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Original Research Article

Clinical Assessment of the Effectiveness of Tacrolimus and Triamcinolone Acetonide in the Treatment of Oral Lichen Planus

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Abstract

Introduction: Lichen planus (LP) is a mucocutaneous, chronic, autoimmune condition that affects the skin, scalp, nails, and genital mucosa. The goal of the study was to assess the effectiveness of topical administration of TA orabase and Tacrolimus (TAC) ointment along with intralesional triamcinolone acetonide (injection TA) for symptomatic cases of OLP.

Materials and Methods: 100 symptomatic OLP patients were enrolled in the prospective trial. For the first four weeks, they received a 0.5 ml intralesional injection of TA once a week, followed by one injection in the sixth week, coupled with 0.1% TA mucosal paste and 0.03% TAC ointment, tapered doses until the eighth week. On a 10 cm visual analog scale (VAS), subjective symptoms including BS and pain were evaluated, while objective markers like the size and location of the lesion were graded using a modified version of the Thongprasom et al. criteria scale. After an 8-week treatment period, differences were compared, and at the 20-week mark, follow-up assessments were made to note any recurrence lesions.

Results: 20 % had partial improvement, and 80 % had complete illness remission. Both the BS and pain VAS scores dramatically increased. The average size of active lesions shrank, and there were fewer treatment sites, both of which were indicators of improvement. In the 20th week, 40% experienced a relapse.

Conclusion: Combining TA with TAC is a helpful treatment strategy for the therapy of symptomatic OLP. Our findings suggest that patients have statistically improved.

Keywords: Intralesional injection, tacrolimus, topical therapy, triamcinolone acetonide.

Introduction

Since a long time, autoimmune lesions have generated debate because certain cells are recognized as foreign bodies because of antigenic changes to their cell surfaces. In the general population, the prevalence of lichen planus, one of the prevalent chronic inflammatory diseases of stratified squamous epithelium, ranges from 0.5% to 2.2%.[1] The trigger factor that may make the oral mucosa more likely to experience apoptosis involving auto-cytotoxic T-cells is thought to be the ambiguous character of T lymphocytes. The condition, which was first identified by Erasmus Wilson in 1869, primarily affects females between the ages of 30 and 70 and commonly affects the skin, mucous membranes, nails, and hair.[2] The buccal mucosa, dorsum of the tongue, gingiva, labial mucosa, and vermilion border of the lower lip all exhibit 15%–35% incidence as

mucosal/oral lesions.[3] While erosive, atrophic, and bullous lesions are usually accompanied by burning sensations (BSs) and discomfort that impair quality of life, the most common reticular variant runs an uneventful course. Oral lichen planus (OLP) typically manifests clinically in a major way, however a biopsy is advised to confirm the diagnosis and rule out malignancy.[4,5]

Although several empirical treatment plans have been used to lower morbidity, a permanent cure has not yet been identified. Drugs that specifically target T cells at various stages of maturation, however, may result in unexpected outcomes, according to current thinking.

While systemic corticosteroids are utilized for widespread involvement of the skin, genitals, esophagus, or scalp, intralesional or topical corticosteroids have anti-inflammatory and immunosuppressive effects on the oral epithelium. Effective symptom relief for OLP has been demonstrated with topical administration of TA, super potent halogenated steroids like clobetasol, and potent fluorinated steroids like fluocinolone acetonide and fluocinonide. Ointments, gels, mouthwash, sprays, and pastes of TA are regarded as acceptable and respectably effective therapy options.[5] According to a study by Suresh et al., there is little proof that one type of corticosteroid is preferable to another in terms of lowering pain and other clinical indications.[6] Although the oral cavity is easily accessible and allows for direct drug delivery, it is equally critical to recognize that complete clinical cure and disease return after drug withdrawal remain ongoing challenges for clinicians. Insufficient drug absorption prevents oral mucosa from reaching therapeutic levels that, in some situations, may contribute to a partial cure. The oral mucosa's viscoelastic quality prevents any foreign compounds, such as paste or gel, from adhering and quickly removes them before being absorbed. Contrarily, intralesional steroid injection is a successful strategy for attaining a high enough local drug concentration for optimal anti-inflammatory effects. The therapeutic efficacy at the site is maintained for a longer period of time with fewer side effects because to the aqueous suspension of TA, which slows down its rate of absorption. Few side effects described in prior research include brief tingling and BS at the injection site with cushioned features.[4]

