ORIGINAL RESEARCH

A comparative study of clinical efficacy and safety of 0.1% tacrolimus ointment versus 1% pimecrolimus cream in the treatment of lichen planus pigmentosus

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ABSTRACT
Background: Lichen planus pigmentosus, an uncommon variant of lichen planus, is an enigma with perplexed treatment. Several treatment modalities has been tried but with variable results. **Objectives**: The primary objective of the study is to compare the efficacy and safety of 0.1% tacrolimus ointment versus 1% pimecrolimus cream in the treatment of LPP. **Method**: 60 patients were randomly divided into 2 groups of 30 patients each. Group A was asked to apply 0.1% tacrolimus while Group B was asked to apply 1% pimecrolimus cream twice daily. The results were evaluated on the of physician's global assessment, patient's satisfaction score, patient's global tolerance and coloured photographs. **Results**: Physician's assessment and patient's satisfaction score were comparable and good to moderate in both the groups but were statistically non significant ($p > 0.05$). Drug tolerability was good to excellent in both the groups. **Conclusion**: Topical calcineurin inhibitors like tacrolimus and pimecrolimus can be considered as a treatment modality of LPP with greater tolerability and negligible adverse effects as compared to systemic treatment. Furthermore, larger prospective studies are required to investigate their outcomes.

Keywords- Lichen planus pigmentosus, Pimecrolimus, Topical, Tacrolimus

INTRODUCTION

Lichen planus pigmentosus (LPP) is an uncommon variant of lichen planus (LP) that tends to occur in middle-aged individuals with darker pigmented skin.[1] The disease is insidious in onset and has a chronic course.[2] Clinically it presents with hyperpigmented, brown to gray-brown macules and patches in sun-exposed areas.[1] Precipitating factors include sun exposure and photosensitizing agents. The histopathological changes of LPP consist of mild, band-like lymphocytic infiltrate with vacuolar degeneration of the basal layer in the epidermis. Dermal changes include marked melanin incontinence with apoptosis or necrosis of keratinocytes.[3] Main differential diagnosis are erythema dyschromicum perstans /ashy dermatosis, pigmented contact dermatitis/Riehl's melanosis, post inflammatory hyperpigmentation, drug induced pigmentation, macular amyloidosis and fixed drug eruption.

LPP has a variable course and refractory to treatment. Various treatment modalities like systemic (oral corticosteroids, vitamin A, dapsone, isotretinoin) [4, 5, 6, 7] and topical (steroids, topical immunomodulators like tacrolimus) [8, 9] have been tried but with inconsistent response. Other treatment modalities that have been practiced are chemical peels and Nd:YAG lasers with variable response[10, 11]. As per our knowledge, there is scarcity of literature on the use of tacrolimus and pimecrolimus in the management of LPP. Due to paucity of studies, we felt that it might be useful to evaluate the efficacy & safety of 0.1% tacrolimus

ointment and 1% pimecrolimus cream and compare with each other in the treatment of LPP.

MATERIAL & METHODS

An open label, randomized, comparative and prospective study was conducted in the pigmentary clinic of dermatology department of a tertiary care centre in North India among 60 biopsy proven patients of LPP in 2018. They were randomly divided into 2 groups of 30 each. In Group A, patients were asked to apply 0.1% tacrolimus ointment twice daily and in Group B, patients were asked to apply 1% pimecrolimus cream twice daily, as monotherapy on affected area till complete clearance of lesions or to a maximum of 16 weeks whichever is earlier. The patients were followed up once a month till the completion of therapy. Photographs was taken before treatment as a baseline and after 16 weeks of starting treatment. Inclusion criteria was patients showing clinical features of LPP, biopsy proven LPP , patients giving informed consent and age equal or more than 18 years. Clinical criteria for LPP – presence of asymptomatic bluish-grey/ black-brown ill defined macules and patches mainly over face, neck and upper extremities.Histological criteria for LPP – minimal atrophy of epidermis, keratinocyte apoptosis and basal cell layer vacuoler degeneration along with band like lymphocytic infiltrate, melanophages and melanin incontinence in the dermis.[9]

Exclusion criteria was patients who do not give informed consent, age less than 18 years, pregnant females, lactating mothers, on immunosuppressant therapy or any other systemic drugs, having other dermatological and systemic disorders. Patients on topical/ systemic treatment for LPP over the past 2 months were also excluded. One skin punch biopsy of 4 mm was performed for all the patients. Patients were also advised to apply broad spectrum sunscreen on daily basis and avoid precipitating factors.

