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Temporary Dermal and Soft-Tissue Fillers Supplement

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A lthough few people still search for Ponce de León’s fountain of youth, the human fascination with defying the effects of aging is alive and well. In fact, staving off wrinkles and folds accounts for the most popular minimally invasive cosmetic procedures performed. Since the 1980s, injectable collagen has been the favored way to fill facial lines. In fact, in 2005 nearly 220,000 collagen procedures were performed. The emergence of new compositions, however, has taken the demand for temporary dermal and soft-tissue fillers to the next level. The American Society of Plastic Surgeons showed an increase of 388 percent in botulinum toxin type A procedures from 2000 to 2005, from 786,911 to over 3.8 million.

With new arrivals in the field of fillers and the growing popularity of less invasive procedures among the public, “often in a younger patient population,” it is more important than ever to understand the soft-tissue injectable filler materials. With this mission in mind, I am proud to present the second supplement in our series on injectable fillers: the Temporary Dermal and Soft-Tissue Fillers Supplement. Whereas the September 1, 2006, supplement focused on the longer-lasting fillers, this supplement has a tight focus on the so-called temporary fillers, including collagens and both animal-based and non-animal-based hyaluronic acids.

To reemphasize the Food and Drug Administration status and indicated uses for the products discussed in this supplement, every article has a separate Food and Drug Administration disclosure on the first page, in addition to the information contained in the article’s text. If more information is required, please visit the Food and Drug Administration’s Web site (http://www.fda.gov), the American Society of Plastic Surgeons’ Injectables At-A-Glance Web page (http://www.plasticsurgery.org/media/press_releases/Injectables-at-a-Glance.cfm), or the American Society for Aesthetic Plastic Surgery’s Injectables Quick Facts page (http://www.surgery.org/download/injectablechart.pdf). All are very thorough information resources, and the latter two provide bullet points of easily referenced information.

This supplement would not have been possible without the tireless efforts and cooperative leadership of the guest editors, Steve Fagien, M.D., and Jim Stuzin, M.D. Because of their strong resolve, prudent editorial decisions, and thoughtful article and author selections, I am confident that this document will be cited as a very important contribution to the literature for years to come.

The guest editors and I also owe thanks to the authors not only for writing significant articles but also for their general adherence to deadlines, their cooperation with the editorial staff, and their flexibility. These men and women are leaders in our field, and their expertise and knowledge have certainly resulted in the significant document before you today.

I would also like to thank Allergan, BioForm, and Medicis for the unrestricted educational grant that made this supplement possible. Without the philanthropy of such corporations, educational documents like the Temporary Dermal and Soft-Tissue Fillers Supplement would not be possible. The content of the supplement was by no means dictated by the sponsors, and all financial declarations and affiliations of the authors have been disclosed both in an appendix and within each article.

I am extremely grateful for the daily efforts of our support team at Lippincott Williams & Wilkins and of my editorial staff, especially Aaron Weinstein, coordinator of supplements and production, and Dan Sullivan, managing editor. Their dedication to the Journal and creativity are truly admirable.

I hope this supplement will be helpful in your daily practice and that it will better your under-
standing and use of the temporary dermal and soft-tissue fillers.

**REFERENCES**


**DISCLOSURE**

The author has no financial interest in any of the products, devices, or drugs mentioned in this article.
Financial Disclosures for the Temporary Dermal and Soft-Tissue Fillers Supplement

Guest Editors’ Financial Disclosures

- Steven Fagien, M.D., serves as a consultant and an investigator to Allergan, Medicis, Dermik Aesthetics, and Mentor, Inc. He is an investigator for Anika Therapeutics and a shareholder in Collagen Matrix Technologies.
- James Stuzin, M.D., has no financial interests in any of the products, devices, or drugs mentioned in this supplement.

A Brief Overview and History of Temporary Fillers: Evolution, Advantages, and Limitations
By Steve Fagien, M.D., and Arnold W. Klein, M.D.

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Injectable Collagens: Lost but Not Forgotten—A Review of Products, Indications, and Injection Techniques
By Seth L. Matarasso, M.D.

Dr. Matarasso has served as a consultant to Allergan (Irvine, Calif.), Inamed Aesthetics (Santa Barbara, Calif.), and Medicis (Scottsdale, Ariz.).

Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations
By Clifford P. Clark, III, M.D.

Dr. Clark has received honorariums for participating in the Inamed Academy.

Non–Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations
By Alastair Carruthers, M.D., and Jean Diana Carruthers, M.D.

Neither author has a financial interest in any of the products, devices, or drugs mentioned in this article.

The Role of Hyaluronic Acid Fillers (Restylane) in Facial Cosmetic Surgery: Review and Technical Considerations
By Rod J. Rohrich, M.D., Ashkan Ghavami, M.D., and Melissa A. Crosby, M.D.

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Calcium Hydroxypatite (Radiesse) for Correction of the Mid- and Lower Face: Consensus Recommendations
By Miles H. Graivier, M.D., Lawrence S. Bass, M.D., Mariano Busso, M.D., Michael E. Jasin, M.D., Rhoda S. Narins, M.D., and Thomas L. Tzikas, M.D.

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Practical Use of Juvederm: Early Experience
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Hyaluronic Acid Injections for Correction of the Tear Trough Deformity
By Val S. Lambros, M.D.
Dr. Lambros was once paid by Medicis to be part of a Restylane expert users group. There are no other conflicts of interest.

Hyaluronic Acid Fillers and Botulinum Toxin Type A: Rationale for Their Individual and Combined Use for Injectable Facial Rejuvenation
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The Role of Autologous Fat and Alternative Fillers in the Aging Face
By Louis P. Bucky, M.D., and Suhail K. Kanchwala, M.D.
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Management of Complications and Sequelae with Temporary Injectable Fillers
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Injectable Soft-Tissue Augmentation: The Present and the Future

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This special supplement to the Journal is dedicated to a review of temporary filler materials for facial soft-tissue augmentation. Contained within is a collection of information that has been contributed by some of the pioneers and innovators of injectable agents. We begin the supplement with a historical perspective followed by an overview of many of the temporary filling agents that are commonly used today. We hope that, after reading through this material, you will have a better understanding of not only how to utilize these agents but also what the future implications and advances are for fillers applicable to facial rejuvenation.

Despite many years of utilizing a variety of agents to fill facial defects, it has only been in the last decade that the salient issues have become clarified regarding what constitutes successful treatment. The indications for injectable filler agents have largely evolved through a better understanding of facial aging, specifically the soft-tissue deflation typically noted between youth and middle age. The limitations of surgical procedures to correct soft-tissue atrophy, as well as the possibility of postponing surgical procedures by early intervention with injectable fillers, have made these agents indispensable in improving the appearance of the aging face. With greater experience and scientific investigation, we now have a clearer understanding of both the short- and long-term effects of these agents. With the improvement in products and techniques, the results with fillers have become more consistent, thereby increasing patient and physician satisfaction.

Just over 25 years ago, we had a relatively modest appreciation of the value of soft-tissue augmentation as a complement to attempts at facial rejuvenation and far underestimated patients’ ultimate acceptance of office-based treatments that had temporary results. In an age of lifestyles that demand minimal recovery after such treatments, the absorbable and biodegradable injectable agents have taken the lead in aesthetic procedures worldwide. Initially, a relative few embraced the use of injectable bovine collagens, Zyderm and Zyplast (distributed by Allergan Aesthetics, Inc., Irvine, Calif.), which were essentially the only materials available (they had no real competition in the marketplace). Compositionally, these agents were fibrillar extractions (fragments) of pepsin-solubilized, atelopeptide bovine collagen in a phosphate-buffered saline containing 0.3% lidocaine. It was with these agents, too, that the concept of cross-linking was introduced as an attempt to make varieties of these products more resistant to biodegradation (Zyplast) and carried through to even the newer products available today. Because these were the first agents introduced in the United States, they were utilized for a growing list of facial aesthetic applications, including the treatment of facial lines, shallow furrows, and scars, with volume augmentation applications essentially limited to lip enhancement. The ease of injectability and the ability to achieve satisfactory results (one of the few phenomena that shared the premise of horseshoes, where “close” was good enough) escalated their popularity, as patients became aware of and sought facial treatments that potentially had dramatic effects and could be performed during a brief visit to the doctor. The promise of “collagen replacement therapy” was appealing to all; yet the reality was that what actually occurred with treatments had little resemblance to it. Results typically lasted in the range of several months, although poor injection techniques and protocols often led to even shorter durations of effects. It was mostly concerns with allergenicity, however, and not lack of persistence that initially led to the pursuit of improved biocom-
compatible materials that could serve as dermal bulking agents. The historical importance of collagen substances and the appreciation of newer and improved varieties looking ahead are just a few of the reasons that these agents are discussed in this supplement.

Newer agents have been developed to address these concerns of allergy or were otherwise known biomaterials that were highly compatible and could serve as dermal filling agents. The first generation of commercially available, injectable human tissue collagen matrix, DermaLogen (Collagen Matrix Technologies, Boca Raton, Fla.), for instance, was a direct reaction to the appreciation of “collagen” as a valid dermal filling agent and the need to have a substance that posed negligible risk for allergenicity. The premise was that an injectable, allogeneic, decellularized human dermis (not simply collagen fragments) would be an ideal replacement for the involutional loss of dermal thickness. CosmoDerm and CosmoPlast (distributed by Allergan Aesthetics, Inc., Irvine, Calif.) were eventually introduced as human tissue analogs with otherwise the exact formulation as ZyDerm and ZyPlast. They also obviated the need for skin testing but offered the identical (sometimes less) persistence as their older siblings. Several other collagen-based products that never gained popularity for a host of reasons are briefly discussed in this supplement.

The relative newcomer to the injectable filler spectrum is the family of hyaluronans. Since their introduction, hyaluronans have become the leading filling agent worldwide and have immensely popularized the use of injectable soft-tissue augmentation as highly acceptable in facial rejuvenation. The hyaluronic acids have been long-awaited as a solution to longevity and allergenicity, as well as being better agents for facial volume augmentation. For many years, these agents had been used for other nonaesthetic applications and had a proven track record of biocompatibility, with both intraocular and intra-articular uses. The awareness of this substance as a primary component of skin, characterized by its hydrophilic properties, as well as the ability to procure or produce it in a variety of ways, sparked the interest of many. As the residence time of hyaluronic acid in its native state was known to be dramatically transient in vivo, this was enhanced with a host of chemical manipulations, including cross-linking techniques and concentration optimization. Sources of hyaluronic acid products continue to draw controversy, and the physical and rheological characteristics of each of these agents contribute to their clinical effects, many of which are discussed in this issue. The more common use of supplemental local anesthesia (none of the hyaluronic acid agents currently available in the United States contain lidocaine), improved injection techniques, and greater product persistence and versatility have facilitated the high level of acceptance of these products as well. Due to their present immense popularity, the hyaluronic acids are a main focus of this supplement. Restylane (distributed by Medicis Aesthetics, Scottsdale, Ariz.) was the first hyaluronic acid product to receive U.S. Food and Drug Administration approval, and others were soon to follow (e.g., Hylaform, Captique, Juvederm, and so on). At the time of publication of this supplement, Restylane was the most commonly used injectable filling agent worldwide. With an evolution of product improvements and an escalating patient demand, we have entered the age of hyaluronic acid filling agents that have now dominated the market. But does it stop here?

The reality is that, at present, although we have a better understanding of the contributors to and pathophysiology of facial aging, nothing truly restores youth. Most of the agents presented and discussed in this supplement simply offer a temporary solution to a permanent problem. We do, however, have a greater opportunity for aesthetic enhancement with the enlarging spectrum of options and techniques, including improved prophylaxis/protection, topicals, injectables, energy-based devices, and surgery, to further enhance outcomes that can bring us closer to a more youthful appearance. Better injectable agents (each with unique characteristics) and techniques are now available to us that are safe, effective, and longer-lasting and that can be delivered in the comfort of an office setting, which is always appealing to our patients. Combined with enhanced knowledge and experience as to “which agents work best where,” safety and outcomes have improved dramatically. What our patients demand is not necessarily a permanent solution but more of the truth regarding safety, efficacy, and persistence at a cost to them that is commensurate with the result. The products of tomorrow will take filling agents to the next level and will offer short- and long-term benefits. The learned and experienced injector realizes that satisfying most patients requires the time to educate
and counsel them on the options available and the ability to deliver on their expectations utilizing a combination of approaches to give the most effective and aesthetic results.

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DISCLOSURES

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A Brief Overview and History of Temporary Fillers: Evolution, Advantages, and Limitations

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Summary: Facial soft-tissue augmentation by injection has become increasingly popular as a minimally invasive option for patients seeking cosmetic facial enhancement. Surgical rejuvenation procedures of the face often relate to a less than comprehensive solution to many of the changes that occur with age. Indeed, the surgical “lift,” while providing the opportunity for soft-tissue repositioning, often fails to provide volumetric restoration to the face that is lost with aging. Appreciating the necessity of replacing depleted soft tissue has allowed for a more comprehensive approach to total facial rejuvenation. Hundreds of filling agents are available worldwide, and the enormity of options has led to confusion about which agents work best, where, and why. The vast array of available soft-tissue filling agents can be distilled into two simple categories: nonpermanent and permanent. In this article, the authors mostly limit their discussion, consistent with the mission of this supplement, to the evolution of nonpermanent filling agents, providing a rationale for their emergence and their individual use. (Plast. Reconstr. Surg. 120 (Suppl.): 8S, 2007.)

We have come to understand facial aging much better in recent years through a combination of revelations, including the actual anatomic and physical changes that occur with time and the failure of traditional surgical methods to address changes. In addition, photographic comparative imaging and morphing techniques, as described and demonstrated by Lambros, have shed more light on the reality of facial change. As has been the case in aesthetic medicine, historically, the cure has related more to available options and the often ill-conceived concepts of causation. Although facial aging has been attributed primarily to soft-tissue descent, we now realize that qualitative and quantitative influences, including a depletion of components present in youth and volume loss, may have comparable relevance. Soft-tissue loss is now better understood and acknowledged as a necessary component that must be addressed in a comprehensive reversal of facial aging. Moreover, the causes of facial volume loss and shifts are many and include contributions from chronic facial animation that were previously less appreciated. The ability now both to address volume depletion and to modify its cause (for instance, with chemodenervation) has yielded a more powerful approach to nonsurgical facial rejuvenation.

HISTORY AND EVOLUTION

One of the earliest agents used for soft-tissue augmentation was autologous fat, which was first used more than 100 years ago. Interest in autologous fat transfer has been renewed by improved applications and techniques, but unlike most of the agents discussed in this article, autologous fat transfer is used primarily for subcutaneous volume augmentation. Of historical interest, most of the early dermal-filling materials were potentially long-lasting (even “permanent”) and were not necessarily native to the intended site. Paraffin, for instance, was used at the turn of the nineteenth century, but it fell into disfavor by the 1920s be-
cause of the appearance of severe granulomas. Nevertheless, its use continued in Asia throughout the 1960s. Pure injectable silicone was utilized by a relatively small group of physicians with markedly mixed reviews.\(^5\)–\(^8\) Others, albeit intuitively and anecdotally, without a strong scientific basis for their claims, felt that permanent agents such as these could cause severe facial distortion over time, hence their personal preferences for nonpermanent filling substances. Due in part to concerns about its use, the U.S. Food and Drug Administration eventually banned silicone for cosmetic procedures.\(^9\) Ultimately, we have come to a greater understanding of the benefits and limitations of a host of filling agents, including the appropriate application and what factors, such as technique, might contribute to untoward events. This is also true for silicone, with experienced injectors showing good results while minimizing complications.\(^10\)–\(^12\) Recently, ophthalmologic 1000 centistokes of silicone was used in an off-label manner as a filling substance.\(^13\)

**“COLLAGEN” PRODUCTS**

In 1958, Gross and Kirk at Harvard Medical School showed the potential for collagen extracted from calf skin to produce a solid gel by gentle warming.\(^14\) In the early 1970s, a group of investigators at Stanford began work on a potentially useful injectable bovine collagen implant. This ultimately led to the development and approval of the Zyderm (Allergan, Irvine, Calif.) bovine collagen implant in 1977.\(^15\) The early claims were that this filler could result in “collagen replacement” and more long-lasting results. Experience indicated otherwise. This led to the development of a more robust (cross-linked) form of the product called Zyplast, followed by the formulation of Zyderm 2, a more viscous form of the original Zyderm formulation that is used to treat moderate fine lines, wrinkles, and scars. These (pioneer) products paved the way for a better appreciation of what could be accomplished with filling agents in an outpatient setting by injection alone, with minimal downtime. Improved injection methods, including serial puncture for implantation and lip augmentation, also contributed to the success (better results and improved persistence) of these products. The lack of satisfactory persistent correction with bovine collagen was more often technique-related than product-related, although the reality was still that these agents, in most individuals, would last for only several months at best. The bovine collagen products, which were really the first widely used, commercially available, injectable soft-tissue augmentation agents, suffered many of the casualties of being “first generation.” Physicians also often used ancillary (staff) help to implant these products, and little attention was paid to the details of implantation, which often yielded suboptimal results. In addition, the rare occurrence of severe localized allergic reactions also raised many questions regarding their usage. Satisfactory results could be obtained with these injectable collagen agents, however, and complaints were related mostly to the lack of persistence and the inability to substantially improve facial volume. There was also the requirement for skin testing, which evolved into double skin testing as physicians’ understanding of collagen reactions became more sophisticated. Complications due to allergenicity were also most disconcerting, and these occurrences were sometimes quite difficult to manage (Fig. 1). Many of these problems were related to the lack of physician appreciation of the most applicable facial regions and injection techniques associated with these products. The theoretic bio-compatibility of bovine collagen rested on the fact that the ultrastructure of type I collagen is quite similar among animal species. The risk of allergenicity due to different species specifications was said to be addressed by modifications of the “exposed” protein segments through a variety of processing techniques. Processing of bovine collagen involves conceptual removal of the nonhelical amino and carboxyl telopeptides in an attempt to reduce the immunogenicity to make the bovine collagen more compatible with human tissue. Cross-linking was also considered to render the collagen fragments more resistant to enzymatic degradation and to seclude other heterogeneous segments. Although severe allergic reactions were, fortunately, relatively rare, there has been inconsistent reporting, and best estimates of a severe reaction place it in the 5 percent range. Satisfactory results could be achieved, and the era of injectable bovine collagen facilitated an awakening of the field of soft-tissue augmentation. Other animal protein collagen-like products were introduced into the market, including porcine-derived collagen (Fibrel) and other bovine products available outside of the United States. The requirement for in-office formulation (Fibrel) and the lack of superiority over the then-available bovine products led to the continued use of the latter.

Concerns regarding the allergenicity of the bovine products led to the concept of creating a nonallergenic human collagen. The first agent commercially available in the United States was...
Autologen (Autogenesis Technologies, Acton, Mass.). Research and development culminated in the ability to extract human dermis with intact collagen fibers for injection from skin obtained during any surgical procedure. With autologous dermal tissue matrix, there was no need for skin testing and concerns about allergic inflammation and potential communicable diseases were eliminated. However, a relatively laborious process was required for skin harvest and procurement of the injectable Autologen (autologous human tissue dermal matrix). The skin was sent in sterile containers for processing, which involved sterilization with a proprietary technology that extracted decellularized dermal components, including collagen fibers, in a viable injectable form.16–20 The required process of custom production for each individual patient was rather costly and heralded the typical inconsistencies of products that lacked mass production. Furthermore, the product did not contain the lidocaine found in the bovine agents; many physicians found it painful to inject, and it lacked the ease of use compared with the familiar bovine collagen. The viscosity of the early prototypes of this product also varied, and good results required a level of precision that at the time was not commonly practiced.

The interest in a readily available injectable human tissue matrix spawned the idea for a cadaver-based allogeneic agent. Dermalogen (Collagenesis, Inc., Beverly, Mass.), identical to Autologen in structure and substance, was created, but the source, rather than being autologous, was skin obtained from approved tissue banks.21,22 One advantage was mass production, which allowed for greater quality assurance, mostly with regard to consistency, and lower costs. In contrast, the source of Autologen was limited, and turnaround of the product to the physician occurred despite slight variations in specifications.

The earlier prototypes of Dermalogen and Autologen were not fibrillar-purified agents but rather dermal extracts with distinctly different flow characteristics compared with the bovine products.23 Dermalogen was refined in several ways. It was available in a 4% (40 mg/dl) range of concentration and could be injected through 27-gauge needles into the dermis. When a precision technique was used to administer the product, the results were highly satisfactory (Fig. 2).

As with the introduction of most injectable products, rare reactions were seen early in the evolution that were related to product impurities; these problems were eventually rectified. Although the many obstacles of the first human collagen injectable product were eventually overcome, its widespread use was limited as many awaited the introduction of newer agents that could both eradicate dermal defects and restore facial volume loss. In many ways, however, Dermalogen paved the way for other agents that could also satisfy the requirements of safety and efficacy with negligible adverse events and avoidance of skin testing.

To address the concerns about allergenicity, CosmoDerm and CosmoPlast (Inamed Division of Allergan, Santa Barbara, Calif.), human tissue analogs to Zyderm and Zyplast, were introduced. In March of 2003, the U.S. Food and Drug Admin-
istration approved the CosmoDerm family of injectable dermal fillers (Allergan). CosmoDerm 1, CosmoDerm 2, and CosmoPlast were the first approved bioengineered human collagen dermal fillers and the first approved fillers, according to the manufacturer, that were nonallergenic and did not require skin testing before use. CosmoDerm 1 has a collagen concentration of 3.5 percent and CosmoDerm 2 has a collagen concentration of 6.5 percent. Both are used to correct fine to moderate lines, wrinkles, and scars. CosmoPlast, which is cross-linked, is a more robust formulation and is indicated to treat deeper lines and folds.

Another collagen-based product is Cymetra (micronized human cadaveric dermis; AlloDerm; LifeCell Corporation, Palo Alto, Calif.). The manufacturer claims a longevity of 3 to 9 months, but this injectable agent is costly. It costs about twice as much as collagen and typically requires multiple office visits. Fascian is an injectable human cadaveric fascia made by Biosystems (Beverly Hills, Calif.). First introduced in 1999, the manufacturer claimed that it lasted from 6 to 8 months. Most physicians, however, feel that its persistence is more comparable to the longevity of bovine collagen. In addition, both Cymetra and Fascian are relatively more difficult to use. In our experience, syringes are easily clogged by the product and the result can be irregular and “lumpy.” In addition, Cymetra and Fascian have not enjoyed popularity similar to that of other “collagen” agents for many reasons, including larger particle size, which requires larger needles that make precise intradermal injection difficult. Ultimately, they have not proven superior with regard to persistence. A new cross-linked porcine collagen, Evolence (Colbar LifeScience, Herzliya, Israel, acquired in July of 2006 by Johnson & Johnson, Inc.), has shown promise, as there appears to be a renewed interest in collagen-based products with greater persistence due to cross-linking and other methods. In its first U.S. clinical trials, Evolence was matched against Zyplast for the treatment of nasolabial folds and showed equal efficacy in the short term and superiority to Zyplast beyond 6 months. Isologen (Isologen Technologies, Inc., Paramus, N.J.), consisting of cultured autologous fibroblasts, has also been reintroduced. With this filler, a dermal specimen is harvested from behind the ear and sent to the Isologen laboratory, where the fibroblasts are cultured and packaged for injection into the patient. A test dose is required and it is reportedly quite expensive. There is no consensus regarding the validity of many anecdotal claims relating to both the real science and persistence. One study, however, reported that after two to three treatments the effects may last for up to 22 months.24

HYALURONIC ACID PRODUCTS

The concept of using hyaluronic acid for tissue augmentation was the result of years of research by Balazs and coworkers.25 Its use was justified because it is a structural and elastic component of skin as well as partly responsible for maintaining skin hydration. Native hyaluronic acid, however, has a short residence time in the skin and likely lasts for only several days after injection. Clinically, hyaluronic acid had been used as a viscoelastic injectable material during intraocular surgery, to protect delicate structures such as the cornea during instrumentation of the anterior segment. Several derivatives of hyaluronic acid, including animal and bacteria fermented products, had been introduced in both the ophthalmology and ortho-
The concept of cross-linking, which was well known in the collagen industry, was then applied to the hyaluronic acid products in an attempt to improve persistence by fortifying the molecule against enzymatic degradation. In the late 1980s, investigators reported the potential for injectable cross-linked hyaluronan to have a prolonged residence time in tissue and yet have the same biocompatibility as hyaluronan. In 1991, Piacquadio initiated a study of cross-linked hyaluronic acid (hylan B) for tissue augmentation.26

The Food and Drug Administration’s approval of Restylane (nonanimal stabilized hyaluronic acid; Medicis, Scottsdale, Ariz.) in December of 2003 began a new era of injectable soft-tissue agents in the United States. This product proved to have several advantages over the existing “collagen” products, mostly due to its greater persistence and because it was an off-the-shelf agent that could be used for volume augmentation. “Nonanimal stabilized hyaluronic acid” simply indicates that the product is derived from a nonanimal source and is essentially “stabilized” by cross-linking. Several independent manufacturers of hyal-
Hyaluronic acid products utilize proprietary cross-linking methods; these products have also been shown to be more resistant to enzyme degradation and, hence, have an improved residence time (compared with “free hyaluronic acid”) when injected into the dermis. The following is an abbreviated list of these agents (in alphabetical order): AcHyal (Tedec Meiji Farma, S.A., Madrid, Spain), Hydra Fill (Allergan), Hylaform and Hylaform Plus (Genzyme, Framingham, Mass.; distributed by Allergan), Captique (Genzyme and Allergan), Juvederm, Juvederm Ultra Plus, and Juvederm Ultra (Allergan), Perlane (Q-Med, Uppsala, Sweden), Purogen (Mentor, Santa Barbara, Calif.), Restylane (Medicis), Restylane Lip, Restylane Fine Line, and Restylane SubQ (Q-Med and Medicis), and Rofilan Gel (Rofil Medical International, Breda, The Netherlands).

To date, Restylane has been the frontrunner in the vast sea of available hyaluronic acid filler products for a variety of reasons, including its earlier Food and Drug Administration approval, satisfactory safety margin, and beneficial effects. Guidelines on the most effective applications and usage were recently reported based on the consensus of a large group of experienced injectors across the aesthetic specialties.27,28

Erroneously, however, there appeared to be the notion that persistence and enhanced aesthetic effect could simply be accomplished by increasing concentration and/or cross-linking. What is also critical is a low-protein load of the source material from which the agent is derived. Furthermore, severely high concentrations of hyaluronic acid, as well as the nature and concentration of the cross-linking agent, can affect the

Fig. 5. (Left) This patient presented in her forties with complaints of the recent onset of obvious nasolabial folds, oral commissures, and aging changes around the chin. (Right) Postoperative view, after 2.0 ml of Restylane was injected into the nasolabial folds and oral commissures, in addition to treatment around the chin. Reproduced with permission from Steven Fagien, M.D.

Fig. 6. (Left) This patient presented with a significant depression along the central chin region and lower facial aging. (Right) Postoperative view, after 2 ml of Restylane was injected into mentum, upper and lower lips, and perimental hollows. Reproduced with permission from Steven Fagien, M.D.
biocompatibility of the agent. A multitude of hyaluronic acid agents are now currently available worldwide with variations that define their unique individual characteristics, including source derivation (animal versus bacterial), cross-linking (both chemical method and degree), concentration, amount of free hyaluronic acid (non–cross-linked), and particle size/uniformity (structure). Practical and theoretic differentiations include superior applicability of certain products to different regions, residence time and persistence, patient comfort and the requirement for anesthetic, rheological and flow characteristics, gel hardness, and injectability. With appropriate and precise injection protocols, highly satisfactory results can be achieved with a variety of hyaluronic acid products primarily for the treatment of facial furrows and volume depletion (Figs. 3 through 6).

It has always been our contention that a good injector can use any of these temporary products and get comparable results (including persistence) once he or she completely understands the nuances of each agent and applies the agent with appropriate precision. For example, a fine-line variety of hyaluronic acid (smaller-particle hyaluronic acid) is more applicable to more superficial rhytides. Although this is not recommended by the manufacturer, by carefully using a 32-gauge needle, Restylane can be applied at the most difficult (superficial) sites. Some evidence indicates that this decreases the bead size, thereby making Restylane useful for superficial applications. This phenomenon holds true for most of the collagen products as well. To date, however, the smaller-particle agents have not been impressive with regard to persistence. They have shown little to no

Fig. 7. (Left, above and below) This patient wished to improve the appearance of her deepened nasolabial folds and oral commissures. (Above, right) One-month postoperative view, after 2 ml of Restylane was injected into multiple planes (deep, mid-dermis, and superficial dermis) because of the depth of the folds and prior mediocre treatments. A satisfactory early result is seen. (Below, right) Four-month postoperative view, after resorption of the deeper injected product with persistence and visibility of the superficially placed product. This reflects an error in the superficial injection, which can result in a dramatically enhanced residence time. Reproduced with permission from Steven Fagien, M.D.
superiority to collagen products placed with precision and herald the risk of visibility (detection) and palpability. These agents are all, however, less advantageous to the deeper dermis, and residence time/persistence is dramatically reduced in the subcutaneous space.

More recently, we have observed a resurgence of the use of “collagen” for the superficial/papillary dermis. Hyaluronic acid agents have simply not worked well in most of these situations, and in fact are at the center of complaints about the use of hyaluronic acid. Visible and palpable nodularities are a manifestation of attempting to place a viscous, clear, amorphous gel in the superficial dermis. The residence time, for all agents in this space, can seem like “forever” and has forced many to either enzymatically degrade (hyaluronidase) or surgically excise or drain the material to satisfy patients. A particular phenomenon is one in which hyaluronic acid products are injected into multiple planes of a particular facial region in an attempt to augment the soft tissue at many dermal levels. Since the residence time and persistence for most fillers is greater the more superficial it is placed, when the deeper placed product dissipates (sooner), despite an initially highly satisfactory result, the residual superficial component remains and can become quite visible (Fig. 7). Collagen from any source (bovine, human, or other) that can be administered through a fine needle is far more utilitarian, effective, and forgiving in this superficial plane. On the other hand, for volume augmentation, the collagens that were once used for this purpose due to a “lack of options” have proven to be dramatically less effective than the hyaluronic acids and, certainly, the more permanent materials in this space. Commonly, practitioners use a combination of agents to optimize results, for instance, by using the “collagen” products in the superficial dermis and the hyaluronic acid product in the deep dermis to dermal/subcutaneous junction. In the final analysis, we have realized that instead of replacing existing products with newer agents, the most comprehensive approach utilizes a palate of products, with each appropriate for the required effect and used in harmony for facial dermal and volume augmentation to yield the best results.

CONCLUSIONS

As we have established, soft-tissue augmentation is a vital component of facial rejuvenation. The aesthetic market continues to be flooded with agents touted as being an improvement over existing products. What we have learned is that newer is not necessarily better, and sometimes, when we look back at some of the older practices that were essentially intuitive or were spawned from a lack of options (after we survive the distraction of the “latest and greatest”), we learn about their limitations. Further clinical experience with most of these agents will eventually dictate what agents work best, and a clearer algorithm for product choice will become more evident.

