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Pimecrolimus versus tacrolimus for the topical treatment of unresponsive oral erosive lichen planus: a 8-week randomized double-blind controlled study.

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Abstract

Objective To assess the efficacy and safety of topical calcineurin inhibitors for unresponsive erosive oral lichen planus (OLP).

Design An 8-week randomized, double-blind controlled trial, followed by a six-month follow-up period.

Setting Outpatients of the Oral Medicine Section, Lingotto Dental School, University of Turin, Italy.

Patients Thirty patients were treated with either pimecrolimus 1% cream or tacrolimus 0.1% ointment, both mixed with an equivalent amount of 4% hydroxyethyl cellulose gel.

Intervention The medications were to be applied twice daily for 2 months as follow: finger rub application on dried lesions after meals without eating, drinking or speaking for at least half an hour afterwards. Each patient was examined at the beginning of therapy, and then every two weeks during the treatment and every 3 months of follow-up.

Main Outcome Measures (i) To compare the effectiveness of topically applied pimecrolimus and tacrolimus; (ii) to evaluate which is more cost-effective; (iii) to determine which drug is faster in reducing signs and symptoms and (iv) which gives the longest remission.

Results Both drugs were effective at inducing clinical improvement, with no statistical difference. Pimecrolimus creams revealed a significantly better stability of the therapeutic effectiveness (P=.031).

Conclusion Both medications would currently appear to be a treatment of choice for patients with unresponsive atrophic-erosive OLP. Pimecrolimus seemed to be more effective in providing long-term resolution of sings and symptoms. Future efforts are however needed to obtain more objective evidence of the benefit of these medications in the treatment of immunologically mediated oral mucosal lesion.

Key words: erosive oral lichen planus, symptomatic, pimecrolimus, tacrolimus.

Introduction and background

Oral lichen planus (OLP) is a chronic inflammatory disease, affecting nearly 1-2 % of the population; its lesions are habitually chronic, potentially premalignant, hardly ever undergo spontaneous remission, and are frequently a source of morbidity.[1] To date, the precise aetiology remains unknown but it possibly represents a cell-mediated immunological response to an induced antigenic change in the skin or mucosa in predisposed patients.[2-4] Proposed therapies are usually symptomatic and numerous drugs have been used, but recently, it has been published that there is insufficient evidence to support the effectiveness of any specific treatment as being superior.[5] To date OLP management is commonly empirical, with no adequate control groups or corrected study designs;[6-9] moreover, although topical steroids are considered first line treatment for symptomatic OLP, no randomized controlled clinical trials have ever compare steroids with placebo.[5]

Clobetasol propionate appeared to be one of the most effective topical steroid, as in an adhesive base led to complete remission in 56-75% of patients with symptomatic OLP.[1,5,10,11] Unfortunately, some patients are refractory to topical corticosteroids. For this reason, recently, topically applied calcineurin inhibitors have been introduced for the treatment of OLP, founded to reduce signs and symptoms associated to OLP with little incidence of adverse effects.[5,12] Pimecrolimus and tacrolimus are topical calcineurin inhibitors that bind to macrophillin-12 and afterwards inhibit dephosphorylation of nuclear factor of activated T cells by calcineurin, reducing the production of TH1 cytokines.[13]

To the best of our knowledge, direct evaluation of the efficacy of topically applied pimecrolimus and tacrolimus in the treatment of atrophic-erosive OLP, refractory to topical steroids, is still lacking. Therefore, the aim of our study was: (i) to compare the effectiveness of topically applied pimecrolimus and tacrolimus for the palliative care of symptomatic OLP in a double-blind and randomized protocol, (ii) evaluating which is more

cost-effective; (iii) to determine which drug is faster in reducing signs and symptoms during the first two weeks of treatment and (iv) to determine which gives the longest remission from signs and symptoms.

Methods

Study design

An 8-week randomized, double-blind controlled trial was designed to measure the efficacy and safety of two different topical calcineurin inhibitors in the treatment of OLP. Local ethical committee approval was obtained before the trial started and all patients gave written informed consent. The study was divided into two phases: phase I consisted of topical treatment for 2 months; phase II was a six-month follow-up period without therapy. Patients were randomly divided into two groups. Randomization was performed using computer-generated random number tables. The first group of patients received pimecrolimus 1% cream mixed with a hydroxyethyl cellulose adhesive gel, whereas the second group of patients received tacrolimus 0.1% ointment in the same adhesive medium. The medication was distributed in identical containers, packed by someone who was unaware of the study. The coded tubes were consecutively numbered according to the randomization list which was prepared and retained by a single clinician (R.B.). During treatment, neither the physicians nor the patients knew which of the two medications they were using.

Patients

Consecutive Caucasian patients, attending the Oral Medicine Section of the Department of Biological Sciences and Human Oncology, University of Turin, between June 2010 and January 2012, were enrolled.