Detailed history regarding age of onset, duration of the disease, site of onset of pigmentation, progression, associated symptoms and family history was recorded. Information regarding related external factors like drug intake prior to onset of disease, use of cosmetics, dyes, mustard oil and amla oil etc. was obtained. Physical examination and detailed dermatological examination including morphology & distribution of lesions, extent of involvement, colour & pattern of pigmentation and changes in oral cavity, hair and nails was performed. Also presence of any other systemic or dermatological disease was ruled out. Following baseline investigations were carried out in each patient - complete haemogram, liver function test, renal function test, HBsAg and anti- HCV, thyroid function test and random blood sugar.

The results were evaluated at the end of therapy on the basis of

1. **Physician's Global Assessment**- the clinical response was assessed by grading the improvement in pigmentation using the following scale[9]- None=0%; Poor=1–25%; Moderate =26–50%; Good=51–75%; and Excellent >75%.
2. **Coloured photographs**- coloured photographs were taken of all the patients in both the groups at baseline and at the completion of therapy. The percentage of pigmentary clearance was evaluated by means of coloured photographs.
3. **Patient's Satisfaction Score**- patients in both the groups were asked to grade their improvement at the end of therapy using the following score- 0-3 – poor response; 4-6 – good response; and 7-10 – excellent response.
4. **Patient's Global Tolerance**- patient's tolerance for the two topical agents was graded as follows- poor, fair, good and excellent.

P value was calculated by applying Chi-square test on results of both the groups (group A- n=30; group B- n=30) for proper statistical analysis.

RESULTS

Total patients recruited in the study were 60, which were divided into two groups of 30 each. The age range of maximum number of patients was between 30-40 years (14 patients, 46.7%) in Group A and more than 40 years in Group B (11 patients, 36.7%). The prevalence of LPP is more common in female [total 55 patients, (91.7%); 28 patients (93.3%) in Group A, 27 patients (90%) in Group B] while only 5 (8.3%) males were affected with it. Patients belonging to rural and urban areas were in almost similar ratio in both the groups.

The duration of LPP was less than 12 months in 14 patients (46.7%) in Group A and in 17 patients (56.7%) in Group B. The most frequent site affected by LLP was neck [27 patients (90%) in Group A and 26 patients (86.7%) in Group B] followed by face [22 patients (73.3%) in Group A and 19 patients (63.3%) in Group B] and then arms and trunk as shown in graph 1. LPP inversus involving groin and axilla were seen in only 2 patients in Group A and none in Group B.

History of some irritant application such as dye, mustard/amla oil was present in 10 patients and 9 patients in Group A and B respectively. Family history of similar disease was negative in all patients. In any of the patients, there was no history of any previous lesions or inflammation in the affected areas.

