Oral Lichen Planus

A Case Series With Emphasis on Therapy

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Background: Oral lichen planus (OLP) is a chronic inflammatory disorder that can cause local irritation and discomfort with attendant poor dentition and nutrition. Although a range of therapeutic options is available, data on the long-term efficacy of treatments for this chronic disease are limited. To identify agents that might be effective in OLP treatment over a longer term, and to explore their sequential use in treatment-refractory patients, we studied patients who received multiple OLP therapies and who were followed up for an average of more than 2 years.

Observations: We performed a retrospective medical record review of 50 patients with histologically confirmed OLP. Patients were treated according to a therapeutic ladder of sequential treatments, beginning with topical corticosteroids and progressing through topical immunomodulators, systemic retinoids, methotrexate, and thalidomide. The best responses were observed in previously untreated patients. Most patients eventually achieved a substantial response with limited toxic effects.

Conclusions: Our results identify low-dose methotrexate as an agent with substantial activity in OLP. We also demonstrate that a laddered therapeutic approach to patients with this disease can achieve substantial lesion regression even in heavily pretreated and treatment-refractory patients.

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Oral Lichen Planus (OLP) is a chronic inflammatory disorder affecting mucosal surfaces. The posterior buccal mucosa is most frequently involved, followed by the tongue, gingiva, and vermilion of the lower lip. Lichen planus may also occur on nonoral epithelial surfaces, such as the skin, genitalia, nails, and hair follicles. The oral form is a relatively common dermatologic condition that affects approximately 1% to 4% of the population. Onset generally occurs in the fifth or sixth decade of life, although all ages may be affected, including children. The disease occurs in all races. There is controversy as to whether there is a female predisposition.

See also pages 463, 472, and 519

Lichen planus is believed to be an autoimmune disorder mediated by T lymphocytes that recognize self-antigens on keratinocytes as foreign, leading to inflammation and keratinocyte cell death. Exogenous factors may also contribute to the pathogenesis of the disease. For example, patients with hepatitis C (but not hepatitis A or B) infection seem, in some series, to have a higher prevalence of LP than uninfected individuals, although the exact nature of the antigen involved in the cutaneous T-lymphocyte reaction has not been identified. In recent studies, however, this association has been challenged. Other exogenous factors, such as contact allergens, particularly those used in dentistry (gold and mercury amalgam), have also been implicated. Most patients with LP have no identifiable exogenous trigger.

Oral LP appears in several forms, including atrophic, bullous, erosive, pigmented, plaquelike, and reticular. Reticular lesions are the most common, but patients with reticular lesions are generally asymptomatic. Atrophic, bullous, and erosive lesions cause discomfort, ranging from mild to severe pain. Although OLP can spontaneously regress, many lesions eventually require treatment. The most commonly used agents for the treatment of OLP are topical corticosteroids. Intral esional and systemic corticosteroids are also used. Topical and systemic medications include immunosuppressants, such as cyclosporine and tacrolimus, and topical or systemic retinoids. The treatment of refractory disease has also been approached with other agents, including thalidomide and even nonpharmacologic agents such as psoralen–UV-A.

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Despite the wide variety of therapeutic agents used to treat OLP, data on the efficacy of these treatments are limited. A review conducted in 2005 identified 11 placebo-controlled, randomized, clinical trials for OLP, with individual studies each containing from 12 to 40 patients. The authors concluded that there was only weak evidence for the effectiveness of any of 4 major therapeutic classes (corticosteroids, cyclosporine, retinoids, or phototherapy) vs placebo, when these agents were used individually.

A limitation of most studies of treatments for OLP is their relatively short duration. Randomized trials were often conducted over only 2 to 16 weeks. Because OLP is a chronic disorder that can persist for years, the durability of response is of interest.

To identify agents that might be effective in treating OLP over a longer term, and to explore their sequential use in treatment-refractory patients, we studied a number of agents in patients followed up for an average of more than 2 years. In addition to standard therapies, such as topical corticosteroids, anti-inflammatory agents, and retinoids, we explored the effectiveness of methotrexate, a drug that has not been well described as a treatment option for patients with OLP.

