Antimalarial Drugs for the Treatment of Oral Erosive Lichen Planus

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Abstract
Background: Treatment of oral erosive lichen planus is considered a therapeutic challenge. Various systemic and topical agents aimed at controlling the symptoms, rather than curing the lesions, have been used with varying results. Objective: To evaluate the response to treatment with antimalarial drugs in patients with oral erosive lichen planus. Methods: Eight patients diagnosed with oral erosive lichen planus were treated with antimalarial agents. The first clinical evaluation was made after a month of treatment and then every 2–3 months. Baseline ophthalmologic examinations were performed, and laboratory values were monitored before and during treatment. Results: All studied patients who had previously been resistant to other treatments responded favorably. Pain relief and reduced erythema and erosions were observed after a mean of 2.4 months. Conclusion: Antimalarials may be useful for the treatment of oral erosive lichen planus. They are easily administered and affordable, with few adverse effects.

Introduction

Lichen planus is an inflammatory disease that often affects the oral mucosa. Although in many cases the disease is asymptomatic, some patients develop erosive and very painful lesions that can be difficult to treat, reducing their quality of life. Topical corticosteroids are the most widely accepted treatment [1], and systemic administration should be reserved for acute exacerbations of the disease [2]. However, a significant number of patients, especially those with extensive involvement, respond poorly to treatment and even develop fungal superinfections due to repeated/prolonged administration [3].

Other therapeutic resources that have proved useful in the management of oral erosive lichen planus (OELP) without consideration of choice include: topical retinoids, calcineurin inhibitors, mesalazine, thalidomide, the polysaccharide nucleic acid fraction of the bacillus Calmette-Guerin, amlexanox, phototherapy, cyclosporine, and aloe vera gel [4].

The use of antimalarial agents in multiple skin diseases has been well documented, and they are considered first-line drugs for the treatment of lupus erythematosus, porphyria cutanea tarda, and chronic ulcerative stomati-
tis. We have also obtained good therapeutic results in patients with polymorphous light eruption, dermatomyositis, sarcoidosis, and generalized granuloma annulare [5, 6] and in some cases of lichen planus of the skin and lichen planus of mucosa [7]. Although they are not usually considered for the management of OELP, there is scientific evidence that antimalarial agents could be useful in the treatment of this disease [8].

In this study, we review the therapeutic response to antimalarial drugs in 8 patients with OELP. All of them had been previously treated with other drugs at the Department of Dermatology of the Instituto Valenciano de Oncología without obtaining a favorable response.

Patients and Methods

Table 1 shows the clinical characteristics of our 8 patients diagnosed with recalcitrant OELP. All of them had varying degrees of erythema and erosions with whitish reticulated lesions of the oral mucosa. None of them had skin lesions of lichen planus, lupus erythematosus, or other inflammatory dermatoses. All of the patients had previously received other topical, intraleral, and/or systemic medications without obtaining an adequate and/or persistent response.

Seven patients received chloroquine (CQ) in doses ranging from 3.5 mg/kg/day (4 patients) to 6 mg/kg/day (3 patients). One patient received hydroxychloroquine (HCQ) at 200 mg twice a day (6 mg/kg/day). All patients underwent a baseline ophthalmologic examination and blood tests that included a complete blood cell count, blood urea nitrogen, serum levels of electrolytes, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin. The first clinical evaluation was performed after 1 month of treatment and then every 2–3 months, along with analytical and/or visual control according to the changes they presented.

Patients were evaluated according to the degree of erythema and erosion in addition to their symptoms. They were graded on a global scale of 0–3 as follows: 0 = no change/minimal improvement (less than 20%), 1 = mild improvement (about 20–49%), 2 = moderate improvement (50–79%), and 3 = almost complete or complete improvement (80–100%).

Results

The therapeutic response of patients to antimalarial agents can be seen in table 1. Six women and 2 men aged 56–82 years (mean 66) received oral antimalarials drugs. The range of favorable clinical responses was 1–5 months (mean 2.4).

As for a global evaluation of the treatment, all patients had satisfactory therapeutic results (global score = 3), i.e. size reduction and reepithelization over 80% of the lesions compared to baseline, as well as relief of subjective pain (fig. 1, 2). By the time the clinical improvement occurred, the medication dose had been decreased by half in most patients.

Moreover, although one patient (No. 7) was a smoker and did not quit smoking during treatment, this did not decrease the effectiveness of the antimalarial drug.

Five patients relapsed: 2 of them as a result of decreasing the dose of antimalarial to half the dose administered at baseline (at 2 and 4 months in patients 4 and 2, respectively) and 3 of them 5, 6, and 24 months after stopping the drug because of marked clinical improvement (patients 5, 7, and 8, respectively).