The inclusion criteria were:

-Histological diagnosis of OLP on the basis of WHO criteria:[14] hyperkeratosis of the superficial epithelial layers, vacuolar degeneration of the germinative layer of the epithelium and band-like sub-epithelial lymphocytic inflammatory infiltrate;

-Presence of painful and atrophic-erosive oral lesions, at the same time with reticular ones;

-Previous failure of therapies with topical steroids;

-Ability to complete the present trial.

The exclusion criteria were:

-Presence of histological signs of dysplasia;

-Use of lichenoid reaction inducing drugs and presence of amalgam fillings close to lesions;

-Therapy for OLP in the 2 months prior to the study;

- Pregnant or breast feeding women;

-Proved or suspected hypersensitivity caused by the tested chemicals.

Preparations

1st arm. Hydroxyethyl cellulose was melted in boiled water and slowly turned. After few hours, the 4% hydroxyethyl cellulose gel was mixed with an equivalent amount of pimecrolimus (Elidel® 1% cream, Novartis Farma S.p.A., Orrigo, Varese, Italy)) to achieve a final concentrations containing 0.5% of the drug.

2nd arm. Hydroxyethyl cellulose was melted in boiled water and slowly turned. After few hours, the 4% hydroxyethyl cellulose gel was mixed with an equivalent amount of tacrolimus ointment (Protopic® 0.1% ointment, Astellas Pharma S.p.A, Carugate, Milano Italy) to achieve a final concentrations containing 0.05% of the drug.

For both groups, every dose consisted of a quantity of formulation (2 ml), so that 0.5 mg per dose of administered medication was obtained.

Intervention

The drugs were applied twice daily for 2 months. All patients were carefully instructed how to apply the medications: finger rub application on dried lesions after meals without eating, drinking or speaking for at least half an hour afterwards. Anti-mycotic treatment was added to the therapy of both groups, consisting of miconazole gel (Daktarin® 2% oral gel, Janssen-Cilag S.p.A., Cologno Monzese, Milano, Italy) applied once daily plus 0.12% chlorhexidine mouth rinse without alcohol (Curasept A.D.S. 0.12%®, Curaden Healthcare S.r.l., Saronno, Varese, Italy) three times daily. Patients were given a written description in which the modalities of application were reported and also a paper in which they had to mark the two daily administrations. At the end of the protocol, they had to give back the marked paper to the examiners. We only accepted cases in which two applications were missed, but not consecutive.

In order to evaluate possible systemic absorption, 8:00 a.m. blood tacrolimus levels were monitored at the beginning and at the end of the protocol; we were unable to monitor the pimecrolimus levels because in our institution is a not a routinely exam possible to prescribed.

Evaluation

Clinical evaluation was performed by a single physician (M.C.). Each patient was examined by means of record chart compilation, oral examination, registration of symptoms and clinical sings, and photo at the beginning of therapy, and then every two weeks during the two months of treatment and every 3 months during the follow up period. The clinical data were scored according to the criteria scale used by Thongprasom and co-workers:[15]

Score 0: no lesions

Score 1: hyperkeratotic lesions

Score 2: atrophic area ≤ 1 cm^2

Score 3: atrophic area > 1 cm^2

Score 4: erosive area ≤ 1 cm²

Score 5: erosive area > 1 cm²

Complete resolution of the clinical signs (complete response) was defined as the disappearance of all atrophic-erosive lesions, regardless of any persisting hyperkeratotic lesions; scores were either zero or one.

The symptoms score was obtained using a Visual Analogue Scale (VAS). The VAS consisted of a 10 cm-horizontal line marked 0 (= no pain) to 10 (= most severe pain ever experienced). Patients were requested to mark the scale at each visit. Complete resolution of the symptoms (no symptoms) was defined as the absence of any discomfort, corresponding to a zero VAS score.

Partial response, worsening, or persisting of the patient's condition meant a decrease, an increase, or no change at all in the patient's score.

The difference between baseline and endpoint scores numerically expresses the clinical and symptomatic improvement.

The stability of the obtained result in the 6 months following the suspension of treatment was assessed; the differences between the two groups, when present, were also evaluated.

Cost assessment

We evaluated the total cost of the two treatments: this included the cost of buying the drugs and the cost of preparing them with the adhesive medium. All the dressings were prepared by the same pharmacy. Each patient used two tubes of a given drug (one per month during the trial). The cost of antimycotics was not included in this evaluation as both the tacrolimus- and pimecrolimus-treated patients used the same amount of antimycotic drugs (data not shown).

Statistical analysis

The sample size was calculated according to previously published[16] data suggesting an overall efficacy of 80% and 30% for topically applied tacrolimus and pimecrolimus, respectively. With a power of 95% and a type I error of 0.05, 30 patients (15 for each arm of the study) had to be recruited. X^2 analysis (with Yates' correction or Mantel-Haenszel's correction) or Fisher's exact test were used to compare the responses between the groups. $P < 0.05$ was considered to be statistically significant.