**METHODS**

A retrospective medical record review of patients seen in the Wake Forest University Health Sciences (WFU) dermatology clinic between January 1, 1997, and December 31, 2005, who were diagnosed as having idiopathic LP, was the starting point of the analysis. This study was then limited to patients with histologically confirmed OLP. The medical record review was performed under an institutional review board–approved protocol. All patients were seen by 1 of us (J.L.J.), who made treatment decisions and performed disease status evaluations. Treatment decisions followed a prospectively designed, laddered, therapeutic approach developed prior to 1998, which remained unchanged during this review (and is described in the “Results” section). Because LP has a variable clinical course punctuated by episodes of improvement and worsening, disease status was scored according to a nomenclature that required a consistent semiquantitative assessment of the change in the OLP lesions in response to treatment. Nursing staff confirmed and recorded all changes in medications. The goal was to eradicate lesions where possible, and to reduce the extent and morbidity of the lesions with a well-tolerated treatment regimen when eradication could not be achieved.

The regimens used for OLP therapy were as follows: (1) topical corticosteroids, 0.05% fluocinonide gel 2 to 3 times per day (prior to WFU) and 0.5% clobetasol gel 2 to 5 times per day (at WFU); (2) intralesional corticosteroid, 10 mg/kg, injection of 0.2 to 0.3 mL; (3) topical tacrolimus, 0.1% tacrolimus ointment, 2 to 3 times per day, alternating with clobetasol; (4) hydroxychloroquine, 200 mg orally twice daily; (5) retinoid, including isotretinoin, 80 mg/d, for a 70-kg patient and acitretin, 25 mg/d, for a 70-kg patient; (6) methotrexate, 2.5 to 12.5 mg/wk, depending on creatinine clearance; and (7) thalidomide, 100 mg every night on average. The adverse effects of these therapies have been described in detail elsewhere. Potential adverse effects were always discussed with the patient in detail, and verbal assent was documented. Patients treated with isotretinoin were in the SMART (System to Manage Accutane-Related Teratogenicity) program (which preceded iPledge), and patients who received thalidomide were in the STEPS (System for Thalidomide Education and Prescribing Safety) program. Monitoring was as per American Academy of Dermatology guidelines for methotrexate.

**RESULTS**

Fifty patients with biopsy-proved OLP were identified, from a group of 225 patients with LP at all sites seen from 1997 to 2005 at the WFU dermatology clinic. This represented all of the cases of histologically documented OLP seen in this period. All patients had erosive disease. There were 35 female and 15 male evaluable patients. The mean age at first WFU visit was 60 years (range, 41-80 years). Of the patients, 45 were white and 5 were African American. Thirty-eight patients presented with only OLP lesions, while 12 had involvement of OLP at sites other than the oral cavity. Of these 12, 2 extraoral sites involved the vaginal mucosa. Most patients at their first WFU visit had previously been treated for OLP, often based on a presumptive clinical diagnosis; 31 (62%) of the 50 patients had received prior OLP therapy at their first visit to WFU, while 19 (38%) did not receive prior OLP treatment. We routinely performed a biopsy to confirm the diagnosis of OLP before implementing further treatment. Most of these patients, when first seen at WFU, had already received topical corticosteroids, although others had more complex and prolonged treatments before their first WFU diagnosis. The mean duration of follow-up at WFU was longer than 27 months.

The overall best response to therapy for each of the 50 patients is summarized as follows: 4 (8%) experienced worsening or no response, 5 (10%) experienced a moderate improvement (25%-75%), and 41 (82%) achieved substantial improvement (>75% or clearing) of their OLP. It sometimes required multiple discrete regimens to achieve these responses.

In general, the patients who had not received prior OLP treatment at their initial evaluation at WFU did better than those who received prior treatment. The first response to treatment at WFU is described in Table 1. Of 19 patients with no prior treatment, 12 achieved substantial improvement, compared with 14 of 31 patients who received therapy prior to their first WFU visit. This differential is even more pronounced if the best response the patient achieved is examined. As seen in Table 1, 19 of the 19 patients in the no prior treatment group eventually achieved a greater than 75% response, compared with 22 of the 31 patients in the prior therapy group.

Response as a function of the type of treatment administered at WFU is described in Table 2. Each treatment course (defined as a change in drug treatment) is examined separately. Ninety separate treatment courses were administered to the 50 patients. Response data for 1 course of therapy in 1 patient could not be retrieved, making the denominator 89 for response assessment by treatment course. Although treatments are placed in categories identified by the predominant drug used, it was often necessary to maintain the previous treatment while the new one was being administered. For example, oral corticosteroids were often continued but tapered as rapidly as allowed to prevent rebound in patients who required more stable regimens to control the disease. In addition, virtually all pa-
Patients received anticandidal prophylaxis, usually in the form of clotrimazole troches (1 per day) after initial fluconazole treatment, 100 mg/wk for 3 weeks.