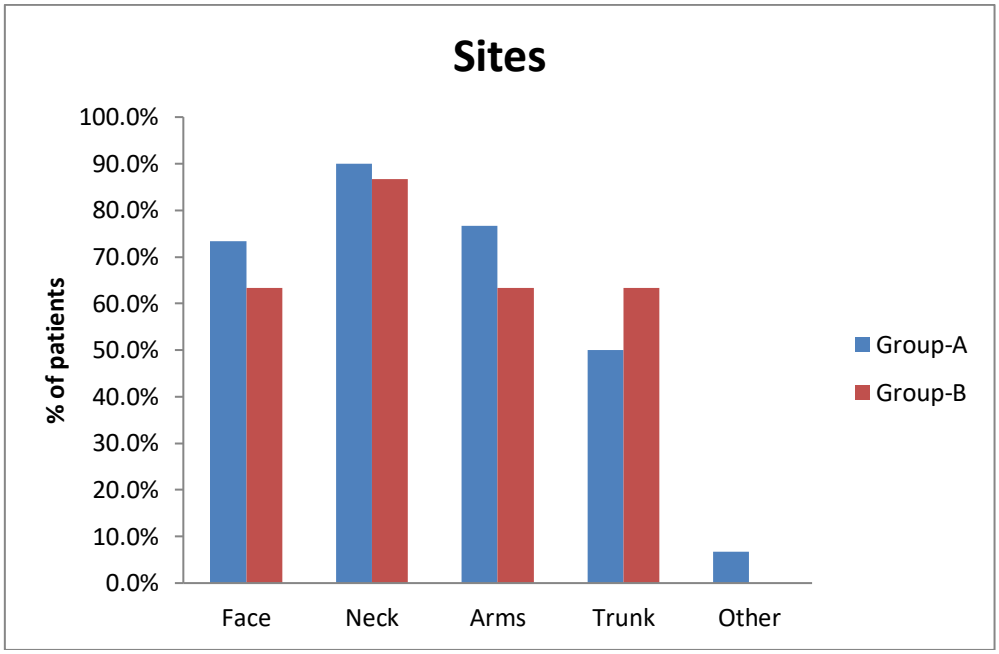
The most characteristic pattern found was diffuse pattern, which was prevalent in 21 patients (70%) and 19 patients (63.3%) in Group A and B respectively. Other patterns, which were seen were blotchy, reticulate, and perifollicular as shown in graph 2. Bluish gray was the typical colour of the lesion found in 24 patients (80%) in each group followed by black brown in 6 patients (20%) in each group. Pruritus was present as initial symptom in 23 patients. Cutaneous/oral LP was seen in 2 patients only.

Most common histological findings seen in 43 patients were minimal change in epidermal thickness, basal cell layer vacoular degeneration along with

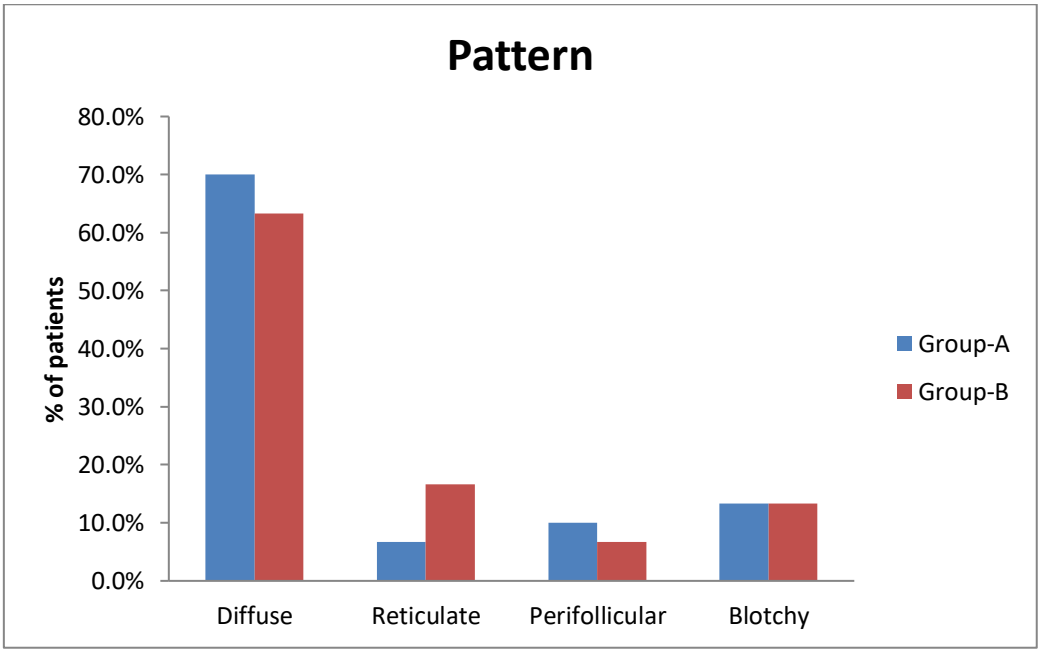
band-like lymphocytic infiltrate, melanin incontinence and melanophages as shown in figure 1a and b.

