femoral neck volumetric BMD to discriminate between fracture and nonfracture cases, and hip strength analysis, which yields several measures including cross-sectional moment of inertia, section modulus, hip axis length, compressive stress, and safety factor, and which explains in part the lower incidence of hip fracture found in Oriental populations [36,37].

Comorbidities

Comorbidity is known to be an important fracture determinant. In a retrospective cohort study of 86 United States residents undergoing renal transplantation between 1965 and 1995, high fracture rates were observed, particularly of the vertebrae and feet [38]. In a multivariate analysis, age and diabetic nephropathy were independent predictors, whereas cumulative corticosteroid, cyclosporin, and tacrolimus use was not.

To test the hypothesis that there is a significant age-independent relation between arteriosclerosis and osteoporosis and that vascular calcification and bone loss progress in parallel, computed tomography was performed at baseline and at follow-up 9 months to 8 years later in a group of 228 women [39]. Aortic calcification was inversely related to BMD and directly to fracture, with women in the highest quartile for gain in aortic calcification having four times greater yearly bone loss. A cross-sectional Norwegian study assessed the relation between BMD and the prevalence and morphology of carotid artery plaques among 5000 men and women aged 55 to 74 years and demonstrated an increased risk of low bone mass with echogenic calcified arteriosclerotic plaques but not radiolucent plaques [40].

Other studies have evaluated the relation between other chronic diseases and osteoporosis. In one study of 909 middle-aged residents of the United Kingdom, bone density was higher in persons with newly diagnosed diabetes, with relations attenuated by adjustment for body mass index [41]. In a population-based retrospective cohort study among 226 residents of Rochester, Minnesota, who were 35 years of age or older when they first received diagnoses of asthma, the 70% increase in overall fracture risk was mainly confined to the subset who also had chronic obstructive pulmonary disease and was influenced by corticosteroid use [42].

A recent Australian population-based study of 569 women with radiologically confirmed incident fracture and 775 control individuals without fracture assessed medication use and lifestyle [43*]. In this group, β-blocker use was associated with a higher BMD at the hip and forearm and a reduced risk of fracture. Adjustment for anthropometry, thiazide use, and lifestyle made little difference, and the authors suggested that β-blockers may stimulate bone formation, inhibit bone resorption, or both.

Finally, further evidence of the detrimental effects of corticosteroids on bone was provided by a meta-analysis of data
from seven cohort studies of 42,000 men and women, which documented a relative risk of hip fracture of 4.42 to 2.48 among previous steroid users [44]. There were no differences according to sex or age. Despite the limitations of the data, the consistency of the association in an international setting is clearly important.

Conclusions
Osteoporotic fractures represent a significant public health burden, which is set to rise in future generations. Life expectancy is increasing worldwide, and it is estimated that the number of individuals aged 65 years and over will increase from the current figure of 323 million to 1555 million by the year 2050. These demographic changes alone can be expected to cause the number of hip fractures occurring worldwide to increase from 1.66 million in 1990 to 6.26 million in 2050. On the basis of current trends, hip fracture rates might increase in the United Kingdom from 46,000 in 1985 to 117,000 in 2016. A report from the Asian Osteoporosis Study has recently demonstrated a moderate variation in hip fracture rates among Asian countries, with highest rates in urbanised countries, suggesting that rapid economic development may prove important in rapidly increasing fracture rates.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

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Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004; 19:893–899. This meta-analysis used seven previously studied patient cohorts that were followed up for 176,000 patient-years.
The use of bisphosphonates in the treatment of osteoporosis

Pierre D. Delmas

Purpose of review
The bisphosphonates alendronate and risedronate, given orally once weekly, are the cornerstone of treatment of postmenopausal osteoporosis, as well as of male and secondary osteoporosis. They reduce significantly the risk of vertebral and nonvertebral fractures; their effects appear early, within 6–12 months, and appear to be sustained. Several questions remain unanswered, however. In addition, data on a new bisphosphonate became available in 2004.

Recent findings
The optimal duration of treatment has not been clearly established. Long-term data with alendronate are now available, indicating a persistence of alendronate effects on bone mineral density and bone turnover markers several years after stopping treatment given for 5 years. Whether these effects translate into sustained reduction of fractures needs to be further analyzed. Because of their efficacy, bisphosphonate use has been explored in other forms of osteoporosis, such as after androgen deprivation therapy for prostatic cancer. The challenge of long-term compliance with treatment of osteoporosis has triggered the use of intermittent bisphosphonate. The effects of intermittent oral and intravenous ibandronate on bone mineral density, bone turnover, and fractures have been recently reported.

Summary
The mechanism by which bisphosphonates improve bone strength is not yet fully understood but probably involves complex effects on different components of bone strength, such as microarchitecture.

Keywords
bisphosphonates, bone turnover, fragility fractures, osteoporosis

Introduction
Among various treatments used in the management of postmenopausal osteoporosis, the two bisphosphonates alendronate and risedronate, available worldwide, play a prominent role. Both have been shown to reduce the risk of vertebral fracture by approximately 50% and to reduce the risk of nonvertebral fracture, including the hip, by 20–50% according to patient characteristics [1]. The efficacy of these two bisphosphonates on bone mineral density (BMD) at the spine and hip as well as on biochemical markers of bone turnover has been shown consistently in postmenopausal women across various ages and severity of the disease. A pooled analysis of data from three randomized double-blind, placebo-controlled, 3-year fracture-endpoint trials performed over 3 years was done to determine the efficacy of risedronate in reducing vertebral fracture risk in women aged 80 and older, with osteoporosis. After 1 year, the risk of new vertebral fractures in the risedronate group was 80% lower than with placebo ($P < 0.01$) and the reduction was 44% after 3 years ($P = 0.003$) [2]. The incidence of nonvertebral fractures was slightly but not significantly reduced with risedronate, probably because of limited statistical power. Importantly, the safety profile was comparable to that of placebo, although patient age ranged from 80–98 years [2]. Most antiresorptive therapy reduced the risk of fracture within 1 year. This is also true with bisphosphonates. In 2442 postmenopausal osteoprotic women from two pooled trials, risedronate was found to reduce significantly the risk of clinical vertebral fractures within 6 months [3]. In a post-hoc analysis of women with osteoporosis women with and without vertebral fractures who had low BMD ($lumbar spine T-score < -2.5$) taken from four randomized placebo-controlled trials, risedronate was found to reduce significantly the risk of major nonvertebral fractures by 6–12 months [4].

The convenience of bisphosphonate dosing has been markedly improved by the once-weekly regimen, as compared with daily dosing. As previously shown for alendronate, the equivalence of risedronate 35 mg once a week vs. 5 mg daily over 2 years has been recently shown, with similar increase in BMD at the spine and hip and similar reduction in bone turnover markers, without safety issues [5]. An important step in obtaining acceptance and full reimbursement of the bisphosphonates is to demonstrate their cost effectiveness in the management of osteoporosis. A health economic study performed in Sweden has shown that alendronate is, indeed, cost effective for treating women with osteoporosis as defined by prevalent

Abbreviations

- **BMD**: bone mineral density
- **CTX**: C-terminal telopeptide of type I collagen
- **FIT**: Fracture Intervention Trial
- **FLEX**: FIT Long-Term Extension trial
- **NTX**: N-terminal telopeptide of type I collagen
- **P1NP**: N-terminal propeptide of type I procollagen

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1040-8711
vertebral fractures or a low BMD (T-score < -2.5) regardless of age [6]. Using a similar Markov model that was adapted to fit a cohort of Swedish men, and assuming a similar fracture risk reduction in men as compared with women over 10 years for a treatment duration period of 5 years, the same group concluded that treating a 71-year-old man with osteoporosis (prior vertebral fracture and low BMD) was cost effective, i.e., associated with the cost of 14 843 Euros per quality-adjusted life year gained [7**]. Using a similar model, risedronate was found to be cost effective in the United Kingdom in elderly women with osteoporosis and low BMD. Treatment was cost effective in women from age 65 years with and without a previous vertebral fracture, as well as in women whose BMD T-score was at the threshold of osteoporosis and who also had an additional risk factor for fracture (e.g., smoking, oral glucocorticoid use) [8**]. Thus, bisphosphonates appear as a first-line treatment of both men and postmenopausal women with osteoporosis.

What is the optimal duration of bisphosphonate treatment?