Response was substantial in all treatment groups (Table 2), including the methotrexate and thalidomide groups, which were the most heavily pretreated and treatment-refractory patients. Responses were also seen to topical corticosteroids, even in the setting of prior topical corticosteroid therapy. However, at WFU, topical therapy was administered intensively, with (class 1) corticosteroids, generally 2 to 5 times a day while awake during the initial treatment period. Topical tacrolimus was used whenever possible. Retinoids were used in topical and oral formulations. Whether responses are examined by patient or treatment course (Table 2), most patients eventually achieved a substantial response.

Overall, toxic effects were limited, and no unexpected toxic effects were observed. Oral corticosteroids resulted in frequent local toxic effects, primarily related to the development of oral candidiasis, which was disturbing for most patients and required treatment with topical and/or systemic antifungal agents. Therefore, the WFU regimen always included elementary baseline oral candidiasis prophylaxis or treatment with oral fluconazole and prophylaxis against recurrence with daily topical clotrimazole troches. The morbidity of oral treatment associated with frequent daily treatments, and the need for oral or topical antifungal prophylaxis or therapy, clearly affected compliance to these regimens, although this was difficult to quantify in this medical record review.

Patients who presented as new untreated cases (ie, no previous treatment) received different treatments than those who had received prior OLP treatment (Table 3). Furthermore, the number of prior treatments at WFU also affected the choice of subsequent WFU treatment, demonstrating the implementation of the therapeutic ladder in this patient population. For example, 36 of 44 patients who received topical corticosteroids either alone or with topical tacrolimus as their first WFU treatment had no prior OLP therapy, while methotrexate was the first choice therapy in only 3 of 18 patients and thalidomide was never a first choice. As patients progressed through a therapeutic ladder of sequential treatments at WFU, therapy choices shifted from topical to oral treatments (usually with continued topical treatment) and eventually to oral treatments with more potential toxic effects (Table 4).

**Table 1. Effect of Prior Therapy on Initial and Best Achievable Responses**

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Worse or No Response*</th>
<th>Moderate Improvement (25%-75%)*</th>
<th>Substantial Improvement (&gt;75% or Clear)*</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Response Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior treatment</td>
<td>6 (32)</td>
<td>1 (5)</td>
<td>12 (63)</td>
<td>19</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>9 (29)</td>
<td>8 (26)</td>
<td>14 (45)</td>
<td>31</td>
</tr>
<tr>
<td>Best Achievable Response Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior treatment</td>
<td>0</td>
<td>0</td>
<td>19 (100)</td>
<td>19</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>4 (13)</td>
<td>5 (16)</td>
<td>22 (71)</td>
<td>31</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Percentages are based on totals for each row.

**Table 2. Response per Course as a Function of Treatment Type**

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Worse or No Response*</th>
<th>Moderate Improvement (25%-75%)*</th>
<th>Substantial Improvement (&gt;75% or Clear)*</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroid with or without intralesional corticosteroid</td>
<td>4 (17)</td>
<td>7 (30)</td>
<td>12 (52)</td>
<td>23</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>5 (24)</td>
<td>6 (29)</td>
<td>10 (48)</td>
<td>21</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>0</td>
<td>2 (40)</td>
<td>3 (60)</td>
<td>5</td>
</tr>
<tr>
<td>Oral retinoid</td>
<td>6 (35)</td>
<td>3 (18)</td>
<td>8 (47)</td>
<td>17</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2 (11)</td>
<td>6 (33)</td>
<td>10 (56)</td>
<td>18</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>0</td>
<td>1 (20)</td>
<td>4 (80)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Percentages are based on totals for each row, and may not total 100 because of rounding.