DISCLOSURES

Steven Fagien, M.D., serves as a consultant and investigator to Allergan, Medicis, Dermik Aesthetics, and Mentor, Inc. He is an investigator for Anika Therapeutics and a shareholder in Collagen Matrix Technologies. Arnold W. Klein, M.D., serves as a consultant and investigator to Allergan and Medicis.

REFERENCES

Injectable Collagens: Lost but Not Forgotten—A Review of Products, Indications, and Injection Techniques

Seth L. Matarasso, M.D.
San Francisco, Calif.

Summary: Soft-tissue augmentation and three-dimensional volume replacement remain a cornerstone of facial rejuvenation. There has been an exponential increase in interest in dermal fillers. Science and technology have kept pace with this demand, and currently there is a wide range of options from which to choose. This is especially well illustrated by the recent introduction of an entirely new class of agents—the hyaluronans. The temporary fillers (the collagens and the Zyderm and CosmoDerm families), however, remain an excellent alternative, as they have a well-documented safety record, there are multiple formulations that make them very versatile, and the admixture of local anesthetic decreases the discomfort of injection. (Plast. Reconstr. Surg. 120 (Suppl.): 17S, 2007.)

The aging face is not a medical condition that necessitates treatment per se. However, when a patient requests an elective aesthetic evaluation, a simple algorithm to present them with is the five “Rs” of facial rejuvenation: redraping of excess skin with surgical manipulation, resurfacing with ablative and/or nonablative mechanisms, recontouring of the structural anatomy, relaxing of the hypertrophic musculature with neurotoxins, and, finally, replacement of the atrophic or diminished subcutaneous tissue. Clearly, these are not mutually exclusive modalities. In fact, the patient must be made aware that to maintain facial homogeneity and proportion, these modalities are often used in concert. The cornerstone of facial enhancement could arguably be viewed as the last option, replacement. It would almost be counterproductive to utilize any one of these modalities as monotherapy without the additional use of three-dimensional facial volume replacement. For instance, a rhytidectomy may be quite successful in removing redundant skin, but the remaining facial concavities would result in an incomplete cosmetic appearance. Similarly, immobilizing the musculature of the upper third of the face without addressing the areas below the zygoma would also be aesthetically incongruous.

Historically, the only options for soft-tissue augmentation were autologous fat transplantation and bovine collagen injections; over the past decade, however, there has been a virtual explosion of new fillers from which to choose. Fueled by patient demand, improved technology, and the remarkable safety and efficacy of botulinum toxin injections above the zygomatic arch, there is now a remarkable selection of injectable products for effacement of rhytides and lip augmentation.

No one agent meets all of the criteria of the “ideal filler” (Table 1), and selection should be based on anatomic parameters as well as the preference of the individual injector (Table 2). Despite the overwhelming list of available fillers,
The product with unequivocally the longest safety profile remains bovine collagen.1

**COLLAGEN PRODUCTS**

Many new forms of collagen are currently under investigation and have the potential for clinical utility, but they have yet to be granted approval by the U.S. Food and Drug Administration. A partial list of implantable collagen is provided below.

*Evolence* (ColBar LifeScience, Herzliya, Israel), a xenogenic product derived from porcine (pig) tendons, is the most recent addition to the injectable dermal collagens. It is produced in vitro by polymerization of porcine collagen followed by “Glymatrix technology,” a cross-linking technology that uses a sugar (ribose) and not chemicals. Porcine collagen is supposedly less immunogenic than its bovine counterpart; furthermore, during production of the porcine product, the allergenic telopeptides are removed, making it highly compatible with human collagen. No allergic responses have been reported in the clinical trials or in post-marketing surveillance follow-up, and theoretically, allergy testing is unnecessary. Each syringe of Evolence contains 30 mg/ml of product without anesthetic. Because it is a collagen, it may have the added benefit of stimulating the clotting cascade, so there may be less bleeding and bruising on injection. The longevity of implanted material is purportedly equivalent to that of Zyplast collagen, and in fact it may be longer, up to 12 months. Evolence was made available for sale in Europe, Canada, and Israel in 2005 and has received U.S. Food and Drug Administration approval for clinical investigation (Fig. 1).

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**Table 1. Partial List of Characteristics of the Ideal Filler Substance**

<table>
<thead>
<tr>
<th>Material</th>
<th>FDA approved</th>
<th>Nonallergenic (decreased risk of hypersensitivity)</th>
<th>Noncarcinogenic/nonteratogenic</th>
<th>No migration</th>
<th>Minimal adverse sequelae</th>
<th>Minimal inflammation</th>
<th>No overt cutaneous change (undetectable)</th>
<th>Reproducible</th>
<th>Durable</th>
</tr>
</thead>
</table>

**Table 2. Soft-Tissue Augmentation Preinjection Considerations**

<table>
<thead>
<tr>
<th>Defect parameters</th>
<th>Medications (anticoagulants)</th>
<th>History of hypersensitivity reaction</th>
<th>History of herpes facialis</th>
<th>Volume required</th>
<th>Location</th>
<th>Alternative/simultaneous treatments</th>
<th>Medical history</th>
<th>Pregnancy/lactation</th>
<th>Autoimmune disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient goals</td>
<td></td>
<td>Degree of improvement (what is of concern to the patient)</td>
<td>Morbidity/downtime</td>
<td>Risk/benefit ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The photographs courtesy of Dr. Gary Monheit.

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*Fig. 1.* Nasolabial folds (above) before treatment and (below) after injection of 1.0 cc of Evolence (porcine collagen). Photographs courtesy of Dr. Gary Monheit.
Permacol (Tissue Science Laboratories, Aldershot, United Kingdom) is a porcine dermal collagen matrix graft. It is primarily manufactured as a firm sheet of material that is used for reconstructing human dermal tissue defects. Injectable Permacol is the cross-linked micronized formulation of the sheet form. It is produced in a saline vehicle with a 60% wet weight per volume and is available in Europe in 2.5-cc syringes. It is intended for urinary bulking for patients with urinary incontinence, but some physicians have used it off-label as dermal filler.

Atelocollagen (Koken Co. Ltd., Tokyo, Japan) is obtained from Australian-bred calves no older than 6 months of age to decrease the risk of transmission of bovine spongiform encephalitis. It is supplied in 1-cc/mg cartridges and injected with dental syringes. It is commercially available outside of the United States and comes in three solutions containing 2%, 3.5%, and 6.5% monomolecular solutions of collagen without anesthesia. It contains approximately 95% type I collagen, but as it is of bovine derivation, allergy testing is recommended. There is limited information available regarding its duration and biologic cosmetic response.

Isolagen (Isolagen Inc., Houston, Texas) is a technology that requires harvesting a 3-mm punch biopsy specimen and transporting it for culture. From a single specimen, cultured fibroblasts will theoretically produce approximately 1.5 cm of endogenous collagen that can be re-injected into the original donor. Because this product is autologous, there is little risk of an allergic response. The procedure is currently under investigation, and Isolagen may soon become commercially available.

Artefill (Artes Inc., San Diego, Calif.) contains a combination of 30-μm to 42-μm microspheres of polymethylmethacrylate suspended in bovine collagen. The collagen serves as both a temporary filler and a vehicle that degrades, leaving intact polymethylmethacrylate beads. The remaining beads induce a localized foreign body reaction and become encapsulated in fibrous connective tissue (fibroplasia), producing long-term, if not permanent, augmentation. It has been approved for use in Canada, and in January of 2004 it received a U.S. Food and Drug Administration approval letter pending collection of 5-year safety follow-up data for the first 1000 patients and compliance with strict Food and Drug Administration bovine collagen manufacturing standards. In October of 2006, Artefill became the first Food and Drug Administration–approved, nonresolvable injectable filler for the correction of facial “smile lines.”

Resoplast (Filorgra Laboratories, Moscow, Russia) consists of solubilized elastin peptides with bovine collagen. Injected intradermally, the material influences the proliferation of fibroblasts to produce collagen. Because there is a bovine component, two negative skin tests are required before treatment. Augmentation is reported to last as long as 12 months. This product is currently available only in Europe and is not approved for use in the United States.

There are three human cadaveric collagens: AlloDerm and Cymetra, both manufactured by LifeCell Corporation (Branchburg, N.J.), and Dermalogen (Collagenesis Inc., Beverly, Mass.). They are allograft materials derived from American tissue banks that are subject to screening for all infectious processes. They primarily contain the acellular dermal layer of cadaver tissue, consisting of intact collagen and elastin fibers. AlloDerm is processed as sheets and is widely used to treat full-thickness burns and blistering disorders, as well as for soft-tissue augmentation procedures. In sheet form, it requires surgical implantation with the patient under local or general anesthesia. Cymetra is the micronized, injectable form of AlloDerm and is reconstituted in the physician’s office with lidocaine. As is the case with AlloDerm, no known hypersensitivity has been reported, so no allergy testing is required. Cymetra is injected deep in the dermis, above the dermal/subcutaneous junction, to treat rhytides and scars and for lip augmentation. Although the manufacturer addressed the original difficulties in reconstituting the product, it nevertheless remains a viscous material that generally requires a larger-bore needle (23 or 26 gauge) for injection. Therefore, local or regional anesthesia is required for placement. According to the manufacturer, the results last between 3 and 6 months. Although theoretically nonimmunogenic and incapable of producing allergic reactions, with the introduction of newer...
fillers, all three of these cadaveric agents seem to have lost much of their initial appeal, and the two injectable forms, Cymetra and Dermalogen, are no longer available.8

There are many forms of injectable collagen, but the two that have withstood the test of time and maintained the widest appeal and diversity are the bovine-derived Zyderm family of products and the newer, human bioengineered form, the Cosmo-Derm family (Table 3). Both were originally manufactured by Inamed (Santa Barbara, Calif.) and are now supplied by Allergan (Irvine, Calif.); they have three concentrations and viscosities of material, with corresponding clinical indications. They are available in boxes of six preloaded, single-use syringes containing opaque white collagen suspended in phosphate-buffered physiologic saline with 0.3% lidocaine; they are stable for up to a year when stored appropriately in a refrigerator (4°C). The manufacturer recommends that any unused product be discarded and not re-stored between patient visits; furthermore, should there be any separation of the microfibril suspension resulting in a nonuniform consistency, the syringe should be returned. The single-use syringes are accompanied by self-adhering labels with a lot number and expiration date that are placed in patients’ charts for tracking purposes. Both 30-gauge 0.5-inch and 30-gauge adjustable-depth gauge needles are provided. The later adjustable-depth gauge needles have the flexibility to be adjusted to alter the distance between the distal end of the needle and the cutaneous surface of the patient.

BOVINE COLLAGEN

The three Zyderm collagen implants, Zyderm I, Zyderm II, and Zyplast, are 95% to 98% type I collagen, with the remainder being type III.9,10

Zyderm I is the least concentrated and contains 35 mg/ml of collagen, and is recommended for very superficial rhytides or to layer on top of a deeper filling agent. Zyderm I should be placed in the superficial papillary dermis. Because a significant portion of Zyderm I is saline, which is rapidly resorbed, the defect should be overcorrected by 150 to 200 percent, to impart a white blanch or peau d’orange appearance to the epidermis. Zyderm II is a more concentrated and viscous form of Zyderm I and contains 65 mg/ml of collagen. It is intermediate in durability between Zyderm I and the more robust Zyplast. Zyderm II is appropriate for deeper lines and wrinkles and is placed deeper in the papillary dermis, with about 100 to 150 percent overcorrection. Zyplast has a collagen concentration of 35 mg/ml but has the longest duration because it is cross-linked by the addition of 0.0075% glutaraldehyde. This characteristic decreases proteolytic degradation by collagenase and enhances its in vivo stability, making it last longer than the 3 months generally anticipated for Zyderm I and Zyderm II. Zyplast is typically placed deeper in the dermis and is recommended for deep rhytides and folds; it should be injected without overcorrection.

Before the patient starts therapy with any of the three bovine products, potential allergenicity must be excluded. It has become the standard of care to reduce the risk of an allergic reaction with double skin testing. A skin test that screens for all three forms of bovine collagen is available in 1.0-cc tuberculin syringes that contain 0.3 ml of Zyderm I. Approximately 0.1 cc is placed subcutaneously in an inconspicuous area, such as the volar aspect of the forearm. Hypersensitivity is manifested by swelling, induration, tenderness, pruritus, and/or erythema at the injection site and resolves as the implant is absorbed. This has been found in ap-

### Table 3. U.S. Food and Drug Administration Approved Collagens

<table>
<thead>
<tr>
<th>Type of Collagen</th>
<th>Collagen Concentration</th>
<th>Indications</th>
<th>Available Syringe (cc)</th>
<th>% Over-correction</th>
<th>Year FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyderm I</td>
<td>35 mg/ml bovine</td>
<td>Fine/superficial rhytides</td>
<td>0.5, 1.0, 1.5</td>
<td>Superficial papillary dermis</td>
<td>150–200×</td>
</tr>
<tr>
<td>Zyderm II</td>
<td>65 mg/ml bovine</td>
<td>Mild/moderate rhytides, scars</td>
<td>0.5, 1.0</td>
<td>Mid-dermis</td>
<td>100–150×</td>
</tr>
<tr>
<td>Zyplast</td>
<td>35 mg/ml bovine</td>
<td>Deep lines and folds</td>
<td>1.0, 2.0, 2.5</td>
<td>Deep dermis</td>
<td>None</td>
</tr>
<tr>
<td>COSMOTHERAPY</td>
<td>85 mg/ml bovine</td>
<td>Fine/superficial rhytides</td>
<td>1.0</td>
<td>Superficial papillary dermis</td>
<td>150–200×</td>
</tr>
<tr>
<td>COSMOTHERAPY</td>
<td>65 mg/ml bovine</td>
<td>Mild/moderate rhytides, scars</td>
<td>0.5, 1.0</td>
<td>Mid-dermis</td>
<td>100–150×</td>
</tr>
<tr>
<td>COSMOTHERAPY</td>
<td>35 mg/ml bovine</td>
<td>Deeper rhytides and folds</td>
<td>1.0</td>
<td>Deep dermis</td>
<td>None</td>
</tr>
</tbody>
</table>
approximately 3 percent of patients and indicates a preexisting allergy to bovine collagen. Despite a negative preliminary test, an additional 1 to 2 percent of patients will develop allergic reactions to the products at subsequent treatments. Therefore, a second challenge 2 weeks after the initial skin test should be performed. This test dose, using a similar volume, can be injected on the contralateral arm or at the periphery of the face (pretragal area, anterior hairline) and should be monitored for an additional 2 weeks. A positive reaction to either skin test is an absolute contraindication to soft-tissue augmentation with bovine collagen. Conversely, a negative skin test allows the patient to proceed with treatment 4 weeks after the initial test or 2 weeks after the second test. An amended protocol is suggested for patients who have previously been successfully treated with bovine collagen but have not had soft-tissue augmentation for a year or more. If these patients do not wish to switch to the newer form of human-derived collagen or a different class of fillers and elect to continue with bovine products, to reduce the risk of bovine collagen hypersensitivity, a single retest with a 2-week observation period is advisable before commencing treatment.11,12

SYNTHETIC HUMAN COLLAGEN

The development of human-derived collagen (CosmoDerm) predates the availability of many of the newest fillers and was prompted by the need for a product that would eliminate hypersensitivity reactions and the concomitant skin testing.13,14 On the basis almost exclusively of the safety profile following their use in burns and wounds, the CosmoDerm family of products was granted approval by the Food and Drug Administration for soft-tissue augmentation. There are three forms: CosmoDerm 1, CosmoDerm 2, and CosmoPlast. They have the same consistency and injection properties as their Zyderm and Zyplast counterparts but are grown from a single human fibroblast cell culture, and unlike other human-derived products (Dermalogen and Cymetra), they are not cadaveric in nature. They are the result of tissue-engineered technology and have undergone extensive pathogen screening for viral and bacterial contamination, to avoid the possibility of disease transmission. As with many of the injectable hyaluronic acids, these products are non–animal-based and have the significant advantage that they do not require initial skin testing to exclude the risk of hypersensitivity before administration. Hence, they can be injected on the same day as the initial consultation. Like Zy-derm I, CosmoDerm 1 has a collagen concentration of 35 mg/ml and is placed into the superficial papillary dermis, with a comparable degree of blanching and overcorrection. It is also primarily indicated for superficial lines and defects. CosmoDerm 2 is 65 mg/ml of product and is applicable to moderate folds and defects. CosmoPlast, like Zyplast, is the most robust of the three forms and contains 35 mg/ml of human-derived collagen cross-linked with 0.0075% glutaraldehyde, which not only increases its durability but also makes it less immunogenic. It is a dermal implant suitable for more substantial folds. Because it is a deeper implant and can be applied to a depth of approximately 2 mm, it does not require overcorrection to improve the defect.

INDICATIONS FOR SOFT-TISSUE AUGMENTATION WITH COLLAGEN

It had been speculated that with the addition of many new fillers, the use of collagen would become outdated. This may have been substantiated by the statistics provided by the American Society for Aesthetic Plastic Surgery in 2004. It was specifically reported that the use of hyaluronic acid fillers increased 700 percent,15 but this should be interpreted correctly. This was the first year that hyaluronic acids were commercially available and included in the survey. What is of paramount importance is that, in fact, the use of all fillers increased significantly. While collagen products may not retain the distinction as the accepted standard, they similarly will not become veritable dinosaurs and face extinction. Their utility lies in the fact that they contain anesthesia and are only mildly uncomfortable upon administration; they have three different concentrations and are therefore diverse, and they have an unparalleled safety history.

Botox (botulinum toxin type A; Allergan, Irvine, Calif.) has become the treatment of choice for dynamic wrinkles in the upper third of the face. The use of Botox in the lower half of the face can be unforgiving; therefore, soft-tissue augmentation alone or in conjunction with small doses of Botox remains the preferred treatment.16 Perhaps the greatest use for collagen remains lip augmentation. The lips are a central focus of the face and are one of the most requested sites for soft-tissue augmentation. The collagen products (Zyplast and CosmoPlast) are an excellent treatment option. Unlike other fillers, they do not require additional injectable anesthesia, and topical preparations sufficiently reduce the injection discomfort; they flow well along the potential space of the vermilion border without inciting too
much edema, and they do not cause significant bruising. Hence, not only are they user-friendly for the physician, but the procedure and the results are not too overwhelming for the patient, especially the first-time patient with little experience with injectables. However, both the patient and the physician should be well versed in the characteristics of the selected agent (Fig. 2). Other areas that are specifically amenable to treatment with collagen (Zyderm I or CosmoDerm 1) include the static superficial periorbital (Fig. 3) and perioral lines (Fig. 4) that radiate from the eyes and lips (lipstick lines). Nondynamic lines that remain after inactivation with botulinum toxin in the glabella and forehead may be treated with Zyderm I or II or CosmoDerm 1 or 2. The oral commissures, vermilion borders, and nasolabial creases are best suited to the thicker products; Zyplast or CosmoPlast, as the non–cross-linked products, do not provide sufficient long-term augmentation (Fig. 5). Nasolabial folds that are very deep may require two agents: a thick product such as Zyplast or CosmoPlast, or even a hyaluronic acid, may be initially placed in the deeper dermis, and a non–cross-linked product such as Zyderm I or CosmoDerm 1 may be simultaneously layered superficially on top. This fully reduces the fold and may increase the longevity of the augmentation. Nonactive, shallow, soft, distensible scars caused by trauma, surgery, or infection, such as varicella or acne vulgaris, respond well to any of the forms of collagen.

Fig. 2. A 24-year-old woman was offered, and agreed to, lip augmentation with “lamb’s collagen” at her hair salon. This resulted in deforming large subcutaneous nodules and granulomas that were painful, that impaired her phonation, and that were permanently irreparable. Biopsy and analysis of the injected product showed that it was approximately 37.75% silicone oil; the remainder consisted of impure contaminants.

Fig. 3. Combination/layering therapy. (Above) Periocular rhytides of a 50-year-old woman before treatment. (Center) Immediately after treatment with 15 U of Botox injected into the orbicularis oculi muscle, 0.25 cc of Zyderm I injected into the static lateral periocular rhytides, and 0.2 cc of Restylane (Medicis Aesthetic, Scottsdale, Ariz.) injected into the infraocular sulcus and inferior brow. (Below) The final result is effacement of both static and photodamaged wrinkles and tissue replacement of the entire periorbita.

While there are few absolutes with respect to selecting collagen, and there can be a great deal of personal physician preference, the one irrefutable contraindication is the use of the thicker fill-
ers, Zyplast and CosmoPlast, in the glabellar complex. The deeper placement required of these products has been associated with vascular compromise and sloughing of the skin (Fig. 6). It should also be kept in mind that the primary Food and Drug Administration indication for any of these collagen fillers is the glabrous (nonmucosal) skin in the perioral area.

**TREATMENT GUIDELINES**

Before any form of soft-tissue augmentation with collagen, it is recommended that patients abstain from medications that can inhibit platelet aggregation and potentiate ecchymosis for approximately 10 to 14 days before their appointment. After the patient signs an informed consent form that specifically relates to fillers, the area to be treated should be photographed, corroborated by the patient with a handheld mirror, and cleansed of all debris and makeup. Percutaneous injections can be painful, especially in the central face and perioral areas, and the patient should be offered anesthesia. Sufficient cutaneous anesthesia can be obtained with various topical preparations. Local anesthesia and nerve blocks are unnecessary, as all of the collagen products already have lidocaine present in the syringe. For adequate pain management, topical anesthetics can be applied liberally and left intact for 15 to 30 minutes. For further cutaneous penetration, occlusive dressings can be used.

Patients should be in a dependent or seated position with their heads upright, so that their lines and folds are accentuated and not blunted upon reclining. To further appreciate the defects, overhead lighting and magnification are helpful.

Before penetration of the skin surface, topical preparations and anesthetics should be removed in a nonabrasive manner with gauze, and then the filler can be injected. Although it is contingent on personal practice style, many physicians find it preferable to bend the needle to a 45-degree angle and insert it with the bevel up, gently and slowly inserting it through a pilosebaceous opening. The material can then be placed in the proper dermal location with the serial puncture technique, linear threading, or a combination of the two approaches. Serial puncture is performed by injecting small, discrete amounts of material at the leading edge of a previously placed deposit. This allows for very precise material placement, but at the expense of multiple punctate cutaneous entry points. Threading is one continuous uninterrupted injection that can yield a more even contour, but because it is more of a closed/blinded procedure, vascular accidents are more common. Postinjection massage helps to locate any residual skip areas, and ice applied to the treated area can reduce erythema and edema. Unlike many other facial procedures, the results are immediate, with few postprocedural restrictions. Patients can reapply makeup and promptly resume their normal daily activities.

**COMPLICATIONS**

A common source of frustration for patients receiving collagen injections is the temporary nature of the correction. The duration of implanted dermal filling substances depends on the volume used, the type of defect, and the mechanical stresses at the implantation site. Patient satisfaction is a combination of not only anatomic defect and physician expertise but also managing expectations. This can be tempered if patients are provided with a range of how long augmentation can be sustained. Although it is quite variable, in general, patients should be provided with a conservative range; they can reasonably anticipate 3 to 4

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**Fig. 4.** A 55-year-old woman (above) before treatment of her perioral rhytides and (below) after injection of 1.0 cc of CosmoPlast into the nasolabial folds, 1.0 cc of CosmoDerm 1 into the radiating “lipstick” vertical lines, and 4 U of Botox into the orbicularis oris muscle of the upper lip.
months of improvement, with gradual diminution of results as the implant descends from its intradermal site of location into the subcutaneous space. Some have found that with repeated treatments, subsequent augmentation has a longer duration. Patients can receive additional treatment or maintenance therapy at any time. To date, there have been very little scientific data in the literature on the use of CosmoDerm products, but it has been noted anecdotally that while the CosmoDerm products have better flow characteristics, which is advantageous for the physician, they allegedly have also been found to have a briefer duration of augmentation.

The adverse treatment responses for both classes of injectable collagen can be nonhypersensitive; in addition, for bovine collagen, hypersensitive reaction patterns may occur (Table 4). Many of the former are technique dependent and include injection-site ecchymosis, superficial placement with apparent beading, and deep placement with intravascular injury. Vascular occlusion following dermal placement of collagen presents as an immediate cutaneous blanch associated with pain. Immediate vasodilation with warm compresses and topical nitroglycerin can reduce the

Fig. 5. Frontal and lateral views before treatment of the perioral area (above) and after injection of 1.0 cc of Zyplast into the potential space of the vermilion border of the upper lip and Cupid’s bow and an additional 1.0 cc of Zyplast into the lateral oral commissures and vermilion of the lower lip (below). There is improvement in the atrophic senescent lip.

Fig. 6. Vascular embarrassment and subsequent cutaneous necrosis and slough in the glabellar area following injection of Zyplast bovine collagen.
vasospasm. Ultimately, if tissue necrosis and slough occur, sustained emotional support and wound care are essential to expedite resolution.

With bovine collagen, there are two forms of true classic type IV hypersensitivity to the implant. They develop in about 1 percent of those with two negative skin tests and who subsequently receive treatment. Caused primarily by Zyderm I and occurring approximately 2 weeks after treatment, the more common reaction is manifested by swollen, indurated granulomas at both the treatment and test sites. Although they resolve spontaneously and without permanent scarring, they can take up to 1 year to completely dissipate. In addition to reassurance, treatment has included nonsteroidal anti-inflammatory medications and intralesional injections of diluted corticosteroids (triamcinolone). There is anecdotal evidence that oral cyclosporine and topical immune modulators (tacrolimus) expedite resolution.18,19 Sterile abscesses are the second form of delayed hypersensitivity reaction that has been associated with bovine collagen. The incidence is low, approximately one to four in 10,000 treatments, and is due in large part to Zyplast (Fig. 7). This adverse reaction is characterized by the sudden onset of pain, usually a few weeks after injection, followed by tense edema and erythema with fluctuant nodules. The lesions can be treated by incision and drainage, intralesional steroids, and oral antibiotics, but scarring can occur. The circulating anti–bovine collagen antibodies that occur in these two scenarios do not cross-react with human collagen products. Furthermore, it is important to stress that there has been no statistical association between bovine collagen injections and the subsequent development of autoimmune connective tissue diseases. It should also be noted that all the bovine collagens are derived from the hides of a closed herd of American cattle; therefore, these cattle do not come into contact with animals exposed to prions that can cause bovine spongiform encephalopathy.20,21

**CONCLUSIONS**

Soft-tissue facial deformities and age-related cutaneous changes have a great effect on psychosocial interactions. There are many causes for these defects, and in the quest for maintaining and enhancing facial appearance, there is a correspondingly wide range of therapeutic options. Most of the vast array of available injectable dermal filler materials, and those on the horizon, are a safe and effective means to improving contour irregularities associated with aging and trauma. The newest class, the hyaluronans, will clearly have a significant role in facial contouring, because they tend to provide longer-lasting and perhaps more three-dimensional volume than collagen products. The collagen family of products, however, whether bovine, tissue engineered, or derived from an alternate source, will continue to be the mainstay in the ever-expanding filler arena.22 They have a significant historical track record; they are associated with little discomfort on administration; they are available in multiple concentrations and, therefore, are versatile, with the capability of being used synergistically with other injectables and facial cosmetic procedures; and they are not restricted to one anatomic area. Finally, with the proper injection technique, it remains an optimal ambulatory procedure, because there is little morbidity and high patient satisfaction, with the ability for patients to quickly resume their normal daily activities.

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**Table 4. Complications Associated with Use of Bovine Collagen**

- Localized hypersensitivity reaction
  - Granulomatous
  - Cystic
- Intravascular injection
  - Tissue necrosis
  - Vision loss
- Infection
  - Herpetic reactivation
  - Acneiform eruption
- Contour irregularity
  - Superficial placement: beading
- Duration and failure to meet patients’ expectations

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**Fig. 7.** Abscess/nodule formation as a hypersensitivity reaction to Zyplast, despite two confirmed negative skin tests.
DISCLOSURE
Seth L. Matarasso, M.D., has served as a consultant to Allergan (Irvine, Calif.), Inamed Aesthetics (Santa Barbara, Calif.), and Medicis (Scottsdale, Ariz.).

REFERENCES
Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations

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Background: Successful clinical application of dermal filler products requires an understanding of their physical characteristics and in vivo behavior. This study reviewed the data for hyaluronic acid dermal filler products derived from an animal source—the rooster comb.

Methods: A review of the hyaluronic acid literature was performed. Clinical experience with the animal-derived hyaluronic acid products was evaluated.

Results: The source of the hyaluronic acid has not been demonstrated to be a clinically important point of differentiation among filler products. Hypersensitivity reactions are rare and are also present in the products derived from bacteria. Variations that effect the hyaluronic acid products’ physical characteristics and clinical performance are more closely related to cross-linking and formulation. Hyaluronic acid gel derived from animal sources is cross-linked by a sulfonyl-bis-ethyl bond and is a soft gel compared with other hyaluronic acid products. There is minimal gel swelling, which results in modest postinjection edema. Optimal clinical application favors patients who desire quick recovery and minimal palpability.

Conclusions: Hyaluronic acid skin filler products derived from an animal source are safe and effective. Successful clinical application should be based on an understanding of the patient’s goals and the choice of a hyaluronic acid product with the optimal characteristics. (Plast. Reconstr. Surg. 120 [Suppl.]: 27S, 2007.)

There has been an unprecedented release of dermal filler products in the United States over the last several years. One category, the hyaluronic acids, was highly anticipated by both physicians and the general public because of the perception that they possessed many of the “ideal” filler qualities. However, our enthusiasm has eclipsed the science readily available to direct the clinical application of these products.

The hyaluronic acid products presently available utilize one of two general sources of raw material: rooster combs or bacteria. Although the merit of the hyaluronic acid source has been the subject of great attention and debate, many of the more important characteristics of the individual products have only recently been appreciated. The differences in rheologic characteristics and clinical performance are significantly more relevant to the application of these products. In this article, the available science of hyaluronic acid products derived from rooster combs (hylan B gel, distributed under the names Hylaform and Hylaform Plus; Inamed Aesthetics, Irvine, Calif.) is discussed.

HISTORICAL PERSPECTIVE

Hyaluronic acid was isolated from the bovine vitreous by Meyer and Palmer in 1934.1 It subsequently took decades to fully characterize this unique substance. It is now appreciated that hyaluronic acid participates in a variety of intercellular functions, such as inflammation, angiogenesis, wound healing, and malignancy.2 The function of hyaluronic acid that is most pertinent to soft-tissue augmentation is its contribution to the viscoelastic properties of connective tissue and skin.

FDA Status and Approved Uses: Hylaform and Hylaform Plus have received FDA approval and are indicated for injection into the mid-dermis to deep dermis for correction of moderate to severe facial wrinkles and folds.
The therapeutic applications of hyaluronic acid began in ophthalmology, with E. A. Balazs and others applying the viscoelastic properties of hyaluronic acid to eye surgery in the 1970s. Balazs et al. extracted a highly purified noninflammatory hyaluronic acid solution from rooster combs that has been available commercially as Healon. This non–cross-linked hyaluronic acid solution continues to be used in retinal and cataract surgery.