In the prevention of osteoporosis in postmenopausal women, alendronate 5 mg or 10 mg daily prevents bone loss at the spine and hip up to 7 years, with a slightly greater effect with 10 mg than with 5 mg. Discontinuation of treatment after 2–5 years is followed by a significant bone loss at the spine and hip [9]. In women with osteoporosis, the long-term effect of alendronate has been assessed in three subsequent extensions of two initial 3-year placebo-controlled trials of alendronate testing three daily doses [10–12]. The final report provides adequate information about changes in BMD and bone turnover markers in patients treated for up to 10 years, but no conclusion can be drawn about the long-term efficacy on fractures, as the placebo group was maintained for only 3 years [13**]. Treatment with 10 mg of alendronate daily for 10 years produced a gradual increase in BMD of 13.7% at the spine, 10% at the trochanter, and 5.4% at the femoral neck as compared with baseline values. In patients who discontinued alendronate after 5 years, there was a small but significant decrease in BMD at most skeletal sites in the subsequent 5 years, but at 10 years BMD values were higher than at baseline. Interestingly, cessation of treatment was followed by a 20% increase in urinary N-terminal telopeptide of type I collagen (NTX) (a marker of bone resorption). The mean values remained 50% lower than at baseline up to 5 years after discontinuation [13**]. These data suggest that the beneficial effect of alendronate may be sustained after cessation of treatment, provided that a sufficient cumulative dose has been reached. As noted by Bjarnason [14] and by Ott [15], however, this study does not allow conclusions to be drawn on the optimal duration of treatment. Some additional information is provided by the FLEX trial (FIT Long-Term Extension), which extends the Fracture Intervention Trial (FIT), in which alendronate-treated patients were randomly reallocated to receive alendronate or placebo. In this extension, more than 1000 postmenopausal women with osteoporosis who were treated with alendronate for an average duration of 5 years were randomly reallocated for an additional 5 years to receive alendronate or placebo. Changes in BMD and bone turnover markers were consistent with the previous study showing that after discontinuation of alendronate, the loss of BMD was slow and the increase in bone turnover was of small magnitude, indicating persistence of alendronate effects on bone [16**]. Fracture incidence during FLEX has been reported in an abstract form [17]. There was no difference in morphometric vertebral or in nonvertebral fracture incidence during years 6–10 between patients who continued and patients who discontinued alendronate, suggesting that the antifracture efficacy of alendronate is maintained after discontinuation and that it might be legitimate to stop treatment after 5 years. Surprisingly, however, the incidence of clinical vertebral fracture was significantly lower in women continuing alendronate, but the number of women with such fractures was low [17]. It is not known whether the pattern of BMD and bone turnover changes after cessation of long-term risedronate is similar to that observed after cessation of alendronate, but preliminary observation suggests that the offset of action on bone turnover is more rapid after both 5 and 7 years of therapy [18].

The use of bisphosphonates in secondary osteoporosis

The use of androgen deprivation therapy for prostate cancer has increased markedly over the past 15 years. This treatment is associated with bone loss and it has been recently shown in a large epidemiologic study that it is associated with a significant increase in the risk of fracture [19]. Neridronate, an amino bisphosphonate that has been shown to be effective in patients with Paget disease of bone [20], was given at the dose of 25 mg intramuscularly every month and compared with the effect of calcium and vitamin D in a randomized study of patients with prostate cancer receiving androgen deprivation therapy. Neridronate was able to prevent bone loss and to prevent the increase in markers of bone turnover (deoxypyridinoline and bone alkaline phosphatase) over 1 year of treatment [21]. Cardiac transplantation is another condition that leads to osteoporosis. A total of 149 such patients were randomly assigned to receive alendronate 10 mg/day or calcitriol 0.5 μg/day from 3 weeks after transplantation and were compared with a reference group of 27 untreated patients who received cardiac transplant within the same period [22]. The degree of bone loss did not differ significantly between the two intervention groups and was markedly lower than in the control group. The incidence of vertebral fracture did not differ significantly among the groups, but the study did not have the statistical power to show such an effect. Because calcitriol treatment requires a
close monitoring of serum and urinary calcium levels, alendronate appears to be a more attractive alternative for the prevention of bone loss early after cardiac transplantation, at least in patients who are at high risk of fracture. Rheumatoid arthritis is associated with low BMD and an increased risk of fracture. Although bisphosphonates have been consistently shown to prevent systemic bone loss in these patients, whether or not they are treated with glucocorticoids, their effects for preventing or slowing bone erosion are contradictory. Herrak et al. [23] have shown in a mice model of tumor necrosis factor-mediated arthritis that bone erosion was retarded by a single dose of zoledronic acid and was almost completely blocked by repeated administration. Although synovial inflammation was not affected by zoledronic acid, synovial osteoclast counts were reduced and cartilage damage was partly inhibited. These data suggest that highly potent bisphosphonates might be useful in the management of rheumatoid arthritis, not only to prevent systemic bone loss but also to reduce peripheral erosion.

**New intermittent bisphosphonates**

Ibandronate is a highly potent nitrogen-containing bisphosphate that has the potential to be administered intermittently with extended between-dose intervals. Oral daily (2.5 mg) and intermittent ibandronate (between-dose interval of >2 months) with a regimen delivering similar cumulative exposures were evaluated in about 3000 women with osteoporosis with prevalent vertebral fracture. As compared with the placebo group, a significant reduction in incident vertebral fracture risk of 62 and 50%, in the daily and intermittent ibandronate groups, respectively, was shown after 3 years (Fig. 1). Overall, the incidence of nonvertebral fracture was not reduced by treatment; however, a post-hoc analysis showed that the daily regimen reduced the risk of nonvertebral fracture by 69% in a higher-risk subgroup, i.e., in those with a femoral neck BMD T-score less than −3 [24]. By 3 months, the rate of bone turnover as assessed by the urinary excretion of C-terminal telopeptide of type I collagen (CTX) and NTX was reduced by 50–70% by both regimens and this level of suppression was sustained throughout the remainder of the study [25]. The increase in BMD at the spine and hip was also similar in the two treatment groups [24]. These beneficial effects contrast with a trial in which patients with osteoporosis received 1 mg and 0.5 mg intravenous ibandronate injections once every 3 months over 3 years. Despite a significant increase in BMD, the incidence of new morphometric vertebral fractures was nonsignificantly reduced by 24% with the highest dose as compared with the placebo group, with no effects on nonvertebral fractures. Although both doses of ibandronate produced a dose-dependent increase in spine BMD (4 and 2.9%, respectively), the residual suppression of bone resorption, measured by the decrease in urinary CTX at the time of injection, was suboptimal and not significantly different from the value observed in the placebo group [26]. In contrast, ibandronate given intravenously every 3 months at the dose of 2 mg induced an increase in spine BMD at 1 year, similar to the oral daily and intermittent arms of the positive fracture study, and induced a marked 60% suppression of urinary CTX [27]. In summary, intermittent oral or intravenous ibandronate given at the adequate dose is an interesting alternative for the treatment of postmenopausal osteoporosis.

**Mechanism of action and safety**

Although antiresorptive therapies, and especially bisphosphonates, induce a significant and consistent increase in BMD at the spine and hip, the magnitude of the increase in BMD may not be a valid surrogate marker of treatment efficacy [28**]. Most studies based on individual patient data suggest that the magnitude of the increase in BMD accounts for only 10–30% of the reduction in vertebral and nonvertebral fracture risk with bisphosphonates. The primary effect of bisphosphonates is to reduce osteoclastic activity and therefore the rate of bone turnover, and a previous study has shown that the short-term (3–6 months’) decrease in bone resorption markers in patients with osteoporosis treated with risedronate is significantly associated with a 3-year reduction in vertebral and nonvertebral fractures [29]. The relation between the change in bone turnover after 1 year of alendronate or placebo treatment and subsequent hip, nonspine, and spine fracture risk among 6186 postmenopausal women with osteoporosis was analyzed using data from the FIT trial [30**]. Each standard deviation reduction in 1-year change in bone alkaline phosphatase was associated with fewer spine (odds ratio 0.74), nonspine (relative hazard = 0.89), and hip fractures (relative hazard = 0.61). Alendronate-treated women with at least a 30% reduction in bone alkaline phosphatase had a 28% lower risk of
nonspine fractures and a 74% lower risk of hip fractures relative to those with reduction below 30%. In contrast, change in spine BMD was not associated significantly with risk of spine, nonspine, or hip fracture. Greater increases in hip BMD were not associated with fewer hip or nonspine fractures, but increases in hip BMD were associated with a reduction in spine fractures [30••]. These and previous data with risedronate suggest that bone turnover markers might be useful in the monitoring of treatment with bisphosphonates. The mechanism by which the reduction of bone turnover by bisphosphonates improves bone strength is complex and is probably mediated, at least in part, by a preservation of trabecular microarchitecture, as suggested by a case report [31] and by a reduction in cortical porosity. An experimental study performed in dogs suggests that the increase in apparent Young’s modulus (an index of bone strength) induced by alendronate and risedronate is related to increased bone mass and altered trabecular architecture rather than to changes in the calcified matrix properties [32]. Further studies should be performed to understand the effects of bisphosphonates on the various components of bone strength, often referred to as ‘bone quality’.