According to physician global assessment, moderate response was seen in 17 patients (56.7%), good response in 5 patients (16.7%) in Group A whereas in Group B, moderate response was seen in 20 patients (66.7%) and good response in 2 patients (6.7%) as shown in figure 2 &3. Patient satisfaction score was good in 16 patients (53.3%) and excellent in 2 patients (6.7%) in Group A while it was good in 21 cases (70%) and excellent in none in Group B. Patient's global tolerance was excellent in most of the patients in both groups (18 patients (60%) in Group A and 22 patients (73.3%) in Group B). All above mentioned assessment and score are shown in graph 3.

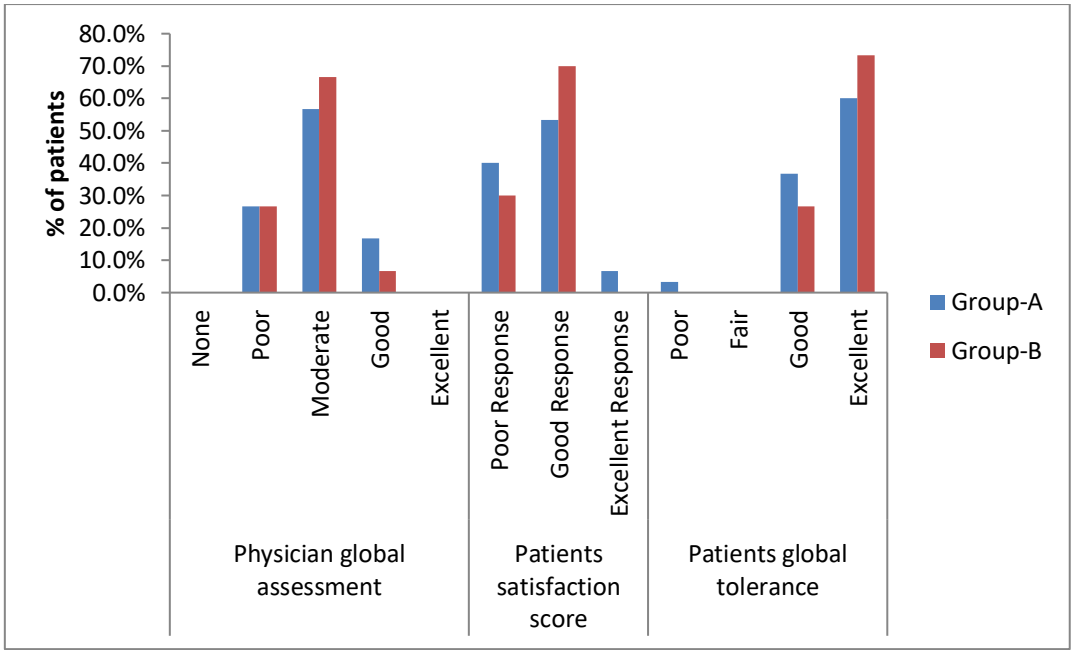
Maximum improvement was present in patients with limited area involvement like face and neck, or neck and upper extremities, and of duration less than 1 year. Poor response was seen in patients with extensive body surface involvement and with longer duration of the disease. Topical drugs were well tolerated and no adverse effects were reported in any of the patients.