Tacrolimus (TAC), pimecrolimus, and other topical calcineurin inhibitors are being evaluated as alternatives, primarily to treat resistant cases of OLP. TAC is up to 100 times more strong and effective than ciclosporin, according to studies, and it has hardly any negative clinical effects.[5,7] By inhibiting the calcium calmodulin-dependent phosphatase calcineurin, which enhances interleukin 2 and tumor necrosis factor by targeting cytosolic FK binding protein, it prevents T-cell activation.[8] According to Zhang and Tao et al., TAC can reduce Treg proliferation and block the NF-B pathway, which has been linked to the pathophysiology of OLP.[9,10] Even though topical use of TAC has demonstrated a greater therapeutic response in resistant instances, it is frequently utilized for a brief length of time due to the possibility of raising the risk of developing oral squamous cell carcinoma.[11]

Combination therapy has been a pillar of cancer treatment in recent years. Such a treatment utilizes a combination of two or more therapeutic drugs to affect numerous pathways. The medications work together synergistically to increase treatment effectiveness in less time, decrease the likelihood of drug resistance, and slow the pace of relapse. Because each treatment only needs to be used at a lower dose than in monotherapy, there are less adverse effects. Comparing drug repositioning to conventional cancer monotherapy has also proven to be advantageous. In order to achieve better therapeutic results, the medications are combined with a

secondary agent that targets the neoplastic cells and a neo-protector agent that protects the normal cell.[12]

Although TA and TAC have been employed separately for the therapy of OLP in a number of trials, a combinational strategy has not yet been tried. As a result, in the current study, we aimed to evaluate improvement in symptomatic OLP patients using combination medications made up of TA injection, TA orabase, and TC paste.

Materials and Methods

Patients who visited the radiology and oral medicine departments participated in the study. By screening patients who visited the outpatient department over the course of a year, a prospective randomized trial was conducted. 56 individuals between the ages of 25 and 72, of either sex, were included in the study. After getting written informed consent, clinical and histopathologic exams were used to diagnose all of the patients. The institutional ethics committee granted this study approval and issued a certificate of clearance.

Inclusion criteria

Patients above the age of 18 who had OLP's clinical and diagnostic criteria were included. The occurrence of ulcerations as well as discomfort and BS after consuming spicy or hot meals were clinical signs. Patients who agreed to get a biopsy and were prepared to take the prescribed medications and attend clinics frequently were chosen.

Exclusion criteria

Patients with other mucosal or skin disorders, hepatic diseases, hematological diseases, infectious or contagious diseases, intractable medical conditions, or radiological abnormalities were not included in this study. Additionally, individuals with a history of cancer, those who have received prior therapy, those who are allergic to corticosteroids, or those whose biopsy results revealed dysplastic characteristics on histopathology were not included. Patients with a history of medication therapy that may have caused lesions resembling OLP or those who were pregnant or nursing were excluded from the trial.

For the first four weeks, each of the 100 patients received a (0.5 ml) intralesional injection of TA (40 mg/mL; manufactured by Abbott health care Pvt Ltd.) and then just one injection in the sixth week. The lesion's surrounding normal mucosa and subepithelial connective tissue were also targeted for injection. The patients were instructed to use TA mucosal paste (5 gm, trade name: Kenacort: Triamcinolone Acetonide (TA) 0.1%. Manufactured by Abbott healthcare Pvt. Ltd.) and TC 0.03% ointment (10 g, trade name: Tacroz: TAC 0.03%. Manufactured by Glenmark Pharmaceuticals Ltd.), three times daily for 4 weeks followed by twice daily application in the next 3 weeks and once-daily application in the 8th week. For at least 30 minutes after application, the patients were instructed not to eat or drink.

