The Journal of Laryngology & Otology (2017), ***131***, *69–76*.

doi:10.1017/S0022215116009658

MAIN ARTICLE

Efficacy of steroidal *vs* non-steroidal agents in oral lichen planus: a randomised, open-label study

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Abstract

Objective: This study compared the therapeutic efficacy of steroidal and non-steroidal agents for treating oral lichen planus.

Methods: Forty patients with clinical and/or histologically proven oral lichen planus were randomly placed into four groups and treated with topical triamcinolone, oral dapsone, topical tacrolimus or topical retinoid for three months. Pre- and post-treatment symptoms and signs were scored for each patient.

Results: Patients in all treatment groups showed significant clinical improvement after three months ($p < 0.05$), with steroidal and non-steroidal agents having equal efficacy. Furthermore, of the non-steroidal drugs, oral dapsone had greater efficacy than topical retinoid ($p < 0.05$). However, no significant differences in outcome were recorded for oral dapsone *vs* topical tacrolimus ($p > 0.05$) and for topical retinoid *vs* topical tacrolimus ($p > 0.05$).

Conclusion: Non-steroidal drugs such as dapsone, tacrolimus and retinoid are as efficacious as steroidal drugs for treating oral lichen planus, and avoid the side effects associated with steroids.

Key words: Dapsone; Lichen Planus; Oral; Retinoids; Tacrolimus; Triamcinolone

Introduction

Lichen planus is an autoimmune disease that can affect the mucosa and the skin and its appendages; it was first described by Wilson in 1869.[1,2] Oral lichen planus affects about 0.5–2 per cent of the population worldwide,[3,4] with a prevalence of 0.1–1.5 per cent in India.[5] The condition is most common in middle-aged patients and affects more women than men[1,6,7]; children are rarely affected.[8]

The disease may involve various mucosal surfaces, either independently or concurrently, with cutaneous involvement or serially. Up to 44 per cent of oral lichen planus patients develop coincident skin lesions, and more than 70 per cent of cutaneous lichen planus patients develop coincident oral lichen planus.[9] Oral lichen planus is more frequent, persistent and treatment resistant than the cutaneous form. Andreasen classified six forms of the disease.[1] The commonly affected sites are the buccal mucosa, dorsum of tongue and gingiva.[11]

The specific aetiology of oral lichen planus is unknown, but it is believed to result from an abnormal cell-mediated immune response that results in T4 and T8 lymphocyte infiltration into basal epithelial cells. Factors known to aggravate the disease include stress, smoking and spicy foods.

The disease is characterised by relapses and remissions, so management should aim to resolve painful symptoms and oral mucosal lesions, reduce the oral cancer risk, and maintain good oral hygiene. In patients with recurrent painful disease, another treatment goal is to prolong the symptom-free interval.[5]

Oral lichen planus also has malignant potential and is classified as a 'probable precancerous condition'.[12] A systematic review of studies over several years found a rate of transformation to squamous cell carcinoma of between 0 per cent and 3.5 per cent.[13]

One problem is that although several groups of drugs (including corticosteroids and immunomodulators) have been used to treat this disease, no standard modality has been established. The multiple management options for oral lichen planus suggest that a single agent is inadequate to provide symptom relief to patients. A systematic review compared the results of 28 randomised controlled trials.[14] The wide range of interventions suggests that there is insufficient evidence that any specific treatment is most effective. Another problem is that prolonged topical corticosteroid use can result in secondary candidiasis.[15]

This study aimed to address these treatment issues by comparing the efficacy of four different drug

Presented at the 67th Annual Conference of Association of Otolaryngologists of India, 9 January 2015, Raipur, India.

Accepted for publication 24 August 2016 First published online 5 December 2016

treatments for oral lichen planus: one steroid and three non steroid agents.

