Low-Dose Excimer 308-nm Laser for the Treatment of Oral Lichen Planus

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Background: Lichen planus is a difficult-to-treat chronic inflammatory disorder that affects mucous membranes, causing inanition, halitosis, and dyspareunia.

Objective: To evaluate the novel use of low-dose 308-nm excimer laser radiation for the treatment of symptomatic oral lichen planus (OLP).

Design: A single-center, before-after trial.

Setting: Academic clinical research center.

Patients: Nine patients with symptomatic, biopsy-proven OLP, unresponsive to conventional therapies, were recruited from the dermatology clinics of the Massachusetts General Hospital in Boston. Eight participants completed the entire study, and 1, despite early improvement, did not complete the study because of hospitalization for an unrelated reason.

Intervention: With a narrow, fiberoptic handpiece to target precisely only diseased sites, 308-nm excimer laser radiation was delivered at an initial dose of 100 mJ/cm² once a week.

Main Outcome Measure: A visual analog scale was used to grade subjective disease severity. Clinical improvement was graded in quartiles as follows: poor (<25%), fair (25%-50%), good (51%-75%), and excellent (>75%). Follow-up visits occurred for up to 18 months. A paired t test was performed to evaluate efficacy of treatment.

Results: Treatments were painless and well tolerated. Five patients demonstrated overall excellent clinical and subjective improvement after 7 treatments. Two participants with nonerosive OLP were deemed fair responders. The only poor responder in the study also had chronic active hepatitis C infection. Overall improvement was statistically significant (P<.05), and for the responders, remission times ranged from 2 to 17 months.

Conclusion: Low-dose treatment with the excimer 308-nm laser can be very effective in treating symptomatic and especially erosive OLP, an otherwise notoriously difficult-to-control disease.

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With an incidence of less than 1%, lichen planus (LP) is an idiopathic, chronic inflammatory, and presumably autoimmune disease that affects the skin, mucous membranes, nails, and hair. Oral LP (OLP) occurs in approximately 60% to 70% of patients with cutaneous LP (CLP) and may be the sole manifestation in 20% to 30% of patients. Such mucous membrane lesions have a predilection for the buccal mucosa, gingiva, and tongue. These lesions may consist of relatively asymptomatic, white, lacy, or erythematous patches or plaques to devastatingly painful erosions, ulcers, and desquamative, foul-smelling gingivitis. Mucous membrane involvement may include oral and anogenital membranes. Symptoms such as pain, burning, and stinging can lead to dysphagia, dysgeusia, inanition, and dyspareunia. Spontaneous remissions after 1 year are known to occur in up to two thirds of cases with cutaneous involvement, but unfortunately mucous membrane lesions are more persistent. In addition, malignant transformation of longstanding, nonhealing OLP lesions has been reported; however, the exact incidence is unclear.

Treatment for these patients frequently requires a concerted multidisciplinary approach by oral pathologists, dermatologists, gastroenterologists, and gynecologists. Therapy for OLP is generally palliative and all too often unsuccessful (Table). Topical potent corticosteroids, which may sting or taste poorly, and painful intralesional injections are often the
first line of therapy. Topical anesthetics may serve an adjunctive role but must be used with caution due to systemic absorption. Moreover, they can lead patients into a false sense of security, causing them to eat hard foods, which subsequently further damage their delicate mucous membranes. Systemic corticosteroids are frequently used to settle severe flares, but their long-term use has a well-known spectrum of adverse effects. Other treatments include topical cyclosporine and immunomodulators, such as tacrolimus.2,8,15,16,32 Both systemic and topical retinoids have been used and found to have limited success.3,24 There are several reports in the literature that support the role of photochemotherapy with psoralen–UV-A (PUVA) in the treatment of both OLP and CLP.26,27,33,34 Two major disadvantages of PUVA therapy include the adverse effects of nausea and dizziness secondary to psoralen and 24-hour photosensitivity when this medicine is taken orally. Also, dosimetry can be difficult within the complicated geometry of the mouth, because PUVA is usually administered on glabrous skin over large, open surfaces.