**COMMENT**

Despite the chronicity of OLP, clinical trials to assess new therapies have traditionally been reported after short follow-up intervals and, therefore, provide incomplete information on the efficacy of therapy. The long duration of follow-up in our study (mean, 27 months) allowed us to observe a pattern of response and exacerbation of OLP in this patient population. It was unusual for remission to be sustained; instead, patterns of response and relapse had characteristics of a chronic disease, which in most patients could be controlled but not eradicated. Furthermore, oral mucosal involvement, particularly in those patients who presented with or progressed to more erosive forms of the disease, was clearly painful and disabling, and required treatment for comfort, ease of eating, and disease control in all patients studied.
ample, complete responses were observed in 68% of patients referred who were receiving this regimen, the regimen was tapered to other therapies. A study of topical retinoids showed complete responses in 19 of 19 patients after long-term follow-up. Our study also confirmed the efficacy of oral thalidomide in this patient population, adding to the limited literature on the use of this drug for patients with advanced OLP.

The primary intent of our study was to evaluate the utility of the therapeutic ladder in OLP therapy. We also noted the surprising activity of the folate antagonist, methotrexate, in this disease. To our knowledge, this is the first report that systematically evaluates methotrexate for OLP therapy. Doses of methotrexate were titrated to achieve maximal effect on the OLP lesions while limiting potential toxic effects to the bone marrow and liver. In our patient population, clinical toxic effects were not observed and reduction of hematological indexes was easily managed. Methotrexate treatment resulted in excellent control of OLP in the group with the most refractory and aggressive disease, and should be considered as part of the portfolio of treatment options for this condition, particularly for patients with treatment-refractory or erosive disease.

One of the striking features of this patient population has been the ability to achieve responses in patients in whom multiple prior therapies failed. The acquisition and maintenance of response in the oral lesions was the result of the application of a graded approach to drug administration, in which the intensity of an individual therapy was varied to achieve lesion regression and at the same time limit oral and systemic toxicity. Eventually, most patients achieved outstanding responses (Table 1). The therapeutic ladder is illustrated in Table 4.

This laddering approach to selecting treatment has another dimension. Because retinoid and anti-inflammatory therapies can be slow to take hold and the results are frequently less than complete, patients often continued to receive topical treatments, even as they were treated with systemic agents. As the systemic agents took hold, topical agents were often gradually tapered by the patient to control cost and increase convenience. However, topical therapies were always encouraged to reduce the dose of systemic therapies.

Although a laddering approach to therapy has not yet been studied in the setting of a randomized clinical trial, to our knowledge, the favorable response rates we observed for individual therapies within the ladder are consistent with others reported in the literature. For example, complete responses were observed in 68% of patients with OLP treated with either systemic plus topical corticosteroids or topical corticosteroids alone. We never selected systemic corticosteroids as a long-term treatment option because of the potential for toxic effects in patients with this chronic disease; rather, for patients referred who were receiving this regimen, the regimen was tapered to other therapies. A study of topical retinoids showed complete responses in 19 of 19 patients after long-term follow-up. Our study also confirmed the efficacy of oral thalidomide in this patient population, adding to the limited literature on the use of this drug for patients with advanced OLP.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jorizzo and McCarty. Acquisition of data: Torti, Jorizzo, and McCarty. Analysis and interpretation of data: Torti and Jorizzo. Drafting of the manuscript: Torti and McCarty. Critical revision of the manuscript for important intellectual content: Jorizzo. Administrative, technical, and material support: Jorizzo and McCarty. Study supervision: Jorizzo.

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REFERENCES


On the Horizon

On the Horizon is designed to showcase a recent finding in the scientific literature that is likely to have a significant impact on our understanding of skin disease pathogenesis and ultimately contribute to more effective disease management. While treatment is an obvious focal point of the section, other elements of improved disease management might include prevention, counseling, and public policy. The section is intended to have a concise, consistent structure. It begins with an abstract reprinted from the scientific literature that represents the focus of the article. This is followed by a short commentary of approximately 500 words and a few relevant references. If crucial to the message, 1 or 2 figures or tables might be included. The content should be focused and contained to a single page of the ARCHIVES.

To achieve our goal of making On the Horizon a monthly feature of the ARCHIVES, we need your help. We know that excitement about advances in dermatology is shared by many dermatologists in and out of academics, as well as fellows, residents, and students. We invite all kindred spirits to submit material to On the Horizon. This is an excellent opportunity for residency program directors and other faculty mentors to get their trainees involved in writing about, not just reading about, scientific advances relevant to dermatology. Submissions may go directly to Gary S. Wood, MD, the section editor, or through one of the assistant section editors.