Ruggiero et al. [33] have reported 63 cases of jaw osteonecrosis in patients treated with bisphosphonates, most of whom received high-dose intravenous pamidronate for multiple myeloma or other cancers that had metastasized to bone. They suggest that jaw lesions may be related to potent osteoclastic inhibition, altered blood flow in bone, or localized antiangiogenesis. Chemotherapy, recent dental alveolar procedures, glucocorticosteroid exposure, and oral infections are possible risk factors, however, that are probably highly prevalent in most of these patients. Whether there is a causal relation is unclear at this stage.

The overall safety profile of bisphosphonates is excellent. There have been concerns, however, that long-term treatment with alendronate may have the risk of oversuppressing bone turnover that could, potentially, impair some of the biomechanical properties of bone. High doses of bisphosphonates result in accumulation of microdamage in the bones of dogs, but the relevance of these findings in terms of bone strength and clinical use is unclear. Nine patients who sustained spontaneous nonspinal fractures while on alendronate therapy for 3–8 years, six of whom displayed either delayed or absent fracture healing for 3 months–2 years during therapy, have been reported [34]. Histomorphometric analysis of iliac crest biopsy specimens in these patients showed a marked suppression of bone turnover in the trabecular and cortical envelopes, suggesting that long-term alendronate therapy may have oversuppressed bone turnover, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures. Although long-term controlled trials have not shown safety concerns, individual cases with severe fractures after long-term bisphosphonate therapy should be investigated carefully. Finally, Ettinger et al. [35] have shown that the teriparatide-induced early increase in N-terminal propeptide of type I procollagen (P1NP), a sensitive and specific marker of bone formation reflecting the anabolic effects of this drug, is transiently blunted in patients previously treated with alendronate, but not in those previously treated with raloxifene. Black et al. [36] had previously shown that the concomitant administration of alendronate blunts the anabolic effect of parathyroid hormone, reducing both the increase in trabecular BMD measured by quantitative CT scanning and the increase in markers of bone formation.

Conclusion
Data now show the long-term effects of bisphosphonate treatment in postmenopausal osteoporosis and raise the question of the optimal duration of therapy. Although clinical trials suggest that 10-year treatment with alendronate is safe, stopping treatment after 5 years, at least in low-risk patients, might be a beneficial alternative, especially if a persisting reduction in fragility fractures is confirmed. Patients on long-term therapy should be monitored closely. New regimens, using intermittent oral or intravenous bisphosphonates, such as ibandronate and zoledronate, represent an interesting alternative that should be available soon.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Metabolic bone disease


New perspectives on parathyroid hormone therapy
Nancy Lanea and Stephen Morrisb

Purpose of review
The prevention and treatment of osteoporosis has traditionally involved the use of antiresorptive therapies. The introduction of parathyroid hormone, an anabolic agent that enhances bone formation, has been accompanied by new treatment strategies. This article reviews combination and sequential therapy approaches with parathyroid hormone and antiresorptive agents to optimize efficacy outcomes.

Recent findings
The distinguishing features of the anabolic and antiresorptive therapies for the treatment of osteoporosis has led to the hypothesis that the appropriate use of both agents, either in sequence or in combination, may result in superior fracture protection compared with either anabolic or antiresorptive treatment alone. This enthusiasm has been tempered by the observations that the transition from daily bisphosphonate therapy may blunt the efficacy of teriparatide. By contrast, more recent studies suggest that once-weekly bisphosphonate therapy may provide a better option with parathyroid hormone either in combination or in sequence. These considerations are critical to understanding the benefits of sequential treatment (parathyroid hormone followed by an antiresorptive agent), which aims to maintain or build on the large gains in efficacy from short-term therapy with parathyroid hormone. Because patients may require an additional treatment course of parathyroid hormone in the future, the choice of antiresorptive agent should be carefully considered. In addition, more recent evidence suggests that the forms of parathyroid hormone may have important differences in action that influence combination and sequence outcomes.

Summary
Combination and sequential therapy with parathyroid hormone offers new options to maximize efficacy in patients at risk for osteoporotic fracture.

Keywords
anabolic agent, antiresorptive agent, combination therapy, parathyroid hormone, sequential therapy

Introduction
Within the past 10 years, there has been exponential growth in both the diagnosis and the treatment of osteoporosis [1]. In the early 1990s, therapies for the prevention and treatment of osteoporosis included hormone replacement therapy (HRT) and calcitonin. By the mid to late 1990s, the approval of additional antiresorptive agents, including the bisphosphonates and the selective estrogen receptor modulator raloxifene, provided more therapeutic options.

Parathyroid hormone [PTH (1-34), teriparatide] was initially approved for the treatment of osteoporosis in women and the prevention of bone loss in men in 2002. It is currently approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. The development and mechanism of action of PTH as a treatment for osteoporosis have been extensively reviewed elsewhere and will be discussed only briefly here [2–4]. PTH (1-34), teriparatide, is the N-terminal peptide of the parent hormone PTH (1-84), which is responsible for serum calcium homeostasis. For the purpose of this review, PTH will be used when referring to the class of agents [both PTH (1-34) and PTH (1-84)]; teriparatide will be used to designate PTH (1-34), and PTH (1-84) for the parent hormone.

Parathyroid hormone is an anabolic agent that stimulates new bone growth on endocortical, trabecular and periosteal surfaces, resulting in an increase in bone strength and a decrease in fracture risk. The actions of PTH are very complex, however, despite this relatively simple outcome.

Parathyroid hormone stimulates osteoblasts to develop and form new bone. Concomitantly, this stimulation results in the production of both receptor activator of nuclear factor-κB ligand (RANKL) and interleukin (IL)-6, proteins that increase the proliferation and maturation of osteoclasts, resulting in resorption of bone [5•]. Thus, PTH treatment increases bone formation, which contributes to the improvement of bone strength, and activates

Abbreviations
BMD bone mineral density
HRT hormone replacement therapy
IL interleukin
PTH parathyroid hormone
RANK receptor activator of nuclear factor-κB
RANKL receptor activator of nuclear factor-κB ligand

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bone resorption. In some models, treatment with these forms of PTH has resulted in an increase in cortical porosity. Collectively, these events could theoretically contribute to a decrease in bone strength, although this has not been observed [6–8]. Adding to the complexity of this analysis, continuous rather than intermittent exposure to PTH appears to compromise bone strength and to result in enhanced fracture risk (i.e., hyperparathyroidism). Although the events stimulated by continuous and intermittent PTH may be similar, intermittent exposure results in a net increase in bone formation, suggesting that the net pharmacodynamics of PTH differ in accordance with the patterns of exposure.

**Rationale: parathyroid hormone in the treatment paradigm**

This review focuses on two distinct configurations of PTH in the treatment of osteoporosis. In the first configuration, PTH is used in combination with an antiresorptive therapy. The second is a sequential approach, in which PTH treatment is followed by antiresorptive therapy. The distinction between the two configurations has been difficult to ascertain with certainty in the literature. In some studies, patients had been receiving prolonged antiresorptive therapy when they switched to PTH. Moreover, study designs to consider this issue have not been uniform, adding further limitations to their interpretation. Nonetheless, it is useful to take advantage of the results that have emerged in the literature and at recent meetings to consider the value of combination and sequential therapy with PTH.