Results

Thirty consecutive Caucasian patients (23 women, 7 men, mean age 67.75) were enrolled in our study; 1 (pimecrolimus group) did not complete the study because of personal choice. Fig. 1 shows participant flow. However, this case has been also added in the statistical analysis and considered as a treatment failure.

Demographics and clinical characteristics are detailed in Table 1. There were no significant differences between the two groups with regards to age, gender, or clinical and symptomatic characteristics at baseline.

Symptoms improved in all tacrolimus and pimecrolimus treated patients (100%) during the first 2 months of therapy, with no statistical differences between the two groups. Complete remission of symptoms occurred in 4 patients in both groups (26% and 28% in tacrolimus and pimecrolimus group, respectively) (Table 2; Fig. 2).

Regarding clinical signs, 14 of the 15 tacrolimus treated patients (93%) improved after 2 months of therapy, while 11 of the 14 pimecrolimus treated patients (78%) had a positive response (Fig. 3 and Fig. 4); however, the difference was not statistically significant ($P > 0.05$, Fisher's exact test). In particular, 5 patients treated with Tacrolimus (33%) and 5 treated with Pimecrolimus (35%) had a complete remission of the athrophic-erosive lesions (score 0 or 1) (Table 3; Fig. 5). Both drugs caused a significant reduction of signs and symptoms after the first two weeks of treatment with no statistical difference.

At the end of the trial, some adverse effects were noted; in the tacrolimus group, 2 patients reported mucosal burning sensation during the first days of the therapy and 1 reported a transient sialorrhoea. In the pimecrolimus group, 2 patients reported xerostomia, 2 experienced episodes of gastroesophageal reflux and one the recurrence of two lesions of herpes labialis. None of these adverse effects was severe enough to require discontinuation of therapy. There was no statistically significant differences between the two groups in the incidence of adverse effects ($P>0.05$, Fisher's exact test). During treatment, blood tacrolimus levels remained undetectable (<1.5ng/mL) or low (<5ng/mL) (data not shown).

Finally, we evaluated a parameter of compliance (e.g. number of missed application) without any significant difference between different groups and also in the same arm (data not showed). None of the patients had particular difficulty in applying the medications.

Six months after the end of the therapy, 11 patients treated with tacrolimus (73.33%) needed to be retreated due to reactivation of the disease, whereas 10 patients treated with pimecrolimus were stable and did not need a new therapy, revealing a significantly better stability of the therapeutic efficacy of the latter (Table 4).

Each patient in both group used an average of 4 ml of drug daily. The cost of a single tube of tacrolimus in adhesive medium was 92.79 €, whereas a single tube of pimecrolimus costs 93.73 €. The daily cost of tacrolimus treatment was 1.65 € and it was comparable to that of pimecrolimus therapy which was 1.67 €.

Discussion

Usually, patients with OLP are treated with medications that were neither developed nor planned for oral diseases, consequently satisfactory efficacy studies are missing. The most habitually employed agents for the treatment of OLP are topical corticosteroids.

However, independently from the active principle used and the way of administration, beyond the half of the responsive patients showed yet again active painful disease, and can need new therapeutic approach, confirming the OLP chronic course and the symptomatic character of therapeutic treatments. Moreover, some patients are refractory to steroid medication and could need a different approach.

The non-steroidal topical calcineurin inhibitors (TCIs) are important treatment option and are indicated in cases where the use of topical steroids is unsuitable, or have failed to adequately control OLP, especially in the acute phase, similarly to other dermatological conditions.[17] Calcineurin inhibitors are microbial derived immunosuppressive medication, mainly used in transplant medicine and in the treatment of immune-mediated diseases. To date however, there is much debate about their long term efficacy and safety and their advantage with respect to conventional therapies.[16] Topical pimecrolimus and topical tacrolimus have been reported to be successful in treating OLP,[18-37] but there are no published data comparing their efficacy. We chose two different concentrations of pimecrolimus and tacrolimus following the recommendations of previous reported works and of pharmaceutical firms.

In the present study, we can say that both drugs, at these doses, were effective at inducing clinical improvement in patients affected by atrophic erosive lesions, with no statistical difference.

The compliance of the tacrolimus arm was slightly better due to the lower incidence of adverse effects, even if this did not reach statistical significant difference and the adverse-effects were however mild in most cases and did not cause patients to leave the study. Topical calcineurin inhibitors occasionally are used within the mouth; the more frequently reported adverse event is transient burning sensation (similar to our cases); other minor adverse events published can vary and in our series the salivary problems,

gastroesophageal reflux and herpes reactivation should have been simply not related effects.