The first cross-linking of hyaluronic acid to form a gel was done in Sweden by Pharmacia AB in the 1960s using an epoxy cross-link, but the gel was not therapeutically useful because of its poor biocompatibility. In the 1980s, Balazs et al. produced the first biocompatible gel. The hyaluronic acid was isolated from the rooster comb and then cross-linked with divinyl sulfone to create a sulfonyl-bis-ethyl bond. This non–water-soluble gel was subsequently known as hylan B gel. Hylan B gel, under the trade name Synvisc (Genzyme Biosurgery, Cambridge, Mass.), is one of the components used to supplement synovial fluid in the arthritic knee joint. Marketed under the name Hylaform, it has been used for skin augmentation in Europe since 1996 and received U.S. Food and Drug Administration approval in April of 2004. In its larger particle size, Hylaform Plus, it was approved by the Food and Drug Administration in October of 2004.

THE SIGNIFICANCE OF THE HYALURONIC ACID SOURCE

Hyaluronic acid has an identical structure in all vertebrates, but concern over protein and nucleic acid contamination during the extraction process has led to much discussion. A comparison of hyaluronic acid from Streptococcus zooepidemicus, rooster comb, human umbilical cord, and bovine vitreous sources shows the protein and nucleic acid content to be highest in human umbilical cord and lowest in bacterial and rooster comb. The DNA content and RNA content were similar for the rooster comb–and bacteria-derived hyaluronic acid, but the endotoxin content was higher for the rooster comb source. The molecular weight of the hyaluronic acid was the same in the bacteria and rooster comb sources in this study, but the starting molecular weight of hyaluronic acid from rooster combs used for Hylaform was two to three times that of the hyaluronic acid from the bacterial source used for Restylane (Medicis, Scottsdale, Ariz.).

The protein content of Hylaform and Restylane was examined in two European studies. An Italian study suggested the protein content of Restylane was four times higher than that of Hylaform. A similar conclusion was reached in a Swiss study in which Restylane demonstrated a greater protein and calcium content than Hylaform. The author suggested, however, that the protein content of the two products was proportional to their hyaluronic acid content, with Restylane containing roughly three times the hyaluronic acid as Hylaform. Restylane has been further refined since the publication of these articles.

The potential for hypersensitivity reactions to cross-linked hyaluronic acid products generated concern over protein and nucleic acid contamination. Micheels skin tested eight patients who had a reaction to the injection of Restylane or Hylaform. Two patients reacted to Hylaform, three reacted to Restylane, and three reacted to both. None of the patients who reacted to Hylaform demonstrated antiavian antibodies. The study theorized that steriometric manipulation of hyaluronic acid through cross-linking could result in a foreign-body reaction in humans.

The orthopedic literature similarly suggests that the occasional reaction to intra-articular hyaluronic acid preparations is due to the cross-linking process, not the source of the hyaluronic acid or contaminants. Animal studies further substantiate the potential immunologic reaction to cross-linked hyaluronic acid but not to non–cross-linked hyaluronic acid from the same source. However, the mechanism of the occasional reaction to hyaluronic acid in humans is still unclear.

RHEOLOGY AND CROSS-LINKING OF HYALURONIC ACIDS

Hyaluronic acid’s viscoelastic properties are determined by the length of the molecular chains, its concentration, the cross-linking, and particle size. A key component to understanding the behavior of hyaluronic acid is the non-Newtonian characteristic, where hyaluronic acid demonstrates decreasing viscosity with increasing applied force. This is important, because hyaluronic acid becomes less viscous when it is pushed through a syringe.

Other physical characteristics to describe the hyaluronic acid gels include gel hardness (G’), and the amount of swelling or accumulation of water that occurs after it is injected. These characteristics are summarized in Table 1 and can be used to make clinical decisions with regard to product choice. The harder the gel, the greater its ability to resist shear, and the greater its ability to exert a deformational force on the surrounding tissues for the correction of defects. However, palpability and a firmness to feel also increase with gel hard-
ness and could limit the potential for increasing this variable.

Hyaluronic acid concentration is also thought to contribute to greater longevity. It has been suggested, however, that the concentration in Restylane is lower than that stated because of the soluble hyaluronic acid component, which is quickly degraded, and dilution of the material during swelling or hydration.\(^\text{10}\) Swelling of the product causes a deformational force that could potentially result in tissue trauma and would appear to result in greater edema clinically.

### FACTORS AFFECTING THE DURATION OF THE COSMETIC EFFECT OF INJECTED HYALURONIC ACID

Our understanding of the factors affecting the duration of the cosmetic effect of injected hyaluronic acid continues to evolve. Both the breakdown and the displacement of injected hyaluronic acid appear to be important factors. Breakdown of injected hyaluronic acid is probably best understood by examining the biodegradation of native hyaluronic acid in the extra cellular matrix of the dermis. In the dermal tissues, hyaluronic acid forms a dense network comprising the extracellular matrix. The matrix is first broken down enzymatically or, more commonly, by reactive oxygen species and free radicals to release short hyaluronic acid chains from the matrix.\(^\text{16}\) Specific receptors on fibroblasts, macrophages, and keratinocytes then bind and internalize hyaluronic acid, where it is further degraded in lysosomes. Specific receptors can also move hyaluronic acid into the lymphatic system for eventual clearance from the circulatory system.\(^\text{17}\)

Injected hyaluronic acid forms a significant mass of cross-linked hyaluronic acid molecules, which can be thought of as similar to the extracellular matrix. It is theorized that the injected hyaluronic acid must be partially degraded from the injected mass to allow clearance from the dermis in a fashion similar to that of the hyaluronic acid of the extracellular matrix. The nature and density of the cross-linking, the concentration, and the particle size of the hyaluronic acid could be significant variables in determining the speed of degradation and, hence, the tissue residence time. Hylaform has a lower concentration of hyaluronic acid and a lower density of cross-linking than other injectable hyaluronic acid compounds, because the gel has reached equilibrium with water.\(^\text{18}\) Conversely, Restylane has a greater hyaluronic acid concentration and cross-link density before injection, but it “unwinds,” or swells, after injection. While swelling contributes to edema, continued swelling after injection could contribute to the duration of the cosmetic effect of Restylane.

In addition to breakdown and swelling of the injected mass, the cosmetic effect of hyaluronic acid also appears to be affected by displacement or dispersal of the injected hyaluronic acid. While the displacement is not completely understood, the clinical observation of botulinum toxin prolonging the cosmetic effect of Hylaform could suggest that displacement is an important factor in determining the duration of the cosmetic effect of hyaluronic acid.\(^\text{19}\) Therefore, decreasing the forces acting on hyaluronic acid, such as concomitant use of botulinum toxin, and increasing its ability to resist shear forces, such as increasing gel hardness, could increase the duration of the cosmetic effect.

Individual patient factors must also play a role in duration of the cosmetic effect, although there is only empiric evidence to suggest this. Individual variations of hyaluronic acid degradation could be driven by differences in the available reactive oxygen species and free radicals, associated inflammation,\(^\text{20}\) and medications.\(^\text{21}\)

### AVAILABLE HYLAFORM STUDIES

Few head-to-head studies have been performed with the various injectable hyaluronic acid products. Interpreting the results of the various individual studies is difficult because of variation
in study design, although consistent trends can be identified.

The biocompatibility and tissue residence time of Hylaform were demonstrated by Piacquadio et al. in a guinea pig model. An inflammatory response was seen by week 2 that diminished by week 9. At week 26, implant sites were palpable in only two of 16 implant sites; however, histologically, implant material was seen in 87 percent of the sites. By week 52, no implant sites were palpable, but 75 percent of sites still demonstrated material histologically.

Further examination of the residence time of Hylaform in dermal tissue was studied in guinea pigs using radiolabeling. Hylaform was detected at all time points through the final 6-month postinjection analysis, with the half-life estimated by linear regression to be 9.2 months.

Clinical evaluation of Hylaform was performed in a multicenter, open-label study conducted in 216 patients and 724 facial sites. Thirty percent of the sites received only one injection, 53 percent received a second touch-up, and 17 percent received a third injection. Both the physician and the patient performed live evaluations. The duration of effectiveness was predicted by linear regression at 21 weeks for wrinkles and folds versus 22 weeks for all scars. Patient assessment was 21 weeks for wrinkles and folds and 36 weeks for scars. The correction duration varied by anatomic area, with a 16-week duration for the nasolabial fold, 25 weeks for wrinkles on the cheeks, 39 weeks for scars on the cheeks, and 59 weeks for scars on the forehead.

A randomized, double-blind study of Hylaform to treat the nasolabial fold was designed to evaluate noninferiority to Zyplast (Inamed Aesthetics, Irvine, Calif.). This study has yet to be published but was submitted to the U.S. Food and Drug Administration and is available in the Hylaform package insert. A total of 261 patients were evaluated for improvement of the nasolabial fold utilizing a six-point scale, with both live and photographic assessment. After initial injection, one touch-up at 2 weeks was performed if less than one point of improvement was achieved. At 12 weeks, the photographic assessment showed results with Hylaform to be equivalent to those with Zyplast, with the peak effect at 2 weeks and both products returning to baseline by 12 weeks. No other studies have used this photographic method to evaluate the efficacy of hyaluronic acid, and the results of photographic assessment have often been incorrectly compared with the results of live assessment studies. The live investigator assessment of Hylaform showed that 85 percent of Hylaform patients and 90 percent of Zyplast patients had not returned to baseline at 12 weeks. This difference was not statistically significant. Adverse initial events included pain, erythema, edema, and bruising.

A randomized, controlled trial was performed with Hylaform Plus using the nasolabial folds in 96 patients. This study has also not been published and is found in the package insert. Touch-up treatments were not performed. In the photographic assessment, both Hylaform and Hylaform Plus patients had returned to baseline by 12 weeks. Utilizing live investigator assessment, 79 percent of Hylaform Plus patients had not returned to baseline at 12 weeks.

A recent survey of experienced injectors suggested that the average duration of the clinical result with Hylaform Plus was 4.4 months for the nasolabial folds and 3.5 months for the lips.

ADVERSE REACTIONS

In the study submitted to the Food and Drug Administration, 41 percent of the Hylaform patients demonstrated bruising, 35 percent had edema, and 63 percent experienced erythema. Hylaform Plus demonstrated bruising in 35 percent, edema in 52 percent, erythema in 76 percent, and lumps and bumps in 22 percent. The Hylaform Plus trial demonstrated sterile nodules in 1 percent of patients.

In a large clinical experience, Lowe et al. treated 438 patients with Hylaform and 271 patients with Restylane. Three patients had a delayed inflammatory reaction at the injection site. Three more patients who had not received injections from Lowe et al. were referred for treatment. Four patients had undergone Hylaform injections and two had received Restylane. These reactions occurred 6 to 8 weeks after hyaluronic acid injection. The authors noted the duration of the nodules was 6 to 24 weeks, with three patients requiring steroid injection.

Michiels treated 219 patients with hyaluronic acid products (133 patients were treated with Restylane and 106 were treated with Hylaform). Eight patients had a delayed reaction of redness, pruritus, and painful swelling of the treated areas. The Hylaform patients showed a negative anti–chicken protein antibody titer.

I have had two delayed inflammatory reactions in more than 722 hyaluronic acid injections. One patient received Restylane and one patient received Hylaform Plus. Oral steroids were effective in the Restylane patient but not in the Hylaform Plus patient. Hyaluronidase was subsequently injected three times and appeared to be effective.
CLINICAL APPLICATION OF ANIMAL-BASED HYALURONIC ACID PRODUCTS

My staff and I used all Food and Drug Administration-approved skin fillers in 933 injections over a 19-month period. Our enthusiasm and indications for each skin filler product changed significantly during that time. As more products become available, treatment algorithms will continue to evolve.

Our collective experience has concluded that no single filler product is suitable for all patients and all anatomic applications. Multiple variables should be evaluated in every patient to define the proper treatment plan. In addition to the analysis of the patient’s anatomic concerns and the expected aesthetic result, the patient’s expectations with regard to downtime, the potential adverse events, and the duration of the result must be managed effectively. The patient’s history with the various injectable products should be reviewed, so that an attempt can be made to choose products that will minimize any previous source of patient concern.

There is minimal postinjection edema with the animal-based Hylaform family of products. For those patients who need to return to function faster, these products could be desirable. The relative decrease in edema is probably due to the absence of in vivo swelling. The analogy has been made that the Hylaform products are partially unwound or hydrated before injection. Clinically, this would suggest that a larger volume of Hylaform should be injected for a given correction, relative to Restylane. Optimally, evaluation of all injections is suggested at about 2 weeks, with further treatment performed if needed to achieve the optimal aesthetic correction. This appears to enhance patient satisfaction and the duration of the cosmetic result.

The hardness, or G’, of the various products provides further characterization of the product. The wet vermilion of the lips and areas that need augmentation in the superficial dermis offer greater patient satisfaction when the product, such as the Hylaform family of products, has less hardness. The more challenging nasolabial folds are less appropriate for softer products. Harder products do better in deeper planes of injection and in anatomic locations such as the malar highlights and nasolabial folds.

Inhibition of product displacement and a synergy of the cosmetic effect can be achieved with the concomitant use of botulinum toxin in indicated areas, such as the radial lip lines and the glabellar lines. Multiple types of skin fillers are also used in a given patient, with various hyaluronic acid products used in addition to collagen products in more superficial dermal rhytides.

CONCLUSIONS

I have found the use of animal-based hyaluronic acid products to be safe and effective. However, no skin filler has universal application for all anatomic locations in all patients. While the marketing of fillers and the continuing evolution of filler products make the logical clinical application of fillers challenging, a scientific approach to the application of each skin filler can lead to an optimal treatment outcome and patient satisfaction.

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DISCLOSURE

Dr. Clark has received honorariums for participating in the Inamed Academy.

REFERENCES

9. Shiedlin, T., Bigelow, R., Christopher, W., et al. Evaluation of hyaluronan from different sources: Streptococcus zooplider-
Non–Animal-Based Hyaluronic Acid Fillers: Scientific and Technical Considerations

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Background: Recent advances in the technology and biocompatibility of the hyaluronans in all skin types mean that they are becoming the temporary facial filling agents of choice for many aesthetic physicians and surgeons.

Methods: The hyaluronan products that have been approved for clinical usage by the U.S. Food and Drug Administration and Health Canada were reviewed with respect to their composition, clinical effects and safety profiles, and potential complications.

Results: The currently approved accepted standard for the hyaluronan family of fillers of nonanimal bacterial origin includes Restylane and Perlane in the United States and Perlane, Restylane Touch, and SubQ in Canada. Also of nonanimal origin, Juvéderm 24HV, 30, and 30HV were approved by the Food and Drug Administration in June of 2006. Another bacteria-derived hyaluronan filler is Captique; the Hylaform group of hyaluronan fillers is of animal origin and appears to be similar in effect and longevity to Captique.

Conclusions: The remarkable biocompatibility of the hyaluronan group of agents in individuals of all skin types, allied with the superior aesthetic result and outstanding longevity of response, promises that patients will continue to demand these recent advances in filler technology. (Plast. Reconstr. Surg. 120 (Suppl.): 33S, 2007.)

There are a number of synthetic and natural filling agents at the aesthetic clinician’s disposal for creating a smoother, more youthful countenance. At the peak of popularity are hyaluronic acid gels that replace or enhance the body’s natural hyaluronic acid. Of the available products, nonanimal stabilized hyaluronic acid (or NASHA) is one of the products least likely to produce allergic reactions; it is available in several forms for specific indications and areas. Used to improve both fine and deeper lines and furrows, increase volume, or sculpt the face, nonanimal stabilized hyaluronic acid is more durable than injectable collagen, easy to manipulate, and well tolerated, thereby providing a superior aesthetic improvement.

HYALURONANS

Found naturally in the skin, hyaluronic acid is a glycosaminoglycan biopolymer that provides structure and holds moisture within the dermis. During the aging process, the amount of natural hyaluronic acid decreases, leading to dermal dehydration and rhytide formation. Hyaluronic acid gels (hyaluronans) were developed for soft-tissue augmentation by cross-linking hyaluronic acid chains. When injected into the dermis, these gels join forces with the body’s own hyaluronic acid to create support and add volume for a period of 4 to 12 months before undergoing degradation and

FDA Status and Approved Uses: Restylane is U.S. FDA approved and indicated for mid- to deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Restylane Fine Lines and Restylane SubQ are not yet U.S. FDA approved but are approved in Canada. Juvéderm 18, Juvéderm 24, and Juvéderm 30 (including the HV formulations) and Captique are all FDA approved. The Juvéderm family is approved in Canada also, but Captique is approved only in the United States. CosmoDerm and CosmoPlast are both U.S. FDA and Health Canada approved.

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clearance by the liver. Each hyaluronic acid gel is stabilized before use in cosmetic enhancement; the stabilization process varies according to manufacturer and explains differences in product longevity and viscosity.

There are a number of advantages associated with hyaluronans, including longer duration of effect, for less frequent touch-ups than injectable collagen, and a low level of hypersensitivity (ideal for patients who are allergic to bovine collagen). Treatment with hyaluronans is easy and quick and can be performed in as little as 30 minutes. The effects are immediate, there is little to no recovery time, and the clinical effects persist for up to a year, depending on the product and density of the hyaluronic acid used.

There are both non–animal- and animal-based hyaluronic acid gels on the market today. One advantage of non–animal-based gels is the small risk of hypersensitivity to, for example, avian proteins; for this reason, many patients prefer them to other animal-based products.

**NONANIMAL STABILIZED HYALURONIC ACID**

There are a number of non–animal-based hyaluronic acid derivatives from which to choose, including Restylane, Restylane Fine Lines, Perlane, and Restylane SubQ (Q-Med, Uppsala, Sweden); Juvéderm 18, Juvéderm 24, and Juvéderm 30 (including the HV formulations; Allergan, Irvine, Calif.); and Captique (Allergan, Irvine, Calif.).

Available in Europe since 1996 and in Canada since 1998, Restylane is produced by bacterial fermentation from a specific strain of streptococci and has been in clinical use for more than 10 years. Approved by the U.S. Food and Drug Administration in December of 2003 for the correction of moderate to severe facial wrinkles and folds, Restylane is now used in more than 60 countries. Designed for injection at different layers of the skin (Fig. 1), each form of Restylane differs in the size of the gel particle (Table 1) and is packaged in sterile, ready-to-use syringes.

Restylane, considered by some to be close to the “ideal” filler, gives a clinical effect that lasts from 4 to 6 months before it is reabsorbed. Perlane may last longer, but more mobile areas (i.e., the lips) usually require touch-ups after 6 months. Perhaps because of its increased particle size, Perlane is associated with more initial swelling and redness compared with Restylane; this reaction (the mechanism of which is not fully understood) can be reduced by the administration of systemic corticosteroids.

Hailing from France and used in the United Kingdom since 2001, Juvéderm is of nonanimal origin and is used in the same areas. Juvéderm 18 works on fine lines (i.e., crow’s feet and perioral rhytides). Juvéderm 24 targets mild to moderate wrinkles (i.e., forehead rhytides, glabellar lines, and mild to moderate nasal furrows), and Juvéderm 30 is used for lip augmentation and to fill deep folds and sculpt the cheeks. The duration of clinical effect for both the Juvéderm and Restylane products is similar. Juvéderm has more recently been introduced in 24HV and 30HV forms (Juvéderm Ultra and Juvéderm Ultra Plus, respectively) in the United States. The HV products are distinguished from the regular Juvéderm by a greater degree of cross-linking and the presence of some non–cross-linked hyaluronic acid as a lubricant.

In December of 2004, the U.S. Food and Drug Administration approved Captique, a new bacteria-derived hyaluronan, for the treatment of moderate to severe facial wrinkles and folds around the nose and mouth. A clear, colorless gel, Captique has characteristics and a safety profile similar to those of Hylaform, a cross-linked hyaluronic acid derived from chicken combs, and is produced by a similar method. It is our impression that the Hylaform/Captique products do not have the duration of Restylane or Juvéderm.

**CLINICAL EFFICACY**

In general, nonanimal stabilized hyaluronic acid has been proven to be an effective, safe, and well-tolerated method of facial rejuvenation. In one of the first studies conducted, Duranti et al. injected 158 patients for facial rhytides, lip augmentation, and/or recontouring with nonanimal stabilized hyaluronic acid and found that 78.5 percent of patients maintained a moderate to marked clinical improvement after 8 months. Photographic evaluation yielded even better results, with an 80.4 percent moderate or marked improvement after 8 months. Immediate, localized, transient side effects occurred in 12.5 percent of patients. Likewise, Bosniak et al. found that almost 61 percent of 1446 consecutive patients who underwent intradermal injection of nonanimal stabilized hyaluronic acid for the enhancement of lip volume and contour and the reduction of visible facial rhytides remained satisfied with results after 9 months. Duration of effect was longest in the glabellar and nasolabial fold areas. Only minimal transient side effects were noted. We studied the use of nonanimal stabilized hyaluronic acid injected using a standardized technique, with nerve block anesthesia to ensure patient comfort, in
15 women with prominent down-turned mouth corners. All women experienced an improvement in the appearance of mouth frown, particularly in the first 3 months after treatment, and 40 percent still noted improvement 6 months after treatment. Side effects included swelling, redness, and some local discomfort for several days after injection.

Results of comparative studies have suggested that the duration of effect associated with non-animal stabilized hyaluronic acid is superior to that of both collagen and animal-based hyaluronic acid. In a randomized, double-blind, multicenter trial that led to the Food and Drug Administration’s approval of Restylane, Narins et al. compared the efficacy and tolerability of Restylane and bovine collagen (Zyplast; Allergan/Inamed, Irvine, Calif.) in 138 patients with prominent nasolabial folds. Less injection volume was required to achieve an “optimal cosmetic result” with non-animal stabilized hyaluronic acid than with collagen. In addition, non-animal stabilized hyaluronic acid was superior in 56.9 and 62 percent on the Wrinkle Severity Rating Scale and Global Aesthetic Improvement Scale assessments, respectively, at 6 months. Side effects, such as lumpiness and the appearance of nodules, were greater in patients treated with collagen; however, swelling, tenderness, pain, and bruising were more frequent in those injected with non-animal stabilized hyaluronic acid. In the first direct comparison of non-

**Table 1. Available Forms of Restylane**

<table>
<thead>
<tr>
<th>Product</th>
<th>Gel Particles/ml</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restylane Touch</td>
<td>200,000</td>
<td>Fine superficial wrinkles</td>
</tr>
<tr>
<td>Restylane</td>
<td>100,000</td>
<td>Larger wrinkles and lip augmentation</td>
</tr>
<tr>
<td>Perlane</td>
<td>8000</td>
<td>Deep folds, scars, and volume augmentation</td>
</tr>
<tr>
<td>Restylane SubQ</td>
<td>1000</td>
<td>Chin or cheek augmentation</td>
</tr>
</tbody>
</table>
animal stabilized hyaluronic acid (Perlane) and hylan B gel (Hylaform) in 150 patients with moderate or severe nasolabial folds, we found that fewer treatment sessions were required with nonanimal stabilized hyaluronic acid to achieve an “optimal cosmetic result.” At 6 months after treatment, a higher proportion of patients injected with nonanimal stabilized hyaluronic acid showed an improvement of one grade or more on the Wrinkle Severity Rating Scale than those treated with hylan B; nonanimal stabilized hyaluronic acid was considered superior in 64 percent of patients. Treatment-related adverse effects (swelling, pain, and redness) tended to occur more frequently in patients treated with nonanimal stabilized hyaluronic acid but were transient and mild to moderate in intensity.

GENERAL CONSIDERATIONS

Nonanimal stabilized hyaluronic acid can be used to fill wrinkles, creases, furrows, and scars, as well as for tissue augmentation. The type of gel used will vary according to the depth of the defect to be treated. Topical anesthetic may be sufficient in certain areas (i.e., crow’s feet region and forehead); however, a local nerve block in combination with a topical anesthetic is recommended for maximal patient comfort, particularly in the lips and around the perioral area. Injections are placed in the middle to deep dermis (except in the lips, where injections are intramuscular, rather than dermal) using 27- to 30-gauge needles, depending on the viscosity of the gel. Heavier gels may be injected deeply, followed by lighter gels placed more superficially in a layering technique for optimal effect. Injection too superficially can cause the appearance of nodules or other irregularities; likewise, injection too deep may be ineffective. Care must be taken to avoid injection into a blood vessel, especially in the periocular region.

Injections into dynamic areas associated with a great amount of movement, such as the perioral region, may lead to less satisfactory results, as the motion will encourage absorption. Subperiosteal injections are not recommended, because injection in this plane is hard to achieve and painful. Injection above the periosteum is very favorable for hyaluronans, and reinflation of natural fat pads, such as the brow, malar, buccal, and mental fat pads, can be long-lasting and well tolerated.

Although hyaluronans provide greater persistence of effect than injectable collagen, they are still similar to natural components of the skin and, as such, will gradually break down and be absorbed, necessitating periodic touch-up treatments to maintain the desired outcome. If insufficient product is injected at the initial treatment session, approximately 80 percent of patients will require a second treatment session 2 to 4 weeks after the initial treatment to build the tissue contours to the desired degree.

INJECTION TECHNIQUES

Technique varies among clinicians; however, it should be noted that complications are often directly related to inexperience in technique and practices. Since the majority of our clinical experience rests with Restylane and Perlane, the remainder of this article refers to those products specifically, unless otherwise noted.

Fine Lines and Rhytides

When used for the treatment of fine to deep lines in the glabella, cheek, and perioral region, nonanimal stabilized hyaluronic acid is injected with a serial puncture technique in the mid-dermis or higher (Fig. 2). We usually use Restylane or Hylaform in the glabella. More often, a combined approach using botulinum toxin type A ex-

Fig. 2. Serial puncture technique in the glabella.
tends the average cosmetic response time from 16 to 18 weeks to 32 weeks, further enhancing subject satisfaction (Fig. 3).

Fine lines around the mouth are often called “lipstick lines,” and women dislike the cosmetic blemish when lipstick proceeds into their cutaneous lip up those lines. We prefer to outline the vermilion cutaneous junction with a collagen product such as CosmoDerm or CosmoPlast (both from Allergan, Irvine, Calif.) and then fill the vermilion lip with a hyaluronan, but hyaluronans, especially Restylane Fine Lines, can be used. After the initial injection, we evaluate the radial lines; by this point, they are often fairly well supported from “behind.” For any residual radial lip lines, we inject CosmoDerm using the serial puncture technique, avoiding reduction of lip projection.

**Nasolabial Folds**

To treat deeper rhytides such as nasolabial folds, we use a heavier nonanimal stabilized hyaluronic acid gel (i.e., Perlane) (Fig. 4). Some clinicians prefer to use a threading technique when injecting in this area, concentrating on the area below the nares and lateral to the ala. It is important to note that the closer one injects to the corner of the mouth, the shorter the duration of effect because of increased mobility.

**Lip Augmentation**

Nonanimal stabilized hyaluronic acid is an ideal product for lip augmentation, one of the most frequently requested procedures (Fig. 5). Since lip injections are painful, many clinicians use nerve blocks or vibration before treatment; others provide patients with 30 mg of prednisone to be taken both before and after treatment to minimize the swelling that is so prevalent after perioral treatment with fillers. The needle is inserted through the lip mucosa close to the ver-
milium, and the plunger is depressed gently. The “push-ahead” technique (using the filler to dissect the area in front of the needle and moving blood vessels out of the way) will reduce the amount of bruising commonly experienced when injecting into the perioral region. Injections are spaced along the length of the lips within the vermilion border, with a total of five to six injections per lip. A lighter gel, such as Restylane Fine Lines, injected more superficially along the vermilion border will create a line of firmness that will define the lip border and resist wrinkling. After injection, gentle massage will help disperse the filler for a smooth and even result. Ice applied for 5 to 20 minutes after injection may reduce swelling.

**Brow Lifts and Facial Contouring**

Nonanimal stabilized hyaluronic acid is an ideal filler to replace volume lost naturally through the aging process in the brow and midface, and it can be used to produce brow lifts, soften the hollows beneath the eyes, enhance cheekbones, sculpt the jaw, and augment the chin. Injections are placed deep in these areas after topical anesthesia using a 30-gauge needle and the “push-ahead” technique described above to minimize bruising (always a risk when injecting deeply).

**COMPLICATIONS**

Most of the side effects of nonanimal stabilized hyaluronic acid are transient and mild and include pain and intermittent swelling, edema, and erythema at the injection site.\(^8\) By far the most common reactions are localized hypersensitivity reactions (Fig. 6), some of which may be delayed by months after treatment. Lowe et al. followed 709 patients treated with Hylaform and Restylane for at least a year and found six patients who developed delayed skin reactions approximately 8 weeks after injection; in four of the five patients tested, results of challenge intradermal skin testing were positive.\(^12\) It is believed that these occurrences are related to protein content in the hyaluronic acid raw material. In a retrospective review of all adverse events data from Europe, Canada, Australia, South America, and Asia from 1999 and 2000, data from more than 400,000 patients treated with nonanimal stabilized hyaluronic acid were examined.\(^13\) In 1999, localized hypersensitivity reactions occurred in approximately one in 1400 patients and adverse events were reported in one in 650 patients (0.15 percent). In 2000, when the amount of protein in the raw product decreased, those numbers fell to one in 5000 for hypersensitivity reactions and one in 1800 for adverse events (0.06 percent). A retrospective study evaluating the incidence of adverse reactions after aesthetic nonanimal stabilized hyaluronic acid injections from 1997 to 2001 described similar findings, with an overall 0.8 percent global risk of

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**Fig. 5.** Before and after lip augmentation with nonanimal stabilized hyaluronic acid.

**Fig. 6.** Localized hypersensitivity reaction after treatment with nonanimal stabilized hyaluronic acid.
hypotheses reactions, of which 50 percent were immediate and resolved in less than 3 weeks.\textsuperscript{14} The rate of delayed reaction was 0.3 percent. After 2000, the incidence of hypersensitivity reactions fell to 0.6 percent. There were no bacterial infections or systemic reactions reported, although herpetic recurrence was possible after lip augmentation due to reactivation of latent herpes virus. We follow standard prophylaxis, with 500 mg of Val- trex (Glaxo Smith Kline, St. Louis, Mo.) twice daily on the day of treatment; we also offer a prescription for 10 days of twice-daily Valtrix to follow, if necessary.

There have been three recent reports of serious granulomatous reactions\textsuperscript{10,15,16} and one case of angioedema-type hypersensitivity following treatment of the upper lip.\textsuperscript{17} Again, the use of impure or contaminated material contributes to the development of infection or a foreign-body reaction.\textsuperscript{18} While granulomas often respond to injected corticosteroids, topical antihistamines, and digital pressure or manipulation,\textsuperscript{10} patients must be advised of the potential risk, as this reaction can have negative aesthetic implications.

**CONCLUSIONS**

One of the most popular products in cosmetic noninvasive facial enhancement, nonanimal stabilized hyaluronic acid targets fine and deeper rhytides and scars and boosts lost volume in the face and lips. As a naturally occurring substance in the body, nonanimal stabilized hyaluronic acid has a low risk of allergic reaction, requires no skin testing before injection, is easy to use and mold, and is more durable than collagen. Moreover, the cross-linked nature of the hyaluronic gel lends itself to a highly versatile product that can be used in multiple forms and treatment areas. Most side effects are transient and mild; more serious adverse events are likely related to oligopeptide contamination of the product or inexperience with injection techniques. In the hands of an experienced clinician, however, nonanimal stabilized hyaluronic acid is a safe and effective choice for facial re-shaping and rejuvenation.