Regarding side effects, we did not find alterations in blood analysis during treatment. Although patient 8 had mild pancytopenia, this finding was attributed to chronic liver disease (cirrhosis secondary to HCV infection) which the patient had previously; nevertheless, we decided to discontinue the medication to prevent further complications. A patient receiving CQ at 250 mg twice a day

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Fig. 1. Patient 1. a Erosions and whitish plaques in the anterior two thirds of the hard palate. b Significant improvement after 5 months of treatment with CQ.
Table 1. Baseline clinical characteristics of the patients, treatments, outcomes, and adverse events

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/ Gender</th>
<th>Duration of the disease</th>
<th>Smoking status</th>
<th>Clinical characteristics</th>
<th>Previous treatments</th>
<th>Antimalarial and dose</th>
<th>Favorable clinical response, months</th>
<th>Global score</th>
<th>Adverse events</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/F</td>
<td>14 years</td>
<td>No</td>
<td>Erosions and whitish plaques in the anterior two thirds of the hard palate, Reticulated plaques and erosions in the buccal mucosa</td>
<td>Topical corticosteroids, Oral corticosteroids, Oral retinoids</td>
<td>CQ 125 mg twice daily</td>
<td>5</td>
<td>3</td>
<td>None</td>
<td>Stable with mild lesions</td>
</tr>
<tr>
<td>2</td>
<td>61/F</td>
<td>7 months</td>
<td>No</td>
<td>Leukoplakic reticulated plaques and erosions on the lateral side of the tongue and the buccal and lower labial mucosa</td>
<td>Topical corticosteroids</td>
<td>CQ 125 mg twice daily for 1 month and then 125 mg daily</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>After 4 months of halving the initial dose</td>
</tr>
<tr>
<td>3</td>
<td>82/F</td>
<td>6 months</td>
<td>No</td>
<td>Scaling and erosions of the lower lip that bleed easily</td>
<td>Cryotherapy, Topical corticosteroids</td>
<td>HCQ 200 mg twice daily for 1 month and then 200 mg daily</td>
<td>1</td>
<td>3</td>
<td>Decreased visual field decibels</td>
<td>Suspended due to adverse effects after 2 months of treatment</td>
</tr>
<tr>
<td>4</td>
<td>65/F</td>
<td>18 years</td>
<td>No</td>
<td>Outbreaks of leukoplakia plaques on the tongue (left side) and buccal mucosa</td>
<td>Topical corticosteroids, Oral antifungals, Topical retinoid</td>
<td>CQ 250 mg twice daily for 1 month and then 250 mg daily</td>
<td>1</td>
<td>3</td>
<td>Moderate gastric intolerance</td>
<td>After 2 months of halving the initial dose</td>
</tr>
<tr>
<td>5</td>
<td>78/M</td>
<td>5 months</td>
<td>N/A</td>
<td>Reticulated whitish lesions in both buccal mucosa, with slight erosion on the left</td>
<td>Topical corticosteroids, Oral corticosteroids</td>
<td>CQ 125 mg twice daily</td>
<td>4</td>
<td>3</td>
<td>None</td>
<td>After 5 months of stopping treatment due to improvement</td>
</tr>
<tr>
<td>6</td>
<td>63/F</td>
<td>4 years</td>
<td>No</td>
<td>Extensive erosions in the buccal mucosas, predominantly on the right</td>
<td>Topical corticosteroids, Oral corticosteroids, Oral antifungals</td>
<td>CQ 125 mg twice daily for 2 weeks and then 125 mg daily</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>Permanent complete response</td>
</tr>
<tr>
<td>7</td>
<td>56/F</td>
<td>1 year</td>
<td>Yes</td>
<td>Reticulated whitish lesion in both the oral mucosa and the sublingual area, Erosions in the left buccal mucosa</td>
<td>Calcineurin inhibitors, Topical corticosteroids, Topical retinoid</td>
<td>CQ 250 mg twice daily for 1 month and then 250 mg daily</td>
<td>5</td>
<td>3</td>
<td>None</td>
<td>After 6 months of stopping treatment due to improvement</td>
</tr>
<tr>
<td>8</td>
<td>63/M</td>
<td>9 months</td>
<td>No</td>
<td>Erosive whitish lesions on the mucosa, Erosion on the lower labial mucosa</td>
<td>Oral, topical, and intralesional corticosteroids</td>
<td>CQ 250 mg twice daily for 1 month</td>
<td>1</td>
<td>3</td>
<td>None, stopped due to pancytopenia secondary to chronic liver disease</td>
<td>After 2 years of stopping treatment</td>
</tr>
</tbody>
</table>

Ages are presented in years. N/A = Not available; M = male; F = female.