Our data confirmed that the reduction of symptoms in OLP patients following treatment with topical pimecrolimus or tacrolimus is generally noticeable; moreover, as previously reported, the side-effects are limited and no serious toxicities have been described.[38] The daily cost of the two medications is similar, less than cyclosporine but still more than five times higher than clobetasol (1,82 € and 0,35 € respectively as reported by Conrotto and co-workers[10]). To date, because of the non-existing evidence that TCIs are better than topical corticosteroids in reducing pain and clinical sings in patients with erosive OLP, and because of their cost, pimecrolimus and tacrolimus should be use as second-line treatment for symptomatic OLP, after failure of topical steroids.

It has been reported that the severity of the oral erosions could impair the barrier function of the mucosa and promote the systemic absorption of tacrolimus.[39] However, systemic absorption of tacrolimus after topical application on the oral mucosa are unpredictable, low and with probably very limited clinical significance.[17] In our series, low blood level of tacrolimus were detected in less than 50% of patients, but this haematological presence was not associated with severe adverse events. For technical reasons, we were unable to monitor the pimecrolimus blood level; however, recent studies did not showed relevant changes in laboratory values of pimecrolimus from baseline,[18,24] suggesting that this drug could be difficulty absorbed by the oral mucosa. Moreover, it has been reported that the permeation of pimecrolimus in corticosteroid pre-treated skin is lower than that of tacrolimus.

As OLP tends to frequently relapse after cessation of treatment, long-lasting property and effects of these new medications have to be carefully analysed. During follow up we observed that tacrolimus patients were less stable than pimecrolimus patients. Pimecrolimus creams revealed a significantly better stability of the therapeutic

effectiveness during a period of six months. As already reported, the ability of pimecrolimus to permeate the skin to a lesser extent than tacrolimus may contribute to the sustained therapeutic effect observed.[19, 40] However, literature data about the long-lasting benefits of TCIs are nowadays missing. Most of the studies have a short follow-up period[19,24] and others do not evaluate patients for relapse of disease after discontinuation of medications.[18] It has been reported that, although topical pimecrolimus and tacrolimus are secure and successful for OLP that not respond to topical steroids, existing evidence suggests that these agents will not provide long-term resolution.[16] Moreover, it has been reported that the maintenance of disease remission necessitates continued intermittent use of topical tacrolimus, in order to obtain a long lasting action of this medication.[34] However, our data demonstrated that probably this is incorrect at least for pimecrolimus, but further studies are needed with more patients and with a long follow-up period.

As previously used with topical steroids,[10,11] we added the hydroxyethylcellulose (HEC) with the drugs, in order to make the application more stable and manageable; HEC is a naturally derived polymer that is used as a thickener in creams and lotions and helps modify viscosity and form gels with water-soluble ingredients.[41] Both drugs were mixed without any particular technical hitches, even if tacrolimus (provided as homogeneous, viscous and semi-solid ointment) was more difficult to incorporate rather than pimecrolimus. Any possible differences due to the incorporation of HEC in the two tested medication were considered as irrelevant, based on the lack of any previously reported changes in the pharmacological properties of ointment or cream after mixing with HEC. However, because of the impossibility to check for the solubility of the two medications in the HEC, our results should be interpreted with caution, and, in future, it would be interesting to know if the statement achieved would be the same with different preparation and different concentrations.

Calcineurin inhibitors have been shown to have oncogenic properties mainly linked to the production of cytokines that promote tumour growth, metastasis and angiogenesis.[18] Usually, however, the systemic forms are known to increase the risk of malignancy[16] and currently there is no strong evidence that topical applications could be associated with an increased risk of tumours.

Of course one of the main limitations of our study is the small sample size, which could result in limited power, particularly for multivariate analyses. However, it is important to remember that our population is exceptionally selected, because of the previous and unsuccessful treatment with topical steroids.

In conclusion, both pimecrolimus and tacrolimus would currently appear to be a treatment of choice for patients with atrophic-erosive OLP, previously treated with topical steroids but unresponsive; moreover, no unexpected adverse events were reported and the rates of adverse events were generally low in both treatment groups. Pimecrolimus seemed to be more effective in providing long-term resolution of sings and symptoms. More research is however needed to obtain objective evidence of the benefit of TCIs in the treatment of immunologically mediated oral mucosal lesion such as erosive OLP, and this work needs to be reconfirmed by a large scale clinical trial.

Author contributions

All the authors had access to the data reported and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study design*: Arduino, Carbone and Broccoletti. *Analysis and interpretation of data*: All authors. *Drafting of manuscript*: Arduino, Della Ferrera, Gambino, Elia, Comba and Conrotto. *Statistical analysis*: Broccoletti and Della Ferrera. *Obtained funding*: Broccoletti. *Study supervision*: Arduino, Carbone, Calogiuri and Broccoletti.

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