Graph 1



Graph 2



Graph 3

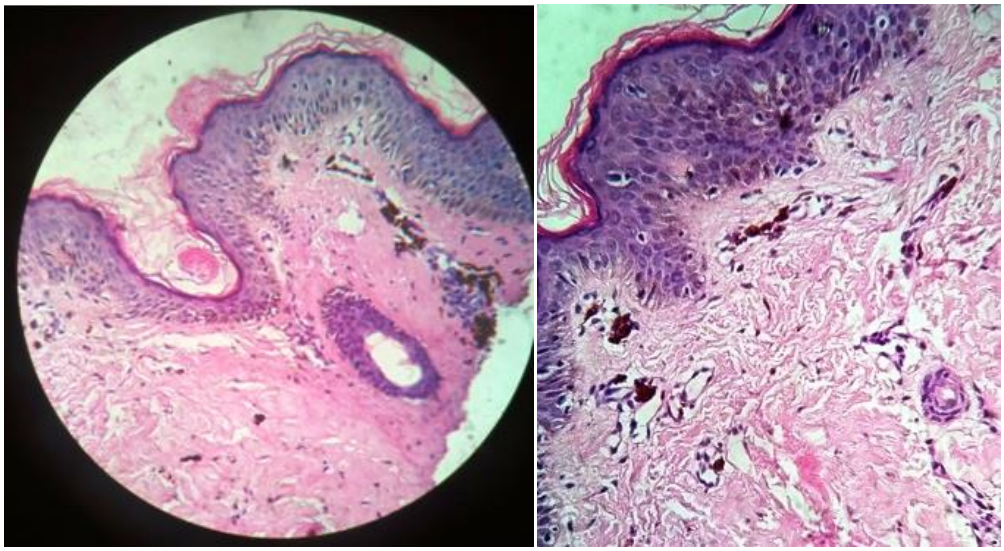


Figure 1 a and b- Epidermis showing mild atrophy, basal cell layer vacoular degeneration with upper dermis showing lymphomononuclear inflammatory infiltrate, melanophages and pigment incontinence.

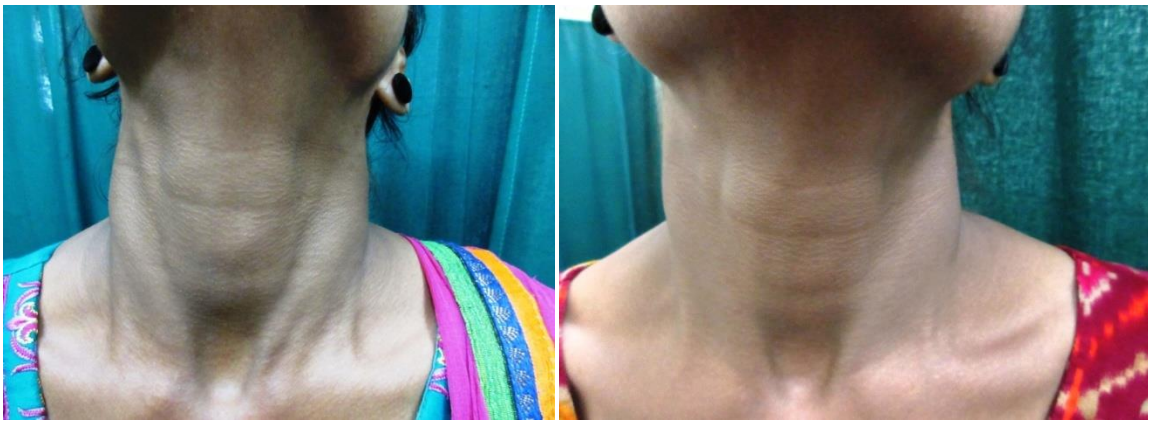


Figure 2a and b – Lesions of LPP over neck showing moderate response with twice daily application of tacrolimus ointment at 0 weeks and after 16 weeks of treatment respectively.