*Drs. Alastair and Jean Carruthers are consultants and investigators for and receive honoraria from Allergan, Inc.; stock holders and members of the advisory board for Artes Medical, Inc.; consultants and investigators for Bioform Medical, Inc.; investigators for BioPelle (formally Ferndale Laboratories, Inc.); consultants and investigators for and receive honoraria from Medici, Inc.; consultants and investigators for Merz Pharmaceuticals; investigators for Organogenesis, Inc.; investigators for Q-Med; and members of the advisory board for Solstice Neurosciences. In addition, Dr. Jean Carruthers is on the advisory board for Lumenis, Inc. Dr. Alastair Carruthers is an investigator with Richard James, Inc., and is on the advisory board for and receives honoraria from Unilever Canada.*

**REFERENCES**

14. Andre, P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA – Q-Medical, Sweden) in European


The Role of Hyaluronic Acid Fillers (Restylane) in Facial Cosmetic Surgery: Review and Technical Considerations

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Dallas and Houston, Texas; and Los Angeles, Calif.

Background: Bioengineered hyaluronic acid derivatives are currently available that provide for safe and effective soft-tissue augmentation in the comprehensive approach to nonsurgical facial rejuvenation. Current hyaluronic acid fillers do not require preinjection skin testing and produce reproducible, longer-lasting, nonpermanent results compared with other fillers, such as collagen.

Methods: A review of the authors’ extensive experience at the University of Texas Southwestern Medical Center was conducted to formulate the salient requirements for successful utilization of hyaluronic acid fillers. Indications, technical refinements, and key components for optimized product administration categorized by anatomical location are described. The efficacy and longevity of results are also discussed.

Results: Bioengineered hyaluronic acid fillers allow for safe and effective augmentation of selected anatomical regions of the face, when properly administered. Combined treatment with botulinum toxin type A can enhance the effects and longevity by as much as 50 percent. Key components to optimal filler administration include proper anatomical evaluation, changing or combining various fillers based on particle size, altering the depth of injection, using different injection techniques, and coadministration of botulinum toxin type A when indicated. Concomitant administration of hyaluronic acid fillers along with surgical methods of facial rejuvenation can serve as a powerful tool in maximizing a comprehensive treatment plan.

Conclusions: Current techniques in nonsurgical facial rejuvenation and shaping with hyaluronic acid fillers are safe, effective, and long-lasting. Combination regimens that include surgical facial rejuvenation techniques and/or coadministration of botulinum toxin type A further optimize results, leading to greater patient satisfaction.

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Plastic Surgeons demonstrated a 150 percent increase from 2002 in the use of soft-tissue fillers, with 744,283 procedures performed in this nonsurgical category.¹² Soft-tissue fillers are particularly attractive to younger, middle-aged patients who display minimal to moderate signs of facial aging and who want minimal downtime.

FDA Status and Approved Uses: Restylane is FDA approved as an injectable gel to treat facial wrinkles. Juvederm is FDA approved. The three product formulations include Juvederm 24 HV, a highly cross-linked formulation for more versatility in contouring and volumizing of facial wrinkles and folds; Juvederm 30 HV dermal filler, a more highly cross-linked...
As the search for an ideal filler material continues, hyaluronic acid derivatives have gained popularity among aesthetic surgeons because of their numerous advantages. An ideal filler material is one that is biocompatible, nonantigenic, nontoxic, easy to use, long-lasting (yet nonpermanent), inexpensive, and reversible. It should demonstrate a high safety profile and produce a predictable result with minimal downtime.

Many of the new fillers available for use in the United States are longer-lasting and have shifted the paradigm between permanent and nonpermanent fillers. Use of permanent or "more permanent" fillers allows less room for error and can produce irreversible changes in facial shape that may not retain the aesthetic changes as the patient ages. With the introduction of hyaluronic acid derivatives for use in soft-tissue augmentation, a safer, longer-lasting, and yet temporary alternative has been made available.

**WHAT IS HYALURONIC ACID?**

Hyaluronic acid is common among many organisms and is present in connective tissues of skin, cartilage, bone, and synovial fluid. Hyaluronic acid is unique in that it is natively present in the intracellular matrix of the dermis and identical in form in all mammalian species. In human skin, it aids in bulk, lubrication, and shock absorption. Its viscoelastic properties and role in cell membrane protection and stabilization make it a natural choice for dermal soft-tissue augmentation. The amount of hyaluronic acid residing in native tissue decreases with age, leading to reduced dermal hydration and increased folding.

Hyaluronic acid is a glycosaminoglycan biopolymer of alternating D-glucuronic acid and N-acetyl-D-glucosamine monosaccharide residues cross-linked into long, repeated, unbranched polyanionic chains. The repeating chains are hydrated and coil upon themselves, providing the substance with elasticity and viscosity. Hyaluronic acid acts by binding water molecules, which leads to increased skin hydration and turgescence. Its hydrophilic properties help the product maintain its volume and viscoelasticity when it is injected.

Exogenous hyaluronic acid is rapidly eliminated by lymphatics and degraded in the liver to carbon dioxide and water. Without cross-linking, the tissue half-life is only 1 to 2 days. Manufacturers, therefore, have had to modify the physical and chemical properties to allow long-lasting results.

The goal of bioengineered hyaluronic acid is to improve its stabilization via increased tissue residency, viscosity, and elasticity while preserving its innate biocompatibility. The bioengineered hyaluronic acid derivative is chemically cross-linked, which alters its solubility and rheological profile so that it becomes a more viscous, water-insoluble gel. This process has dramatically improved its stability when it is injected into tissue. The hyaluronic acid gel properties are, therefore, controlled by varying the molecular weight, concentration, and degree of cross-linking. This process helps retain the biological compatibility of the native polymer, slow its dissolution rate, and increase its residence time when it is injected into dermis.

Hyaluronic acid derivatives first received Food and Drug Administration approval in the United States for soft-tissue augmentation in December of 2003 with the introduction of Restylane (Medicis Aesthetics, Inc., Scottsdale, Ariz.) followed by Hylaform (Inamed, Santa Barbara, Calif.) in April of 2004, Hylaform Plus in October of 2004, and Captique (Allergan, Santa Barbara, Calif.) in December of 2004. The majority of the long-term experience with these filler products can be found in both the European and Canadian literature, with up to 9 years of experience in more than one million patients. The hyaluronic acid derivatives available in these countries include Hylaform Gel, Hylan Rofilan Gel, Achyal, Restylane, Restylane Fine Lines, and Perlane. These various hyaluronic acid derivatives differ in particle size, molecular weight, and degree of cross-linking, making each optimal for injection into specific dermal layers and facial regions (Table 1).

For example, Restylane Fine Lines is a lower-density, less viscous filler that is indicated for the more superficial dermis (dermoeepidermal junction), whereas Restylane is composed of medium-density particles, more viscous, and better suited for augmentation of the mid-dermis. Perlane is a high-density, longer-lasting hyaluronic acid filler,
that is very useful for deep dermal injection. Perlane is currently the largest hyaluronic acid compound available. Perlane is an effective, long-lasting filler indicated for augmentation of the deeper dermal level. However, thicker hyaluronic acid fillers (i.e., larger particle size) can be less forgiving in more superficial dermal layers and can produce lumpiness and more erythema if caution is not used.

**COMMERCIALY AVAILABLE HYALURONIC ACID PRODUCTS (UNITED STATES)**

**Restylane**

Restylane is a partially cross-linked hyaluronic acid derivative obtained from a bacterial (*Streptococcus*) fermentation process that forms a viscoelastic, transparent gel. Because it is a non-animal-derived compound, there is no risk of transmitting diseases and minimal risk of allergic reactions, so the need for preinjection skin testing is eliminated. As with other bioengineered hyaluronic acid derivatives, Restylane binds water with great affinity and can maintain its bulk as it undergoes “isovolemic degradation.” This stability is provided by the high degree of cross-linking, which allows for its long-lasting effect (up to 4 to 6 months, depending on the location and injection technique).17 Restylane is indicated for mid- to deep dermal implantation for moderate to severe facial wrinkles and folds/nasolabial folds.14,17 Restylane is provided in 0.4-ml and 1.0-ml preloaded, 30-gauge, 1.5-inch-long needle syringes containing 20 mg/ml of stabilized hyaluronic acid.18,19 The product syringes have a shelf life of 1.5 years.

**Hylaform/Hylaform Plus**

Hylaform and Hylaform Plus, both hyaluronic acids derived from avian proteins, were approved by the Food and Drug Administration in April and October of 2004, respectively.15 These products are indicated for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles and folds. Both products are supplied in individual treatment syringes, with 30-gauge needles packaged for single-patient use and ready for injection. Each syringe contains a solution of hyaluronic acid gel mixture (5.5 mg/ml), sodium chloride (8.5 mg/ml), and water. Hylaform Plus has a larger particle size compared with Hylaform.15,20–22 As with other hyaluronic acid derivatives, no skin testing is required.

**Juvederm**

Juvederm (Allergan, Inc., Irvine, Calif.) was approved by the Food and Drug Administration in June of 2006 for use as a dermal filler. The makers of Juvederm consider it to be “next generation” hyaluronic acid–based dermal filler.22 It possesses all the benefits of a hyaluronic acid–based filler and reportedly comes in a smooth gel form that is different from other hyaluronic acid fillers that use particle suspension technology.22 In addition, the manufacturer states that it contains the highest concentration of nonanimal and cross-linked hyaluronic acid currently available.22 There are three formulations available; Juvederm 24 HV, a highly cross-linked formulation; Juvederm 50 HV dermal filler, a more highly cross-linked robust formulation intended for deeper filling; and Juvederm 30, for more shallow and superficial dermal augmentation.

**Captique**

Captique is a newer hyaluronic acid derivative, manufactured and packaged in the same manner as Hylaform. It was approved by the Food and Drug Administration in December of 2004 based largely on the approval of Hylaform. Captique differs from Hylaform in that it is derived from a bacterial source rather than an avian source. Captique is indicated for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles.13,22

**Efficacy**

The efficacy of hyaluronic acid fillers has been demonstrated in numerous clinical trials. Olenius16 found in his series of 100 patients treated with Restylane that 60 percent of the effect was present at the 12-month follow-up. In a prospective, randomized, controlled study using a non–animal-sourced hyaluronic acid [or NASHA (Restylane)] in combination with botulinum toxin type A (Botox; Allergan,
Irvine, Calif.), Carruthers and Carruthers demonstrated an improved and longer-lasting aesthetic response for glabellar rhytides when Restylane was used in combination with Botox. At a follow-up of 16 weeks, 83 percent of the Restylane group, compared with 95 percent of the Botox/Restylane group, had aesthetic improvement. This finding may be explained by the reduction in dynamic muscle action that could reduce filler deformation within the dermis. In addition, the subjects in the study commented on more “instantaneous” results when Restylane was added to Botox treatment for severe glabellar folds.

In a pivotal one-to-one randomized, double-blind, multicenter trial, Narins et al. compared the efficacy of Zyplast (bovine collagen [Allergan, Santa Barbara, Calif.]) to that of Restylane in the treatment of nasolabial folds. Using a Wrinkle Severity Rating Scale and a Global Aesthetic Improvement Scale, the authors found that Restylane required less volume and fewer treatments to achieve an “optimal cosmetic result,” as evaluated by blinded investigators. In addition, both Restylane and Zyplast demonstrated a similar safety profile.

The pivotal trial for Hylaform compared the safety and efficacy of Hylaform viscoelastic gel with those of Zyplast for the correction of nasolabial folds in a prospective, multicenter, randomized, double-blind, parallel-group study conducted during an initial 12-week treatment phase. Hylaform gel was found by an independent review of photographs to be equivalent to Zyplast (control filler) in the correction of nasolabial folds. As of this writing, there have been no clinical trials involving the use of Captique; Food and Drug Administration approval of this product was based on trials involving other hyaluronic acid fillers.

**LONGEVITY**

One significant advantage of hyaluronic fillers over more traditional nonpermanent fillers, such as fat and collagen, is their increased tissue longevity (Table 2). In our clinical experience, the purported longevity of 6 months has not been seen in all areas of injection. In the tear trough, malar, and glabellar regions, the longest longevity we have seen has been approximately 6 months. This has been enhanced to as long as 9 months with concomitant Botox treatment in the glabellar and forehead regions. In the nasolabial fold, adjunctive injections are usually necessary within 4 to 6 months and are required less often as injection sessions proceed. A layering technique in this area can also prolong injection intervals. The shortest duration, of approximately 3 to 4 months, has been seen in the lip region in our patients, chiefly in long-lip patients with minimal initial bulk. Before injection, all patients are informed of the inherent variability in duration of effect; this is a critical part of the informed consent process. Re-injections (not including touch-ups) of specific areas are usually performed 4 to 6 months after the initial injection. In our experience, an additive effect is evident as the number of injections increases. Often, progressively less product volume is required with each subsequent injection.

**INDICATIONS**

With aging, the skin loses its viscoelasticity, which is maintained in part through the innate properties of hyaluronic acid. Volume loss, especially in the lips, nasolabial, and malar regions, is seen with advanced age. Useful, more objective methods of rating the severity of facial rhytides and the corrective results have been described by Fitzpatrick et al., Glogau, and Lemperle et al. Lemperle et al. developed a 0- to 5-point rating scale to assess results after soft-tissue augmentation with fillers (Table 3).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Areas Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No wrinkles</td>
<td>Horizontal forehead lines</td>
</tr>
<tr>
<td>1</td>
<td>Just perceptible wrinkle</td>
<td>Glabellar frown lines</td>
</tr>
<tr>
<td>2</td>
<td>Shallow wrinkles</td>
<td>Periorbital lines</td>
</tr>
<tr>
<td>3</td>
<td>Moderately deep wrinkle</td>
<td>Preauricular lines</td>
</tr>
<tr>
<td>4</td>
<td>Deep wrinkle, well-defined edges</td>
<td>Cheek lines</td>
</tr>
<tr>
<td>5</td>
<td>Very deep wrinkle, redundant fold</td>
<td>Nasolabial folds, Radial upper lip lines</td>
</tr>
</tbody>
</table>

The lips and perioral region are the central aesthetic component of the lower third of the face. Lips express emotion, sensuality, and vitality. In evaluating the aesthetic lip, it is critical to assess the surrounding soft tissues as well as the maxillofacial harmony (Fig. 1). Some of the characteristics of an aesthetic and youthful lip are listed in Table 4 and shown in Figures 1 through 5. With aging, the lips undergo changes in vermilion bulk (pout) and exposure (thin lips) that can be exaggerated by bony retrusion and changes in denticion (Fig. 4). Patients who require subtle refinements in lip fullness, projection, and degree of eversion are ideal candidates for augmentation with hyaluronic acid fillers (Fig. 5). In addition, marionette lines, the deep mental groove, and the anterior jowl line must also be evaluated and augmented when indicated, to optimize overall lip and perioral aesthetics.

With increasing nasolabial fold depths, the face appears older and lacking in midface support. Hyaluronic acid fillers are ideal for blunting prominent nasolabial folds. Malar atrophy, resulting from fat, muscle, and skeletal atrophy, and soft-tissue descent contribute to the aging appearance of the middle third of the face (Fig. 6). Combining both surgical and nonsurgical options to provide support and fullness to the midface can result in marked rejuvenation in this facial region. It is not uncommon to perform a face lift and inject hyaluronic acid filler into the lips, nasolabial folds, and malar or nasojugal areas. Hyaluronic acid aug-

**Fig. 1.** Aesthetic upper-to-lower lip height balance. The upper lip is approximately one-third of the height and the lower lip is two-thirds of the total lip height. This corresponds to the relative volume differences between the upper and lower lips.

**Fig. 2.** The Cupid’s bow is sharp and well defined in youthful lips.

**Fig. 3.** Youthful lips have full philtral columns that add upper lip-to-nasal base fullness.

**Table 4. Comparative Features of the Youthful/Aesthetic Lip and the Aging Lip**

<table>
<thead>
<tr>
<th>Aesthetic Lip</th>
<th>Aging Lip</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-third upper to two-thirds lower lip height</td>
<td>Upper and lower lips equal out, thin, and stretch out</td>
</tr>
<tr>
<td>ratio</td>
<td>Loss of Cupid’s bow</td>
</tr>
<tr>
<td>Distinct Cupid’s bow</td>
<td>Thin, uniform, contoured upper lip</td>
</tr>
<tr>
<td>Central fullness of the upper lip</td>
<td>Convex, ill-defined sloping projection from the nasal base and labiomental groove</td>
</tr>
<tr>
<td>Concave sloping of the upper and lower lips</td>
<td>Equalized projection of the lips</td>
</tr>
<tr>
<td>Upper lip 1–2 mm anterior to the lower lip</td>
<td>Loss of vermilion-cutaneous pout</td>
</tr>
<tr>
<td>Vermilion-cutaneous borders thickened with a pout</td>
<td>Philtral columns flattened</td>
</tr>
<tr>
<td>Philtral columns prominent and full</td>
<td>Commissures downturned</td>
</tr>
<tr>
<td>Commissures slightly upturned</td>
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</tbody>
</table>
mentation can be beneficial for rejuvenation of numerous regions of the face (Table 5).

Combining fillers with Botox adds to the harmonious facial aesthetic balance. The amplified aesthetic result was shown by Carruthers and Carruthers, as discussed above. In our opinion, optimum efficacy is achieved by coinjection of Botox in numerous facial regions when indicated, including the brow/lateral canthal area, depressor angular oris, and glabella (Fig. 7). Hyaluronic acid can then be used to fill the nasolabial and deep glabellar folds, augment the lips, and blunt the tear trough (Fig. 1). In our experience, using Botox to relax the upper face and hyaluronic acid fillers to fill the lower face has provided our patients with an excellent aesthetic result that is further enhanced by up to 50 percent (Table 2).

**TECHNIQUE**

Annually, the senior author (R.J.R.) injects more than 350 patients with hyaluronic acid fillers at University of Texas Southwestern Medical Center. The majority of experience has been with Restylane alone or in combination with Botox. Satisfactory injections require a thorough understanding of the product’s potential and the patient’s expectations. Product knowledge includes proper technique, preparation, and training for the physician and office staff, as well as an understanding of the product’s characteristics and guidelines. Patient knowledge includes expectations, prior experience with injected filler material(s), and perceived downtime. Close patient follow-up is paramount to successful incorporation of fillers into one’s practice. In the senior author’s practice, all patients are seen at 2 weeks after injection to ensure treatment success. Touch-up injections at this time are needed in less than 5 percent of patients, and the next visit is scheduled at 3 to 4 months. Regular follow-up allows for lower filler volume requirements with subsequent visits, especially in the perioral and nasolabial fold regions.

The depth of hyaluronic acid injection is a critical consideration in optimizing the aesthetic result. Hyaluronic acid fillers with smaller gel particles are best suited for injection into the superficial or upper part of the dermis. These fillers are

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**Fig. 4.** (Left) Aged lips with ill-defined and convex upper and lower lip sloping. (Right) Youthful lips demonstrate gentle concave sloping from the nasal base and labiomental groove. This provides the lips with a pleasing “pouty” appearance.

**Fig. 5.** The upper lip should project 1 to 2 mm anterior to the lower lip.
used to correct superficial lines, such as forehead ("worry" lines), peri-orbital, and perioral (vertical) rhytides. More moderate facial areas, such as glabellar and forehead lines, nasolabial folds, and atrophic scars, are best augmented in the mid-dermis level with hyaluronic acid fillers with medium-sized gel particles. Layering the filler(s) at different depths can further improve the final contour and efficacy.

Before injection, informed consent is obtained from the patient. The majority of patients receive a combination of topical, local, and regional anesthesia. Topical anesthetic creams include benzocaine, lidocaine, and tetracaine (New England Compound, Farmingham, Mass.) and are applied 20 minutes before injection of local anesthesia. Regional anesthesia includes infraorbital and mental nerve blocks with 1% lidocaine and 1:200,000 epinephrine, or septocaine, which we have found to produce less discomfort and stinging. Supplemental, low-volume local anesthetic is given in the perioral area, with an average requirement of 1.5 cc of 0.5% lidocaine per side with 1:200,000 epinephrine, buffered with 0.5 cc of bicarbonate, and injected via a 30-gauge needle. In our experience, this does not distort the treatment area.

The following are guidelines for injection into specific facial regions based on our institutional experience. As mentioned earlier, injection around the nose and mouth is approved by the Food and Drug Administration. All other areas of injection are considered off-label use.

### INJECTION TECHNIQUES

Various injection techniques have been described. Familiarity with all of these techniques is

<table>
<thead>
<tr>
<th>Primary Treatment Area</th>
<th>Injection Site</th>
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</thead>
<tbody>
<tr>
<td>Lips*</td>
<td>Mental groove</td>
</tr>
<tr>
<td>Nasolabial folds</td>
<td>Infraorbital and supraorbital hollows</td>
</tr>
<tr>
<td>Glabellar lines</td>
<td>Soft acne or other scars</td>
</tr>
<tr>
<td>Marionette lines</td>
<td>Temporal hollow</td>
</tr>
<tr>
<td>Nasojugal fold (&quot;tear trough&quot;)</td>
<td>Malar region</td>
</tr>
<tr>
<td>Forehead lines</td>
<td>Philtral columns</td>
</tr>
</tbody>
</table>

*"Lips" includes the vermillion-cutaneous border, volume enhancement, and vertical rhytides.

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Fig. 6. (Left) Descent of the oral commissures is seen with aging. (Right) Commissure downturn is also seen on the lateral view, along with flattened upper lip sloping.

Fig. 7. Botox injected into the upper lip orbicularis oris and depressor anguli oris (DAO) muscles is combined with Restylane soft-tissue augmentation to enhance efficacy.
vital to improving efficacy and aesthetic results (Fig. 8).

Serial Puncture

Serial puncture is optimal for the glabella, for philtral column enhancement, and for fine rhytides. It can also be used for the nasolabial folds. Multiple injections are made serially along the fine wrinkle or fold. The injection sites should be close together, so that the injected material merges into a smooth, continuous line that ultimately lifts the wrinkle or fold. It is helpful to pull the skin slightly away and out from the injection area while injecting. No spaces should remain between the serially injected material. If some minimal gaps are present, postinjection molding and massage can be used to blend the material into a smooth layer.

Linear Threading

The vermilio-cutaneous border and nasolabial folds are best treated using linear threading. The full length of the needle is inserted into the middle of the wrinkle or fold to create a channel. The product is usually injected while the needle is slowly pushed forward, so that “threads” are deposited along the length of the wrinkle or fold. One can inject while advancing the needle, which may push blood vessels out of the way, or one can utilize a retrograde injection technique, inserting product while withdrawing the needle from the tissue. Which approach to use is largely the preference of the surgeon.

Fanning

We have not found fanning to be particularly useful. The needle is inserted in a fashion similar to that used in the linear threading technique, but immediately before the needle is withdrawn, its direction is changed and a new line is injected (without withdrawing the needle tip from the skin). The fanning pattern of lines should be evenly spaced in a progressive clockwise or counterclockwise direction, so that the contour is evenly filled and shaped. This technique is best suited for deep malar injection.
Cross-Hatching (Cross-Radial)

Cross-hatching is especially effective for filling the oral commissures. The needle is inserted in a fashion similar to that used in the linear threading technique, but before beginning the procedure, the cross-hatching lines should be carefully demarcated. A series of linear threading injections is made in the treatment region. The pattern of lines should be evenly spaced in a progressive grid so that the contour is evenly filled and shaped. This technique is used when a relatively large area requires correction (i.e., facial contours) to maximize filler coverage of the treatment area. This technique is particularly useful for the perioral area.

**TECHNIQUE REFINEMENTS**

**Lips**

As with all aesthetic procedures, accurate and comprehensive aesthetic analysis is the first step (see above). Any asymmetries, previous injection sites, irregularities, and scars should be noted and pointed out to the patient and improved upon if feasible. Hyaluronic acid fillers are more viscous than collagen material, and injection may be more difficult until familiarity with the product is attained. While materials with smaller particle sizes, such as Restylane Fine Lines, flow more easily from the syringe and demonstrate less tissue resistance when injected in the proper plane, it is still imperative to release the material from the syringe in a smooth and even fashion to avoid lumping and surface irregularities.

Optimal lip rejuvenation involves two main components: volume enhancement and vermilion-cutaneous border enhancement. Volume filling is often required in older patients and those who have thin lips. Vermilion-cutaneous enhancement is usually required in younger individuals who have enough volume, but it is also indicated in older patients, along with volume augmentation.

Linear threading and/or serial puncture techniques are implemented starting at the oral commissures and proceeding in a lateral to medial direction. Marionette lines are a key element in overall lip enhancement; otherwise, results are destined to be disappointing to both the patient and the physician. A cross-radial technique is used around the oral commissure and marionette line to enhance and “lift,” or fill in, the corners of the mouth. Botox injection into the depressor anguli oris can further enhances this lifting effect. The dermal level is, once again, the mid-dermis. A range of 0.5 to 1.5 cc is often needed for each lip.

Care should be taken to avoid superficial injection in this region, as a light blue hue may become visible. Intravenous and postinjection palpation for surface irregularities is important. If material tracks away from the intended injection plane and created tunnel, then immediate massage is necessary to recontour the area. Massaging should be instituted immediately by the physician, as this is the best time to achieve molding and shaping. This avoids later discomfort that can be present if the patient is given that task.

Injection of the lip itself can be accomplished at the submucosal level, within the superficial orbicularis oris muscle mass. Placing the hyaluronic acid in this deeper level decreases its visibility and augments lip volume. Minimal augmentation of the philtral columns can further enrich the periorbital and lip augmentation. Restylane can also be used to refine the white rolls, which will enhance the overall aesthetic result. More superficial, finer vertical rhytides are augmented with smaller-particle hyaluronic acid (Restylane Fine Line) or collagen. Concomitant injection of 2 to 4 U of Botox will further improve the longevity of lip rejuvenation by as much as 50 percent.

The final result of overall lip rejuvenation should be evident immediately after the injections, unless excess bruising and edema are present (Fig. 9). Immediate swelling is uncommon and may be a result of histamine release or immediate particle expansion by water absorption. Bruising, if present, should be controlled with compression during the injection so that there is no compromise of the final result from blood staining or volume due to extravasated blood.

**Nasolabial Fold**

An assessment of the depth and character of the nasolabial fold is critical to a successful outcome. Lemperle et al.26 provide a useful classification system for grading nasolabial fold depth. A concomitant face lift will also affect the degree to which the fold will require soft-tissue filler augmentation (blunting). The fold will never fully correct, and this would be unnatural even if it were possible. Nevertheless, a 50 percent or more correction is attainable with proper technique and patient selection. Soft-tissue augmentation of a deep fold can be a powerful tool when combined with a midface or face lift technique that also addresses the nasolabial region.

A combination of serial puncture and linear threading in the mid- to deeper dermis is used in this region, while the nasolabial fold is held taut.
Serial puncture injections should be aimed medially away from the large cheek fold, beginning inferiorly and moving superiorly. The dermis is often thicker as one moves superiorly. Beveling the needle up assists with etched-in lines, as does injection of smaller-particle hyaluronic acid in a layered fashion. Molding of the hyaluronic acid by immediately massaging it will help soften and smooth out the blunted fold. Overcorrection can result in an awkward, paradoxically aged appearance when smiling, as a softness in the upper one-third of the nasolabial fold is natural and youthful (Fig. 10).

Approximately 0.5 to 2.0 cc is used per patient for the nasolabial region. As stated above, complete fold correction is not desirable, is difficult to attain, and should not be the goal in this region (Fig. 11). Subsequent touch-up layering or further blunting of fold depth can be accomplished at follow-up visits.

**Glabellar Folds**

Optimal treatment of the glabellar region often requires combined treatment with both hyaluronic acid and Botox (Fig. 12). This combined treatment modality can increase the longevity of the treatment to as long as 9 months. A serial puncture technique is used in this region for the deep and/or wider folds, while staying in the mid-dermis. Injection along the rhytide(s) is performed while the needle is being pulled out. The finer etched-in lines can be treated with a dermal-epidermal level injection of small-particle hyaluronic acid (or collagen), with a precise serial puncture technique and subsequent linear injec-

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**Fig. 9.** Before and 4-month follow-up after administration of 3 cc of Restylene (1.5 cc at the vermilion-cutaneous border and lip rhytides and 1.5 cc to the nasolabial folds bilaterally) and an adjunctive 35 percent moderate-depth trichloroacetic acid chemical peel.

**Fig. 10.** Before and 6 months after 2 cc of Restylene was added to the vermilion-cutaneous border and marionette lines.
tions to disrupt the fold and provide complete geometric filling. It is important to compress the supratrochlear vessels with the nondominant hand while injecting, to prevent inadvertent intravascular injection and minimize bruising. Approximately 0.5 cc is used per patient in this region.

**Forehead Lines**

The forehead is similar to the glabellar region, but a linear threading technique is better suited for this region. This is a highly dynamic area and is particularly amenable to coinjection with hyaluronic acid and Botox. Combined treatment will dramatically increase the longevity of the results, as previously stated. Once again, smaller-particle hyaluronic acid is indicated for dermal-epidermal injection of the finer etched-in furrows that remain despite Botox chemodenervation of the underlying musculature. Thin-skinned patients or those previously injected with Botox may display filler visibility as lumps and irregularities.

As with other regions, using a layering technique and combining injection techniques can maximize the amount of correction achieved. The volume of filler necessary in this area depends on the depth and number of folds, which often relates to skin texture and thickness and whether the patient has received previous Botox treatment in this region. With very deep rhytides, the folds may need to be mechanically disrupted using a “pickle fork” before filling and chemodenervation. As mentioned previously, comprehensive treatment with hyaluronic acid fillers, Botox, and surgical facial rejuvenation techniques can provide powerful aesthetic results.

**Tear Trough/Malar Region**

This area, as with the nasolabial fold, can be further enhanced when augmentation is combined...
with a face lift or other surgical lift (Fig. 13). Although fat injections can be used easily in this area, along with surgical modalities, hyaluronic acid augmentation is an alternative that may be more predictable, with less risk of postinjection irregularities. This is particularly true of the tear trough region. Serial and linear threading is used in this region starting from a lateral to medial direction, with molding of the filler as one proceeds. The injection plane is supraperiosteal. Often, approximately 0.5 to 1.0 cc is all that is required in the tear trough region, but up to 2.0 cc of hyaluronic acid may be used for malar augmentation. The malar injection plane is also just superficial to the periosteum. Larger-particle hyaluronic acids, such as Perlane, once approved for use in the United States, will be especially useful for deeper augmentation planes.

Light massage of the area after injection allows the implanted material to conform to the contours of adjacent tissues. The tear trough region is prone to bruising because of the thin skin and increased vascularity of the periorbital area. Placing cold compresses over the area of injection for the first 24 hours can reduce ecchymosis and swelling.

**POSTTREATMENT CARE**

Massaging should preferably be performed by the injecting surgeon immediately after injection. We find it unpredictable and suboptimal to bequeath the molding and massaging to the patient. The use of cooling eye packs, such as Swiss Eye Therapy (Invotec International, Inc., Jacksonville, Fla.), for 20 minutes at a time in the first 24 to 48 hours can help decrease postinjection bruising and swelling. The patient’s head should be elevated at approximately 30 degrees for the first 24 hours. Oral antihistamines can blunt the histamine release and resultant early edema and may be most useful in patients who develop more edema than usual or redness immediately after injection.

