Topical Tacrolimus for Effective Treatment of Eosinophilic Folliculitis Associated With Human Immunodeficiency Virus Infection

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 31-year-old man of Thai origin with human immunodeficiency virus (HIV) (Table, patient 1) was seen for pruritic lesions that had appeared 7 months earlier and had localized on his face (Figure 1A). At the time of presentation, he was profoundly immunosuppressed (CD4 cell count, 9/mm³ and viremia, HIV-1 RNA load of 100 000 copies/mL) and had been seen for a flare-up that had occurred 2 weeks earlier. Despite introduction 2 months later of treatment with highly active antiretroviral therapy (HAART) (indinavir, ritonavir, stavudine, and lamivudine) and topical clindamycin phosphate and ketoconazole, the lesions and pruritus persisted. The patient developed a secondary spread of lesions to his trunk and upper limbs 2 months after HAART was begun. Findings from a physical examination revealed multiple papules and pustules on his forehead, cheeks, neck, and upper part of his trunk and upper limbs. The diagnosis of HIV-associated eosinophilic folliculitis (HIV-EF) was confirmed by histologic examination of skin lesions, and a diagnosis of infectious folliculitis was excluded by negative findings from bacterial and fungal cultures. At this point, treatment with topical mometasone furoate and montelukast sodium produced transient improvement. He had a relapse 4 weeks after the partial change of the HAART (indinavir and ritonavir were discontinued and replaced with efavirenz in association with stavudine and lamivudine).

CASE 2

A 40-year-old HIV-positive Haitian woman (Table, patient 2), was seen for a pruritic eruption on her face that had begun 1 month earlier. She was severely immunocompromised (CD4 cell count, 77/mm³ and viremia, HIV RNA load of 391 000 copies/mL) at the time of presentation. On examination, she had papules, microcysts, and pigmented macules localized on her face only. A diagnosis of inflammatory folliculitis was made in the absence of superficial bacterial, viral, or fungal infection. Results from a skin biopsy confirmed the diagnosis of HIV-EF. Various topical treatments (erythromycin, tretinoin, clindamycin phosphate, adapalene, and metronidazole) as well as H1 receptor antagonists were ineffective. Subsequent treatment with oral doxycycline and topical clobetasone propionate gave some improvement. Treatment with HAART ( stavudine, lamivudine, lopinavir, and ritonavir) was introduced 2 months later, but the symptoms became more severe.

HIV-EF is characterized by erythematous papulopustules that are often heavily excoriated and have a distribution that is mainly truncal with frequent facial and cervical involvement. It is a common condition in immunosuppressed HIV-positive patients. The most serious symptom is intense and debilitating itching. Treatment of patients with HIV-EF is challenging, and various regimens have been attempted. Results are variable and often followed by recurrence once treatment is discontinued; isotretinoin,2 cetirizine hydrochloride,3 UV-B phototherapy,4-6 itraconazole,7 permethrin,8 metronidazole,9 and minocyclin hydrochloride are used in treatment.10 Potent topical corticosteroids, such as betamethasone dipropionate and clobetasol propionate, have been reported10 to be successful in the treatment of these patients but are associated with skin atrophy and hypopigmentation after prolonged use. The treatment of patients 1 and 2 described herein presented additional challenges as a result of severe facial involvement and dark phototype that made the prolonged use of topical corticosteroids inadvisable.
The face and neck lesions of patient 1 were treated with topical 0.1% tacrolimus once daily for 2 weeks; then applications were reduced to once every 2 days and then once every 3 days during each of the following 2 weeks, respectively. Topical mometasone was applied daily for treatment of the lesions of the trunk and arms during this same period. The resolution of the lesions was characterized by a rapid disappearance of pruritus; at the end of the 1-month treatment period, the lesions had cleared, leaving only pigmented scars. All topical treatments were discontinued at this point. Twenty-four months after the start of the effective topical treatment, patient 1 showed persistence of remission and had no residual scarring in the absence of further treatment (Figure 1B).

For patient 2, an initial trial with topical pimecrolimus applied once daily for 2 months gave only limited improvement of symptoms. Subsequent introduction of topical 0.1% tacrolimus once daily for 2 months led to rapid improvement, and applications were gradually decreased to once every 2 days for 2 weeks and then once every 3 days for another 2 weeks before treatment was stopped completely. The patient’s symptoms were still in remission 6 months after treatment ended.

In addition to these 2 cases, another 8 patients with HIV-EF were treated and followed up at our outpatient clinic (Table). The group comprised 6 women and 4 men; most were of African or Asian origin. Their mean ± SD age was 39.4 ± 7.8 years (age range, 27-55 years). Diagnosis of HIV-EF was confirmed in each case by histologic evaluation of a skin biopsy stained with hematoxylin-eosin. Results from periodic acid–Schiff and gram staining were negative in fixed tissue. Bacterial and fungal cultures from pustules or crusts as well as corresponding cultures were performed to exclude a diagnosis of infectious folliculitis. The average duration of symptoms before treatment with topical tacrolimus was 10.1 ± 13.2 months (range, 1-36 months). Topical 0.1% tacrolimus was applied daily by 6 of the 8 patients for periods ranging from 2 weeks to 4 months, followed by a reduction in the frequency of application to once every 2 to 3 days for a few more weeks. In most cases, pruritus subsided within a few days. The average time to clearing of lesions was 2.6 ± 1.4 months (range, 1-5 months). The average duration of remission observed is 12.3 ± 8.1 months (range, 6-36 months). An absence of residual scarring was observed in all patients treated successfully with tacrolimus (Figure 2 and Figure 3). Patients 9 and 10 received only topical corticosteroids because the lesions were pruritic just on the trunk.