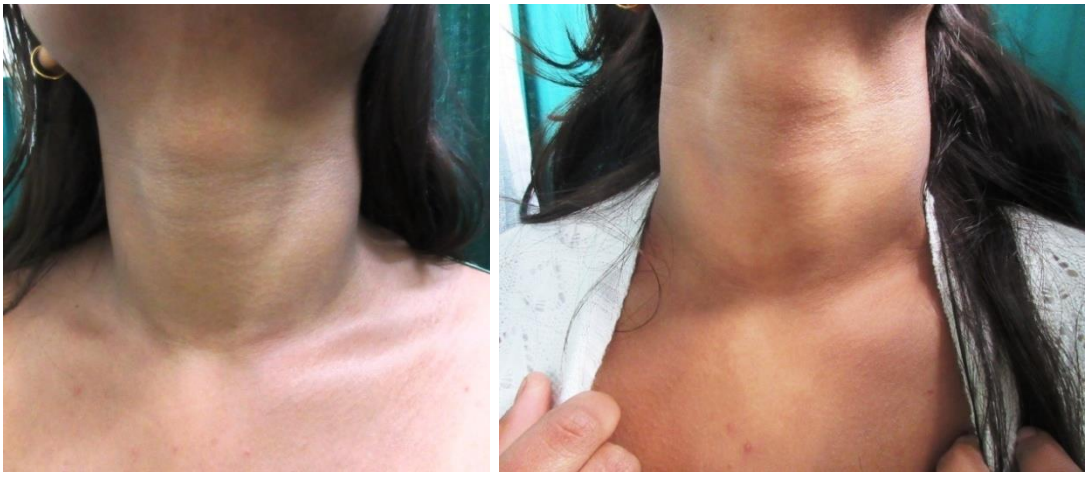


Figure 3a and b- Lesions of LPP over neck showing moderate response with twice daily application of pimecrolimus cream at 0 weeks and after 16 weeks of treatment respectively.

DISCUSSION

LPP was first reported in a series of Indian patients in 1974 by Bhutani et al. They described the clinical and histopathological features of LPP in 40 patients.[12] LPP is thought to be a type IV hypersensitivity reaction to unknown antigen with lichenoid inflammation, leading to melanin incontinence and superficial dermal pigmentation.[13] Precipitating factors include sun exposure and photosensitizing agents. Bhutani et al[12] found application of mustard and amla oil in most of their patients as mustard oil contains allyl thiocyanate which is a potential photosensitizer. Tienthavorn et al reported that 36.36% cases of LPP had positive patch test results which further supports the role of contact allergens in the pathogenesis of LPP.[14] In a study conducted on 124 Indian LPP patients by Kanwar et al,[15] similar observation was noted. They also found use of henna and hair dyes for a variable period of time in 21% of their patients. LPP has also been observed as paraneoplastic phenomenon as it was found to be associated with acrokeratosis of Bazex.[3] In a study conducted by Karn et al on 54 LPP patients, 20 were associated with abnormal thyroid function tests.[16] The frequency of LPP in general population is very limited with insidious onset of hyperpigmented, brown to gray-brown macules and patches in sun- exposed areas with mean duration around 12 months in our study.

The demographic profile shows that LPP occurs in young adults (20-40 years) with female preponderance as shown by Muthu et al[7] (17 females to 10 males in age Group 20-40 years). This was consistent with our study which shows 24 patients were between 30-40 years and 19 patients less than 30 years. Out of 60 patients in our study, 55 patients (91.7%) were females. In a study conducted by Al-Mutairi et al in 2009 in Kuwait, there was male preponderance as among 33 patients, 21 were males and rest were females.

Most common sites affected were neck (53(88.3%) followed by face (41(68.3%) and arms and trunks. It collaborated with other studies[7,9] in the literature which showed the face, neck and upper limbs being the most common sites affected. The majority of the patients in our study presented with bluish gray pigmentation (24 patients in each group) while 6 patients (20%) of each group had a black-brown pigmentation. Muthu et al[7] showed that 77.8% patients had bluish-slate grey pigmention while Al-Mutairi et al[9] observed that 81.8% patients had dark-brown pigmentation. LPP can present with different patterns with diffuse pattern being most prevalent in the present study followed by blotchy, reticulate and perifollicular pattern which was similar to other studies.[7,9]

Various chemical agents have been incriminated in the causation of LPP like dyes, mustard/amla oil in the literature.[12,14,15] In our study, total 19 patients (31.8%) had similar history of irritant applications. In the study by Muthu et al[7], history of mustard oil application and consumption was positive in 24(88.9%) followed by amla oil in 2 cases and henna application in one. While Al-Mutairi et al[9] found no positive association between sun exposure, drugs cosmetics, trauma and LPP.