**Combination therapy**

The consideration of combination therapy originates from the observation that PTH treatment alone increases not only bone mass but also bone remodeling, manifested by an increase in bone turnover. The PTH-associated increase in bone remodeling may be an integral component of the efficacy of PTH in improving bone strength; however, the stimulation of remodeling also results in enhanced resorption of cortical bone (activation on endocortical and intracortical areas). Such a possibility led to the concept of ‘cortical steal’ (i.e., moving mineral from cortical to trabecular surfaces) with potentially unhelpful clinical consequences [9]. To address these theoretical concerns, investigations have targeted the potential for combination therapy with PTH and an antiresorptive agent to reduce cortical bone turnover, prevent cortical steal, limit cortical porosity, and thereby focus the effects of PTH on bone formation.

With the widespread clinical use of PTH, these original assumptions have been challenged. Thus, it is not clear that the concerns of cortical steal and skeletal fragility with monotherapy have been realized. Jiang et al. [6] obtained iliac crest biopsy specimens at baseline and after 2 years of teriparatide therapy. As expected, they observed an increase in bone mass, but they also noted a dramatic thickening of the cortex with an apparent increase in cortical cross-sectional area after the teriparatide treatment. The increase in periosteal and endosteal bone mass was found to far outweigh the loss in bone strength that might have occurred from the increased porosity.

Additional studies of combination therapy, reviewed in Table 1, suggest that there may be benefits of combination therapy that are dependent on the properties of the specific antiresorptive agent chosen for this purpose. Accordingly, there continue to be opportunities for further evaluation of this approach.

**Sequential therapy**

The theoretic basis for considering sequential therapy appeared well before the clinical use of PTH as put forth by Frost [10] and others [11,12]. The initial stimulation of remodeling with PTH analogs followed by a depression of osteoclast function with an antiresorptive agent was thought to be beneficial by coordinated mobilization of remodeling cycles (the activation-depression-free-repeat regimen). Nonetheless, early experimental studies failed to confirm this theory. This concept and its application were not reconsidered until subsequent preclinical studies revealed that the anabolic effects of intermittent PTH therapy, manifested by bone mineral density (BMD) build and improved bone strength, markedly decreased within months after withdrawal from treatment [13,14]. Importantly, when withdrawal from PTH was followed immediately by antiresorptive therapy, the beneficial effects of PTH manifested by BMD or other surrogate markers were either maintained or improved [13,14]. Hence, the benefit of the sequential approach was viewed not so much as improving the efficacy of PTH but rather as preserving its benefits.

Additional studies have suggested that the bone-building effects of teriparatide therapy may occur within a relatively short time (6–12 months) [15–17]. Moreover, it has been reported that prolonged exposure to teriparatide may produce bone of inferior quality [15]. These data suggest that the concept of limited exposure, which originated from concerns about osteosarcoma, may be linked to treatment efficacy; however, these observations have been challenged by the recently reported influence of PTH (1-84) on continuous bone formation even at 18 months, suggesting that there may be important differences in the anabolic activities of the different PTH therapies [18]. Therefore, consideration of the duration of PTH therapy, the nature of the anabolic agent, and the subsequent use of an antiresorptive agent is important to optimize osteoporosis treatment.
Table 1. Combination studies of parathyroid hormone and an antiresorptive agent

<table>
<thead>
<tr>
<th>Study</th>
<th>Study characteristics</th>
<th>Treatment (n)</th>
<th>Spine BMD</th>
<th>Hip BMD</th>
<th>Resorption</th>
<th>Formation BTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al. [20]</td>
<td>Design: Prior HRT (7.6 and 10.6 y) add on PTH (1–34) 25 μg/d or placebo</td>
<td>HRT + PTH (17)</td>
<td>↑13.0% 36 mo (4.3%/y)</td>
<td>↑2.7% 36 mo (0.9%/y)</td>
<td>NTX ↑80% at 6 mo (24–4 ng/mL)</td>
<td>OST ↑100% 6 mo at 36 mo</td>
</tr>
<tr>
<td>Mean age: 62</td>
<td>Duration: 36 mo</td>
<td>HRT (17)</td>
<td>NS ↓</td>
<td>NC</td>
<td>↓ BL</td>
<td>NC</td>
</tr>
<tr>
<td>Cosman et al. [21]</td>
<td>Design: Prior HRT (4.5 and 6.1 y) add on PTH (1–34) 25 μg/d or HRT alone</td>
<td>HRT + PTH (27)</td>
<td>↑13.4% 36 mo (4.5%/y)</td>
<td>↑4.4% 36 mo (1.5%/y)</td>
<td>NTX: ↑71% at 6 mo</td>
<td>BSAP ↑44% 36 mo at BL</td>
</tr>
<tr>
<td>Mean age: 60</td>
<td>Duration: 36 mo</td>
<td>HRT (25)</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Hesch et al. [22]</td>
<td>Design: 14-d cycles: PTH, PTH + calcitonin, PTH, PTH + calcitonin, calcitonin</td>
<td>Cyclic PTH + calcitonin (8)</td>
<td>QCT of spine: 12–89% increase over 14 mo</td>
<td>NR</td>
<td>NR</td>
<td>PTH alone and combination with calcitonin produce equivalent and continuous ↑ in AP over 14 mo</td>
</tr>
<tr>
<td>Mean age: 60</td>
<td>Duration: 36 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reeves et al. [23]</td>
<td>Comparison with PTH alone:</td>
<td>HRT + PTH (12)</td>
<td>NR</td>
<td>NR</td>
<td>OH-P no change</td>
<td>AP ↑5.3%</td>
</tr>
<tr>
<td>Mean age: 64</td>
<td>Duration: 12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reeves et al. [24]</td>
<td>Design: PTH 500 units/d</td>
<td>PTH (21)</td>
<td>NR</td>
<td>NR</td>
<td>OH-P ↑26% over 6 mo</td>
<td>AP ↑15% over 6 mo</td>
</tr>
<tr>
<td>Mean age: 56</td>
<td>Duration: 12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Finklestein et al. [16]</td>
<td>Design: ALN alone 10 mg/d, PTH (1–34) 37 μg/d, or ALN (6 mo) add PTH (24 mo)</td>
<td>ALN (28)</td>
<td>↑7.9% 30 mo (2.2%/y)</td>
<td>↑14.8% 30 mo (1.9%/y)</td>
<td>NR</td>
<td>AP ↓25% by 6 mo and remained depressed to 30 mo</td>
</tr>
<tr>
<td>Mean age: 58</td>
<td>Duration: 30 mo</td>
<td>PTH (20)</td>
<td>↑19.1% 30 mo (9.1%/y)</td>
<td>↑16.4% 30 mo (3.2%/y)</td>
<td>NR</td>
<td>175% by 12 mo and declined to 25% by 30 mo</td>
</tr>
<tr>
<td>Black et al. [25]</td>
<td>Design: ALN alone 10 mg/d, PTH (1–84) 100 μg/d, or both</td>
<td>ALN (60)</td>
<td>↑4.6% 12 mo</td>
<td>↑13.0% 12 mo</td>
<td>CTX ↓58% 1 mo and remains depressed</td>
<td>PINP ↓59% 3 mo and remains depressed</td>
</tr>
<tr>
<td>Mean age: 70</td>
<td>Duration: 12 mo</td>
<td>PTH (119)</td>
<td>↑6.3% 12 mo</td>
<td>↑10.3% 12 mo</td>
<td>175% at 3 mo and remains elevated</td>
<td>130% 3 mo and remains elevated</td>
</tr>
<tr>
<td>Neer et al. [17]</td>
<td>Design: ALN alone 10 mg/d, PTH (1–34) 37 μg/d, or ALN (6 mo) add PTH (24 mo)</td>
<td>ALN (31)</td>
<td>↑6.8% 30 mo (2.7%/y)</td>
<td>↑13.1% 30 mo (1.2%/y)</td>
<td>NR</td>
<td>AP ↓15% at 18 mo</td>
</tr>
<tr>
<td>Mean age: NR</td>
<td>Duration: 30 mo</td>
<td>PTH (31)</td>
<td>↑18.5% 24 mo (9.3%/y)</td>
<td>↑16.4% 24 mo (3.2%/y)</td>
<td>NR</td>
<td>179% at 12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALN + PTH (31)</td>
<td>↑14.8% 24 mo (7.4%/y)</td>
<td>↑5.3% 24 mo (2.7%/y)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Clinical outcomes of parathyroid hormone therapy

The clinical outcomes of parathyroid hormone therapy differ between combination therapy and sequential therapy.