Informed consent that describes the usual postinjection course should be reviewed with the patient before injection and can be re-reviewed by the surgeon and/or staff after treatment. Swelling may last up to 3 weeks, but it typically lasts 1 to 2 days. This can be particularly troublesome in the lips. Patients need to be informed that the lips may temporarily look overcorrected as a result of swelling. Bruising may last a little longer than a week and can be markedly minimized with cessation of aspirin, nonsteroidal anti-inflammatory drugs, and other, similar medications for 2 weeks before injection. Asymmetric animation may occur as a result of any local anesthetic that has been used and should be mentioned before injection of the local anesthetic. Discomfort is usually minimal. Nonsteroidal medication and any medications that can increase bruising should be avoided. A combination of cooling treatment and acetaminophen are typically all that is required. All patients should be seen within 2 weeks after treatment, so that touch-ups can be initiated if necessary. Hyaluronidase injections and/or massaging may help correct any irregular lumps and bumps that are visible and/or palpable (see Complications, below).

**COMPLICATIONS**

Potential adverse reactions are minimal and are mainly injection-related and self-resolving. These include local bruising, purpura, erythema, tenderness, itching, and swelling. A major adverse event that has been reported is hypersensitivity, but true immunoglobulin G- and E-mediated reactions are rare. Friedman et al. reviewed the adverse events data on non–animal-based hyaluronic acid from 1999 to 2000 in Europe, Canada, Australia, South America, and Asia. They found...
that of the 144,000 patients treated in 1999 and 262,000 treated in 2000, a reported 0.15 percent and 0.06 percent, respectively, experienced adverse events. The majority of these events were attributed to trace proteins found in prior lots of less purified product available at that time and included impurities of bacterial fermentation.

Two cases of injection site necrosis were reported and attributed to compression of the vascular supply from excessive use of the product at the time of injection. Manna et al. demonstrated transient adverse events in 12 to 13 percent of patients treated with Restylane and showed a higher protein load per milliliter of gel in Restylane versus Hylaform. However, no long-term sequelae resulted. The majority of these reports predate improved purification by manufacturers and therefore may not be relevant to the product line presently available.

Numerous reports have described a prolonged hypersensitivity with a granulomatous-like, foreign-body reaction. Biopsy specimens usually demonstrate a granulomatous foreign-body reaction with multinucleated cells surrounding a blue, amorphous material. Brody reported a case involving a granulomatous-like reaction with persistent nodularity that was recalcitrant to a steroid regimen (injection and oral therapy) and antibiotic therapy, even at 5 months after injection. The nodularity finally responded to an injection of 15 U of hyaluronidase. Complete resolution without recurrence was noted within 24 hours. The hyaluronidase was prepared by diluting 0.5 cc of 150 U/cc (75 U) with 1.5 cc of 1% lidocaine with epinephrine. Lambros and Vartanian et al. have also reported on the benefits of hyaluronidase injection for both a chronic granulomatous-like reaction and misplacement of material. Hyaluronidase is a soluble protein enzyme that hydrolyzes hyaluronic acid by breaking the glucosamine bond between C1 of the glucosamine moiety and C4 of glucuronic acid. It is often used to augment the affected area during injection of local anesthesia as well as to increase the hypotonic effect of local anesthesia in ophthalmologic procedures. Although the bovine-derived hyaluronidase (Wydase; Wyeth-Lederle Pharmaceutical, Philadelphia, Pa.) is no longer available, recent forms of the drug have been approved by the U.S. Food and Drug Administration.

Large injection volumes can theoretically result in the formation of a sterile abscess, although we have not witnessed this. Papulocystic nodules can develop and can be secondarily infected with frank pus. Patients with prior telangiectasias can be prone to developing increased postinjection telangiectasias, and this should be discussed with the patient before treatment. Prolonged edema, if present, can be treated with a Medrol Dose pack (Pfizer, New York, N.Y.). Perhaps the most severe complication would be an intra-arterial injection, which can theoretically lead to blindness, but fortunately, this has never been reported.

Aesthetic complications include asymmetry, lumpiness, surface irregularities, undercorrection, and overcorrection. In our extensive experience, we have not observed any significant adverse reactions to injection with hyaluronic acid fillers.

CONCLUSIONS

Nonsurgical facial rejuvenation through soft-tissue augmentation with bioengineered hyaluronic acid derivatives has resulted in a major shift in the facial rejuvenation algorithm. With the increasing popularity of nonsurgical cosmetic procedures, new products aimed at soft-tissue augmentation and rejuvenation are being introduced every day that have different particle sizes, are more concentrated, and possess smaller protein loads. Hyaluronic acid fillers provide both patients and physicians with a biocompatible, easy-to-administer alternative that requires no preinjection skin testing and produces reproducible, long-lasting results. At our institution, we have experienced excellent results by combining soft-tissue augmentation with hyaluronic acid fillers, Botox, and surgical techniques to restore the youthful ideal facial aesthetic.

DISCLOSURE

The authors received no financial benefit from any commercial entity in support of this article.

REFERENCES


Calcium Hydroxylapatite (Radiesse) for Correction of the Mid- and Lower Face: Consensus Recommendations

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Mariano Busso, M.D.
Michael E. Jasin, M.D.
Rhoda S. Narins, M.D.
Thomas L. Tzikas, M.D.
Roswell, Ga.; New York and White Plains, N.Y.; and Coconut Grove, Tampa, and Delray Beach, Fla.

Summary: Restoring volume in the middle and lower portions of the face is becoming an indispensable component of modern facial rejuvenation. Radiesse (BioForm Medical, San Mateo, Calif.) is an injectable filler material composed of synthetic calcium hydroxylapatite microspheres (30 percent) suspended in an aqueous carrier gel (70 percent). At present, Radiesse is indicated in the United States for correction of moderate to deep nasolabial folds and for correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. Its off-label use in other facial aesthetic indications is widely reported in the literature. The ability of Radiesse to provide immediate and durable effects has fueled interest in its use for expanded aesthetic applications, particularly in the middle and lower face. The authors’ consensus panel, consisting of a cross-section of experts in plastic surgery, facial plastic surgery, and dermatology, was convened to review the scientific literature and compare clinical experiences regarding the use of calcium hydroxylapatite. This report describes the characteristic effects of aging in the middle and lower face and reviews the composition of calcium hydroxylapatite, its safety and durability, and its appropriate use in a variety of facial applications, including nasolabial folds, correction of human immunodeficiency virus–associated lipoatrophy, augmentation of the malar, submalar, and zygomatic regions, and correction of oral commissure defects, marionette lines, and prejowl sulcus. Recommendations for Radiesse use in each area, including anesthesia, and injection techniques are provided. Measures for enhancing patient comfort, anticipating and minimizing potential complications, and optimizing aesthetic results are also discussed. (Plast. Reconstr. Surg. 120 [Suppl.]: 55S, 2007.)

Facial aging is a complex process characterized by thinning of the epidermis, atrophy of subcutaneous fat layers, and a degree of bone resorption, as well as progressive loss of organization of elastic fibers and collagen and weakening of underlying muscles. Fillers are increasingly being used in novel ways to address some of these age-associated changes throughout the face. Fillers approved for aesthetic uses include collagen products, such as Zyderm, Zyplast, Cosmoderm, and Cosmoplast, and hyaluronic acid products, such as Restylane, Perlane, Juvederm (Ultra and Ultra Plus), HylaForm, HylaForm Plus, and Captique. Longer-lasting synthetic fillers include poly-L-lactic acid (Sculptra), calcium hydroxylapatite (Radiesse), and polymethylmethacrylate (ArteFill). Autologous fat can also be used and requires surgical harvesting. Fillers such as Silikon are used off label. Other novel approaches include the layering of several types of fillers and combined use of fillers and botulinum toxin type A.

Optimal aesthetic results can be achieved by understanding the unique profile of each of

F A D A Status and Approved Uses: Radiesse is approved by the FDA and indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. It is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.
these fillers. This article presents consensus recommendations on the use of calcium hydroxyapatite in the middle and lower face. It includes cosmetic uses for aesthetic purposes and reconstructive uses for persons living with facial lipoatrophy.

**CALCIUM HYDROXYLAPATITE**

**Composition**

Radiesse (BioForm Medical, San Mateo, Calif.) is an injectable filler material composed of synthetic calcium hydroxyapatite microspheres (30 percent) suspended in an aqueous carrier gel (70 percent). These uniform microspheres (25 to 45 μm) are smooth in shape and are identical in composition to the mineral portion of human bone and teeth.5–7

The components of calcium hydroxyapatite occur naturally in the body and therefore are inherently biocompatible. Results from extensive in vitro and in vivo safety studies and in several retrospective physician reports, including toxicology assessments, standardized biocompatibility testing, and a 3-year animal study, demonstrate that injectable calcium hydroxylapatite is biocompatible, nontoxic, nonirritating, and nonantigenic.6 Patient sensitivity testing is not required before use.6

**Applications of Calcium Hydroxylapatite**

Calcium hydroxylapatite has been used for more than 20 years in various forms in surgery and dentistry.8 In the United States, injectable calcium hydroxylapatite has been used for several years for correction of oral/maxillofacial defects, for vocal fold augmentation, and as a radiographic tissue marker. In 2006, Radiesse was approved in the United States for correction of moderate to deep nasolabial folds, and restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

**Nasolabial Folds Pivotal Trial**

The use of Radiesse in nasolabial folds is based on a multicenter, evaluator-blinded, randomized, bilateral (split face) comparison, in which 117 patients with moderate to deep nasolabial folds received injections of calcium hydroxyapatite on one side and human collagen (Cosmoplast; Allergan, Irvine, Calif.) on the other.9 No significant difference in adverse events was observed between the calcium hydroxyapatite folds and the collagen folds. At 6 months, significantly more patients who received Radiesse (82 percent) showed improvement compared with control subjects (27 percent) ($p < 0.001$), and the fold treated with Radiesse was rated more improved in 79 percent of calcium hydroxyapatite patients, compared with 5 percent of control patients ($p < .0001$).9 The 12-month results of this study have been submitted for peer-reviewed publication.

**Facial Lipoatrophy**

A pivotal study of Radiesse for facial lipoatrophy in patients with human immunodeficiency virus receiving highly active antiretroviral therapy showed that 100 percent of patients who received Radiesse to correct lipoatrophy reported significant improvement at 12 months. Eighty-four percent of these patients were very much improved or much improved, and the remaining 16 percent were rated as improved. At 18 months, 91 percent of patients reported significant cosmetic improvement. Furthermore, quality-of-life data collected at 12 months indicated that 100 percent of patients found that Radiesse treatment had been beneficial.10

**Mechanism of Action**

When placed into soft tissue, Radiesse provides immediate correction. Over time, the carrier gel is gradually absorbed and the calcium hydroxyapatite particles remain. Local histiocytic and fibroblastic response at the site appears to result in the production of new collagen around the microspheres.11 Preclinical canine studies (Fig. 1, above) have demonstrated histologically progressive integration of collagen fibers in and around the calcium hydroxyapatite microspheres up to 78 weeks after implantation (Fig. 1, center and below).

Further studies by Marmur et al.11 verified preclinical data by demonstrating dermal matrix integration in biopsy samples harvested from human volunteers. Interestingly, these histological findings were accompanied by evidence of maintained clinical improvement. There was no evidence of granuloma formation, ossification, or foreign body reactions at 1 month or 6 months.

**Durability**

Over time, calcium hydroxyapatite particles are broken down into calcium and phosphate ions via normal metabolic processes and eliminated through the body’s normal excretory processes. In one long-term animal study in the bladder neck, the particles remained intact at the site of injection throughout the entire 3-year study period.12 Our experience with calcium hydroxyapatite use for facial soft-tissue augmentation has shown re-
Results lasting an average period of a year or more in most patients. In vivo, durability depends on factors such as injection technique, site of material placement, and patient age and metabolism. The reported longevity of aesthetic correction in the face ranges from 10 to 14 months, with an average
correction of 1 year in several studies.\textsuperscript{13,14} Other sources report longevity of correction of 12 to 18 months.\textsuperscript{5,15}

**PREPROCEDURE AND POSTPROCEDURE CONSIDERATIONS**

**Preoperative Procedures**

As with any aesthetic procedure, patient satisfaction can be optimized by keeping in mind certain treatment considerations and by carefully discussing expectations with each patient when planning treatment. The patient’s medical history should also be reviewed, with a focus on use of prescription and nonprescription medications, allergies, history of cold sores, presence of autoimmune disorders, previous facial operations or dermal filler treatments, and whether the patient is pregnant or nursing. Patients should also be asked about history of herpesvirus infection, and treatment should be delayed if there are active lesions. Prophylactic antiviral therapy (e.g., acyclovir or valacyclovir) may be prescribed for patients with a history of facial herpesvirus.\textsuperscript{16}

Generally, patients should be told to avoid any medications or supplements that might increase bleeding (e.g., salicylate drugs, nonsteroidal anti-inflammatory drugs, high doses of vitamin E, and certain herbs).\textsuperscript{16} Anecdotal evidence of use of Arnica montana, bromelain, and 1% vitamin K1 (phytonadione) cream as prophylaxis against bruising has been reported.

**Preinjection Procedures**

Before injection of any filler, the patient should be counseled about what to expect in terms of any discomfort that may occur during or after injection, possible adverse events, the results that he or she can expect immediately after treatment, and the likely durability of correction. Informed consent should be obtained.

Before beginning the actual procedure, the injection site may be identified with a washable marker, with the patient sitting upright, to take into account the normal effect of gravity on the facial contours. Pretreatment photographs may be taken after the marking.

**Anesthesia and Other Patient Comfort Measures**

Patient comfort can be enhanced by the appropriate use of anesthetics during injection of any filler; this may be especially true in the case of calcium hydroxylapatite and other fillers that are delivered with a larger (e.g., 27-gauge) needle and/or injected below the superficial layers of the skin. The choice of infiltration, nerve block anesthesia, topical anesthesia, infiltration of tiny amounts of local anesthetic directly into the area, or some combination thereof depends on the preferences of the operator and the patient.\textsuperscript{17} The treatment site should be marked before administration of anesthetic, as infiltration may distort the skin surface and an infraorbital nerve block may blunt or efface somewhat the nasolabial crease.\textsuperscript{17}

**Local Infiltration**

Depending on the area to be filled, minimal amounts of lidocaine 1% with epinephrine (1:100,000) may be infiltrated subcutaneously.\textsuperscript{18}

**Nerve Block**

Nerve blocks have the advantage of producing complete anesthesia while causing minimal alterations in superficial contours.\textsuperscript{18} Blockade of the infraorbital nerve can produce anesthesia extending from the area of the lower lid, through the cheeks, and the upper lip. This branch of the trigeminal nerve exits the maxilla through the infraorbital foramen. It most often can be found approximately 1 cm inferior to the orbital rim at the midpupillary line.\textsuperscript{18} Infraorbital nerve blocks can be performed via direct transcutaneous infiltration of anesthetic agent or via intraoral injection up to 3 to 4 hours before filter injection, depending on type of anesthetic agent used. If the intraoral technique is used, patient comfort can be enhanced by applying topical anesthetic to the oral mucosa before injection.\textsuperscript{18}

Sensation of the lower lip and chin is provided by the mental branch of the trigeminal nerve. The mental nerve may be blocked intraorally, in a fashion similar to that used for the infraorbital nerve.\textsuperscript{18} Nerve blocks in either location create profound anesthesia within minutes of injection and may last between 3 and 4 hours.\textsuperscript{18}

In addition, some physicians elect to use facial cooling systems in lieu of blocks (e.g., the Zimmer Chiller [Zimmer Medical Systems, Irvine, Calif.] or the Aqueduct Facemask [Aqueduct Medical Inc., San Francisco, Calif.]). Topical anesthesia and ice packs may also be used.

**Injection Technique**

Because of the relative viscosity of calcium hydroxylapatite, a 27-gauge, 0.5- or 1¼-inch needle is recommended. Calcium hydroxylapatite should ordinarily be injected at the subdermal plane, especially when filling creases, wrinkles, and deep lines. Injection depth can be just in the subcutaneous space but superior to the periosteum. The
injection can also be placed on the periosteum if the intent is to augment the facial bony skeleton. Placement on the periosteum will not stimulate bone growth in the area.

Depending on the area being treated, calcium hydroxylapatite may be injected in a retrograde fashion using a linear, threading, fanning, and/or crosshatching technique. Supraperiosteal placement usually entails a bolus or depot type of injection, followed by massage or molding of material to desired effect. Injection volumes vary with the location of the treatment site, the size of the area being treated, and individual patient characteristics.

In our experience, a lesser volume of calcium hydroxylapatite may be required to provide the same degree of correction as hyaluronic acid and collagen. Two studies support the finding of smaller volumes in calcium hydroxylapatite than in several other soft-tissue fillers. For example, in a split-face study of calcium hydroxylapatite versus collagen for the nasolabial folds, on average, the collagen-treated side of the face required twice the volume of material (2.35 ml) to produce optimal correction as compared with the calcium hydroxylapatite–treated side (1.22 ml) \((p < 0.0001)\). In another study, approximately 30 percent less volume of calcium hydroxylapatite was required than hyaluronic acid for full correction of the nasolabial folds.9

Massage to ensure no palpable lumps may be appropriate. Some physicians routinely mold the injected area after treatment; other physicians reserve molding for correction of undesired shapes in an effort to avoid the amplification of edema and erythema that molding sometimes creates.

**Posttreatment Care**

Posttreatment photographs may be taken as soon as the injections have been completed and the washable markings removed. The typical protocol for posttreatment care involves immediate placement of ice onto the injected areas to reduce and limit tissue edema and ecchymosis. Some of the authors recommend to their patients that they remain upright for the remainder of the day and sleep with the head elevated to reduce the degree of edema. In our respective practices, patient follow-up visits are typically scheduled 2 to 12 weeks later to document any adverse events and provide refinement treatments as necessary.

**Adverse Effects**

The duration and severity of adverse events associated with calcium hydroxylapatite gel are comparable to those seen with other filler agents (e.g., collagen and hyaluronic acids) and chiefly associated with the delivery of the material rather than the material itself. In our experience, redness, swelling, and bruising are the most commonly reported adverse events and are widely seen with nearly any soft-tissue filler. Further, these events resolve relatively soon after the injection procedure (1 to 2 weeks). Bruising and swelling can be minimized by treating the tissue with care and taking time to provide necessary cosmetic augmentation. There have been no reported granulomas in the injected areas nor migration of calcium hydroxylapatite gel to other parts of the face. In addition, we have no reason to believe that calcium hydroxylapatite, when placed in soft tissue, exhibits any osteogenic properties. In the previously cited study of nasolabial folds, there was no significant difference in adverse events between the folds treated with calcium hydroxylapatite and those treated with collagen, and there was no evidence of granuloma formation with either material. In addition, only one nodule was noted in the calcium hydroxylapatite folds, compared with three in the collagen-treated folds.9

**CALCIUM HYDROXYLAPATITE FOR CORRECTION IN THE MIDFACE**

In the midface area, biometric volume loss plays just as important a role in the appearance of aging as the development of wrinkles and skin laxity. As many clinicians and patients have observed firsthand, simply redraping or lifting skin here is often not sufficient to restore a youthful appearance. Likewise, superficial fill often leaves correction incomplete. Use of a volumizing filler such as calcium hydroxylapatite in this area can immediately restore volume as well as fill and correct specific creases and defects.

**Augmentation of the Malar and Submalar Regions**

With age, volume loss and the descent of malar fat pads may lead to flattening or dropping of the front of the cheek and distribution of excess skin into adjacent areas. Younger patients who present with prominent nasojugal folds or midface soft-tissue or bony deficiency are also good candidates for midface augmentation. Augmentation of the malar and submalar regions can reduce the shadowing effect that aging and deficiency exert on this area, reduce skin surplus from the nasolabial, suborbital, marionette, and jowl regions, and re-balance midface proportions. Because cheek augmentation may affect the face as a whole, malar/
submalar augmentation should be performed first when treating multiple facial areas. Although it is not an approved indication at this time, cheek augmentation with calcium hydroxylapatite has been reported in the literature.

Procedures and Techniques for Malar and Submalar Augmentation

Anesthesia
To enhance patient comfort during filler injection, administration of an infraorbital nerve block is recommended. Only a small amount of anesthetic, 0.2 to 0.3 ml per side, followed by massage, is necessary. Some operators use infiltration to provide additional anesthesia during the procedure.

Injection Technique
If the transcutaneous technique is being used, the area should be approached inferiorly to superiorly with a plan in mind for sequential injection in the malar area, selecting insertion points just lateral to the nasolabial fold and at the zygoma and then proceeding with injection into the submalar soft tissue. The injector may start superficially and then work deep, or vice versa, depending on the injector’s preference. Injections can be started in the deep dermis, or above or on the periosteum, with crisscrossing linear thread injections. Crosshatching and layering of material in the subdermal and subcutaneous planes provide structural support and projection. The fanning/threading pattern into the malar area roughly approximates the shape of an inverted right triangle. Care should be taken not to inject calcium hydroxylapatite into the soft tissue above the orbital rim, as the orbicularis oculi contraction may cause clumping of particulate materials. Although calcium hydroxylapatite has been used for fill of the tear trough, hyaluronic acid products may be more appropriate for this application.

Another technique, the intraoral-suprapieroskeletal approach, is similar to infraorbital and mental nerve blocks for placement of Radiesse. Infraorbital cheek flattening is more common than malar hypoplasia in the aging population. The intraoral injections lessen the need for transcutaneous filling of the nasolabial fold and marionette lines and may provide equal or better results. As a consequence, less bruising and swelling are likely than with transcutaneous injections.

For best aesthetic results, the entire malar area should be augmented, not merely the areas where soft-tissue deficiency is most obvious. Busso and Karlsberg recommend extending the correction laterally and slightly inferiorly along the zygoma to provide better support for crow’s feet and to enhance the triangular shape of the face. A second pass of injection to create a crosshatch is usually not required for the zygoma. As is the case with the malar region, injection should not extend beyond the orbital rim (Fig. 2).

Figure 3 shows a 55-year-old woman before and 1 month after injection of 1.8 ml of calcium hydroxylapatite for infraorbital/medial cheek augmentation and 0.6 ml for perioral correction.

Facial Augmentation in Human Immunodeficiency Virus–Associated Lipoatrophy

Human immunodeficiency virus–associated lipoatrophy can be quite severe and affect substantial areas and thus may benefit most from fillers with volumizing properties. The areas most often affected are the temporal and infraorbital regions, the submalar and malar regions, and the nasolabial folds. In addition to the previously described registrational trial, the use of calcium hydroxylapatite for human immunodeficiency virus–associated facial lipoatrophy has also been reported elsewhere in the literature.

Anesthesia
Adequate anesthesia should be provided. Typically, an infraorbital block, a “mini-block,” and/or field infiltration is used, depending on operator and patient preference.
Injection Technique

Using a 25- or 27-gauge, 1½-inch needle, calcium hydroxylapatite is deposited into the deep dermis of the submalar region using a fanning technique (Fig. 4). To provide adequate volume, additional threads may be layered into a deeper plane.

While the chief area of concern for human immunodeficiency virus lipoatrophy patients is typically the submalar region, we find that extending correction to the malar eminence and periorbital region may provide more complete correction. The volume of material injected depends on the extent or severity of disease.

Figure 5 shows a 37-year-old man at baseline and 1 month after injection of 7.2 ml of calcium hydroxylapatite for correction of human immunodeficiency virus–associated facial lipoatrophy.

CALCIUM HYDROXYPATITE FOR CORRECTION IN THE LOWER FACE

Calcium hydroxylapatite may be particularly apropos for the lower face because of its ability to reliably fill lines and creases of varying depth and replace lost volume. Areas of common application in the lower face area include the nasolabial folds, oral commissure, marionette lines, prejowl sulcus, labiomental crease, lateral chin (perimental hollows), and the mandible.

Augmentation of the Nasolabial Folds

Typically, nasolabial fold creases begin to appear in individuals in their 20s and deepen as aging continues. Their appearance is exacerbated by the descent of fat from the malar and medial cheek pads. We find calcium hydroxylapatite to be particularly appropriate for these folds because it can be injected deep into the dermal plane to splint the line as well as deeper in the subdermal plane to provide structural support to the fold. It provides relative durability despite the dynamic motion of this area.

Procedures and Techniques for Correction of Nasolabial Folds

Anesthesia

Anesthesia techniques used when treating the nasolabial folds vary depending on operator and patient preference. At a minimum, a topical an-
esthetic cream and preinjection cooling may be appropriate. Local infiltration or infraorbital block may also be considered.

**Injection Technique**

For correction of the nasolabial folds, calcium hydroxylapatite gel is injected into the subdermal plane with a 27-gauge, 1¼-inch needle using a linear threading and fanning technique. In our experience, depositing calcium hydroxylapatite gel in a V or triangular shape can provide greater support in this area and enhance correction of the entire fold.24 Crosshatching the area with transversely oriented threads of filler helps to flatten the skin of the upper part of the fold. Because the gel provides 1:1 correction, overcorrection is not necessary.

**Durability**

In an open-label study of 22 patients who received calcium hydroxylapatite for the nasolabial folds, 14 patients reported a duration of cosmetically significant correction longer than 12 months, and four reported correction lasting 10 to 12 months (four patients were lost to follow-up).24 No patient reported correction lasting less than 10 months. In this study, the most commonly reported adverse events were redness, swelling, and bruising. Redness and swelling resolved without treatment within 1 to 5 days and bruising within 4 to 10 days (with one exception lasting 15 days). There were no visible nodules or granuloma formation.

In addition, two-thirds of the patients (six out of nine) in the study who had been injected with hyaluronic acid in the past preferred calcium hydroxylapatite because of its longevity of effect and because the patients found the results to be more “aesthetically pleasing.”24

**Published Studies of Calcium Hydroxylapatite for Correction of Nasolabial Folds**

Table 1 lists several published studies in which patients received calcium hydroxylapatite for correction of nasolabial folds.2,7,9,13,21,24–26

Figure 6 shows a 63-year-old man before and immediately after injection of 2.2 ml of calcium hydroxylapatite for correction of human immunodeficiency virus–associated facial lipoatrophy. (Photograph courtesy of Todd Owsley, M.D.)
hydroxylapatite for correction of nasolabial folds and 0.7 ml for the medial cheek.

Chin and Lip Support
Evaluation of the chin and lip position should include overall assessment of the diffuse volume deficit as well as the individual lines and depressions. Often individual areas, such as the marionette lines and the corners of mouth, cannot be adequately addressed without adding additional support by augmenting the prejowl and perimental areas.

Oral Commissure
Atrophy of soft tissue at the oral commissure causes inversion and results in “parenthesis” lines. The corners of the mouth can descend, giving a negative curve to the lip. The loss of volume at the commissure includes the labial mucosal side as well as the cutaneous portion, which dissolves into the marionette line.27 The appearance of the oral commissure can often be ameliorated by the skilled physician with the appropriate use of fillers, including calcium hydroxylapatite. Correction of this area requires volume to fill the lines and folds as well as to provide a lifting effect to the corners of the mouth. Calcium hydroxylapatite for the oral commissure has been widely reported in the literature.7,17,25,28,29

Procedure and Technique
Before injection, the area should be anesthetized via infiltration or block of the mental nerve. Threads of small amounts of calcium hydroxylapatite (approximately 0.05 ml) are then placed in a fanning and crisscross pattern into the deep dermis inferior to the corner of the mouth and extending into the contiguous marionette line. Crisscrossing threads are then placed in deeper layers to add bulk, splint the depression, and elevate the corner of the mouth. The mucosa of the commissure should also be augmented in a C shape, as this corrects the inversion and elevates the corner of mouth.17

A hyaluronic acid or collagen product carries less risk of palpability or nodularity in this area. If they are deeper, individual “parenthesis lines” can be filled with calcium hydroxylapatite, but the superficial component also needs a hyaluronic acid or collagen.

Figure 7 shows a 56-year-old woman before and 1 month after injection of 1.4 ml of calcium hydroxylapatite for correction of the oral commissure, marionette lines, and prejowl sulcus, 1.0 ml for correction of perioral rhytides, and 1.2 ml for correction of nasolabial folds.

Marionette Lines
Successful use of calcium hydroxylapatite for the marionette lines has been reported in the literature.7,15,17,21 These lines tend to be difficult to efface completely. Some panel members recommend layering of fillers for this area. Typically, calcium hydroxylapatite is injected at the subdermal level, with Restylane or another hyaluronic acid–based filler layered above it.17,30

Procedure and Technique
Anesthesia for this area is provided by infiltration or block of the mental nerve. Calcium hydroxylapatite is then injected into the dermal and subdermal planes, again with the use of fanning and crisscrossing threads in each of these layers. After injection, the area should be gently massaged and contoured to ensure that there are no
palpable lumps. Use of conservative volumes of calcium hydroxylapatite is recommended in this area, along with a staged, multiple-injection-sessions approach.

Figure 8 shows a 73-year-old woman before and 3 months after injection of 3.9 ml of calcium hydroxylapatite for correction of the cheeks, nasolabial folds, and marionette lines.

Figure 7. A 56-year-old woman before and 1 month after injection of 1.4 ml of calcium hydroxylapatite to correct the oral commissure, marionette lines, and prejowl sulcus, 1.0 ml to correct the perioral rhytides, and 1.2 ml to correct the nasolabial folds. (Photograph courtesy of Michael Jasin, M.D.)

Prejowl Sulcus, Perimental Hollows, Labiomental Crease, and Chin Projection

The development of the prejowl sulcus, perimental hollows, labiomental crease, chin pad ptosis, and deflation reflects bone loss, tissue atrophy, and descent of soft tissue around fixed folds (i.e., nasolabial, marionette). Reinfation of the entire chin complex may include some or all of these areas and may also be necessary to provide a base of support for the corners of the mouth. Filling the prejowl area also provides camouflage of the jowl by smoothing the mandibular border, whereas filling the perimental hollows and labiomental crease adds additional support for the area.

Procedure and Technique

To correct the prejowl sulcus, calcium hydroxylapatite is placed in the deep dermis and/or subdermal plane. The key to correction is re-creation of the inferior border of the mandible rather than simple volume fill along the body of the mandible. In addition, the facial vein must be avoided to prevent substantial ecchymosis. For the best aesthetic results and to create a smooth correction that blends well with the adjacent chin and jaw contours, the material should be injected incrementally and gently massaged. Calcium hydroxylapatite can be used along the periosteum of the inferior mandible to add volume to the atrophic jawline.

Intraoral, supraperiosteal bolus placement of Radiesse is another approach. This placement
provides correction with minimal bruising and swelling. This approach also gives correction to the marionette lines, reducing the need for subdermal/dermal injections.

Figure 9 shows a 60-year-old woman before and 16 months after injection of 1.6 ml of calcium hydroxylapatite for correction of the prejowl sulcus and 1.0 for correction of the oral commissure and lateral chin. (Photograph courtesy of Michael Jasin, M.D.)