Our experience with 311-nm, narrowband UVB (NB-UVB) phototherapy at the Khosrow Momtaz Phototherapy Center of the Massachusetts General Hospital in Boston has been favorable for certain inflammatory skin disorders mediated by lymphocytes, for example, psoriasis and CLP. In fact, NB-UVB phototherapy has similar efficacy compared with the well-established and potentially PUVA photochemotherapy.35,36 Also, it may possibly (although unproven yet) be associated with less carcinogenicity.37 To our knowledge, NB-UVB, 311-nm phototherapy has not been previously studied for OLP, primarily because there are no existing delivery systems for oral exposures using conventional 311-nm fluorescent tubes. The 308-nm excimer laser has already been established to clear rapidly stable plaque-type psoriasis,38-41 and other inflammatory papulosquamous dermatoses. The operational 308-nm radiation of the excimer laser is close enough to be photobiologically similar to its neighboring 311-nm wavelength. Therefore, we decided to examine this new modality for the treatment of symptomatic OLP by taking advantage of a flexible fiberoptic delivery system for directing the UV radiation selectively on the affected mucosa.

### METHODS

The protocol was reviewed and approved by the Institutional Review Board at Massachusetts General Hospital. Written informed consent was obtained from each subject. Adult patients with symptomatic, biopsy-proven OLP, unresponsive to previous or current therapies, were enrolled from our dermatology clinics. The only exclusion criterion was a known underlying hypersensitivity to natural sunlight in the UV-B spectrum such as occurs in xeroderma pigmentosum. During the initial evaluation, a pertinent medical and dental history preceded a physical examination with special attention to the oral mucosa. All recent medications, including those that antedated by 1 year or less the onset of the OLP, were documented. Concurrent topical or systemic drug therapy for OLP did not preclude participation in the study. Our intent was to focus on treatment-resistant OLP.

### STUDY DESIGN AND EVALUATIONS

This pilot study used once-weekly applications of the 308-nm excimer laser. Our clinical assessments included investigator and subject data. All participants were encouraged to document their daily dietary habits in a journal, with special attention given to any change in their ability to tolerate certain foods with regard to taste and texture. Given the often complex and subjective nature of the various symptoms of OLP, a 100-mm visual analog scale was used to assess the severity of disease (Figure 1) according to subjective symptoms. Patients were asked to grade the overall severity of their baseline symptoms on the visual analog scale with respect to a composite of burning, pain, and dysphagia. During the study, participants were reassessed weekly using the same scale. The difference between these scores in millimeters was expressed as a percentage to document any improvement from the patient’s view. For discussion purposes, we arbitrarily categorized the overall response given to any change in their ability to tolerate certain foods with regard to taste and texture. Given the often complex and subjective nature of the various symptoms of OLP, a 100-mm visual analog scale was used to assess the severity of disease (Figure 1) according to subjective symptoms. Patients were asked to grade the overall severity of their baseline symptoms on the visual analog scale with respect to a composite of burning, pain, and dysphagia. During the study, participants were reassessed weekly using the same scale. The difference between these scores in millimeters was expressed as a percentage to document any improvement from the patient’s view. For discussion purposes, we arbitrarily categorized the overall response given to any change in their ability to tolerate certain foods with regard to taste and texture. Given the often complex and subjective nature of the various symptoms of OLP, a 100-mm visual analog scale was used to assess the severity of disease (Figure 1) according to subjective symptoms. Patients were asked to grade the overall severity of their baseline symptoms on the visual analog scale with respect to a composite of burning, pain, and dysphagia. During the study, participants were reassessed weekly using the same scale. The difference between these scores in millimeters was expressed as a percentage to document any improvement from the patient’s view. For discussion purposes, we arbitrarily categorized the overall response given to any change in their ability to tolerate certain foods with regard to taste and texture.