We observed that the absence of recurrence of HIV-EF after tacrolimus treatment depends on keeping the HIV infection under stable control with a parallel, well-conducted HAART. For instance, in patient 3, for whom control of HIV viremia could not be achieved because HAART was not strictly indicated, regular application of topical tacrolimus helped to clear each flare-up but did not permit maintained remission.
Table. Clinical Characteristics of and Treatment Response for Human Immunodeficiency Virus–Associated Eosinophilic Folliculitis (HIV-EF) (cont)

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>Duration of Symptoms Prior to Treatment With Topical 0.1% Tacrolimus, mo</th>
<th>Time to Clearing of Pruritus With Topical 0.1% Tacrolimus, wk</th>
<th>Time to Clearing of Folliculitis With Topical 0.1% Tacrolimus, mo‡</th>
<th>Adverse Effects of Treatment With Topical 0.1% Tacrolimus</th>
<th>Treatment With Topical Pimecrolimus</th>
<th>Resolution of HIV Infection During Follow-up</th>
<th>Duration of Remission After End of Treatment, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/31 31</td>
<td>12</td>
<td>&lt;1</td>
<td>1</td>
<td>Burning sensation for 3 d</td>
<td></td>
<td>HAART 2 mo after start of follow-up</td>
<td>24</td>
</tr>
<tr>
<td>2/F/40 40</td>
<td>36</td>
<td>3</td>
<td>3</td>
<td>Burning sensation during the first week</td>
<td>Trial for 2 mo with partial response; subsequent introduction of topical 0.1% tacrolimus effective</td>
<td>Improved control of HIV infection with late introduction of HAART</td>
<td>6</td>
</tr>
<tr>
<td>3/M/40 3</td>
<td>3</td>
<td>&lt;1</td>
<td>4</td>
<td>None</td>
<td></td>
<td>No HAART</td>
<td>Relapse after 2 mo</td>
</tr>
<tr>
<td>4/F/42 42</td>
<td>1</td>
<td>&lt;1</td>
<td>5</td>
<td>None</td>
<td></td>
<td>HAART effective</td>
<td>12</td>
</tr>
<tr>
<td>5/F/27 27</td>
<td>1</td>
<td>&lt;1</td>
<td>3</td>
<td>None</td>
<td></td>
<td>HAART effective</td>
<td>12</td>
</tr>
<tr>
<td>6/F/36 36</td>
<td>24</td>
<td>2</td>
<td>1</td>
<td>None</td>
<td></td>
<td>Improved control of HIV infection with HAART</td>
<td>24</td>
</tr>
<tr>
<td>7/F/35 35</td>
<td>2</td>
<td>&lt;1</td>
<td>2</td>
<td>None</td>
<td>Relay treatment after end of topical 0.1% tacrolimus effective</td>
<td>Improved control of HIV infection with new HAART</td>
<td>6</td>
</tr>
<tr>
<td>8/F/43 43</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>No treatment with tacrolimus; partial clearing after 3 mo of treatment with mometasone furoate</td>
<td>None</td>
<td>HAART effective</td>
<td>12</td>
</tr>
<tr>
<td>9/M/55 55</td>
<td>1</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td>HAART effective</td>
<td>Partial response maintained after 12 mo</td>
</tr>
<tr>
<td>10/M/45 45</td>
<td>5</td>
<td>NA</td>
<td></td>
<td>No treatment with tacrolimus; clearing after 4 mo of treatment with mometasone furoate</td>
<td>None</td>
<td>Improved control of HIV achieved with HAART</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; NA, not applicable.

*At time of presentation.
†All topical treatments unless stated otherwise.
‡Time to clearing includes the initial treatment period, which consisted of once-daily applications as well as the subsequent treatment periods with applications once every 2 days and 3 days, respectively.