DISCUSSION

Volume enhancement is rapidly becoming an indispensable component of modern facial rejuvenation. It is ideal for the patient who is not yet inclined to procedures involving surgical lifting. It is equally useful for patients who have already undergone surgical lifting. Volume enhancement does require judicious use of the appropriate product, however. It is our opinion that calcium hydroxylapatite can be the filler of choice for patients in whom subdermal fill and/or volumizing is needed. Depth of injection and injection volumes tend to be site-dependent.

Calcium hydroxylapatite provides immediate correction of lines and wrinkles and appears to restore lost volume. We have found it to be particularly useful for filling areas such as the nasolabial folds, marionette lines, oral commissure, and prejowl sulcus and for augmenting the malar and submalar areas. As such, it can play a key role in nonsurgical rejuvenation of the middle and lower face, an area where botulinum toxin type A has limited utility.

Clinicians who are in the early stages of adoption should keep several considerations in mind when using calcium hydroxylapatite. First, our own experience, supported by the clinical literature, suggests that smaller volumes are needed to provide the same degree of correction, compared with collagen and hyaluronic acid–based products. It should also be noted that calcium hydroxylapatite provides 1:1 correction. Nonetheless, some operators prefer to bring patients gradually to full correction or to offer follow-up injections 2 weeks to 3 months after initial treatment. Finally, when layering calcium hydroxylapatite with other fillers, such as hyaluronic acid, smaller volumes of calcium hydroxylapatite than usual may be needed.

Our experience has also shown calcium hydroxylapatite to be safe. This observation is borne out by the clinical literature, which demonstrates that the most common adverse events associated with the material are similar to those observed with other fillers, tend to be short-lived, and resolve without treatment. Importantly, there is no evidence of granuloma formation or osteogenesis when calcium hydroxylapatite is placed in soft tissue. A recent study by Carruthers et al. also confirmed that use of calcium hydroxylapatite does not interfere with the interpretation of radiography.

In conclusion, calcium hydroxylapatite has emerged as a versatile, durable, and safe durable filler whose use is anticipated to grow as more clinicians and patients gain firsthand experience with it.

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DISCLOSURES

Drs. Graivier, Bass, Busso, Jasin, Narins, and Tzikas are members of the BioForm Medical Clinical Advisory Board. Drs. Graivier, Bass, Busso, Jasin, and Tzikas have received compensation for educational presentations about Radiesse. Drs. Busso, Narins, and Tzikas have stock options in BioForm Medical.

REFERENCES


Hyaluronic acid dermal fillers, alone or in combination with botulinum toxin type A, have been shown to be effective in treating deep resting rhytides and folds.1–5 Juvéderm Ultra and Juvéderm Ultra Plus (Allergan, Inc., Irvine, Calif.) injectable gels have been on the market in most European countries and Canada since 2003, and in some markets longer, and were introduced to the U.S. market in 2007. They are cohesive, homogenous gels made from hyaluronic acid, which is derived from bacterial fermentation, and are cross-linked using the butane-diol-diglycidyl-ether chemistry which is also used in the preparation of particulate gel suspension fillers. Juvéderm Ultra and Juvéderm Ultra Plus were formulated with the goals of providing optimal flow, predictable delivery of product to the treated area, and prolonged duration of cosmetic benefit.

FDA Status and Approved Uses: Juvéderm 30, 24HV, and 30HV are injectable gels approved by the FDA and indicated for injection into the middle to deep dermis for correction of superficial facial lines and scars.7,8 The more viscous Juvéderm Ultra Plus formulation is optimized for deep dermal injection and also for placement of depots of material (e.g., in the supraperiosteal...
area) in cases where restoration of volume is desired on the upper cheeks or elsewhere (Fig. 1). Recent data from a large-scale clinical trial in nasolabial folds (presented at the 2007 Annual Meeting of the American Society for Aesthetic Plastic Surgery, April 19 through 24, 2007) demonstrated that the benefit of treatment with Juvéderm Ultra lasts for up to 9 months or longer, while the effect of Juvéderm Ultra Plus may last 12 months or longer. The U.S. Food and Drug Administration recently announced a label extension for Juvéderm Ultra and Juvéderm Ultra Plus, indicating that the cosmetic benefit from both products may last for about 1 year—longer than clinical studies supporting Food and Drug Administration approval of other hyaluronic acid fillers.

Juvéderm Ultra and Juvéderm Ultra Plus, marketed by Allergan, are supplied in syringes with a volume of 0.8 ml.

**CLINICAL APPLICATIONS**

**General Considerations for Injection**

Juvéderm Ultra can be injected through a 30-gauge needle, but I usually find it optimal to use a 1.25-inch, 27-gauge needle when injecting either preparation (the same is true for gel-particle suspensions). The longer needle allows for a smaller number of insertions, which I have found reduces the risk of bleeding and bruising and facilitates the creation of a long, smooth, linear deposit of material rather than the series of deposits that result when a half-inch needle is used.

**Treatment of Fine Lines**

When treating very fine and superficial lines (e.g., perioral lines, transverse “necklace” lines, and transverse lines on the forehead), Juvéderm Ultra is optimally injected through a 31-gauge needle. A particularly effective and well-tolerated technique that has evolved in my practice is to load 0.1-ml aliquots of Juvéderm Ultra into the proximal barrel of a 0.3-ml BD-II diabetic syringe with a swedged-on 31-gauge, 0.8-cm needle. The plunger is put back into the syringe, air is expelled from the barrel, and then the needle can be used to perform a series of very finely controlled injections. There is excellent control of the extrusion rate because the very small barrel diameter of this syringe provides a high degree of mechanical advantage for the injector (Fig. 2). The small amount of shear the product is exposed to while passing through the 31-gauge, 0.8-cm needle does not seem to significantly degrade the duration of cosmetic benefit.

**Choosing between Juvéderm Ultra and Juvéderm Ultra Plus**

In my experience, patients who are new to lip enhancement have been more satisfied with Juvéderm Ultra, which is somewhat softer and more malleable than Juvéderm Ultra Plus. Experienced patients and those with thick lips (particularly men) appear to do very well with Juvéderm Ultra Plus. I have found the latter to be optimal for deep dermal injections in areas such as the nasolabial folds, for supraperiosteal injections in areas such as the prejowl sulcus, and for volume restoration in the upper cheeks (Fig. 3). Juvéderm Ultra can also be layered over Juvéderm Ultra Plus in cases where there is a superficial line overlying a deeper defect or crease, most commonly in the nasolabial folds.

*Fig. 1. Cheek renewal before (left) and 10 days after (right) treatment with Juvéderm Ultra Plus (2.0 ml per cheek). (Photographs courtesy of Kent Remington, M.D.)*
Juvéderm Ultra is the preferred product for use in thin-skinned areas such as the tear trough.

**Correction of Errors and Complications with Hyaluronic Acid Fillers**

Compared with the various non–hyaluronic acid fillers, an advantage of using hyaluronic acid fillers such as Juvéderm or hyaluronic acid gel-particle suspensions is that areas of excess fullness, inadvertent superficial placement of filler, and some other rare problems can be corrected simply by injecting hyaluronidase.\(^{10–12}\)

When administering any type of filler, it is important to carefully examine the treatment site by visual inspection and palpation to detect any pre-existing asymmetries or subcutaneous masses, and to discuss these observations with the patient. Inspection and palpation are also important immediately after treatment. Any areas of excess fullness or superficial placement of filler should be identified and massaged into the correct state before the patient leaves the office. Application of water-based ultrasound gel to the gloved fingers before pretreatment or post-treatment examination or manipulation of the treated area can enhance tactile feedback as well as improve the sensation experienced by the patient during examination.
COMPARISON OF INJECTION TECHNIQUES AND OUTCOMES WITH HYALURONIC ACID GELS AND GEL-PARTICLE SUSPENSIONS

In my experience, one subtle difference between the injection of cohesive, homogenous gel fillers such as Juvederm and granular hyaluronic acid suspensions is that homogenous gels are generally easier to inject at a slow and consistent rate with steady thumb pressure. The rheological (flow) properties of granular suspensions can require a relatively high level of pressure on the plunger to initiate flow, followed by a somewhat lower thumb pressure after flow is established and during extru-
The need for continuous modulation of thumb pressure to obtain the desired extrusion rate of particulate gel fillers can result in variances in flow rate. By contrast, the flow properties of Juvederm facilitate gentle, gradual delivery of product to the treated area. As with any filler, if too much force is applied, excessive hydrostatic pressure in the syringe can cause disengagement of the needle from the hub. To prevent this, injectors can ensure that the needle is firmly attached to the syringe, that injection is gradual, and that steady, rather than heavy, force is applied to the plunger. I have also found that the moderate rate of flow causes more gradual distension of tissue, resulting in less patient discomfort. Gradual, steady flow of product into the treated area also facilitates correct placement of the filler.

An important difference, in my experience, has been that Juvederm remains in the area where it is injected, because of its cohesive nature and high viscosity, and does not flow away from the injection point to an appreciable degree. Gel-particle suspension fillers, on the other hand, are slurries, and so tend to behave like fluids during the injection process. I have noticed that gel-particle suspensions sometimes flow away from the injection point, following the path of least resistance. This can cause filling of unintended areas and waste of product (Fig. 4). My experience has been that because cohesive gel implants such as Juvederm tend to stay where they are injected, and they fill more precisely and more efficiently. Precise and efficient filling also logically translates into smaller volumes of filler needed to achieve the desired degree of correction compared with gel-particle suspension hyaluronic acid fillers.

I have also noticed that Juvederm blends in completely with the treated area within a few days, thereby improving patient satisfaction with treat-
ment results. Final integration of gel-particle suspensions with the treated area often seems to take longer, possibly reducing patient satisfaction. The relatively short time to integration of Juvederm with the treated area increases the likelihood of creating a good “first impression,” which may positively influence the patient’s subsequent assessment of procedures. Photographs comparing the duration of cosmetic benefit of Juvederm Ultra Plus with a gel-particle suspension are shown in Figure 5.

I have also noted less swelling during the night following the procedure with Juvederm, particularly after lip enhancement. I attribute this finding to differences in the amounts of free (“non–cross-linked”) hyaluronic acid in the products and in the rates at which tissue is exposed to this free hyaluronic acid. About 10 percent of the hyaluronic acid in Juvederm is non–cross-linked, and this smaller fraction is homogenously distributed and sequestered within the mass of cross-linked hyaluronic acid. This may result in the free hyaluronic acid component of Juvederm not being exposed as a bolus to the injected tissue. Rather, it appears to gradually diffuse from the gel mass into the injected area, probably over a period of weeks to months.

By comparison, particle-based products tend to contain a considerably larger amount of free hyaluronic acid (typically around 20 percent of the total hyaluronic acid in the syringe), and all of this free hyaluronic acid is found in the vehicle system (where it is used as a gelling agent to keep the particles in suspension). All of this free hyaluronic acid is exposed to patient tissues within minutes to hours after injection. Thus, it may be that the differences in swelling during the 24-hour period after injection are related to differences in the rate at which tissues in the injected area are exposed to the free hyaluronic acid of the injected product.

Guidelines for the use of hyaluronic acid fillers of any type are listed below (these guidelines apply to all filler injections):

1. Application of firm, steady pressure to the injected area for 5 full minutes, starting as soon as possible after the needle is withdrawn from the skin, can significantly reduce the incidence and severity of bleeding and of late-presenting bruises.
2. Patients should be instructed to go about their normal activities, including eating, washing, and applying makeup, but to strictly avoid massaging or manipulating the treated area. Disturbance of the site may displace the injected material and could also increase the chance of a bruise developing from a traumatized blood vessel.
3. Standardized pretreatment photographs should always be obtained. In general, when photographing patients before treatment with fillers, it is ideal to have symmetrical lighting of the patient, either by dual flash or flood lamps or simply by being positioned so that ambient light falls in a symmetrical manner on the patient’s face. To facilitate this procedure, it is helpful to place a mark on the floor where patients should stand while being photographed.
4. A good practice is to stop after treating one side of the face to let patients examine themselves with a large hand mirror. At this point in the procedure, patients can easily appreciate the difference between the treated and untreated sides of the face.
5. It is also wise to see new patients 2 weeks after their first treatment in order to obtain timely feedback about their perception of the procedure. Satisfaction can often be enhanced by holding the patient’s pretreatment photograph beside his or her face as the patient looks into a large hand mirror. Additional treatments are often requested following this before-and-after comparison.

**SUMMARY AND CONCLUSIONS**

Juvederm Ultra and Juvederm Ultra Plus are cohesive, homogenous injectable gels made from hyaluronic acid derived from bacterial fermentation. They have a well-established record of safety in Europe, Canada, and elsewhere, and have recently been introduced in the United States. Their proprietary application of butane-diol-diglycidyl ether cross-linking chemistry and post–cross-linking processing of the gel produces smooth flow, predictable delivery, and prolonged duration of cosmetic effect of approximately 1 year—longer than clinical studies supporting Food and Drug Administration approval of other hyaluronic acid fillers.

An advantage of using hyaluronic acid fillers such as Juvederm and hyaluronic acid gel-particle suspensions, compared with the various non–hyaluronic acid fillers, is that areas of excess fullness or inadvertent superficial placement of filler can be corrected by injecting hyaluronidase.

Based on my experience, there appear to be four basic, clinically relevant differences between Juvederm and hyaluronic acid gel-particle suspen-
sions. Juvederm encourages administration by gentle, gradual, and precise placement of product. Juvederm also tends to remain in the treated area and does not flow into unintended areas, which I attribute to its properties as a cohesive, homogenous gel as compared with a fluid-like slurry. In addition, there appears to be less nocturnal swelling after the use of Juvederm, particularly after lip enhancement. This observation may be explained by the presence of a smaller amount of free hyaluronic acid and a slower rate at which tissue in the treated area is exposed to free hyaluronic acid. Finally, Juvederm blends with the treated area within a few days, contributing to rapid patient satisfaction with the feel and look of the treated area.

The foregoing conclusions are based on clinical experience alone in an effort to provide early information about the use of Juvederm. Additional experience and research are needed to properly define the validity and relative importance of these differences in the clinical setting. Trials to further explore the clinical properties of Juvederm are ongoing.

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DISCLOSURES

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REFERENCES


Hyaluronic Acid Injections for Correction of the Tear Trough Deformity

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**Background:** The tear trough, though small in physical dimensions, sits at the perceptual epicenter of the face. Because small changes here make large changes in how other people interpret one’s state of being, it would be beneficial to have a simple way of addressing the area. Despite the complexities of cause, the solution is to level the hollow and smooth the junction between the lid and the cheek.

**Methods:** Hyaluronic acid injections are used to address the tear trough deformity. Very small quantities, 0.2 to 0.4 cc, are used per side, and the placement is in the orbicularis oculi muscle or at the periosteum. The key is to inject deep to the dermis and to massage the injected area smooth.

**Results:** All patients were improved roughly in proportion to their skin quality. The best patients for the treatment are those with young, thick skin and a definite hollow. The duration of the effect is often more than 1 year at this location. Minor bruising and irregularities were self-limiting or treated with light massage. Large overfills or irregularities are correctable with injection of hyaluronidase.

**Conclusions:** Tear trough injection with hyaluronic acid products is relatively simple, effective, and safe, and can offer significant improvement in this difficult area. It can be performed for primary deformities or to improve a surgical result. (Plast. Reconstr. Surg. 120 (Suppl.): 74S, 2007.)

Robert Flowers, who gave the tear trough its name, describes it this way: “The deep groove that commonly occurs near the junction of the eyelid and the cheek is the most consistently ignored major deformity of the orbital region. With a characteristic length of but 2 cm, it extends downward and lateral from the inner canthus of the eye . . . . Whether limited or extended it gives the face a dissipated, unhealthy, and tired—even haggard—appearance . . . .”

The aging face shows a kind of relativity between areas that indent and adjacent areas that enlarge, compounding the effect between the two. For example, the jowl and the anterior prejowl sulcus develop in such a way. The nasolabial crease and the lateral fold behave similarly. The tear trough, at the convergence of several anatomical areas and dynamic processes, is perhaps the most important such area, as most people think it projects information about one’s state of being.

The cause of the tear trough deformity is multifactorial, and separating its components exactly may be difficult. The main components of the tear trough are the hollow itself; the fat bulge just superior to it; and the very distinct change of skin quality, color, and thickness between the lid and the cheek.

In comparing the tear trough area in younger and older patients, there seems to be an intrinsic loss of tissue just superior to the lid–cheek junction (which I define as the junction of the thin pigmented lid skin and the thicker cheek skin). In older patients, one gets the impression that the entire lower lid may have lost tissue volume, which is disguised by the enlarging fat pads but visible at the tear trough.

The intrinsic loss at the tear trough is magnified by the overlying fat pad, which as it enlarges increases the shadowing and apparent depth of the tear trough. For reasons probably related to

**FDA Status and Approved Uses:** Hyaluronic acid products are FDA approved for filling moderate to severe facial wrinkles and folds around the nose and mouth. This article discusses off-label uses of the product.
septal containment and ligamentous support, the fat pads do not transgress the borders of the tear trough.2

A third component of the tear trough is the local skin quality and color. The tear trough sits just superior to the border of the thin pigmented lid skin and the usually lighter-colored thicker dermis and “subcutaneous rich” cheek skin just inferior. The apparent pigmentation of the lid skin increases with time and increases the contrast between lid and cheek. It looks as if the lid–cheek junction drops or enlarges, but recent studies using matched photographs over time indicate that the actual skin borders are stable and unmoving.3 Moreover, in the presence of the tear trough deformity, the skin of the overhang is viewed at a steeper angle, increasing apparent skin pigmentation and sitting in the shadow of the fat bulge. Other anatomical aspects of this complex area have been analyzed by Loeb and Flowers.1,4

It is unclear which component of the tear trough is the most responsible in general, but fortunately, as with most facial cosmetic surgery, understanding the cause of a deformity is not necessary to undertake its correction. In theory, treatment of the area consists of no more than filling or leveling a hollow, but unlike injecting a nasolabial crease, the breadth of the hollow, the very thin skin of the area, and the presence of adjacent fat pads make it technically more demanding than other sites on the face.

INDICATIONS

Cosmetic surgery is largely an empirical endeavor; the main indication for leveling the tear trough is the presence of enough deformity to make a visual difference by its improvement. It is usually obvious to the patient and the physician when treatment is necessary. The patients who do the best with the “tear trough injectoplasty” are those who do best with other cosmetic operations of the face. In general, they have thick, smooth skin, and in particular, they have a well-defined tear trough, without overly large lower lid fat pads that one is trying to compensate for. Patients with extremely wrinkled skin and less of an actual indentation to fill do less well with injections. The larger the overhanging fat pads, the more the injection becomes a compromise procedure, as one tries to correct for the shelving of the fat and the intrinsic indentation of the tear trough.

The presence of hyaluronic acid in the tear trough does not diminish the intrinsic color of the overlying lid skin, though it does diminish the shadow. People with deep pigmentation should be advised of this, although an indentation in the presence of dark pigmentation usually appears better corrected.

PATIENTS AND METHODS

Anesthesia

I prefer to use infiltration anesthesia, because I believe that with vasoconstriction, less bleeding and bruising will result. Also, the possibility of an unintended vascular injection, already extremely uncommon, would theoretically be less plausible in a vasoconstricted environment. Although skin blanching is apparent when using topical anesthetic, one cannot be sure of its depth. Because injections in the tear trough area are intramuscular or preperiosteal, I prefer to have the whole volume of tissue vasoconstricted. If a small volume of anesthetic is used, the area will not be distorted.

After the borders of the tear trough are marked, ice is firmly applied to the most inferior area of the marked lid skin. The eyelid itself is not as sensitive to needle sticks as the thicker cheek skin just below. After 4 to 5 seconds, when the ice is removed, the skin will be blanched for 1 or 2 seconds. Injecting during the blanch greatly reduces the pain of the needle. Using a 1-cc syringe and a half-inch, 30- to 32-gauge needle, 0.2 to 0.4 cc of 0.5% lidocaine with epinephrine is injected into the orbicularis oculi muscle and up the tear trough. I have come to inject the muscle rather than the skin, finding a lower incidence of cutaneous hematomas.

Finger pressure flattens the area injected and walks the local anesthetic up the tear trough. The other side is injected, and several minutes of light finger pressure allows for vasoconstriction and dispersal of the local anesthetic.

Personal Technique

This discussion concerns the tear trough itself, although injections can be performed around the periphery of the lower lid. The goal here is to fill the depression and smooth the junction between the medial and inferior lid and the cheek. Usually, one is trying to increase the elevation of the tear trough by 2 to 3 mm. There are different means to the goal, most having to do with injector preference,5 but the common thread in all successful techniques is to inject well deep to the dermis and to smooth out the injection with massage. Dermal injection will result in highly visible bumps that will last for approximately 1 year untreated.
I have found that the injections are far more accurately performed under local anesthesia and with the patient vertical. When the patient is supine, as is often the case when tear trough injections are carried out in combination with other procedures in the operating room, I find there to be more irregularity and malposition of the injection. I normally inject the tear trough separately rather than combine injections with open lid procedures for the same reason.

When the area is marked and numb, I place the half-inch, 30-gauge needle through the skin at the most lateral extent of the tear trough, advancing fully and even indenting the skin with the hub for a little extra reach. A very small amount of product is then placed while the needle is withdrawn, although usually the needle is not withdrawn through the skin. Another parallel injection at the same depth is made below and another above. The process is repeated to the apex of the deformity. When one places a needle on a syringe of product and clears the air from the needle, the small bead that develops on the needle is an approximate indicator of the speed and pressure of injection. The rate of injection should be slow with very little pressure, although the needle should be moved rather quickly. A heavy hand is not an advantage here.

The tear trough is not an area for beginners; most injectors will have already found out that starting an injection with a stationary needle will result in an overfill bump. Similarly, the withdrawal injection should not continue to the skin or one will be left with a superficial dermal bump.

The superior tear trough is then injected in a similar manner all the way to the top of the deformity. Although I was reluctant to inject this high at first, with anesthesia and some practice, it became routine.

Because the skin muscle and bone are all within a few millimeters of each other at the tear trough, when the needle is not scraping bone and not in the dermis, I presume the needle to be in the orbicularis oculi muscle, which I prefer as an injection plane, although others have reported success injecting at the periperiosteal level. The goal here, as mentioned, is to achieve smoothness, and any technique that does this is acceptable.

The area is then inspected and palpated. Additional small passes are made as needed to create the necessary contour. Every attempt is made to have the injection perfect, but even placement of hyaluronic acid by injection alone is difficult and it is likely that there will be some areas where smoothness could be increased. Accordingly, the area is massaged lightly and compressed with finger pressure and rolled with a cotton applicator. The more forceful the compression, the more bruising that will occur. Forceful compression will also push the product away from its intended location and push it up into the lid fat pad and down into the cheek, exaggerating the deformity. In my experience, injection should be performed rather quickly and the area should be massaged for several minutes. Typically, in the tear trough itself, the average amount of hyaluronic acid placed per side will be on the order of 0.1 to 0.4 cc. Ice is used on the evening of injection. Patients are not instructed to massage the area, because they might overly disperse the product. The material can be easily manipulated and reshaped for at least several weeks, and the patients are encouraged to return if they perceive any irregularities. A few minutes of in-office manipulation usually solves minor irregularities.

RESULTS

The results of this technique are primarily visual, and representative cases are shown in Figures 1 and 2. As of this writing, approximately 200 patients have been treated, with the effect of treatment lasting up to 2 years. As with all aspects of cosmetic surgery, a range of results is seen. Patients are told that they will be improved and not perfect. The older and more crepe-like the skin, the less well the treatment works. In very wrinkled skin, the tear trough is obliterated, but there will be a skin fold at the superior edge of the injection that looks like a tear trough.

In the tear trough, hyaluronic acid lasts far longer than it does in the lips and nasolabial folds. One to 1½ years is not uncommon. I have noticed that other nondynamic sites, such as the temple and the nose, have a similarly long duration.

Complications

Complications have been minor in my practice. Bruising can occur whenever needles are placed in the lids. I have the distinct impression that there is less bruising with infiltration of local anesthesia than with no local anesthesia. It seems to me that there is less bruising when the initial injection is made into the orbicularis oculi rather than into the skin.

Several patients have had irregularities that were massaged away either at the time of injection or several weeks later. When irregularities occur, they are usually treatable with massage.
Fig. 1. A 60-year-old woman before (left) and 6 months after (right) injection of tear troughs with 0.3 cc of Restylane per side.

Fig. 2. A 34-year-old woman before (left) 3 months after (right) injection of 0.4 cc of hyaluronic acid. The injection should have gone to the apex of the deformity on the right side.
The closer one inspects the area, the more effects of the injection that can be seen. Social and casual inspection reveals a smooth contour. If one looks very closely, one can see the sites injected by virtue of very subtle changes in the reflectivity of the skin and its contours. Typically, patients do not notice this degree of imperfection.

I have noticed a faint bluish discoloration in some people with superficial injections of hyaluronic acid products (another reason to stay deep). I am not sure whether this represents an optical phenomenon, an expansion of the pigmented lid skin, or blood degradation products in the expanded extracellular space.

Hyaluronidase selectively hydrolyzes and dissolves hyaluronic acid. If there is a substantial irregularity that cannot be manipulated away or if for other reasons the patient wishes for an overfill to be corrected immediately (Fig. 3, below, right), the problem area may be dissolved with hyaluronidase. This should not be the first method used; with experience, it should almost never need to be used, but having it available will give a sense of security to the novice injector. I have used 75 units of hyaluronidase in 3 cc of local anesthetic for almost immediate dissolution of hyaluronic acid–induced bumps. Others have reported using smaller amounts to avoid losing all of the injected hyaluronic acid6 (Fig. 4).

DISCUSSION

I like to think of the face as having an expressive foreground and a structural background. The expressive foreground consists of the elements that send emotional signals, such as glabellar frown lines, the relative height of the medial and lateral brows, and marionette lines, among others. The structural background of the face, although it

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**Fig. 3.** A 54-year-old woman before injection (above, left), 1 month after injection (above, right), and 11 months after injection (below, left) into the tear troughs, showing the extended longevity of the product in this location. (Below, right) The hyaluronic acid injections left her with a discoloration of the left lower lid and a slight mass that could be seen in vertical light. Fifty units of hyaluronidase in 3 cc of local anesthetic was injected into the lower lid. One can see the dissolution of the mass effect and the loss of the dark color 2 days after injection. In my experience, the mass effect is actually gone almost immediately after injection.
may include some of the former, really is the expressively neutral structure of the face—what it looks like.

Certain lines and furrows, primarily the glabella frowns lines, marionettes lines, and tear troughs, have effects on the perception of the face far beyond their size. Relatively small changes in these areas alter the emotionally projecting foreground of the face because they mimic expressions or emotional states.

The tear trough area is prominent in so many people and alters the expressive foreground of the face so much that an easy, safe, and reasonably lasting correction would be of great benefit. Of course, this is not a new concept, and the problem has occupied plastic surgeons’ thoughts for quite a while.

The names most associated with the tear trough are Loeb, Flowers, and Hamra. Loeb transferred pedicled fat beneath the area to elevate it. Hamra expanded on the concepts of Loeb to reset the orbital septum and support the lateral canthal area. Flowers is the most perceptive and thoughtful of the observers of the periorbital region. Among his other innovations, he pioneered the use of silicone implants to improve the tear trough and to address the flat infraorbital area. These approaches are highly successful in the hands of experienced surgeons. They all require open surgery and a learning curve in the unforgiving lower lid. They have the advantage of being as permanent as any soft-tissue surgery of the aging face, but the complications from uninitiated (and even experienced) operators in the area can be profound. Moreover, surgery in this area works least well in the medial and superior tear trough, at the side of the nose where the shadowing can be most intense.

Injected fat has been used in this area, and some recommend placing it superficially between the skin and muscle. Injected fat in the lower lid and tear trough can reduce the dark discoloration of the area, but it is so unpredictable in lumping and creating unnatural contours that I no longer support its use in the tear trough. Problems, when they occur, are difficult to treat.

Much feared is the possibility of an intra-arterial injection, with skin injury or even blindness. The incidence is unknown, and at this time there are no reported cases of blindness with hyaluronic acid, although there are a few cases of intra-arterial injection with skin injury. Certainly they are extremely rare, less than the incidence of blindness with blepharoplasty. Coleman reviewed this subject and recommended using blunt cannulas in a vasoconstricted environment and not injecting more than 0.1 cc per pass. The use of custom-made, 27- to 30-gauge blunt cannulas has been reported in an attempt to further reduce the possibility of intravascular injection. It is hard to determine the true risk of such an infrequently occurring complication and whether any preventative measures will actually reduce the incidence. The tried and true method of avoiding an intravascular injection with local anesthetic—a constantly moving needle with very slight injection pressure—will, in theory, also reduce the risk with hyaluronic acid injections, and to me, this makes the most sense.

Fig. 4. A 59-year-old patient before (left) and 4 months after (right) injection of 0.3 cc of hyaluronic acid per side.
CONCLUSIONS

I find that the use of hyaluronic acid in the tear troughs has the following benefits: Injection is relatively easy to perform. The very medial and superior tear trough is where this treatment works the best; it is the area where surgery works the least well. There is a high degree of patient satisfaction. The material is very long-lasting (1 year or more) in the tear trough. Most complications are self-limiting and can be treated by massage. In the event of an unsatisfactory effect, the material can be dissolved away. If a larger operation provides a less than total correction, hyaluronic acid injection can nudge the result to make a more pleasing contour. There is a distinct group of patients who will benefit more from leveling of the tear troughs than from modification of the fat pads. With this method, the young patient can avoid surgery completely.

The disadvantages of hyaluronic acid in the tear trough are as follows: it is not permanent. It is by nature a compromise procedure. The larger the fat pads, the more of a compromise it becomes, and in those cases, only moderate improvement is possible. There are no associated improvements in the lower lid as can be obtained with surgery. There is a distinct group of patients who will have more improvement by direct fat pad modification than by filling below them.

On balance, I find this procedure to add flexibility to my practice of cosmetic surgery; it adds a group of patients whose appearance can be improved without the need for large and more risky operations to accomplish relatively small anatomical changes. It is a replacement for lower lid surgery in relatively few patients; it is complementary in many more. It allows me to touch up a lower lid blepharoplasty to achieve additional improvement without additional surgery. It can be used all the way around the eye and can even substitute for a tear trough implant. Although there is a learning curve, it is not a long one, and irregularities at the injected site can always be reduced with the use of massage or hyaluronidase, offering a level of security that is not present in most surgical procedures. Considered together, I believe that hyaluronic acid injections in the tear trough are a safe way of achieving considerable patient improvement with little risk.

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DISCLOSURE

The author was once paid by Medicis to be part of a Restylane expert users group. There are no other conflicts of interest.