Combination therapy

Table 1 summarizes studies that addressed the impact of combination therapy with PTH and antiresorptive agents on BMD and bone turnover [16,17,19–25]. The studies differ not only in the nature of the antiresorptive agent but also in the duration and type of PTH used. In addition, as noted above, with the exception of studies by Black et al. [25] for alendronate and Hodsman et al. [26] for calcitonin, patients who received combination treatment had been receiving prolonged antiresorptive therapy (at least 6–12 months with alendronate and 7–10 years with HRT). In addition, most efficacy measurements were related to either BMD measurements (either areal or quantitative) or bone turnover markers. Although these are valuable aids to understanding the efficacy of osteoporosis therapy, they are not universally recognized as interchangeable with the ultimate goal of therapy, which is fracture protection.

Studies by Reeve et al. [23,24] evaluated teriparatide therapy alone and with estrogen. Although separated by time and lacking comparison with HRT treatment alone (HRT treatment initiated 4 months after the start of teriparata
tide), these data show that combination therapy demonstrated no change in bone formation rate (hydroxyproline) but a slight increase in alkaline phosphatase levels as well as measurements of whole body bone formation (strontium), all of which were accompanied by small decreases in osteoid and eroded surfaces on biopsy. On the basis of these data, the authors concluded that antiresorptive therapy with HRT may have a blunting effect on the anabolic response of teriparatide.

By contrast, an additive benefit of HRT and teriparatide was observed in studies by Lindsay et al. [20] and Cosman et al. [21]. As shown in Table 1, combination therapy resulted in greater increases in lumbar spine and total hip BMD than did HRT alone. Fracture data from these studies are consistent with the positive benefit of teriparatide added to HRT in that more vertebral fractures occurred in the HRT-only groups. Of note, HRT, which characteristically decreases turnover and bone turnover markers, did not, in combination, depress the increases in bone turnover markers characteristic of PTH administered alone [16,25]. Similar findings were reported by Fogelman et al. (unpublished data) with PTH (1-84).

The observations from studies with PTH and HRT are in contrast to those from trials of PTH and the bisphosphonate alendronate. In a group of men with low BMD, concomitant teriparatide and alendronate therapy produced increases in lumbar spine and hip BMD between those

<table>
<thead>
<tr>
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<td>Design: Prior ALN 70 mg/wk (≥1 y) then add PTH (1–34) 25 μg/d or daily PTH for 3 mo followed by no PTH for 3 mo, or ALN alone</td>
<td>ALN + PTH daily</td>
<td>↑4.3% 9 mo (5.7%/y)</td>
<td>NR</td>
<td>More modest increase at 3 mo compared with bone formation</td>
<td>↑Within first 3 mo and continuous elevation to 9 mo</td>
</tr>
<tr>
<td>All groups n = 83</td>
<td>Design: On HRT for &gt;6 mo, given PTH (1–84) (100 μg/d) or placebo</td>
<td>ALN + PTH cyclic</td>
<td>↑3.8% 9 mo (5.1%/y)</td>
<td>NR</td>
<td>↑During PTH treatment and declined off PTH</td>
<td>↑On PTH and declined off PTH</td>
</tr>
<tr>
<td>Fogelman et al. (unpublished data)</td>
<td>Mean age: 59</td>
<td>HRT (67)</td>
<td>↑1.2% 12 mo</td>
<td>↑1.2% 12 mo</td>
<td>↑16% (NS)</td>
<td>↓68% (NS)</td>
</tr>
</tbody>
</table>

ALN, alendronate; AP, alkaline phosphatase; BL, baseline; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; BTM, bone turnover marker; CTX, C-terminal telopeptide to type I collagen; HRT, hormone replacement therapy; NC, no change; NR, not recorded; NS, not significant; NTX, N-terminal telopeptide of type I collagen; OH-P, hydroxyproline; OST, osteocalcin; PINP, N-propeptide of type I collagen; PTH, parathyroid hormone; QCT, quantitative computed tomography.
for either alendronate or teriparatide alone at the end of the observation period. [16] Over the course of the study, however, combination therapy tended to produce greater increases in hip BMD, especially in the first year. Changes in lumbar spine BMD were approximately 8%, 18%, and 15%, for alendronate, teriparatide, and combination therapy, respectively, at the end of the study and 5%, 6.5%, and 8%, respectively, at the end of the first year. The PTH (1-84) and alendronate (PaTH) study yielded similar findings in postmenopausal women with regard to the influence of combination therapy on PTH (1-84)–mediated increases in BMD [25]. Collectively, these data further substantiate not only the different outcomes in the actions of teriparatide or PTH (1-84) at cortical in comparison with trabecular sites but also the possibility that combination treatment with an optimal antiresorptive agent may shift the benefit in the direction of cortical bone build.

Bisphosphonate therapy also results in uniform decreases in bone formation and resorption. In both alendronate-treated and combination-treated postmenopausal women, there was an overall depression in N-propeptide of type I collagen and C-terminal telopeptide of type I collagen compared with sustained elevations in the PTH (1-84) group [25]. Whereas C-terminal telopeptide of type I collagen was depressed at the earliest time points in the combination group, there was an initial rise in N-propeptide of type I collagen with combination therapy at 1 month that was thereafter depressed, suggesting a difference in the kinetic effects of alendronate on the cellular elements targeted by PTH (1-84).

Although it is generally recognized that bisphosphonates are more effective in reducing bone turnover than HRT, this recognition must be tempered by the results from a head-to-head trial of HRT and alendronate. Bone et al. [27] reported similar suppression of bone-specific alkaline phosphatase in both alendronate-treated and HRT-treated patients. Therefore, suppression of bone turnover alone may not account for the differences observed with these agents in combination with PTH.

Estrogen down-regulates the synthesis of IL-1, IL-6, and tumor necrosis factor-α, which promote bone resorption [28,29] and suppresses the osteoprotegrin (OPG)/RANKL/RANK pathway that mediates the final step in osteoclast differentiation [30,31]. This involves up-regulation of OPG, which in turn neutralizes the osteoclast differentiation pathway [32,33]. Bisphosphonates have also been shown to down-regulate IL-6. Their effects on OPG/RANKL expression are controversial. The extent to which the two classes of antiresorptive drugs differ with regard to the cellular elements responsive to PTH remains to be determined but may hold clues to the marked differences seen in combination and sequence trials with PTH.

The beneficial effects of bisphosphonates have been mainly attributed to their inhibitory effects on osteoclast apoptosis, with inhibition of the osteoclastic mevalonate pathway accounting for their antiresorptive effects [34]. Several lines of evidence, however, suggest that bisphosphonates may also regulate osteoblastic expression by modulating important cellular functions, including proliferation, differentiation, and synthesis of extracellular matrix proteins, secretion of various growth factors and cytokines, and formation of mineralized nodules [35–38].

Given that alendronate appears to be one of the most potent suppressors of bone turnover as well as an agent with a long half life, other bisphosphonates with less potency or shorter half lives may be better candidates for coadministration with PTH. Thus, the studies discussed to this point (Black et al. [25] and Finkelstein et al. [16]) used a daily alendronate dose. In a study by Cosman et al. [19], patients who had taken alendronate weekly were subsequently challenged with teriparatide either continuously or in a cyclic fashion. Notably, in this framework, a sustained depression in bone turnover was not observed, but rather an increase temporally tied to teriparatide administration.

Collectively, these data support an optimal level of turnover suppression with antiresorptive drugs beyond which PTH may lose its effectiveness. Although the absolute magnitude of bone turnover changes may correlate with vertebral fracture efficacy in clinical trials of antiresorptive agents, this relation may not reflect the action of PTH on osteoblasts and osteoclasts [39,40].