Figure 1. Patient 1. A, Before treatment with topical 0.1% tacrolimus; B, after treatment.
To analyze whether topical tacrolimus is systemically absorbed, we measured the serum level of tacrolimus of each patient 48 hours after the start of treatment. In patient 5, who applied a total of 15 g of topical tacrolimus over a 3-day period because of her need to treat a large surface, the serum level of tacrolimus was 2.2 µg/L (reference range, 5-15 µg/L). Patient 3 did not show any detectable serum level of tacrolimus after application of a total of 10 g of topical tacrolimus over a 2-week period. Regardless of the duration of treatment by topical tacrolimus, no patient applied more than a total of 60 g of topical 0.1% tacrolimus.
Topical 0.03% tacrolimus and topical pimecrolimus gave poor results for initial treatment of HIV-EF. Patient 8 applied topical 0.03% tacrolimus for 1 month without improvement but responded rapidly to the subsequent introduction of topical 0.1% tacrolimus. For patient 2, a trial treatment with topical pimecrolimus applied once daily for 2 months gave only a partial relief from symptoms and was followed by complete regression of lesions; remission occurred only after subsequent introduction of topical 0.1% tacrolimus. For patient 7, topical pimecrolimus was successful as a relay treatment once the lesions began to clear after initial treatment with topical 0.1% tacrolimus.

**COMMENT**

The etiology of HIV-EF remains unclear. Treatment is challenging, and pruritus is resistant to most therapeutic options. HIV-EF is a chronic inflammatory skin disorder associated with HIV infection and usually presents at advanced stages of the disease when a patient’s CD4 cell counts are lower than 250/mm³. HIV-EF seems to be an important clinical marker of HIV infection and identifies patients at increased risk of developing opportunistic infections.11 HIV-EF has also been described as a manifestation of the immune restoration syndrome.12 We observed this phenomenon in patients 4, 5, and 8, who developed lesions shortly after introduction of HAART, and in patient 2, whose preexisting HIV-EF worsened with the introduction of HAART.

Light microscopy study of HIV-EF shows a mixed inflammatory infiltrate with a predominance of eosinophils and lymphocytes surrounding and invading the follicular and sebaceous epithelia, resulting in destruction of the sebaceous gland (Figure 4). We observed that histologic findings showed varying degrees of eosinophilic infiltrate (depending on the stage of the inflammatory process) as well as the presence of mucinosis, as seen in patients 6 and 7; these findings should be integrated in the wider spectrum of HIV-associated inflammatory folliculitis. HIV-EF cannot be distinguished clinically from other types of folliculitis, and therefore skin biopsies as well as routine swabs and cultures must be performed to exclude a diagnosis of infectious folliculitis. So far, in our experience, only potent topical corticosteroids have been shown to be effective in the treatment of patients with HIV-EF. However, our report describes a small series, and no controlled and randomized studies have been conducted to our knowledge.

Topical corticosteroids may lead to skin atrophy as well as hypopigmentation, particularly in patients with phototypes IV to VI. Because most of our patients are of African or Asian origin and their lesions involve predominantly the head and neck, the use of potent topical corticosteroids is particularly problematic because of the hypopigmentation that they induce on the treated areas, leading to heterogeneous pigmentation of the face. Systemic treatments consisting of histamine H₁ and histamine H₂ receptor antagonists, as well as a leukotriene inhibitor (montelukast sodium) were administered alone or in association with other treatments but were ineffective in the control of pruritus or skin lesions.

Topical 0.1% tacrolimus gave a rapid and complete response in our group of patients with HIV-EF. Tacrolimus, a calcineurin inhibitor, is a potent anti-inflammatory and immunosuppressive molecule devoid of the undesirable adverse effects of topical corticosteroid therapy. Tacrolimus has already been used successfully in a wide range of inflammatory dermatoses, including atopic dermatitis; amicrobial pustuloses, such as pyoderma gangrenosum; and erosive pustular dermatosis of the scalp.12-15 In addition, topical tacrolimus has already been shown to be effective in 1 case report16 describing the treatment of Ofuji disease, an eosinophilic folliculitis in the absence of HIV infection.

No relapse of HIV-EF was observed in patients with well-conducted HAART. This suggests that HIV-EF responds successfully to a combination therapy that includes topical 0.1% tacrolimus with a well-conducted HAART. However, HAART alone was insufficient to obtain a remission of HIV-EF in our patients, as shown by the persistence of symptoms prior to treatment with topical tacrolimus. In our experience, neither topical pimecrolimus nor topical 0.03% tacrolimus was sufficient to induce clearing of lesions.

The absence of detectable serum levels of tacrolimus demonstrates that absorption of tacrolimus and thereby potential systemic effects linked to its immunosuppres-
sive properties are negligible. This supports a previous observation that tacrolimus has a poor permeability in skin with an intact barrier function, which is expected in patients with HIV-EF given the clinical presentation of their lesions. Furthermore, we did not encounter secondary bacterial, fungal, or viral (particularly herpetic) infection of the skin of patients treated with tacrolimus, which is a concern in immunocompromised individuals. Nevertheless, patients must be followed up closely and given clear explanations about the possibility of herpetic or bacterial colonization of the skin.

In conclusion, our experience suggests that topical 0.1% tacrolimus is a valuable treatment for patients with HIV-EF; it induced rapid disappearance of pruritus and maintained remission of skin lesions in the absence of residual scarring. It proved to be well tolerated in our group of patients and is a safe alternative to topical corticosteroids without the undesirable adverse effects. This observation needs confirmation by a randomized controlled study involving a greater number of patients to establish the efficacy of topical tacrolimus in the treatment of HIV-EF.

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REFERENCES


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