REFERENCES

Hyaluronic Acid Fillers and Botulinum Toxin Type A: Rationale for Their Individual and Combined Use for Injectable Facial Rejuvenation

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Summary: Soft-tissue augmentation has seen a renaissance of interest, as an increasing number of patients seek aesthetic improvement without major downtime. Although injectable agents for soft-tissue augmentation have been widely available for more than 20 years, the renewed interest has been fueled in part by the introduction of botulinum toxin type A. The unequivocal establishment of predictable and aesthetic results, initially and primarily in the upper face, created a need for an agent that would work equally well in the lower face and that could be administered in an office setting. The marriage of these two injectables (hyaluronic acid and botulinum toxin type A) began with the escalating popularity of both of these substances individually and the realization that a more global aesthetic enhancement is provided by combining these agents in custom proportions to achieve maximum aesthetic effects. Although the authors discuss most of the related, available hyaluronic acid and botulinum toxin agents, their clinical experiences, and the scientific data regarding these products, they realize that the discussions have been weighted toward the products that have been available for use in the United States the longest. In this article, they attempt to explain some of the results of prior (to U.S. Food and Drug Administration approval) studies that have been the subject themselves of some confusion, and provide a rationale for using hyaluronic acids and botulinum toxin for facial enhancement independently and in combination. (Plast. Reconstr. Surg. 120 [Suppl.]: 81S, 2007.)

As physicians became more sophisticated in their understanding of facial aging, the search began for solutions that provided for the complexities that included surgical repositioning, chemodenervation, and volumetric restoration. When performed in the appropriate combinations, rejuvenation can be most closely approached. The next level of results obtained with surgery has then naturally evolved to use some form of volume replacement that has become one of the central tenets of the field of soft-tissue augmentation. The deflationary effects of aging have also been better understood and their contribution to the mechanics of animation have been well established.

The traditional concepts of soft-tissue descent associated with aging (for which the lift was the solution) have been supplemented with the reality that the illusion of descent is often a manifestation of regional volume depletion. Filling can augment and even, at times, replace or delay surgery. Volume replacement by injection can also give the appearance that the area has been lifted despite the fact that no actual lifting has taken place. Ex-

FDA Status and Approved Uses: Hyaluronic acid products are FDA approved for filling moderate to severe facial wrinkles and folds around the nose and mouth. Restylane is FDA approved as an injectable gel to treat facial wrinkles. Juvéderm (Ultra and Ultra Plus) is FDA approved. Hylaform is approved by the FDA for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). Captique is FDA approved for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles. Botox is FDA approved for use in the glabellar region. All other uses are considered off-label.

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amples of this are seen in the eyebrow (Fig. 1), cheeks, nasolabial folds, perimental hollows, and lips (Fig. 2). Volume augmentation of the perioral region (including lips) performed in a variety of ways for a host of presentations remains the number one presentation and indication for soft-tissue augmentation. The influence of regional volume loss by repetitive motion not only is a significant factor in aging but also relates to the persistence of treatment by injectable soft-tissue agents and must be addressed for optimal effects.

**RATIONALE FOR USING HYALURONIC ACID AGENTS FOR SOFT-TISSUE AUGMENTATION**

There is an abundance of support for the safe and effective use of botulinum toxin type A in both the therapeutic and the aesthetic arenas. There are now over 100 known agents used worldwide that are considered soft-tissue fillers. The scientific support for the use of any substance for soft-tissue augmentation, however, is critical to establish safety and efficacy, which the majority of such substances lack. It is used to substantiate the cosmetic application of such agents and also helps define the adverse events profile and purity of the agent. Ultimately, we must rely on both real science and clinical experience to achieve a greater comfort level to offer particular agents among the options available to our patients. The concept of “read before you inject,” however, has proven also to be problematic, in that the accuracy of the literature surrounding many injectable agents also leaves much to be desired. Even specific to certain

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**Fig. 1.** (Left) This patient had previously undergone upper and lower blepharoplasty elsewhere and presented for options to improve the deflationary effects for overzealous soft-tissue excision. (Right) Restylane was injected to the lateral infrabrow region and tear trough. No Botox was administered. (Reproduced with permission from Steven Fagien, M.D.)

**Fig. 2.** (Left) This patient presented for treatment of nasolabial folds and lower facial aging. (Right) Two milliliters of Restylane was injected into the nasolabial folds, lips, and perimental hollows. (Reproduced with permission from Steven Fagien, M.D.)
groups of seemingly related agents, a high degree of variability exists. The rationale for the use of hyaluronic acid products, for instance, relates to the fact that the substance is ubiquitous in human tissue. Commercially available hyaluronic acid products have a molecular weight between 1 and 10 million daltons. In the human body, with the exception of intraocular use, they have a very fast turnover rate. They are produced from enzymes in the cell membrane contained in what has been theorized to be a specific organelle. Their usefulness for aesthetic indications therefore requires manipulation of the chemical structure that is achieved mostly through cross-linking and/or other modifications to substantially increase residence time and persistence of clinical effects in tissues. These agents are produced by tissue extraction or biosynthesis from a nonanimal source. These cross-linked hyalin gel derivatives of hyaluronan retain the biocompatibility and biological properties of the natural hyaluronan and are nonimmunogenic. Furthermore, the method of cross-linking of agents can also significantly affect longevity. For example, Hylaform (Allergan, Inc., Irvine, Calif.) and Restylane (Medicis, Scottsdale, Ariz.) use different chemicals to cross-link, which contributes to the residence time differential between these two products. These differences in all of the properties of the various hyaluronic acid agents, especially with regard to factors such as injectability, tissue reactions and edema, palpability, and persistence relate to the seemingly minor (although perhaps not) differences in source, particle size, cross-linking, and concentration, to name just a few. In contrast, they all share in the extremely low immunologic potential (development of neutralizing antibodies). Regarding these concerns, studies in mice, rabbits, primates (owl monkeys), and guinea pigs in various tissue compartments (intramuscular, intravitreal, intraperitoneal, intradermal, and subcutaneous) did not produce symptoms of sensitization or immune response.\textsuperscript{6–8} If there is any immunologic response to these products, it is most likely a response to protein contaminants or additives rather than to the hyaluronan itself. Reactions to these agents have also been attributed to excessive concentration and cross-linking.\textsuperscript{9–11} Although intuitively it may appear that increasing these two variables would increase the persistence/residence time, a critical balance must be achieved to minimize these adverse events.\textsuperscript{9,13,14} Several hyaluronan formulations have been U.S. Food and Drug Administration approved and are commercially available in the United States. Restylane, Captique (Genzyme, Cambridge, Mass.), and the newly approved Juvederm family of products (Allergan, Irvine, Calif.) are produced from bacterial fermentation sources; whereas Hylaform (Genzyme) and Hylaform Plus (Genzyme) are produced from nongender chicken combs.

Restylane has been available in the United States since December of 2003, whereas Hylaform, Hylaform Plus, and Captique were approved in April, October, and November of 2004, respectively. The family of Juvederm products received U.S. Food and Drug Administration approval in June of 2006 and became commercially available in the United States at the end of that year. Both Restylane and Juvederm products are stabilized using 1,4-butanediol diglycidyl ether as the cross-linking agent. The manufacturers of both products claim a low protein load and few additives. With Juvederm products, there are claims of greater cross-linking and less free, non–cross-linking hyaluronic acid. Both qualities likely contribute to their individual unique characteristics. The preliminary experience has been, however, with the exception of some inconsistent anecdotal details relating to injectability and immediate postinjection observations (e.g., bruising, swelling), that the product appears to perform much like Restylane, which presently remains the benchmark for all hyaluronic acid products. The approved indication is the same for all of the products. Each product is U.S. Food and Drug Administration approved for mid- to deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. All other uses are considered off-label, including lip enhancement. In contrast to bovine collagen fillers, no skin testing is required.

Many factors contribute to the varied performance of any particular hyaluronic acid filler. For instance, with Restylane, the stabilizing, cross-linking process results in a specific percentage of cross-linked hyaluronic acid in the final product. The process also increases the hyaluronic acid concentration approximately fourfold to 20 mg/ml and produces the small gel particle size (400 μm). The concentration of Hylaform is 5.5 mg/ml, and when compared with agents by concentration, it corrects for variations in molecular weight. Native hyaluronic acid is rapidly degraded and cleared from the skin. Restylane begins as hyaluronic acid biosynthesized and isolated to a high degree of purity from bacterial (\textit{Streptococcus}) fermentation cultures. A low level of impurities contributes to allowing Restylane to be produced at relatively higher concentrations of hyaluronic
acid, and the stabilizing process produces hyaluronic acid with a minimal degree of cross-linking. Therefore, greater cross-linking does not necessarily translate into greater longevity and persistence. These features seem to distinguish Restylane from the other hyaluronic acid products. Therefore, whereas on the “science” side, concentration contributes most to longevity, on the “art” side it is proper injection technique. On the contrary, the manufacturer also claims that Restylane is more biocompatible with native hyaluronic acid because of its limited cross-linking and achieves maximum implant residence time based on clinical evaluation because of concentration as well. The resulting continuous three-dimensional molecular network can be formed into various gel shapes and bead sizes. The actual amount of hyaluronic acid in a Restylane gel bead is approximately five times greater than what is needed to maintain its volumetric correction. Therefore, the size and shape of the implant are maintained for an extended period of time.

Early clinical and efficacy studies of Restylane were reported from Italy and Sweden.14–16 The Swedish study reported that, based on physician evaluations, treatment sites maintained an average of 82 and 69 percent corrections (visual analogue scale, 0 to 100 percent) at 12 and 26 weeks, respectively. The Italian study reported that 78 percent of patients maintained moderate to marked improvement after 8 months, with nasolabial folds sustaining the best result. Nevertheless, these studies were performed long before Europeans had truly appreciated the greater influence of outcomes in improved and methodical injection techniques such as serial puncture. This injection technique and other methods17 that deliver these products precisely and efficiently have dramatically improved the performance of these products. In this Italian study, reactions included redness, swelling, darkening of the treatment site, and slight pain occurring in approximately 13 percent of patients. Ongoing analysis of the Q-Med Aesthetic events databases indicated that, in 1999, with an estimated 144,000 patients treated with Restylane, only one of every 650 patients (0.15 percent) reported redness, swelling, localized granulomatous reactions, bacterial infection, or acneiform lesions.18 In mid-1999, Restylane was reformulated with a source material of lessened protein load. Therefore, there was a large decrease in patients experiencing adverse events: 0.15 percent in 1999 and 0.06 percent in 2000. This reformulation in mid-1999, with one-sixth trace proteins with a strong decrease in adverse events. Indeed, adverse events were 5.9 times more frequent with the old batch than with the new. Delayed implant hypersensitivity reactions were reported in several case series at low incidences (0.4 to 3.7 percent) in early non-U.S. studies. It was subsequently realized that the batch and the nature of the injection technique strongly influenced adverse reactions. This has resulted in some of the European studies being withdrawn by their authors. Furthermore, reports of suspected hypersensitivity reactions to the World Health Organization International Database also have decreased.

Recently, there has been a series of reports of theorized hypersensitivity reactions, which are more likely a treatment-associated response to hyaluronans. One article attributed extreme angioedema of the lips to a hypersensitivity reaction that was short-lived. A true allergic reaction to a product, however, would not likely resolve spontaneously within a week. The more likely response was treatment-associated and could generally be avoided by injecting the agent slowly and gently. No antibody tests were reportedly performed in this particular case to support the author’s claim of a hypersensitivity reaction. Many authors also discuss the work of Micheels as it relates to hypersensitivity responses.19 The reference to Micheels work on hypersensitivity to hyaluronans, however, may be based on significant inaccuracies. Micheels reported that the immunoglobulin G and immunoglobulin E responses to hyaluronic acid can occur and are responsible for hypersensitivity to these hyaluronic acids. In his article, the specificity to hyaluronic acid of these antibodies was not confirmed through skin testing and rechallenge reported allergic response; patients elicited no positive skin response. Finally, skin tests in the article by Micheels are performed after the hyaluronic acid fillers are digested with hyaluronidase, which leaves no hyaluronic acid, suggesting that the original skin test is not the original filler (i.e., it is no longer there). Lowe (personal communication) also no longer supports the conclusions of his own article on hyaluronic acid allergy as valid, based on his observations over the past 4 years.

Another recent article20 reported a granulomatous reaction to nonanimal stabilized hyaluronic acid, making the suggestion, without evidence, that the possible mechanism of the reaction was allergic. They also did not perform antibody studies and, again, cited the article by Micheels. The Micheels article is often referenced by those who associate every adverse response to hyaluronic acids as allergic in nature. Attempts to
shift these objective photographic observations onto the U.S. Food and Drug Administration Hylaform study of global assessment also make little sense. Lumps with Hyaluronan can be caused by focal abundance of material or inflammatory nodules that may be a result of less precise, forceful injection of these agents. We tend to believe firmly that time should be spent injecting, not massaging. Postinjection massage frequently results in a decreased final correction because of the forceful displacement of the material deep both peripherally and into the subcutaneous space. We also personally feel that inflammatory nodules can be related to forceful implantation techniques.

The availability of hyaluronidase (Vitrase; Ista Pharmaceuticals, Inc., Irvine, Calif.) now makes treating lumps or misplaced hyaluronic acids very simple and convenient21 and is rarely necessary. More often, these lumps and irregularities are not adverse reactions but rather misplaced filler. Finally, we must approach every adverse event in patients who present with presumed longstanding allergy to hyaluronic acid with caution and a dose of skepticism. Not infrequently, patients present with clinical “reactions” or a history thereof, and as responsible physicians, we must first confirm that the agent used was indeed a hyaluronic acid and inquire about what other agents have been injected over the prior years. It is not uncommon that further investigation indicates that other filler substances have been applied. Ultimately, the unique physical properties of the hyaluronan products translate into their clinical effects. Differences in rheologic properties differentiate the heartier Restylane hyaluronic acid variety from the more forgiving and less long-lasting Hylaform product, whereas there is also less swelling and potential “lumpiness” with the latter, but this comes at the cost of lesser persistence and residence time. The Juvederm family offers several different products with varying viscosities, and it remains to be seen how well these will fare by comparison. Preliminary experiences, however, suggest that these products may be less likely to yield visible lumps when injected more superficially.

Finally, combining botulinum toxin type A and injectable hyaluronic acid for facial aesthetic enhancement has taken on many forms.22 Initially, the former was touted for use primarily to the upper third of the face and the latter reserved for injectable aesthetic improvement to the lower face. Still, most patients present for facial rejuvenation inquiring about what injectable agents or treatments they can receive (all at once) for maximum aesthetic effects while a combination of agents and other treatments are applied to independent facial regions. The synergistic effects, however, of combining hyaluronic acids with botulinum toxins in the same region where this may be appropriate for this treatment has also taken injectable facial rejuvenation to the next level. Facial regions that more obviously benefit from combination treatment are those areas that have transitioned from dynamic to static lines, furrows, and depressions. Common examples of this are glabellar forehead furrows that are present at animation and at rest and the “downturned” corner of the mouth. Monotherapy with botulinum toxin,
at this point, typically has only a modest effect, as the surface contour changes are present even with complete chemodenervation. Soft-tissue augmentation and supplementation used in conjunction with chemodenervation can yield dramatically improved effects. Furthermore, as the volume loss is more commonly associated with areas having greater movement (animation), it has been well
demonstrated that longer lasting effects with injectable fillers can be achieved with the concomitant use of botulinum toxin type A, which also decreases dissipation of the implant. Such regions include the brow, lips, chin, and perimental hollows (Figs. 3 through 5).

It is one author’s (S.F.) approach to perform a comprehensive aesthetic evaluation for the assessment of the treatment required (botulinum toxin or which filling agent or both), appropriately mark the area as indicated, and inject an appropriate amount of local or regional anesthetic to the treatment area followed by injection of the filling agent and lastly the botulinum toxin. This sequenced approach allows for maximum comfort (both the filling agent and botulinum toxin are administered in a pain-free environment) and the ability to provide both treatments at the same setting, and provides for a more accurate destination for the toxin (after the filling agent has been administered). Hyaluronic acid fillers are also commonly used at the time as facial surgical procedures to complement and enhance the overall result (Fig. 6). Most commonly, to achieve the highest level of aesthetic improvement of the face, these agents are used in combination in the same region and individually in separate regions. The surgeon may use hyaluronans in the lips, nasolabial folds, chin, cheeks, brows, and periorbital hollows, while also using botulinum toxin around the lips, jaw line, neck, chin, nose, and periorbita. It is our opinion that when botulinum toxin is used in combination with hyaluronans in the appropriate patient in the same region, the botulinum toxin reduces the muscular movement of the face, which allows for greater tissue residence of the hyaluronan and restoration of the balance of lower facial movement and position. In our practices, it is now far less common to treat a patient with a single agent. Rather, the combination use of botulinum toxin in conjunction with hyaluronans and other injectable soft-
tissue agents has become the standard of care for patients who present for global facial aesthetic enhancement by injection.

CONCLUSIONS

All of the hyaluronic acid substances are used in an attempt to temporarily restore lost volume with an amorphous gel that is both ubiquitous in human tissue and highly biocompatible. These agents have been proven to be safe and effective but ultimately require periodic maintenance therapy to maintain the desired effects. The substances and applications/techniques for soft-tissue augmentation are increasing at an accelerated rate. This is attributable mostly to a greater appreciation and understanding by the cosmetic physician that the three-dimensional aspects of the face must be preserved or replaced to achieve an optimum aesthetically pleasing result. Nonsurgical facial rejuvenation can be achieved by injectable soft-tissue augmentation with hyaluronic acid products and by chemodenervation with botulinum toxin used both independently and in combination for the most comprehensive results. It is critical that one have a thorough understanding of all the techniques and materials, and how they work in combination, to provide patients with the best outcome. Inevitably, it is not what is used but how it is used that is the most important aspect. A physician should not be a jack of all trades and a master of none. As newer injectables are developed, the methods of soft-tissue enhancement will continue to evolve, possibly bringing even greater results and satisfaction to our patients.

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DISCLOSURES

Arnold W. Klein, M.D., serves as consultant and investigator to Allergan and Medicis. Steven Fagien, M.D., serves as consultant and investigator to Allergan, Medicis, Dermik Aesthetics, and Mentor, Inc.; is an investigator with Anika Therapeutics; and a shareholder with Collagen Matrix Technologies.

REFERENCES

The Role of Autologous Fat and Alternative Fillers in the Aging Face

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Summary: Soft-tissue fillers can be used successfully to restore volume loss caused by facial aging. Injectable fillers can be used in isolation or in conjunction with other facial rejuvenation procedures. To achieve a superior aesthetic result, the plastic surgeon must understand the key components of facial aging: soft-tissue atrophy, gravitational descent, and loss of skin tone. An accurate assessment of the relationship of these factors will determine the role of soft-tissue augmentation through the use of fillers. Because the majority of facial volume loss through aging is attributable to fat loss, the authors believe that autologous fat represents the ideal soft-tissue replacement. The authors describe the appropriate use of autologous fat and improvements in technique that have enhanced the predictability of facial fat grafting. When autologous fat is not an option, alternative facial fillers including calcium hydroxylapatite and hyaluronic acid may provide excellent results. The authors’ algorithm for filler selection is based on relative morbidity, recipient-site characteristics, and the physical characteristics of each filler. This algorithm is discussed in the following anatomical regions: the nasolabial folds, glabellar crease, malar region, nasojugal groove, and lips. When used appropriately, soft-tissue fillers can contribute significantly to overall facial rejuvenation. (Plast. Reconstr. Surg. 120 [Suppl.]: 89S, 2007.)

Early attempts at facial rejuvenation relied exclusively on lifting procedures that did not address the soft-tissue atrophy component of facial aging. Specifically, skin-lift procedures served to flatten and tighten the face rather than provide significant volume augmentation. Further advances in lifting procedures, specifically, the superficial musculoaponeurotic system lift and midface lift, allowed significant improvements in volumetric repositioning and contouring of the aging face but did not address soft-tissue atrophy. Lifting atrophied tissues improved contour, but overall facial volume was not restored.

All the tissues of the face undergo age-related deterioration. These changes begin at 30 years of age and progress rapidly in the perimenopausal years in women. In addition, facial aging is associated with loss of skin elasticity and ptosis of the soft tissues. Although there remains controversy as to the degree of skeletal atrophy in aging, there is little debate that the majority of facial volume loss is attributable to soft-tissue atrophy. Because the majority of atrophy in the face is attributable to fat loss, we believe that autologous fat represents an ideal soft-tissue filler. Recently, numerous injectable fillers have been marketed as alternatives to facial fat grafting, with various claims of clinical efficacy. Because the injection of soft-tissue fillers is easily performed without significant recovery, many practitioners are using fillers not only to address facial volume loss but also to compensate for gravitational and skin elasticity changes. The “overinjection” of fillers can yield disappointing and unnatural results.

We believe that the goals of soft-tissue augmentation in the aging face can be simplified as follows:

FDA Status and Approved Uses: Restylane (hyaluronic acid), no unapproved uses discussed; Hylaform (hyaluronic acid), no unapproved uses discussed; Sculptra (poly-L-lactic acid), no unapproved uses discussed; Juvederm (hyaluronic acid), no unapproved uses discussed; Perlane (hyaluronic acid), no unapproved uses discussed; Radiesse (calcium hydroxylapatite), discussed a complication of use in the lips, which is an off-label use of Radiesse.
(1) to diminish the depth of various grooves and creases throughout the face (i.e., the nasolabial fold, glabellar crease, and nasojugal groove), and (2) to provide volume augmentation to atrophied tissues (i.e., malar and submalar regions and lips) (Figs. 1 and 2).

Plastic surgeons are uniquely positioned to appropriately diagnose and treat the integral components of facial aging. This article focuses on identifying the critical components of facial aging to treat soft-tissue atrophy in the appropriate fashion. Specifically, our aim is to use soft-tissue fillers to address facial atrophy and not to replace lifting procedures for gravitational descent or skin resurfacing procedures for loss of skin tone. We describe an algorithm for the use of soft-tissue fillers based on specific aesthetic goals and anatomical regions.

**PREDICTABLE FACIAL FAT GRAFTING**

We have had extensive experience with facial fat grafting. Fat has had many periods of enthusiasm and disappointment because of its often unpredictable volume maintenance. Fat has had many periods of enthusiasm and disappointment because of its often unpredictable volume maintenance. Through recent improvements in procurement, processing, and infiltration, autologous
Fat has become reliable once again. We describe our technique for achieving consistent results using autologous fat. Autologous fat transplantation has become a workhorse for soft-tissue augmentation throughout the body for both cosmetic and reconstructive indications. Because autologous fat is typically abundant and the process of purification and injection is fraught with minimal complications, we have found autologous fat to be a versatile filler. We have used autologous fat as a filler to treat facial aging, contour defects of the reconstructed breast, and patients with hemifacial atrophy and craniofacial disorders (Fig. 3). Unlike many synthetic fillers, viable fat remains soft, has significant longevity, and is dynamic. Living fat changes size in proportion to the patient’s weight gain and loss.

Despite significant clinical advantages with the use of autologous fat, there are numerous variables that determine the predictability of its use. These variables can be grouped into harvesting, purification, and infiltration. Through a variety of clinical and basic science research performed in our laboratory, we have been able to identify numerous variables that affect the reliability of fat grafting and have been able to improve our results based on this understanding.

**FAT GRAFTING TECHNIQUE**

Armed with our laboratory experience, we have modified our technique to improve our results. Our technique is based on a method originally described by Sydney Coleman. The goal is to minimize chemical and mechanical trauma to the autologous fat transplant, thereby decreasing the damage to adipocyte and preadipocyte architecture.

**Harvest**

Autologous fat grafts are typically harvested from abdominal, thigh, or buttock donor sites using a blunt cannula (Byron Medical, Inc., Tucson, Ariz.) attached to a 10-cc syringe using low-pressure suction. Minimal anesthetic infiltration with 1% lidocaine is advocated, and large-volume tumescence techniques should be avoided.

**Purification**

Purification of fat is performed by the atraumatic rolling of fat on absorbent Telfa pads according to the following guidelines:

1. No saline or lactated Ringer’s solution is used.
2. There is limited exposure to air.
3. Fat is purified by rolling it on a dry Telfa pad until a meringue texture is achieved and the fat is its natural yellow color.
4. Fat is immediately transferred to 1-cc tuberculin syringes in preparation for injection.
5. We do not advocate freezing fat for storage purposes, as this has been shown to lead to diminished persistence when compared with freshly harvested fat.

**Injection**

The injection of purified fat is performed using injection cannulas that are tailored to the specific region being treated. A blunt injection cannula is used for generalized volume augmen-
tation. The V-dissector cannula is designed to release a deep crease and is therefore ideal for use in the nasolabial fold or the glabellar crease. Lastly, a 20-gauge microinjection cannula is reserved for those areas requiring the greatest precision, such as the nasojugal groove and lips. To facilitate the revascularization of fat grafts and promote long-lasting results, small aliquots (<0.1 cc) of fat should be injected into multiple subcutaneous planes. There appears to be a diffusion limit to the survival of autologous fat grafts; therefore, minimal overinjection of less than 10 percent should be performed. Lastly, we have observed that autologous fat grafting has greater success in younger patients (<40 years) than in older patients (>60 years).10

**FILLERS BY ANATOMICAL REGION**

Because the unique characteristics of the recipient site play an integral role in determining both the choice and the efficacy of a given filler, it is helpful to categorize our discussion by anatomical region. In addition, recipient sites can be further separated into two broad groups: those that are amenable to groove or crease effacement, such as the nasolabial fold and glabellar crease; and those that require volume enhancement, such as the malar region, jaw line, and the lips.

The best results of clinical fat transplantation occur in sites with minimal motion when compared with mobile or dynamic areas. We hypothesize that diminished motion leads to better revascularization and have observed that fat survival in the malar, periorbital, superior nasolabial fold, and parasympophysial regions is better than in any other area of the face. In contrast, fat grafts to areas with significant motion, such as lips and marionette lines, have diminished survival and typically require secondary injections.

Despite improvements in fat grafting technique, there remains an element of variability with the use of autologous fat. As a result, alternative injectable fillers have been used extensively and have many appealing characteristics, including diminished preparation time, lack of donor-site morbidity, and relative ease of injection. We have had experience with the use of large-particle, cross-linked hyaluronic acid (Perlane, Medicis, Scottsdale, Ariz.; Juvederm, Allergan, Irvine, Calif.), smaller particle, non-cross-linked hyaluronic acid (Restylane, Medicis, Scottsdale, Ariz.), calcium hydroxylapatite (Radiesse, BioForm Medical, San Mateo, Calif.), and poly-L-lactic acid (Sculptra; Dermik Laboratories, Berwyn, Pa.) for soft-tissue augmentation in the face. In addition to longevity profile, the physical characteristics of these injectable fillers ultimately determine their suitability for a particular anatomical region.

**Nasolabial Folds**

The goal for the treatment of the nasolabial fold is to diminish the depth of the crease. The effacement of the nasolabial fold can be performed with the widest array of fillers because of the thickness of overlying skin and underlying skeletal support from the maxilla. The key to successful treatment of the nasolabial fold is to accurately diagnose the cause of the deep fold. Some portion of the nasolabial fold is attributable to gravitational descent of the overlying cheek, and another portion is attributable to soft-tissue atrophy. To determine the amount of fold that is attributable to soft-tissue atrophy versus gravitational descent, we use a manual displacement test (Fig. 4). The cheek is pulled superolaterally. If gentle manual displacement results in significant effacement of the nasolabial fold, the use of soft-tissue fillers alone will probably not be effective.

The treatment of the nasolabial fold with fat injection requires the release of the dermal attachments creating the fold. We advocate the use of the V-dissector cannula (Byron Medical) for this purpose. The V-dissector device allows one to infiltrate small fat aliquots while simultaneously releasing the fibrous attachments to the nasolabial fold. Typically, 2 to 3 cc of fat is injected per side in a fan-like distribution. The majority of the fat is placed beneath the crease and medially. When combined with lifting procedures, both the gravitational component and soft-tissue atrophy component of the nasolabial fold is addressed (Fig. 5). When performing fat grafting to the nasolabial fold in conjunction with a face lift, it is unnecessary and often detrimental to carry the face-lift dissec-
tion across the nasolabial fold. A more limited dissection tends to minimize facial flattening, ecchymosis, and potential bleeding.

Alternative soft-tissue fillers are also quite effective in treating the nasolabial crease. Because of its improved longevity profile, Radiesse is our first choice of injectable filler in the nasolabial fold. Radiesse has a firm, robust character once injected and is therefore highly effective in treating men with thicker skin. However, care must be taken to avoid superficial injections of Radiesse because of the possibility of contour irregularities. An important drawback to the use of Radiesse is relatively increased discomfort when compared with other injectables. Hyaluronic acid is also effective in the nasolabial crease. We have had particular success with the use of longer-lasting, large-particle hyaluronic acid products: Perlane and Juvederm. We have found these agents to be comparable to Radiesse in this region. Lastly, we reserve smaller-particle hyaluronic acid (Restylane) for shallow nasolabial creases and for small touch-ups.

**Glabellar Crease**

The glabellar crease is another anatomical region where soft-tissue fillers are principally directed at wrinkle effacement. Despite the advantage of underlying skeletal support, the motion of the corrugator muscles limits the persistence of fillers in the glabella. Our early experience with fat grafting in this region was fraught with unsatisfactory results and a decreased persistence of fat grafts at 6 months. However, we were able to significantly enhance the survival of fat grafts by the preinjection blockade of corrugator muscle function with Botox (Allergan, Inc., Irvine, Calif.).

We typically inject Botox into the corrugators 1 week before fat grafting. Using the V-dissector cannula to release the furrows in the glabellar region, approximately 1 cc of fat is subsequently infiltrated under the crease in a fan-like fashion.
This feathering is important to diminish palpability. If corrugator motion can be diminished with Botox for 3 months, ample time for graft survival is provided. Using this method, long-term (>1 year) survival can be achieved with a single treatment, well beyond the effect of Botox (Fig. 6).

Radiesse injections into the glabellar region have proven to be an excellent alternative to autologous fat grafts. Injections of Radiesse into the glabellar region are most effective because the injection is placed in a preperiosteal plane. Radiesse in this region is particularly effective in those individuals with a deep crease and is also enhanced with the concomitant use of Botox. Hyaluronic acid is also well tolerated in this region; however, its greatest limitation is the need for subsequent injections when compared with autologous fat and Radiesse. For this reason, hyaluronic acid fillers are less effective when used in the glabellar region.

Lower Lids

The nasojugal groove or tear-trough deformity is often described as a relative concavity associated with the junction of the thin eyelid skin and thick cheek skin. It can be exaggerated by the adjacent convexity of superior lower lid fat. The nasojugal groove represents an excellent region for soft-tissue augmentation because of decreased motion–increased vascularity. These characteristics, in addition to thin skin, also lead to the potential for greater complications, including persistent contour irregularities.

Fat grafting to the lower lid region can be highly effective but requires meticulous technique to avoid a nodular appearance. Because of the delicate nature of the thin lower lid skin, small amounts of fat should be injected deep to the orbicularis oculi muscle, superficial to the underlying periosteum. Typical amounts of fat injected in these regions range from 0.3 to 1 cc per side. The use of the small, 20-gauge cannula (Storz; Bausch & Lomb, Rochester, N.Y.) allows for the injection smaller aliquots of fat in a less traumatic manner. This has led to the reduced incidence of visible and palpable fat nodules (Fig. 7). Once again, feathering around the deepest aspects of the nasojugal groove is suggested to avoid linear palpability. There have been theoretical concerns regarding potential fat embolism to the central retinal artery during fat grafting to the lower lids and glabella. Although we have never experienced such a complication, care is taken to minimize this potential complication by the use of a blunt cannula with a side-facing injection port.

In addition, gentle infiltration is of paramount importance.