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**Figure 1.** Improvement in burning sensation and pain as determined from the visual analog scale. Our visual analog scale is a bar subdivided into 4 equal segments. Subjects point to where they think they are in terms of their symptoms.
starting dose was arbitrarily set at 100 mJ/cm², the lowest dose we were dealing with already painful and delicate mucous membranes or until clearing, whichever came first. Given that we Subjects were scheduled to receive a maximum of 30 treatments, both the subject and the laser operator are required to wear UV-protective safety goggles.

After each use, the tip is removed and cleaned with discide ultradisinfecting Towlettes (Palmero Health Care, Stratford, Conn), then washed with soap, and rinsed in hot water. Each tip is kept in a plastic bag labeled for subsequent use on that same individual. During treatment, both the subject and the laser operator are required to wear UV-protective safety goggles.

TREATMENT PROTOCOL

Subjects were scheduled to receive a maximum of 30 treatments or until clearing, whichever came first. Given that we were dealing with already painful and delicate mucous membranes, for which UV-B dosimetry has not been established, the starting dose was arbitrarily set at 100 mJ/cm², the lowest dose the laser emits and, analogously, a typical low starting dose for NB-UVB, 311-nm phototherapy. Subjects received a laser treatment to the affected areas once a week. Prior to each treatment, participants were carefully reevaluated to assess possible effects from the previous session. We followed a treatment protocol akin to that for standard NB-UVB phototherapy in that the dose on subsequent treatments was gradually increased. More specifically, if the subject noted no intensification in discomfort temporally related to the laser treatment, the dose was increased by 50 mJ/cm², the lowest possible increment allowable by the laser. If, however, the subject reported mild increase in discomfort temporally related to the last treatment, but lasting less than 24 hours, the dose was held constant. If symptoms intensified within 24 hours of the last laser exposure, then treatment was withheld and the subject was reevaluated at the next scheduled visit. A maximum dose of 400 mJ/cm² was administered at any given session.

STATISTICAL ANALYSIS

Using the Wilcoxon matched-pairs signed-rank test, a non-parametric test that tests whether the difference between 2 variables is 0, improvement scores were calculated at 7, 14, 21, and 28 treatments.

RESULTS

Nine volunteers with biopsy-proven, symptomatic, and treatment-refractory OLP were enrolled in this study. These subjects included 6 men and 3 women. Eight of the patients were white and 1 was African American. One of the 9 enrollees, despite early improvement, did not complete the study due to hospitalization for an unrelated reason. Consequently, 8 OLP subjects completed the protocol, 4 of whom also had active CLP. All subjects had typical symptomatic oral lesions, varying from extensive lacy, white plaques (2/8) to erosive plaques (6/8) on the buccal mucoae, gingiva, lips, and tongue. The mean age of disease onset was 68 years (range, 37-87 years). All the participants had failed previous therapies, including potent class 1 topical steroids and topical analgesics such as lidocaine. Other former treatments included intralesional steroids, systemic steroids, hydroxychloroquine sulfate, and cyclosporine (Table). As for dental work, only 1 subject had ever had an amalgam filling, but onset of her OLP had occurred 24 years prior to the procedure. Six of the 8 participants had a history of smoking (5 former and 1 current), and 2 had never smoked. As for medications, 3 of the 8 enrollees were taking drugs known to exacerbate OLP, such as angiotensin-converting enzyme (ACE) inhibitors, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, and hydroxychloroquine.

On analyzing the data, we found a highly significant direct correlation between the subjective data as reported on the visual analog scale by the participants and the investigator’s clinical evaluations. Given the high degree of reproducibility and reliability associated with such analog scales, only the subjective data were tabulated and subsequently plotted vs time to illustrate response. Figure 3 demonstrates the composite percentage improvement in pain and burning sensation as a function of the number of treatments as determined by the inves-
The mean number of treatments given was 21 (range, 7-30). During each laser session, most subjects reported no discomfort or sensation at all. Each treatment took less than 1 minute to complete. There were no adverse effects. For the 8 participants, the Wilcoxon matched-pairs signed-rank test was also performed to evaluate efficacy of treatment. The mean improvement and the 95% confidence intervals were calculated, and improvement was statistically significant at 7, 14, 21, and 28 treatments with *P* values of .02, .002, .02, and .11 and *n* values of 8, 8, 7, and 3, respectively. Improvement was also statistically significant at 30 treatments for the responsive group only.