Each patient was persuaded to give up bad oral habits like chewing tobacco or smoking and cut out spicy foods from their diets. To prevent further mechanical harm, care was also taken to promote oral health through oral prophylaxis, rounding of sharp cuspal edges, removal of cracked teeth, and correction of any ill-fitting prostheses 1 month prior to the start of the treatment. Throughout their tour, the patients received psychological treatment and were inspired and motivated.

Prior to the initiation of the treatment and after 8 weeks, the reaction was clinically evaluated. Clinical results were evaluated using both objective and subjective criteria. On a 10-cm visual analog scale (VAS), the subject graded the intensity of their BS and discomfort. The number of sites involved (site score) and the severity of the lesion in accordance with the standards outlined by Thongprasom et al. were both included in the lesion

score.[13] The seriously affected site score was taken into account in patients who had numerous sites of involvement. The patients were called back once a week for the first month, then once every other week for the following month. The absence of pain and BS (VAS 0), as well as the removal of atrophic/erosive/reticular lesions at all locations, were regarded signs of complete remission (Score 0). For the following three months, the disease recurrence was evaluated in all patients.

Initial side effects included transient BS and a change in taste, which disappeared within a few days of treatment. By identifying the growth of candida in culture, antifungal medication was administered.

The results of the data's statistical analysis were presented as mean standard deviation. To determine the results' significance, the pre-treatment group's observations were compared to those from the post-treatment group using a paired t-test. Statistics were deemed significant at P 0.05.

Results

Finally, out of 102 cases, 100 patients with an average age of 47 years and a range of 30 to 65 years finished the study, while 2 patients were unable to follow the instructions. The gender split was 1:1 with 50 females and 50 males.

At the end of 8 weeks, complete remission was seen in 80% whereas partial response was seen in 20%. Though the disease was less severe than the initial lesion, the secondary sequelae were seen in 40% patients.

Over the course of the trial, the pretreatment values for BS and pain gradually decreased. The mean BS score was 6.5 at baseline, but by the end of 8 weeks, it had dropped to 0.50. At the beginning of treatment, the mean score for pain intensity was 2.5, and it was found to be 0.10 towards the conclusion. When compared from the baseline score to the end of two months, the mean of the BS and pain scores were statistically significant.

With therapy, the mean scores of the number and size of lesions decreased. According to the initial observations, 20% of patients had a single site of participation, 60% had involvement at two sites, and 20% had involvement at more than two sites, with a mean site score of 1.8. Eighth-week observations showed that 9 % of patients had bifocal site involvement and 11% had unifocal lesions, with a mean score of 0.2 indicating a statistically significant difference in the number of sites implicated.

During treatment, there was a noticeable improvement in the resolution of the reticular, erosive, and atrophic kinds of OLP. When therapy first began, observations showed that 44% of patients had white striae with erosive region and 56% of patients had erythematous area, providing a mean score of 3.1. The mean score attained at the conclusion of 8 weeks was lower than the starting score with a statistically significant difference of (P 0.01).

Table 1: Active lesions at various intervals

Clinical Parameters	Mean ± SE			P value
	Baseline	At 8th weeks	At 20th week	
Burning sensation	6.5±1.11	0.60±0.89	3.5±0.78	<0.01
Pain	2.5±2.23	0.10±0.45	2.1±1.1	<0.01
Site score	1.8±0.56	0.30±0.56	1.1±0.23	<0.01
Size of lesion	3.1±0.98	0.20±0.34	1.6±0.45	<0.01

Discussion

The most widely accepted pathogenic mechanism to start anomalies among histocompatibility antigens like the HLA-