Sequential therapy
Several recent studies evaluated the benefits of PTH therapy first followed by antiresorptive treatment (Table 2) [26,41–45]. In general, these studies showed similar trends in surrogate measures of efficacy, namely bone turnover and BMD changes. Given the limited size and duration of the studies, as well as the absence of optimal placebo arms, there is little evidence of effect on fracture. Similarly to the limitations observed in combination studies, the reported sequential studies differ with regard to study design. Certain generalities can be put forth, however. First, the concept of treatment with PTH followed by an antiresorptive agent appears effective in preserving and even increasing the anabolic effects of PTH as reflected in BMD (Table 2). There is some suggestion that this relation requires some optimal period of PTH exposure. For example, Kurland et al. [46] reported that teriparatide therapy significantly increased markers of bone turnover after 18 months; however, bone turnover levels returned to baseline after 30 months of therapy. If the target of bisphosphonate therapy after PTH treatment is to reduce modeling space and increase bone volume and mineral content, then greater bone turnover and
Table 2. Sequential therapies of parathyroid hormone followed by an antiresorptive agent

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study characteristics</th>
<th>Sequence</th>
<th>Spine BMD (starting off PTH)</th>
<th>Hip or femoral neck BMD (starting off PTH)</th>
<th>Resorption BTM</th>
<th>Formation BTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurland et al. [41]</td>
<td>Design: Following 18 mo PTH (1–34) 25 μg/d assigned to BP or placebo</td>
<td>PTH to BP (12)</td>
<td>5.1% 12 mo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 12 mo</td>
<td>PTH to none (7)</td>
<td>−3.7% 12 mo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaufman et al. [42]</td>
<td>Design: Following 12 mo PTH (1–34) 20 or 40 μg/d, off therapy</td>
<td>PTH 20 μg to BP (22)</td>
<td>2.0% 30 mo (0.8%/y)</td>
<td>2.0% 30 mo (0.8%/y)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 30 mo</td>
<td>PTH 20 μg to none (85)</td>
<td>−3.0% 30 mo (1.2%/y)</td>
<td>NC</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rittmaster et al. [43]</td>
<td>Design: Following 12 mo placebo, 50, 75, or 100 μg/d PTH (1–84) assigned to ALN 10 mg/d</td>
<td>Placebo to ALN (19)</td>
<td>5.7% 12 mo</td>
<td>4.2% 12 mo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 12 mo</td>
<td>PTH 50 μg to ALN (12)</td>
<td>6.3% 12 mo</td>
<td>5.5% 12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 30 mo</td>
<td>PTH 75 μg to ALN (17)</td>
<td>6.2% 12 mo</td>
<td>2.8% 12 mo</td>
<td>75% (all doses) from 102 nmol/L mmol Cr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black et al. [44]</td>
<td>Design: Following 12 mo PTH (1–84) 100 μg/d alone for 12 mo assigned to placebo or ALN 10 mg/d</td>
<td>PTH to placebo (60)</td>
<td>−1.7% 12 mo</td>
<td>0.03% 12 mo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 12 mo</td>
<td>PTH to ALN (59)</td>
<td>4.9% 12 mo</td>
<td>3.6 % 12 mo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zanchetta et al. [45]</td>
<td>Design: Following PTH (1–34) 20 or 40 μg/d (median 21 mo) assigned calcium and vitamin D</td>
<td>PTH 20 μg to placebo (37)</td>
<td>−0.9% 18 mo (−0.6%/y)</td>
<td>−1.1% 18 mo (0.7%/y)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Mean age: 71</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 12 mo</td>
<td>PTH 40 μg to placebo (25)</td>
<td>−4.3% 18 mo (2.9%/y)</td>
<td>−2.4% 18 mo (1.6%/y)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hodsman et al. [26]</td>
<td>Design: PTH (1–34) (800 IU) in 90-d cycles. 28-day course of PTH followed by 60 d with placebo or for the first 42 days with calcitonin SC (75 U)</td>
<td>PTH alone (14)</td>
<td>10.2% 24 mo (5.1%/y)</td>
<td>2.4% 24 mo (1.2%/y)</td>
<td>OH-P ↑41% 1 y, ↑12% 2 y OH-P and NTX: initial rise and fall with each cycle</td>
<td>AP, BSAP and OST initial rise and fall within cycle NS change over 24 mo</td>
</tr>
<tr>
<td></td>
<td>Mean age: 67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 18 mo</td>
<td>PTH with cyclical calcitonin (16)</td>
<td>7.8% 24 mo (3.9%/y)</td>
<td>−1.8% (0.9%/y)</td>
<td>OH-P ↑48% 1 y, ↑12% 2 y OH-P and NTX: initial rise and fall with each cycle</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

ALN, alendronate; AP, alkaline phosphatase; BL, baseline; BMD, bone mineral density; BP, bisphosphonate; BSAP, bone-specific alkaline phosphatase; BTM, bone turnover marker; Cr, creatinine; CTX, C-terminal telopeptide of type I collagen; NC, no change; NR, not recorded; NTX, N-terminal telopeptide of type I collagen; OH-P, hydroxyproline; OST, osteocalcin; PTH, parathyroid hormone; SC, subcutaneous.
remodeling space would presumably be present after 18 months compared with 30 months of PTH. As yet, no published studies have compared short-term and long-term exposure to PTH and the consequences of discontinuation on preservation of BMD.

Findings from the second year of the PrTH study support the concept that antiresorptive agents may be necessary to sustain the benefits of PTH (1-84) [44]. Patients who received alendronate therapy after 1 year of PTH (1-84) treatment realized additional gains in BMD, because the large area of remodeling space made available by PTH (1-84) was allowed to mineralize. Changes in volumetric spinal BMD were even more dramatic, with increases of 34% with PTH (1-84)–alendronate sequential therapy compared with 13% in the PTH (1-84)–placebo arm. Although there are currently no fracture data from this treatment, the addition of alendronate therapy after 1 year of PTH (1-84) to sustain the benefits of PTH (1-84) [44]. Patients who received alendronate therapy after 1 year of PTH (1-84) monotherapy [19].

As noted previously, previous exposure to alendronate may negatively affect the magnitude or kinetics of subsequent PTH benefits. Given the possibility that a patient may benefit from multiple exposures to PTH over a lifetime, careful consideration must be given to the choice of bisphosphonate during those periods between PTH exposures to ensure the most efficacious outcome (i.e., to target an optimal degree of bone turnover that preserves the benefits of PTH without unduly compromising a rapid and efficient outcome in the event of future exposure to PTH). In a different approach, Hodson et al. [26] evaluated cycles of sequential teriparatide-calcitonin and teriparatide-placebo therapy. In this regimen, the addition of calcitonin after teriparatide exposure diminishes the bone turnover that preserves the benefits of PTH. As yet, no published studies have compared short-term and long-term exposure to PTH and the consequences of discontinuation on preservation of BMD.

Conclusions

The quest for the optimal use of PTH is driven by two factors. First, fracture protection is not realized in all patients receiving therapy. Second, PTH cannot be used indefinitely because of both compliance (injectable formulation) and theoretic issues (lack of evidence for continued bone growth). Studies indicate that not all antiresorptive agents (HRT, calcitonin, and bisphosphonates) are equivalent in their interactions with PTH. The determination of the maximum antiresorptive and the bones in which they are found is particularly attractive. In this regard, the optimum combination of antiresorptive agents (PTH, calcitonin, and bisphosphonates) is necessary but not sufficient to ensure the most efficacious outcome (i.e., to target an optimal degree of bone turnover that preserves the benefits of PTH without unduly compromising a rapid and efficient outcome in the event of future exposure to PTH).

The benefits of PTH may be sustained for some time after therapy has been discontinued, even without subsequent antiresorptive treatment. Zanchetta et al. [45] found that after patients stopped taking teriparatide for 18 months, BMD levels declined but remained significantly higher than pretreatment values (by 3.8% and 4.6% in the 20-μg teriparatide-placebo and 40-μg teriparatide-placebo groups, respectively). In a follow-up study of men initially treated with either placebo, or 20 or 40 μg teriparatide (total 12 months), the drop in BMD at both the spine and hip after discontinuation was essentially reversed in those who made the transition to bisphosphonates [42].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest


Genetic determinants of osteoporosis
Stuart H. Ralston

Purpose of review
Osteoporosis is a common disease with a strong genetic component characterised by reduced bone mass and an increased risk of fragility fractures. Several advances have been made over recent years in understanding the genetic basis of susceptibility to osteoporosis. This paper will review recent developments in this area.

Recent findings
Twin studies have shown that genetic factors contribute to osteoporosis by influencing bone mineral density and other determinants of fracture risk such as ultrasound properties of bone, skeletal geometry, and bone turnover. In the normal population, many different genes contribute to the regulation of these phenotypes by interacting with environmental factors such as diet and exercise. Whereas the effect size of individual genes is small, meta-analysis has been successfully used in many cases to define the role of individual polymorphisms in predisposing to osteoporosis. Linkage studies in humans and experimental animals have identified several quantitative trait loci that regulate osteoporosis-related phenotypes, and many genes that cause monogenic bone diseases have been identified by use of this approach. It has been found that subtle polymorphisms in some of these genes also contribute to regulation of bone mass in the normal population.