Five subjects had excellent responses (Figure 4 and Figure 5). Three of these same 5 subjects achieved excellent results as early as between treatments 7 and 14. The fourth demonstrated only fair improvement initially but showed excellent improvement after 21 treatments. The fifth was unique in that his progress occurred more slowly. Still an active and heavy smoker (>1 pack per day), this African American patient reached an excellent response by 30 treatments.

In this excellent response group, 4 of the 5 volunteers had duration of disease less than 2.5 years. The age at onset of disease ranged from 57 to 87 years. Four candidates had quit smoking 15 years or more ago, and 1 was still an active smoker. Remarkably, these 5 participants also reported an improvement in dietary intake and/or weight gain since treatment began. Having cleared erosive OLP lesions, each of these subjects described being able to eat foods, such as spicy or sour ones, that they previously could not have. As for the follow-up of the excellent response group, 1 participant remained in remission for more than 1 year (17 months). Two subjects were still symptom free as of 6 and 10 months. The last 2 subjects achieved remission times of only 2 months. One of these subjects developed various dental problems that required several procedures and subsequently noted recurrent symptoms. The other participant noted a mild recurrence in an area adjacent to what had been treated.

With respect to the fair response group, there were 2 subjects. Both were young nonsmokers with multiple medical problems and had OLP for a very long time (20-24 years). Notably, one of these volunteers had been taking a daily regimen of an ACE inhibitor and an NSAID prior to and during his OLP. The other had chronic abdominal complaints of unclear etiology. These 2 fair responders had low-grade chronic mucosal symptoms to begin with and OLP lesions consisting of only nonerosive erythematous patches.

Only 1 subject had a poor response. He had extensive erosive disease involving both the buccal mucosa and gingiva. He also had a diagnosis of hepatitis C virus (HCV) and granulomatous nephritis of 10 years’ duration.

**COMMENT**

The treatment of symptomatic OLP, especially the erosive variant, represents a perplexing therapeutic challenge. Despite numerous existing remedies, there are many treatment failures. Our clinical experience at Massachusetts General Hospital has consistently been that 311-nm, NB-UVB
phototherapy is a highly successful treatment for CLP. Although it is easy to speculate that this 311-nm wavelength would also be useful for treating OLP, there are currently no good delivery systems for using this radiation intraorally. Therefore, it seems logical to evaluate the role of the 308-nm excimer laser, operating at a nearby wavelength, because it has a flexible fiberoptic delivery system. A handpiece allows the operator to treat specific areas of involvement easily, selectively, and efficiently, thus sparing the adjacent uninvolved mucosa and surrounding tissues from unnecessary UV-B exposure (Figure 5).

In this study, 5 of the 8 completers experienced significant relief in their symptoms and obvious improvement in the extent and severity of their erosive oral lesions by clinical examination. In this excellent response group, the one who took the longest to respond was still an active smoker. This subject had also tried a plethora of other prior remedies, such as potent topical steroids, anesthetics, hydroxychloroquine, and topical cyclosporine. On initial evaluation, he was actively receiving a drug therapy regimen for both OLP and hypertension. His medication list included 3 potential trigger factors for OLP, namely, allopurinol for 2 years, nadolol for more than 10 years, and hydroxychloroquine for 8 months. His delayed response to the excimer laser treatment may possibly be related to the continued use of multiple potential pharmacologic trigger factors.