DR complex associated with band-like infiltration of lymphocytes in OLP is the cell-mediated immune response to surface antigens. When unidentified etiological factors activate CD8+ and a small number of CD4+ T cells, they move toward the basal keratinocytes by chemokine-mediated migration. The major histocompatibility complex-1 on the keratinocyte is further altered by antigen binding to CD8+ cells to enable basal cell death. The released cytokines from the activated CD8+ T cells break the vicious cycle by luring more lymphocytes to the lesion.[14] Complete or partial lesion clearance secondary to palliative cure is the main aim of treatment. The initial management strategy should include essential steps including patient counseling, dental hygiene improvement, and giving up bad oral habits.[1] Several techniques have been employed to reduce morbidity, including topical and systemic corticosteroids, griseofulvin, topical retinoids, hyaluronic acid, tetracyclin, and topical cyclosporin.[7] Topical application to the primary site is advised as a treatment method because it offers immediate availability and ease of application, however the complicated oral environment and salivary secretions reduce the therapeutic efficiency of topical drugs/agents. Topical medications are rinsed quickly and incompletely within a few seconds by the action of salivary flow due to the barrier-forming effect of saliva. Longer contact time with the medicine at the application site is necessary to ensure greater bioavailability by allowing drug penetration into the epithelium's deepest layers.[7,15]

Applying TA, a midpotency corticosteroid topically, is thought to be beneficial in treating OLP. Application of corticosteroids has demonstrated dual anti-inflammatory effects on the afflicted epithelium. It helps to stabilize the intracellular membranes that surround lyzozymes and hinders the release of those enzymes from granulocytes. By inhibiting hydrolytic enzymes, it also regulates cell damage and stops the spread of inflammatory tissue damage in the nearby area.[16] Two formulations of TA 0.1% (mixed with Orabase [Colgate-Palmolive, New York, NY, USA] and as a mouthwash) were found to be classified as Class I (treatment is useful and effective) by Al-Hashimi et al.[1] Although occurrences of oral candidiasis are the most frequently noticed adverse effect and are typically treated topically with ketoconazole, topical treatments are less expensive and less prone to cause major side effects.[13,17] In most research, the amount of time that TA is applied varies from 2 to 4 times per day for a length of 4 to 8 weeks. Using TA ointment, Arunkumar et al. found a 92% reduction in the mean scores of BS.[18] In contrast, Laeijendecker et al. and Malhotra et al. found that 45% and 66% of patients, respectively, demonstrated improvement with topical TA.[19,20] In the current study, 79% of patients reported total relief from pain and BS, while 21% of patients experienced a steady improvement in their VAS scores. While TA orabase helped to overcome the low therapeutic drug concentration in the intermediary phase, injectable TA was chosen to deliver the medication directly in the submucosa.

Numerous studies of the immunosuppressive effects of calcineurin inhibitors have been published in the literature, and they have demonstrated clinical advantages in the treatment of immunologically induced illnesses of the oral mucosa. Calcineurin inhibitors have mostly been utilized to prevent graft-versus-host disease in allogeneic hematopoietic stem cell transplant patients as well as rejection in organ transplant recipients.

Only patients who experienced a complete objective response and attained asymptomatic state were examined for relapse. After the end of the treatment, all patients were monitored for a period of 12 weeks. In 41% of patients, the data showed that the oral lesion had returned.

This is consistent with the findings made by Lee et al., who found that 40% of relapses happened after experiencing drug withdrawal after receiving TA intralesionally.[4] In contrast, Malhotra et al. found that 22% of patients using topical TA experienced relapse.[20] While Laeijendecker et al.'s study discovered a greater rate of recurrence among 72% of TAC patients and 78% of TA patients after therapy stopped.[19] Compared to the initial lesion, the size and number of sites implicated were less severe.

Due to their wide-ranging therapeutic qualities and diverse impacts on a variety of immune-mediated disorders, both TA and TC are regarded as reasonably safe, nontoxic, and effective alternatives for many conventional medications. The usage of this protocol led to statistically significant improvements in the clinical signs and symptoms.

Conclusion

Combination therapy is an advantageous and reasonably priced pharmacological regimen that has proven successful in treating OLP. Additionally, solo treatment increases the risk of drug resistance since it causes changed cells to recruit alternate salvage mechanisms, which could lead to more frequent recurrence and an increase in the disease's malignant potential. Achieving a biological cure with no relapse of the disease in the future is still difficult for dental experts because of the unprecedented multi-exacerbations. To make any firm conclusion, more research involving a bigger patient population, followed by a longer follow-up time, is necessary.

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