Summary
Research has recently begun to clarify the genes and genetic variants that predispose to osteoporosis and regulation of bone mass. Clinical applications of this research include the identification of genetic markers for assessment of fracture risk and the identification of novel molecular targets for the design of drugs that can be used to treat bone disease.

Keywords
fracture, genetic markers, osteoporosis

Introduction
Osteoporosis is a common disease characterised by reduced bone mass, micro-architectural deterioration of bone tissue, impaired bone strength, and increased fracture risk. Osteoporosis is defined to exist when bone mineral density (BMD) values at the spine or hip fall 2.5 standard deviations (T-score values) or more below the population average in young adults [1]. Although osteoporosis is rare in the third and fourth decades, approximately 50% of Caucasian women have osteoporosis by the age of 80 because of age-related factors. Phenotypes such as BMD, femoral neck geometry, quantitative ultrasound properties of bone, and biochemical markers of bone turnover are largely under genetic control. Twin studies and family-based studies have indicated that as much as 60 to 85% of the variance in BMD is genetically determined, and heritability estimates for other risk factors for fragility fracture such as quantitative ultrasound, femoral neck geometry, and bone turnover markers range between 50 and 80% [2–5]. A family history of fracture is a significant risk factor for fracture, but the heritability of fracture itself is relatively low (25–35%), reflecting the importance of fall-related factors in the pathogenesis of fracture [6–8].

Quantitative trait loci for regulation of bone mineral density
Several genome-wide linkage scans have been performed in attempts to identify loci that regulate BMD. A variety of study designs have been used, including analysis of families with a history of osteoporosis, families or sibling pairs drawn from the normal population, and sibpairs who are discordant for BMD values. The most important quantitative trait loci (QTL) for BMD identified by genome-wide linkage scan are summarised in Table 1. Few of the genome-wide scans so far performed have identified QTL that meet the criteria for genome-wide significance, and there has been limited replication of QTL between different studies. Moreover, only one gene that regulates

Abbreviations
BMD bone mineral density
COL1A1 the gene encoding α1 chain of type 1 collagen
LRP5 lipoprotein receptor-related protein-5
PPAR-γ peroxisome proliferator-activated receptor-γ
QTL quantitative trait loci
TGF transforming growth factor
VDR vitamin D receptor
susceptibility to osteoporosis has been identified by this approach: the BMP2 gene, which encodes bone morphogenetic protein 2 – an important regulator of osteoblast differentiation [9]. Some important findings have emerged from these studies, however, including the realization that QTL for regulation of BMD differ at different skeletal sites; are gender specific, and may also be age group specific [10,11]. The lack of replication between studies may simply reflect that fact that genes that regulate BMD have effects that are difficult to detect by conventional linkage analysis. Technical advances such as the development of densely spaced panels of single-nucleotide polymorphisms for genome-wide scans are likely to improve the chances of detecting genes of modest effect size in the future [12]. There is also a prospect that meta-analysis of genome-wide scans may reveal significant QTL that have not been detected by individual studies [13].

### Animal models

Linkage studies in mice have resulted in the identification of several QTL that regulate BMD in mice, and the same approach has been used to localise QTL for other phenotypes relevant to the pathogenesis of osteoporosis such as circulating levels of insulin-like growth factor-1, bone structure, bone shape, and bone strength [14]. Most investigators have focused on the detection of QTL for BMD regulation, and such loci have now been identified on almost all mouse chromosomes, with replication of several QTL across different strains. The studies in mice have clearly shown that the genes that regulate BMD have effects that are site specific and gender specific [15,16]. Identifying the genes and genetic variants responsible for these effects is technically challenging because mouse QTL are usually large, requiring successive rounds of selective breeding to narrow the region of interest to a manageable size. Even then, identification of the causal variants remains difficult because the predisposing genetic variant is in complete linkage disequilibrium with all adjacent variants on the same chromosomal segment. One important success has been the identification of Alox15 as an important candidate gene for the regulation of BMD by linkage analysis in mice [17**]. The Alox15 gene lies within a BMD QTL on chromosome 11, initially identified by genome-wide scan in a cross of DBA2 and C57BL/6 mice. Alox15 was identified as the gene likely to be responsible for part of the linkage signal in this region by micro-array analysis of RNA extracted from renal tissue prepared from the parental mouse strains. This experiment showed that DBA2 (low BMD) mice had a 20-fold increase in expression of the Alox15 mRNA in comparison with C57BL/6 (high BMD) mice, indicating that Alox15 might act as a negative regulator of bone mass. The authors confirmed this hypothesis by finding that Alox15 knockout mice had increased BMD in comparison with wild-type control mice and by showing that a pharmacologic inhibitor of Alox15 protected against ovariectomy-induced bone loss. At present the exact mechanism by which Alox15 reduces BMD is unclear, but the Alox15 gene encodes for the 12/15

### Table 1. Quantitative trait loci for bone marrow density detected by genome-wide linkage scan

<table>
<thead>
<tr>
<th>Study</th>
<th>Chr</th>
<th>cM</th>
<th>Nearest marker</th>
<th>Lodscore</th>
<th>Skeletal site</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng et al. [44]</td>
<td>4q31</td>
<td>152</td>
<td>D4S424</td>
<td>3.08</td>
<td>LS-BMD</td>
<td>Family-based study, probands with low BMD</td>
</tr>
<tr>
<td></td>
<td>13q33</td>
<td>103</td>
<td>D13S285</td>
<td>2.43</td>
<td>LS-BMD</td>
<td>Study of female premenopausal sibpairs; unselected for BMD</td>
</tr>
<tr>
<td></td>
<td>10q26</td>
<td>170</td>
<td>D10S1651</td>
<td>2.29</td>
<td>FN-BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Koller et al. [45]</td>
<td>1q21</td>
<td>169</td>
<td>D1S484</td>
<td>3.11</td>
<td>LS-BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Wilson et al. [46]</td>
<td>1p36</td>
<td>17</td>
<td>D1S214</td>
<td>2.38</td>
<td>Total Hip BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td></td>
<td>3p22</td>
<td>76</td>
<td>D3S1289</td>
<td>2.72</td>
<td>Total Hip BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Karak et al. [47]</td>
<td>21q22.2</td>
<td>40</td>
<td>D21S2055</td>
<td>2.39</td>
<td>Total Hip BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Devoto et al. [48]</td>
<td>2p22–24</td>
<td>17</td>
<td>D2S149</td>
<td>2.25</td>
<td>LS-BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Strykarsdottir et al. [9]</td>
<td>20q12</td>
<td>20</td>
<td>D20S905</td>
<td>2.89</td>
<td>LS-BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Karasik et al. [49]</td>
<td>9q22</td>
<td>120</td>
<td>D9S930</td>
<td>2.71</td>
<td>FN-BMD</td>
<td>Family based study, probands with low BMD</td>
</tr>
<tr>
<td>Kammerer et al. [10]</td>
<td>6q27</td>
<td>190</td>
<td>D6S281</td>
<td>2.27</td>
<td>Trochanter BMD</td>
<td>Family based study, unselected for BMD. All of the major QTL identified were specific to males</td>
</tr>
<tr>
<td></td>
<td>2pter</td>
<td>0</td>
<td>D2S1780</td>
<td>3.98</td>
<td>FN-BMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8p21</td>
<td>48</td>
<td>D8S1771</td>
<td>2.15</td>
<td>FN-BMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13q14</td>
<td>55</td>
<td>D13S788</td>
<td>3.46</td>
<td>Trochanter BMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13q14</td>
<td>60</td>
<td>D13S788</td>
<td>2.51</td>
<td>LS-BMD</td>
<td></td>
</tr>
</tbody>
</table>

The loci shown are those identified by genome-wide scan where lodscore values exceeded the threshold for suggestive linkage (+2.2). LS-BMD, lumbar spine bone marrow density; FN-BMD, femoral neck bone marrow density.
lipoxygenase enzyme, which converts arachidonic and linoleic acids into ligands for the transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ). It is thought that activation of PPAR-γ reduces bone mass by promoting the differentiation of mesenchymal cells to adipocytes rather than osteoblasts. In keeping with this, mice with insufficiency of PPAR-γ have increased BMD [18]. Research is currently in progress to determine whether genetic variation in the human homolog of PPAR-γ is also associated with bone mass.