(patient 4) presented transient gastric intolerance, which resolved spontaneously without cessation of treatment. The patient receiving HCQ (patient 3) showed a decrease in visual field decibels in the ophthalmic evaluation, so the medication was discontinued after 2 months of therapy; however, clinical improvement in the patient was already evident after 1 month of treatment (fig. 3).
Discussion

In this study, we observed that antimalarial agents can significantly improve the symptoms of OELP. All patients had a satisfactory objective clinical response and significant pain relief. These results were evident after a mean time of 2.4 months.

The mechanism by which antimalarial drugs are effective in the treatment of OELP is unknown. This also occurs in lupus erythematosus or rheumatoid arthritis, diseases in which the use of these agents is far more common but without a well-characterized pharmacological effect. Their usefulness is probably due to the anti-inflammatory effects of stabilizing lysosomal membranes and inhibition of prostaglandin synthesis and other hydrolytic enzymes [9, 10]. Moreover, it appears that an immune dysfunction mediated by T cells can play a crucial role in the development of oral lichen planus, and increased regulatory T cells in the blood and tissues of patients with oral lichen planus are significantly higher than in healthy controls; antimalarial treatment decreases the expression of these regulatory T cells, which constitute a new therapeutic target in this disease [11]. A more potent effect of antimalarials was recently noted on inhibition of endosomal Toll-like receptor (TLR) signaling resulting in reduced B-cell and dendritic cell activation. This mode of action may also explain the beneficial effects of these drugs in other T-cell-mediated dermatoses such as lupus erythematosus and granulomatous dermatoses like sarcoidosis and granuloma annulare [12].

Interestingly, the use of antimalarials in OELP is not widespread among dermatologists despite the existence of previous publications showing its effectiveness [8, 11, 13] especially if we consider the alternatives available. Thus, systemic therapies, such as oral retinoids and cyclosporine, are scarce, of questionable efficacy, and with significant adverse events [14–18]. As for the local therapies available, there is not strong evidence for the effectiveness of any single treatment, including topical corticosteroids, which are currently the first-line accepted therapy for OELP [1].

The 2 synthetic antimalarials used in dermatology are CQ and HCQ, and there is a third drug, i.e. quinacrine, which is not commercialized in Spain. Antimalarials are not free of side effects, and the most common are gastrointestinal symptoms but these are usually mild and are controlled by decreasing the dose of the drug [6]. They can also induce mild ophthalmic disorders, but definitely the most serious and irreversible adverse effect is retinop-
athy. It appears in 1% of cases [19] after 5 years of treatment, and the risk is greater with CQ than with HCQ. The American Academy of Ophthalmology (AAO) screening guidelines recommend that patients be placed on HCQ at ≤6.5 mg/kDa/day or CQ at ≤3 mg/kg/day [12]. In our study, we stopped the treatment in a patient because of a decrease in visual acuity. We thought it was a degenerative process caused by the age of the patient. However, we chose to suspend the treatment due to improvement in the vision of the patient and the report of the ophthalmologist. Moreover, we must not forget that smoking has been linked to a decrease in the efficacy of antimalarial drugs in several studies [20, 21], so it is important to advise patients about the need to give up smoking. Considering our case series, we think that a longer duration of antimalarial therapy at a higher dose may be necessary due to the relapse of 5 patients, 2 of whom relapsed after 5 and 6 months of treatment (patients 5 and 7).

The limitations of our study include its retrospective design, the small number of patients, and that there was no control group with another treatment considered first-line to compare results. However, the response in these patients contributes clinical evidence about the therapeutic effectiveness of antimalarial agents in the treatment of OELP as previously described by other authors [8, 13]. These data may be useful for the design of future studies in a prospective manner to validate our results.

In summary, we report a series of 8 patients with OELP treated with antimalarial agents. We suggest antimalarials as a good therapeutic option for OELP due to their easy method of administration, good tolerability, affordable price, and few adverse effects. Although they are not considered first-line drugs for OELP, our results make it a promising and useful choice for patients who suffer from a recalcitrant disease and/or are unresponsive to current therapies. In addition, this treatment could generate a synergistic effect when attached to other drugs that have previously been ineffective as monotherapy. This is the case of topical, oral, and intralesional corticosteroids.

**Statement of Ethics**

The authors have no ethical conflict to disclose.

**Disclosure Statement**

The authors declare no conflict of interests. There were no funding sources.

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**References**


5. Oelph as previously described by other authors [8, 13].