Although the use of microinjection at the preperiosteal level has reduced the incidence of nodules caused by misplaced fat, there remains an incidence of persistent irregularities. These irregularities are typically caused by inadvertent fat placement superficially within the orbicularis muscle. The best treatment for visible fat irregularities includes direct excision through small incisions. Steroid injection should be avoided because of the absence of efficacy and potential further soft-tissue atrophy. Because of the sensitive nature of the lower lid region, fat grafting should be reserved for when one has achieved significant experience with fat grafts to other regions of the face.

The hyaluronic acid fillers are an excellent alternative to fat in the cheek–lid junction because of their ease of use, excellent safety profile, and limited nodularity. Hyaluronic acid appears to have improved longevity in this area compared with its use in other regions such as the nasolabial fold and perioral region. Restylane in the lower lid typically lasts 6 to 8 months. Restylane is most safely injected deep to the orbicularis muscle. Frequently, mild irregularities can be massaged to diminish nodularity. Finally, because the effect is not permanent, contour irregularities will certainly improve with time.
Malar Region

Because of the underlying skeletal support, the malar region is an excellent region for volumetric highlighting. The principal cause of age-related changes in the malar region is soft-tissue atrophy and to a lesser extent gravitational descent. Therefore, the principal goal of soft-tissue fillers in this region is to restore overall volume and contour rather than to fill a particular depression.

Fat grafting in the malar region is successful because of the limited motion in this region and a moderate degree of skeletal support. We typically inject 1 to 2 cc of fat per side in a feathered manner in the deep subcutaneous plane using a blunt cannula. Fat grafting in the malar region can highlight the cheek bones, similar but to a lesser degree than the use of malar implants. In addition, feathering the augmentation into the submalar hollow is quite effective in diminishing age-related atrophy in this region.

Autologous fat grafting represents the ideal replacement for lost volume in the malar region; however, alternative fillers such as Sculptra can be effective when fat grafting is not an option. The use of Sculptra requires multiple treatments over a several-month span, and our long-term follow-up for this relatively new filler is somewhat limited. Importantly, Sculptra has received U.S. Food and Drug Administration approval for volume augmentation in the malar region associated with human immunodeficiency virus lipoatrophy. Appropriately selected patients can achieve successful soft-tissue augmentation in the malar and submalar regions, but we believe the results are more subtle compared with fat (Fig. 8).

Lips

Volume augmentation to the lips is an important component of facial rejuvenation. Nevertheless, the ideal treatment for thin, atrophied lips has yet to be discovered. Autologous fat grafts to the lips can have excellent results but are limited by more variability in their persistence and prolonged edema when compared with their use in other recipient sites. Furthermore, the injection of autologous fat grafts to the lips is associated with a 2- to 3-week recovery, where there is often significant ecchymosis and edema (Fig. 9). We typically reserve autologous fat grafting to the lips for those patients undergoing a simultaneous procedure so that they may share the recovery time.

We have found improvements in postoperative edema resulting from the use of a smaller, 20-gauge side-port injection cannula (Storz). Infiltration is performed by means of an entry site at the base of the ala and at the oral commissure at the border of the wet and dry vermilion. One to 3 cc of fat can be placed in the upper and lower lips. The key to successful fat grafting to the lips remains an understanding of aesthetic principles.
to restore shape and a soft/natural result. The upper lip is associated with greater fullness centrally and near the commissures, whereas the lower lip is associated with increased fullness paramedially. Typically, the lower lip tends to maintain its volume to a greater degree than the upper lip.

Because of the increased morbidity and variable persistence of fat grafts in the lips, we have relied heavily on hyaluronic acid as an alternative in this region. Ease of infiltration, shorter recovery, and an excellent safety profile are the main advantages of the hyaluronic acid fillers (Fig. 10). Unfortunately, their longevity is limited to 4 to 5 months. Radiesse is not recommended in the lips because of an increased incidence of visible and palpable granuloma formation in this region.

CONCLUSIONS

To fully appreciate the role of soft-tissue augmentation in the aging face, it is important to delineate the various components of facial aging. We believe the three principal age-related changes in the face are gravitational descent, soft-tissue atrophy, and loss of skin elasticity. As a guiding principle, we believe that each of these changes should be addressed individually through separate procedures to provide the most natural result in facial rejuvenation.

It is clear that the replacement of atrophied soft tissues plays an integral role in facial rejuvenation and reconstruction. Despite variable results, facial fat grafting is well accepted by a majority of patients and has a low morbidity. Recent improvements in harvesting, purifying, and injecting autologous fat have made the process of facial fat grafting significantly more reliable. Future investigations concerning the variables that affect fat survival should yield even greater improvements with fat transplantation. Although volume augmentation is important, it can also be overdone. Unlike human immunodeficiency virus–associated lipoatrophy, which can result in profound soft-tissue atrophy, age-related changes are more subtle. Therefore, overcompensating for gravitational descent and skin changes can be unnatural. When used appropriately, facial fat grafting can provide a long-lasting and aesthetically pleasing solution for the soft tissues lost through aging or disease.

Despite the success of facial fat grafting in many areas of the face, plastic surgeons must be familiar with the use of alternative fillers. When autologous fat is not an option, our choice of filler depends heavily on relative morbidity and recipient-site characteristics. In regions of good skeletal support and relatively thick overlying skin, such as the nasolabial fold and the glabellar crease, we favor the use of Radiesse and large-particle hyaluronic acid (Perlane and Juvederm) because of their longevity. Nevertheless, in thin-skinned individuals or in superficial creases, we prefer small-particle hyaluronic acid (Restylane). Also, we favor hyaluronic acid products as an alternative to fat in the nasojugal groove because of the thin nature of the overlying skin. Similarly, hyaluronic acid remains our treatment of choice for thin, atrophied lips. For larger-volume augmentation, as in the malar region, autologous fat remains the best filler. We have, however, seen modest improvement with the use of Sculptra for regional volume augmentation. Improvements in predictable soft-tissue augmentation will allow plastic surgeons to provide comprehensive facial rejuvenation.

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Fig. 10. Lip augmentation with Restylane. (Above) Preoperative view. (Below) Three months after 1.5 cc of Restylane to the upper lip and 1 cc to the lower lip.
DISCLOSURE

Neither of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

REFERENCES

Management of Complications and Sequelae with Temporary Injectable Fillers

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Background: Injectable nonpermanent soft-tissue augmentation materials are extremely well-tolerated products that can be used safely in virtually all patients who are candidates for facial augmentation. In this article, the authors review the management of the few common and minor undesirable effects that may be associated with temporary fillers; in addition, the authors mention the rare incidence of serious complications.

Methods: The authors conducted a MEDLINE-based (1990 to 2005) review of complications and side effects of nonpermanent injectable filler materials. This review was supplemented with evidence presented at recent plastic surgery and dermatology scientific meetings and unpublished information made available to the authors.

Results: Nonpermanent injectable soft-tissue augmentation materials are extremely safe substances that are unlikely to cause more than mild injection discomfort, transient redness and swelling, and occasional short-term bruising when used for facial augmentation. Symmetry can usually be maintained with judicious bilateral use of injectant, and injection-site necrosis is rare and treatable. Proper technique minimizes the already very low risk of visible implants, nodule formation, and hypersensitivity reactions. Other serious effects are exceedingly rare, and retinal artery thrombosis, previously associated with injectable collagen, has not been seen with newer fillers.

Conclusions: Injectable nonpermanent fillers are extremely safe substances. Attention to injection technique further minimizes the low risk of adverse events, which are usually minor, spontaneously resolving, and easily treated. (Plast. Reconstr. Surg. 120 (Suppl.): 98S, 2007.)

Prepackaged injectable soft-tissue augmentation materials are extremely safe substances.¹ In vivo, they are associated with benign and remitting short-term effects. Medium-term effects are infrequent, and given the nonpermanent nature of the injectables, long-term effects are virtually absent. Interestingly, despite the differences in composition among the various common soft-tissue augmentation materials, they are remarkably similar in the type and frequency of their undesired effects.

FDA Status and Approved Uses: Restylane (Perlane, Juvederm/hyaluronic acid derivative), CosmoPlast (CosmoDerm/human collagen), Zyderm (Zyplast/bovine collagen), Sculptra (poly-L-lactic acid), and Radiesse (calcium hydroxylapatite) are FDA approved for soft-tissue augmentation. Radiesse (calcium hydroxylapatite) is FDA approved for use in the urinary bladder and larynx/vocal cords and as a radiopaque marker but not for facial soft-tissue augmentation. Bioform, Inc., the manufacturer of Radiesse, has submitted a FDA application for facial soft-tissue augmentation and may receive approval for this indication before publication of this supplement.
less, quick, uncomplicated, and unnoticeable that they can find even the most minor unanticipated outcomes to be disconcerting and upsetting. For this reason, it is desirable to discuss before treatment some of the most common potential sequelae (e.g., bruising and swelling) that have now been well described in the literature[3-4] and that can be temporarily socially embarrassing. In addition, it behooves the injector to take steps to minimize these minor outcomes.

**SHORT-TERM UNDESIRED EFFECTS**

**Injection-Associated Discomfort**

Short-term effects of injectables include discomfort on injection and postinjection skin redness, swelling, and bruising. With regard to injection-associated discomfort, some amount is experienced with all fillers. One factor associated with greater discomfort is the viscosity and consequent injection pressure associated with the injectant. Thicker hyaluronic acid preparations (e.g., Restylane; Medicis, Scottsdale, Ariz.)[5] and calcium hydroxylapatite preparations (e.g., Radiesse; BioForm Medical, San Mateo, Calif.) are among the more viscous fillers. On injection, these firmly displace surrounding tissue, thus inducing pain. Another relevant factor is the caliber of the needle. Calcium hydroxylapatite requires at least a 27-gauge needle, and poly-L-lactic acid requires at least a 25- to 27-gauge needle; in the latter case, the thicker needle is necessary not because of a uniformly elevated viscosity but rather because of the tendency of the reconstituted solution to contain thick, focal inclusions that tend to clog thinner needles. Obviously, thicker needles tend to injure more tissue on injection and thus to elicit greater injection discomfort. The anatomical site of injection also modifies pain. Perioral injections, injections of the lip, and injections of the periorcular skin, especially lower eyelids, are among the most painful because of the increased sensory innervation at these sites.

Several mechanisms can be used to diminish injection pain. Immediately before injection, application of ice or a vibratory sensation during injection can decrease discomfort. In the case of vibration, a hand-held vibrating back massager or similar device can be used. The efficacy of this procedure is predicated on the fact that vibratory sensation and sharp pain are transmitted through common neural pathways, with transmission of one type of sensation reducing concurrent experience of the other. If a vibrating device is not available, piercing it with a needle can be of benefit. Topical anesthetic preparations, both commercially prepackaged types (e.g., LMX; Ferndale Laboratories, Inc., Ferndale, Mich.) and custom preparations produced by compounding pharmacies, may be of some use in providing relief. If topicals are to be used, they should be applied before injection for at least 30 to 60 minutes and usually under occlusion of transparent dressings [e.g., Tegaderm (3M, St. Paul, Minn.), Saran Wrap (S. C. Johnson & Son, Racine, Wis.)] or repeatedly rubbed into the skin every 10 to 15 minutes. In general, however, injection pain is experienced beneath the level that can be treated by topical anesthetics. Thus, this modality is usually more effective at convincing the patient that the physician is concerned about pain management than at markedly reducing physiologically experienced pain. It should also be noted that topical anesthesia should be used sparingly or not at all on mucosal surfaces, such as the wet part of the lip, as systemic absorption can occur. Nerve blocks, in contrast, can be extremely helpful. The most commonly placed blocks are those of the infraorbital nerve, for treatment of the nasolabial folds and upper lips, and the mental nerve, for treatment of the lower lip and marionette lines. Full blocks can be easily placed intraorally, with a 30-gauge needle attached to a 3-cc syringe containing 0.5 to 2.0% lidocaine with 1:100,000 or 1:200,000 epinephrine. Alternatively, articaine 1% with 1:100,000 epinephrine may be injected. With a pH of 7 and an onset of action of 1 to 2 minutes, it is less painful and faster acting than lidocaine. Usually, 0.5 to 1 cc to each infraorbital foramen and 0.2 to 0.4 cc to each mental area is sufficient. Miniblocks, which consist of placement of as little as 0.1 cc of anesthetic solution into the sulcus superior to the third incisor bilaterally with an additional injection into the mucosa above the frenulum in the midline, can also achieve excellent anesthesia of the fibers of the infraorbital nerve. Some physicians may prefer to place blocks transcutanuously without having patients open their mouths. Although patients will still feel some pain after nerve blocks, they may tolerate this residual discomfort better if they are instructed that complete anesthesia with intradermal injection would be counterproductive. Specifically, they should understand that full infiltration with injected anesthesia would result in undesired filling of the potential spaces and rhytides that are targets for augmentation. Consequently, less filler material would be
placed, and only an incomplete and shorter lasting correction would be possible.

In an off-label use, some augmentation materials may be mixed with small quantities of lidocaine prior to injection to reduce injection discomfort without excessively increasing bolus volume. For instance, a 1.3-cc syringe of calcium hydroxylapatite can be attached, via an appropriate connector, to a syringe containing 0.1 to 0.2 cc of 1% or 2% lidocaine with epinephrine; the back-and-forth motion of the two syringes produces a smooth slurry that is easy to inject and that patients report hurts less upon delivery.

Patients have widely varying pain tolerance for injectable augmentation materials. Some fillers, such as collagen [e.g., CosmoDerm (Inamed Aesthetics, Irvine, Calif), CosmoPlast (Inamed Aesthetics), Zyderm (Inamed Aesthetics), and Zyplast (Inamed Aesthetics)], are minimally viscous, come prepackaged with anesthetic, and are well tolerated by virtually all patients. Nerve blocks are often preferred by patients when injecting hyaluronic acid derivatives, calcium hydroxylapatite, and poly-L-lactic acid. A small subset of extremely sensitive patients paradoxically find nerve blocks more distressing than filler injections without anesthesia; these patients complain of persistent numbness and strange sensations after nerve blocks and, needless to say, should not receive these in the future.

Redness and Swelling

Redness and swelling (i.e., erythema and edema) tend to result immediately after injection with many fillers. Both are local effects of puncture trauma and associated inflammation and the hygroscopic properties of the filler being used. Redness will usually persist for a few hours to overnight, but swelling can last longer, up to 1 to 2 days. When the lip is injected, swelling may be more noticeable and usually lasts 1 to 3 days and occasionally longer. Likewise, following multiple injections with poly-L-lactic acid, especially when used for diffuse facial lipoatrophy, edema or fat redistribution manifesting as an elevated contour may persist for several days to 1 week. In general, the more material that is injected, the greater the duration and extent of swelling.

As with mild injection-associated discomfort, redness and swelling are best managed by apprising patients in advance of these likely outcomes. In addition, careful injection technique can reduce the degree of both redness and associated edema. Whether the filler is placed by means of a serial injection technique or by linear tunneling with threading, minimizing the number of skin punctures limits the associated trauma. Even when poly-L-lactate is injected in multiple small aliquots, the needle may be partially withdrawn and redirected instead of completely removed and reinserted. Of the hyaluronic acid products, Restylane appears to induce more swelling than Hylaform (Inamed Aesthetics) and Hylaform Plus (Inamed Aesthetics).

Postinjection application of ice packs for 5 to 10 minutes definitely reduces the risk of swelling. Concerned patients may be allowed to use ice packs at home every few hours on the day of the injection but warned to avoid excessive use, which may cause cold injury to their skin. If patients are returning to work or social engagements immediately after injection, they should be encouraged to apply concealing makeup until the redness spontaneously remits. Makeup with a greenish tint is most able to camouflage red coloration. It is, however, the swelling that typically limits social activity on the day of treatment.

Bruising

Bruising (i.e., ecchymosis) is an inadvertent and occasional effect of soft-tissue augmentation. One cause of bruising is needle-associated perforation of vessels, usually dermal veins, during filler injection. In addition, crushing or rupture of vessels secondary to the pressure of adjacent firm tissue materials can result in localized or widespread ecchymoses. If bruising occurs, it may be evident immediately after injection but, often, notably in patients taking platelet disaggregators, bruising is delayed. Resolution may be gradual, over approximately 5 to 10 days. Even when it does occur, bruising tends to be localized and not markedly disfiguring. It is important for patients to understand that bruising does not interfere with the clinical result.

Needle perforation of vessels can be avoided by understanding the superficial anatomy of the face and also studiously refraining from impinging on visible dermal medium-caliber vessels. Side lighting and cleansing the skin with alcohol pads can illuminate bluish dermal vessels. Ecchymoses caused by firm fillers compressing nearby vessels are more difficult to prevent, especially if large quantities of thicker filler materials are used. One technique entails canalization of the superficial fat with a 1.25-inch needle; this allows injection of viscous materials over a wide area without having to reperforate the dermis repeatedly, thus minimiz-
ing the risk of hematoma or bruising. Injection at the level of the superficial fat is also inherently less likely to cause bruising because of the decreased density of this layer and its relative dearth of vessels per unit volume compared with the dermis.

When bruising does occur, immediate firm pressure over gauze should be applied to the involved area for a few minutes. Ice packs may also be used. Pressure, and to a lesser extent ice, can limit the extent of the bruise. The most common locations for bruises are the perioral rhytides and the lower eyelids, with injections of poly-L-lactate or hyaluronic acid derivatives under the eye reliably inducing bruising; the upper third of the nasolabial fold; the upper lip; and the lateral edge of the lower lip. Patients should be reassured that the effects are transient and will not impair the final correction associated with the filler. At the same time, they should understand that the bruise may darken for a day or so before it slowly resolves over a week to 10 days.

An adverse effect similar to bruising is frank bleeding. This can result when a vessel of moderate caliber is perforated by an injection needle. Almost without exception, firm pressure for 1 to 5 minutes will stop pinpoint bleeding. Cautery and ligation are exceedingly rarely, if ever, required.

**Overcorrection and Undercorrection**

Because the goal of fillers is to improve aesthetic appearance, precision regarding the site and quantity of injection is imperative to ensure the most attractive result. Potential problems include overcorrection, undercorrection, and asymmetry.

With the exception of the least viscous forms of collagen (e.g., CosmoDerm, Zyderm), significant overcorrection is not necessary with injectable fillers and should be avoided. Relatively little of these fillers will dissipate immediately after injection. All facial anatomical sites are, however, subject to some immediate swelling on injection, and this should be taken into account when determining the degree of appropriate correction. For instance, the lips will swell on needle trauma even in the absence of any delivered material, and postinjection swelling for 2 to 3 days is not uncommon. Patients should be reassured that their “Angelina Jolie” lips are a transient phenomenon on the way to desired lip size within a day or two. In general, undercorrection is a less serious problem than overcorrection because patients can always be asked to return in 1 to 2 weeks for a touch-up procedure to replete any missed or incompletely treated areas. When injecting patients who are acutely concerned about looking unnaturally injected or receiving fillers for the first time, it may be prudent to deliberately undercorrect at the first visit.

Maintenance of symmetry is important regardless of how much material is delivered. There are two measurements that are helpful in maintaining right–left symmetry: quantity injected and visible correction. On the one hand, when using the traditional 1-cc syringe of injectable, the injector should ensure that approximately equal amounts are delivered into corresponding structures, such as the lips or nasolabial folds, on each side of the face. On the other hand, given that most faces are slightly asymmetrical to start, visual inspection should be used to verify that both sides look comparably filled. That is, to give the appearance of equality, exactly equal quantities need not be injected into right and left sides. Alternating small aliquot injections on either side may collectively permit achievement of symmetry.

**Injection-Site Necrosis**

One uncommon but significant undesired effect that may be causally related to placement of filler materials is injection-site necrosis. Inadvertent injection of the angular artery (nasolabial fold area) or supratrochlear artery (glabellar area) with viscous fillers induces an ischemic response with violaceous bluish gray discoloration, pain, erosion, and ulceration. Resolution without pain is routine except when a large bolus of material is injected, with ensuing full-thickness necrosis. On recognition of this side effect, immediate application of nitroglycerin paste may reduce the size and extent of the area affected by ischemia. Injections at the glabella with newer injectable fillers have not been reported to cause retinal artery thrombosis, an embolic phenomenon reported in the distant past following use of Zyplast collagen.

**MEDIUM-TERM UNDESIRED EFFECTS**

**Visible Implants**

Implanted material that remains visible near the surface of the skin is an aesthetically problematic undesired outcome. Typically manifesting as a blanched or white papule, or as a palpable lump, visible injectant is invariably a result of injections that are too superficial or excessive in quantity. If medium-term fillers such as thicker collagens (e.g., CosmoPlast and Zyplast), hyaluronic acids, poly-L-lactate, and calcium hydroxyapatite are injected into the high (e.g., papillary) dermis or
epidermis, they may be sequestered in a layer where they are not easily metabolized. Visible blanched or bluish areas can persist for months, even after the remainder of the implant effect has disappeared.

Care must be taken to avoid this problem. When injections are placed using the serial puncture technique, the injector should ensure that at least the mid dermis is reached before the syringe plunger is depressed and that injection ceases as the needle is pulled back out. During injection, it is extremely important to watch the skin near the needle tip to ensure the absence of blanching indicative of superficial placement; rapid ascertainment and needle repositioning can mitigate the problem. Once a blanched area has been created, firm massage may help to break this up. The patient should be asked to open their mouth, and extremely firm pressure should be applied by the physician between the thumb and forefinger to flatten and spread the superficial focus of injectant. At the same time, the patient should be warned that this maneuver may induce a bruise. If hyaluronic acid fillers are placed too high in the papillary dermis, a visible blue papule may become evident, sometimes immediately, occasionally a few days later; this can be very easily corrected by puncturing the site with a 25- or 27-gauge needle and expressing the material. Notably, injections of the thinnest form of collagen (e.g., CosmoDerm, Zyderm) can be placed high in the dermis without problems. Indeed, thin collagens are designed to fill fine skin lines, and injection-related yellow-colored blanching is a good sign, confirmatory of adequately superficial placement.

Nodule Formation

An uncommon but troublesome outcome of injectable augmentation is nodule formation. Historically, nodules were believed to be associated with hypersensitivity reactions. For instance, there have been other anecdotal reports of post–hyaluronic acid hypersensitivity and granulomatous reactions, including abscess-like nodules and foreign body reactions on the nasolabial folds and lips.8–13 A retrospective cohort study of 709 patients treated with Restylane and Hylaform between 1996 and 2000 found that both substances were associated with sporadic cases of injection-site skin reactions (four with Hylaform and two with Restylane), including indurated nodules (three with Hylaform and one with Restylane).14 Nodules appear to emerge either immediately after treatment, likely a result of superficial injection or excessive injection to a given location, or several weeks later as a result of local inflammatory or granulomatous foreign body reactions, which have been seen in the histopathology of some of these nodules. Nodules have also been noted with use of poly-L-lactate, with rates of nodule formation ranging from 6 to 52 percent in a series of five open-label clinical studies from Europe and the United States.15–18 The majority of nodules, described as palpable but nonvisible subcutaneous micronodules, occurred within the first year, and most resolved. Palpable but not visible small subcutaneous nodules occurred in as many as half of patients, with onset at an average of 218 days (range, 9 to 748 days). Nodule formation from poly-L-lactic acid can be reduced by diluting the material with 5 to 8 ml rather than the lower volume (4 ml) used in these studies. In one study with calcium hydroxylapatite, 56 percent of patients had no nodules, 36 percent had minimal nodule formation, 8 percent had moderate nodule formation, and 0 percent had severe nodule formation.19 Submucosal nodules following calcium hydroxyapatite tended to occur at the lips, with all except 8 percent remitting within 4 to 6 weeks of treatment.

Treatment of nodules is similar regardless of the causative filler material. Nodules are treated by squeezing aggressively, massaging for several days, injecting corticosteroid, and ultimately considering puncture and aspiration. Dermabrasion has been used to reduce nodules, but even if induration is successfully reduced by this technique, textural abnormalities, pigmentary abnormalities, and scarring may result because the injectant is often localized in the deep dermis, not the epidermis. In some cases, resolution has been attained by treatment with allopurinol20 or by surgical excision. Either uniformly hard or cystic in composition, nodules may express the contained filler on aspiration. Thus, when a nodule associated with calcium hydroxyapatite injection is incised, a powdery, pasty, white material is often easily extruded, in a manner similar to the expression of an imbedded milium. Poor technique, such as uneven injection pressure and superficial injections, is especially likely to lead to lumps on the lips, including the wet and dry vermilion. Deeper injection, taking care to avoid vasculature and thus bleeding, can prevent this problem. It should be noted that although nodules of the inner wet lip are not visible and thus not disfiguring in the eyes of others, they can be equally troublesome to the affected patients: patients may inadvertently bite down on the overlying, protrud-
ing mucosa or they may obsessively palpate these annoying nodules with their tongues. Intradermal or intraoral nodules of the lips can be resistant to simple corrective treatments such as steroid injections. In general, steroid injections can be useful for diminishing the inflammatory response and possibly rupturing a nodule so as to express its contents and lead to resolution; at the same time, injudicious placement or inadvertent overtreatment with injectable corticosteroids can easily result in an indented, atrophic scar that may be difficult to correct. Most nodules will eventually remit with time. The most conservative management entails gentle at-home massage, reassurance of the patient, and close follow-up. If nodules do not spontaneously involute over some predetermined time interval (usually, the lifetime of the filler involved), more aggressive corrective action may be needed.

When nodules are composed of hyaluronic acid fillers, they can be dissipated by injection of hyaluronidase, which is commercially available as a solution in injection-ready vials. Because the surrounding skin has a low concentration of hyaluronate, the enzyme dissolves the unwanted aliquot of injectable material without harming the skin substrate. This technique is particularly helpful when hyaluronic acid derivative injections into so-called tear-trough depressions result in excessive, asymmetric swelling under the eye that would otherwise last months.

The conservative approach to managing nodules presupposes that there is no associated hypersensitivity response, necessitating further evaluation and management. This assumption is now believed to be usually correct. That is, nodule formation is typically a manifestation of superficial or excessive injection and, as such, an error in technique rather than an immune response.

Hypersensitivity Responses

Nonetheless, there is some evidence that hypersensitivity responses can occasionally be elicited by nonpermanent fillers. Most significantly, injectable bovine collagen can cause cutaneous allergy, and patients must be skin-tested twice, 1 month apart, to reduce the likelihood of this outcome. However, a study in which 428 patients received injection of human-derived collagen (e.g., CosmoDerm) into the forearm and were followed for 2 months found no instances of cutaneous hypersensitivity; this has led to relaxation of the skin-testing recommendation when human collagen is used. Although skin testing before use of human collagen is not deemed necessary by the U.S. Food and Drug Administration, the package inserts for human collagen (CosmoDerm and CosmoPlast) continue to note that use in people with a known allergy to bovine collagen has not been studied.

The noncollagen fillers are much less likely to induce immune responses. This derives from the fact that these materials are believed to be highly biocompatible. Specifically, calcium hydroxylapatite granules are biodegraded in a manner analogous to the turnover of bone mineral; hyaluronic acid is a complex sugar that occurs naturally in human skin; and poly-L-lactate is a resorbable polymer similar in composition to commonly used polyglactin 910 (Vicryl; Ethicon, Inc., Somerville, NJ.) suture. A few cases of local hypersensitivity after injections of hyaluronic acid derivatives have been reported; these may have been caused by residual proteins, given that hyaluronic acid is derived either from cocks’ combs of domestic fowl or from fermentation using streptococci bacteria. Data presented at the 11th Conference on Retroviruses and Opportunistic Infections in February of 2005 indicated that, in a cohort of 94 patients treated with injectable poly-L-lactate, 1 percent had an anaphylactic reaction.

Overall, cutaneous hypersensitivity reactions associated with nonpermanent filler materials are relatively uncommon. Moreover, it is difficult to ascertain whether such reactions are attributable to a true allergic diathesis or local irritation associated with the quantity and location of a bolus of injectant. Whatever the cause, there are a significant number of reports of red indurated bumps over areas treated with Restylane and Perlane (Medicis) that appear up to 3 months after treatment. Lasting several months, they clear up spontaneously, but topical application of tacrolimus ointment (Protopic; Astellas Pharma US, Deerfield, Ill.) speeds healing, as it does with delayed hypersensitivity after collagen injection. Local reactions may also respond to topical or intraleisional steroids, or to incision and drainage.

RARE, SERIOUS, AND POSSIBLY UNRELATED UNDESIRED EFFECTS

Prepackaged injectable fillers are extremely safe and widely used. As a consequence, it is difficult to know whether the few rare effects reported are truly related to the fillers or incidental, unrelated findings in patients who happen to have received augmentation. In addition, each filler material has specific recommendations for injection technique that can minimize problems with use; for
example, poly-L-lactate is a thick, heterogenous solution that clogs needles and syringes, which consequently need to be frequently changed to avoid inadvertent placement of excessively large aliquots into the skin.

Relatively commonly reported undesired effects that are difficult to ascribe to fillers themselves include headache, sinusitis, and other respiratory symptoms. These may be a sign of concurrent unrelated mild illness or respiratory infections. In some cases, headache may result from the injection process itself; it has been shown by others that needleling of the forehead in the absence of injection of any material can occasionally induce headache.

Itch, acne, and herpes simplex virus reactivation (e.g., cold sores) have been reported in a few instances and may be associated with inadvertent skin irritation during the injection process. However, these effects may also be unrelated and reported by patients only because they incorrectly believe them to be related. Cutaneous bacterial infection and resulting scar may rarely be associated with extrusion of superficially placed implants. Management of implant-related infection entails use of topical and oral antibiotics; scarring is best managed by prevention.

Rare, serious effects that have been seen in patients treated with fillers include collagen vascular disease and facial nerve palsy. The infrequency of reports of these makes it impossible to speculate regarding their cause or causal connection to filler materials.

One rare but serious undesired effect that may be causally related to injection of filler materials is injection-site necrosis. Observed rarely after glabellar injections with hyaluronic acid derivatives, this is localized and treatable. This is not associated with embolic phenomena resulting in retinal artery thrombosis, one case of which was reported in the distant past following use of Zyplast collagen.

Another potential adverse event is alteration or degradation of injectable fillers caused by treatment of the overlying skin with lasers, lights, and energy devices. Specifically, it has been suggested that nonsurgical tightening by radiofrequency modalities may result in deeply penetrating heat delivery that may cause liquefaction, migration, or destruction of injectable implants. At least one human study has found this not to be the case, with biopsy specimens of recent hyaluronic acid injections showing that these are unaffected by monopolar radiofrequency treatment; the cosmetic effect of calcium hydroxylapatite injections may actually be augmented by the same treatments.  

CONCLUSIONS

Overall, prepackaged injectable soft-tissue augmentation materials are extremely safe and well-tolerated materials that provide many options for facial rejuvenation. Undesired effects tend to be minor and prone to spontaneous resolution within a few days to 1 week. Rare is the patient who encounters more than mild discomfort, with possible transient redness, swelling, and bruising. Lumps and nodules occur infrequently, are usually easily treated, and are only rarely associated with immune responses or cutaneous hypersensitivity. Discussion of benefits and risks with patients before injection, coupled with a thorough understanding of the specific techniques required for use of particular fillers, should enable surgeons to use these materials with few problems.

DISCLOSURES

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REFERENCES