**Candidate gene studies**

Candidate gene association studies have identified several polymorphisms that are associated with BMD, bone loss, or osteoporotic fractures. The field of osteoporosis genetics continues to be dominated by these studies, although most have been underpowered, with the result that there has been little consistency between studies [19]. Some of the candidate genes that have been implicated in the pathogenesis of osteoporosis are discussed below.

**Vitamin D receptor**

The vitamin D receptor (VDR) was the first candidate gene to be studied in the osteoporosis field, and most attention has focused on polymorphisms situated at the 3’ flank of VDR recognised by the restriction enzymes BsmI, ApaI and TaqI. A recent meta-analysis of association studies that genotyped the BsmI polymorphism concluded that there was evidence of an association between spine BMD and alleles at this site, equivalent to approximately 0.15 Z-score units between the BB genotype and the other genotype genotypes [20*]. No association with femoral neck BMD was observed. This meta-analysis did not include all the studies available, however, and an important omission was the Rotterdam study, in which more than 1700 subjects were genotyped for VDR polymorphisms [21].

**Collagen type 1 α1**

The gene encoding the alpha 1 chain of type 1 collagen (COL1A1) is an important functional candidate for the pathogenesis of osteoporosis because type 1 collagen is the major protein of bone. Previous research identified associations between BMD and polymorphisms within the proximal promoter of COL1A1 and within the first intron of COL1A1 [22–24]. Most interest has focused on a polymorphism within intron 1, which is situated at a binding site for the transcription factor Sp1. Two meta-analyses of association studies have been conducted for this polymorphism, one for osteoporotic fracture and another for BMD and osteoporotic fracture. Both studies concluded that this ‘s’ allele of the Sp1 binding site polymorphism was associated with reduced BMD and an increased risk of fracture [25,26]. Interestingly, the association between COL1A1 alleles and fracture cannot be fully explained on the basis of reduced bone density, implying that the Sp1 allele also acts as a marker for bone quality. This is supported by functional studies indicating that the osteoporosis-associated ‘s’ allele is associated with dysregulation of collagen production, impaired bone mineralization, and reduced bone strength [27].

**Oestrogen receptor**

The oestrogen receptor α, encoded by the ESRI gene, is another important functional candidate for the regulation of bone mass. Many investigators have looked for evidence of an association between ESRI alleles and BMD, mostly focusing on two polymorphisms within intron 1, recognised by the XbaI and PvuII restriction enzymes; and on a TA repeat in the promoter. A meta-analysis of published studies showed evidence of an association between the XbaI polymorphisms and both BMD and fractures, with higher BMD values in XX homozygotes and a reduced risk of fractures in association with this genotype [28]. More recently, a prospective meta-analysis of data from more than 18,000 participants in the Genetic Markers of Osteoporosis (GENOMOS) study confirmed that XX homozygotes have a reduced risk of fracture [29*]. Interestingly, in this study, no association with BMD was observed, indicating that ESRI might influence fracture risk by mechanisms that are independent of BMD.

**Transforming growth factor beta-1**

Several polymorphisms of the TGFβ-1 gene have been identified, and some of these have been associated with BMD and/or osteoporotic fracture in various studies [30,31]. The best functional candidate is a C/T polymorphism, which causes a proline-to-leucine amino acid substitution at position 10 in the TGFβ-1 signal peptide. This has been associated with circulating TGFβ-1 levels, although the underlying mechanisms have not been investigated at a molecular level.

**Lipoprotein receptor-related protein-5**

Inactivating mutations of the lipoprotein receptor-related protein-5 (LRP5) gene are the cause of osteoporosis pseudoglioma syndrome, a rare recessive disorder, whereas activating mutations in the same gene causes autosomal dominant inheritance of high bone mass [32]. The involvement of LRP5 in these rare monogenic bone disorders has led several investigators to evaluate the role of LRP5 as a candidate gene for BMD regulation in the normal population. Five studies have now been published showing evidence of an allelic association between polymorphisms in LRP5 and BMD [33*,35–36,37**]. The polymorphisms associated with BMD have differed in different populations, and their functional effects on LRP5 signalling remain unclear at present. One consistent
feature to emerge from these studies is that the association between LRP5 alleles and BMD is stronger in male individuals, which suggests that LRP5 may regulate bone mass in a gender-specific manner [33,*37**].

**Sclerostin**

Mutations affecting the SOST gene, which encodes sclerostin, are the cause of the sclerosing bone dysplasias Van Buchem disease and sclerosteosis [38–40]. Polymorphisms of SOST have been evaluated in relation to BMD in two studies. In one study using a case-control design, no association between SOST polymorphism and BMD was found in perimenopausal women [41]. In another study of older subjects evidence of an association with BMD was observed in men and women, with effects that increased with age [42**]. These data suggest that SOST polymorphisms may regulate BMD, especially in older people.

**TCIRG1**

The TCIRG1 gene encodes the APT6i subunit of the osteoclast-specific proton pump. Inactivating mutations in TCIRG1 are responsible for a subset of patients with recessive osteopetrosis. Recent work indicates that polymorphisms of TCIRG1 might contribute to regulation of BMD in the normal population; a study by Sobacchi et al. [43*] showed evidence of an association between a polymorphism affecting an AP1 binding site in the TCIRG1 promoter and BMD in perimenopausal women. Functional studies need to be performed to identify the mechanisms that underlie this association, however, and to replicate the finding in other populations.

**Conclusions**

Genetic factors play a key role in the pathogenesis of osteoporosis by regulating phenotypes that predispose to fracture, including BMD, bone turnover, bone geometry, and bone quality. Some of the genes and genetic variants that regulate BMD have been identified, but most of the genes remain to be discovered. Many techniques have been used to identify osteoporosis-susceptibility genes, including linkage analysis in humans and mice and candidate gene association studies. Important findings to emerge over recent years have been the observation that different genes are responsible for the regulation of BMD in both genders and at different skeletal sites and that many of the genes that are mutated in rare bone diseases such as osteopetrosis and sclerosing bone dysplasias also contribute to the regulation of BMD in the normal population. Important directions for future research will be to better define the functional mechanisms by which candidate gene polymorphisms affect bone cell function and bone mass. From the clinical point of view, potential applications of genetic studies in osteoporosis are in the area of fracture risk assessment and in the identification of molecular targets for the design of new drugs. The observation that some candidate gene polymorphisms predispose to fracture my mechanisms independent of BMD indicates that these might be of particular value clinically in providing information on fracture risk, over and above that obtained by bone densitometry [27,29**].

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• of special interest
** of outstanding interest


This is the first example of a gene that regulates BMD identified by genetic mapping and positional cloning in mice. The key to identification of Alox15 came from microarray analysis, which showed 20-fold upregulation of Alox15 mRNA in the low BMD-associated mouse strain. Further studies in Alox15-null animals confirmed elevated levels of BMD compared with wild type control animals, consistent with a model whereby Alox15 lowers BMD. Further suggestive evidence of a role for Alox15 in bone was gained by the observation that Alox15 inhibitors partially protected against ovariectomy-induced loss in mice.
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LRP5 haplotypes and a 1-year gain of bone mineral content in boys, but not girls.

The data are consistent with the hypothesis that LRP5 polymorphisms influence skeletal growth and attainment of peak bone mass in men but not women.

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40 Balemans W, Ebeling M, Patel N, et al. Increased bone density in scleroste-


42 Utterlinden AG, Arp PP, Paever BW, et al. Polymorphisms in the Scleroste-
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This large-scale association study involved almost 2000 subjects from the Rotterdam study, which demonstrates that polymorphisms at the SOST locus are associated
with BMD. Different single nucleotide polymorphisms were associated with BMD in men and women, and the associations were largely observed in older subjects from the study cohort. The data suggest that SOST regulates BMD with effects that in-
ncrease with age. The authors also reported an interaction between SOST alleles and COL1A1 alleles in regulating BMD, illustrating the potential of using multiple polymor-
phisms to predict BMD.


This moderate-size association study demonstrated an association between a polymorphism at a putative AP1 binding site in the TCIRG1 promoter and BMD in perimenopausal women. This study adds to accumulating evidence that subtle polymorphism in monogenic bone disease genes contribute to BMD reg-
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- Papers considered by the reviewers to be of special interest.
- Papers considered by the reviewers to be of outstanding interest.

The number in square brackets following a selected paper, for example [7], refers to its number in the annotated references of the corresponding review.

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