Another one of these excellent responders had also been diagnosed with non-Hodgkin lymphoma (NHL) 2 years before the diagnosis of OLP. Subject 1 initially developed biopsy-proven CLP and within a few weeks manifested oral disease consistent with OLP. He achieved an excellent response during the first 7 laser treatments. Notably, there are extensive case reports in the literature suggesting that both OLP and CLP can be associated with neoplasia. In one report, 5 of 6 subjects with paraneoplastic pemphigus were also found to have NHL. Also, Castlemain tumors, which are benign, mostly intrathoracic lymphomas, have also been associated with various immunological diseases, including LP. It is possible in some cases that lichenoid eruptions represent immune phenomena that predispose to an associated paraneoplastic condition. This study, however, illustrates that even a patient with OLP in the setting of neoplasia such as NHL fared well with 308-nm excimer laser treatment.

On review of the fair responsive group, 2 subjects had OLP symptoms spanning 15 to 24 years. One had no obvious, identifiable trigger factors, but the other had exposure to a potentially exacerbating drug. Prior to onset of his disease, he was taking an ACE inhibitor. Even today, he continues to take daily lisinopril and also an NSAID for osteoarthritis and fibromyalgia. Both NSAIDs and ACE inhibitors are known potential activators of LP. Other drugs that have been cited as potential activators or so-called triggers of oral LP include gold salts, antimalarial agents, penicillamine, thiazide diuretics, methyldopa, quinidine, allopurinol, and chlorpropamide.

Finally, the only patient who had a poor response also had HCV and granulomatous nephritis of 10 years’ duration. His OLP may represent an extrahepatic manifestation of HCV infection. Such a variant may possibly be more resistant to therapy or may require therapy that targets the viral basis of their disease. The literature has also suggested a possible relationship between erosive OLP and HCV-related chronic hepatitis, indicating that patients with such oral disease merit a systematic workup for possible HCV infection.

Worthy of emphasis is the long symptom-free and/or disease-free follow-up that was seen in 3 of 5 subjects in the excellent treatment response group. Remarkably, the longest remission period was seen in our first patient, who also had a concurrent diagnosis of NHL.

Another intriguing observation that emerged from this study was the generally impressive excellent response to therapy seen in subjects with the erosive variants of OLP, which is often associated with the most serious symptoms. One possible explanation might be that because the mucosa lacks the overlying epithelial layer, a higher and consequently more effective UV dose is allowed to reach the infiltrating lymphocytes compared with those who had noneroded erythematous patches. The authors speculate that perhaps higher doses are needed in those with symptomatic OLP of the noneroded variant. Because this pilot study used much lower doses than standard phototherapy, perhaps higher doses with standardized dose increments could result in more rapid improvement. In addition, a biweekly treatment schedule could potentially enhance the clearing response and result in a lower overall cumulative dose.

Transformation to squamous cell carcinoma may occur in a small percentage of OLP patients, but the true incidence and potential causative cofactors have not been clearly elucidated. In terms of reducing the risk of malignant transformation in erosive lesions, long-term follow-up is clearly needed for such excimer laser–treated cases of OLP. However, the known carcinogenic risks of any type of UV radiation, presumably also that of the 308-nm excimer laser, must be balanced against the enhanced quality-of-life factor and reduced time in the eroded, nonhealing state.

Traditionally, UV light therapy has been an area of expertise developed by dermatologists. UV radiation is an excellent, well-established steroid-sparing treatment for inflammatory dermatoses, causing apoptosis and lympholysis. Its adverse effects on the skin are well documented, whereas those effects on mucous membranes are less well understood. Despite the success of UV phototherapy in dermatology, there has been minimal progress in therapeutic UV radiation application for internal inflammatory conditions, perhaps due to a lack of a successful delivery system. An interesting concept that this investigation has highlighted is that UV light can be therapeutically directed to sites of inflammation that lie beyond the skin. This particular device enabled us to access and treat the oral mucosa very efficiently. This success leads one to speculate about the numerous possibilities of how UV radiation could be used to treat other inflammatory conditions in other specialties, such as oral pathology and dentistry. It seems likely, for example, that the 308-nm excimer laser would work on the LP-like eruption associated with graft-vs-host disease. Future studies could possibly investigate the potential benefits of fiberoptic delivery of UV radiation to the mucosa in disorders such as gastritis and inflammatory bowel disease. Although the do-

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