Family history of similar disease was negative for all patients in the studies by Muthu et al and Al-Mutairi et al[7,9] which was consistent with our study. In our study, 23 patients (38.33%) had pruritus at the onset of the disease but no elevated red border was present on examination. 9 patients reported mild pruritus with no active red border in a study by Al-Mutairi et al.[9] In a study by Muthu et al[7] done in PGI Chandigarh, pruritus was noted in 23 patients (85.2%) with active disease. Cutaneous/oral LP was seen in 3 patients (5%) and Inversus type LPP was seen in 2 patients (3.33%) in the current study. While in the study by Al-Mutairi et al,[9] 8 patients (24.24%) had associated LP & 7 patients (21.21%) has inversus type of LPP and Muthu et al[7] described 4 patients (14.8%) with associated LP. Palms, soles, scalp and nails were spared in all the patients in our study which

corresponded with Al-Mutairi et al,[9] although Muthu et al[7] reported one patient with palmoplantar LP.

In Al-Mutairi et al,[9] most common biopsy findings were epidermal thinning, vacuolar degeneration of basal layer, band like inflammatory infiltrate. Melanin incontinence and melanophages were constant findings, and which were similar with the present study. As described by Muthu et al,[7] histological features in 74% of the patients were basket weave hyperkeratosis, apoptotic cells, basal cell layer vacuolation and degeneration, dense lymphocytic infiltrate along with mild pigment incontinence.

Type IV hypersensitivity reaction is a T lymphocyte mediated response that occur in response to different antigens such as against chemical compounds.[17] The released cytokines lead to inflammation & melanogenesis. As LPP is thought to be a type IV hypersensitivity reaction, topical immunomodulators may help in reducing the inflammation and pigmentation & preventing further progression of disease without their systemic side effects. Topical calcineurin inhibitors like (tacrolimus and pimecrolimus) acts by blocking the action of calcineurin which ultimately results in suppression of transcription and responsiveness of T-cells.[13] This forms the basis of their use in LPP. Tacrolimus has been documented in dermatology text books for the treatment of LPP.[18] Recent evidence also suggests that topical immunomodulators can have a beneficial role in the management of LPP. In our study we have used 0.1% tacrolimus and 1% pimecrolimus in patients of LPP for 16 weeks and there have been improvement in physician global assessment, patient satisfaction score and patient's global tolerance. Topical immunomodulators can provide a breakthrough in treatment of LPP as shown in our study.

In a study by Al-Mutairi et al,[9] 33 LPP patients were recruited. 13 patients which fulfilled the inclusion criteria were treated with twice daily 0.03% tacrolimus ointment. After 16 weeks of treatment – 7 out of 13 patients (53.8%) showed improvement in pigmentation and rest 5 did not show any improvement. Excellent response was seen in 4 patients (57.1%), good in 3 (47.9%).

Muthu et al[7] described 32 patients of LPP which were started on fixed low dose oral tretinoin (20mg/day) daily for 6 months. Out of 27 patients which completed the study, 15 patients (55.7%) had moderate improvement (25-50%), 7 had good and 2 had mild response. Patients with limited body surface area involvement and lesions limited to face and neck, responded better which was consistent with our study.

In a case series of linear LPP of the forehead by Rodriguez, Eliyah et al (2023), [19] they reported that treatment with topical tacrolimus can lead to significant reduction in the size, pigmentation and erythema of the affected region which also was consistent with prior reported cases of facial linear LPP.

Chaoui et al[20] discussed a case of 45 year female having LPP in whom partial improvement was seen after using tacrolimus 0.1% ointment twice daily along with sunscreen for 4 months.

In our study, moderate improvement and good response were the most common affair in both the groups as analysed by physical global assessment and patient satisfaction score respectively. Most of the cases were confined to poor to moderate improvement by physician global assessment and poor to good response by patients satisfaction score. Patients global tolerance was good to excellent in both the groups. Results in terms of Physician global assessment (p value = 0.466) and patients satisfaction score (p value = 0.212) of both the groups were comparable and statistically non significant ($p > 0.05$) which were calculated by applying Chi-square test. Earlier reports have also showed similar results with topical calcineurin inhibitors but as per our knowledge, no data/study comparing topical tacrolimus and pimecrolimus in the management of LPP has been reported yet.

CONCLUSION

Topical tacrolimus and pimecrolimus has a variety of indications but their application in the treatment of LPP is relatively recent and good to excellent response has been shown with respect to patient's global tolerance. These calcineurin inhibitors can be kept in the armamentarium of the dermatologists for the management of LPP as these can offer a relatively safe and non-invasive option.

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None

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