Materials and methods

Study design

This study was conducted in the ENT department of a tertiary care centre in Allahabad from April 2013 to April 2014. Inclusion criteria were clinically and/or histologically proven oral lichen planus. Patients aged under 20 or over 60 years, pregnant women, nursing mothers, patients with serious systemic illnesses and those with lesions showing dysplastic or malignant changes were excluded. A total of 40 patients were enrolled into the study and randomly allocated to four treatment groups (i.e. 10 patients in each group): the topical steroid, oral dapsone, topical tacrolimus and topical retinoid groups. The results were recorded and analysed for all 40 patients (no treatment dropouts). The study design was open label, parallel and comparative. All patients gave written informed consent to participate in the study. All patients received the allocated intervention and none was lost to follow up or discontinued treatment. Data from all 40 patients were included in the analysis (Figure 1).

This study was approved by the institutional ethics committee. It did not involve human or animal experimentation, compared established drug treatments for oral lichen planus, and complied with institutional ethical guidelines.

Patient characteristics

A detailed medical history was taken for each patient, including their particulars (name, age, sex, address and occupation) and any addiction, major complaint (along with the duration and severity, i.e. symptom score), significant previous illness, systemic illness or drug use, or significant family history of disease. All patients underwent a complete general examination (particularly, to identify concomitant skin lesions), a systemic examination and a thorough examination of the oral cavity to assess oral hygiene, the lesion site, the clinical subtype and severity (sign score), and any features suggestive of malignancy such as induration or fixity to underlying structures, painlessness, bleeding, infiltration and inexorable growth.

Disease scoring

Pre- and post-treatment symptoms and signs were scored. Symptoms such as pain and a burning sensation in the oral cavity were scored according to Raj *et al*. as: 0, no symptoms; 1, mild (occasional symptoms); 2, moderate (e.g. while eating spicy food); 3, severe (i.e. while eating any food); or 4, intolerable (always present).[16] Signs were scored according to Kaliakatsou *et al*. as: 0, no lesion present; 1, only white striae present; 2, white striae plus erosion of less than 1 cm^2; 3, white striae plus erosion of more than 1 cm^2; 4, white striae plus ulceration of less than 1 cm^2; and 5, white striae plus ulceration of more than 1 cm^2.[17] The effect of treatment on disease downstaging was determined by combining the symptom and sign score for each patient before and after treatment: 0, no disease; 1–3, mild disease; 4–6, moderate disease; and 7–9, severe disease. In this system, symptom and sign scores were weighted equally (e.g. a total score of 6 could result from a combination of 2 plus 4, 3 plus 3 or 4 plus 2). Differences in the combined score were used to assess disease downstaging.

Histopathological analysis

If the lesion appeared to be oral lichen planus by clinical inspection and the patient agreed to enroll in the study, the lesion was biopsied for histopathological confirmation. The histopathological characteristics of oral lichen planus are thickening of the stratum corneum with or without the presence of nuclei (parakeratosis or orthokeratosis, respectively; parakeratosis is more common in oral lichen planus); thickening of the stratum granulosum; thickening of the stratum spinosum (acanthosis); liquefactive degeneration of the stratum basale; and T cell infiltration in a band-like pattern into the dermis 'hugging' the basal layer. When more than one clinical subtype of lesion was found in the same patient (such as the reticular and erosive subtypes), then the lesion was classified as the most severe form (i.e. erosive in this example).

Of the 40 patients enrolled into the study, 24 had histologically proven lichen planus, while the others had a chronic inflammatory lesion requiring clinical confirmation of lichen planus.

Patient randomisation

The first author was responsible for patient randomisation and allocation to treatment groups. Manual randomisation was performed by assigning each patient a number from 1 to 40: those numbered 1, 5, 9, etc. were allocated to the topical steroid group (twice daily local application of 0.1 per cent triamcinolone acetonide buccal paste); those numbered 2, 6, 10, etc. were allocated to the oral dapsone group (100 mg twice daily plus iron and folic acid tablets); those numbered 3, 7, 11, etc. were allocated to the topical tacrolimus group (0.1 per cent, applied twice daily); and those numbered 4, 8, 12, etc. were allocated to the topical retinoid group (applied twice daily).

Treatment

Over a 3-month treatment period, patients were examined every 15 days. At the end of three months, post-treatment symptom and sign scores were recorded. Patients were subsequently followed up every month to identify any side effects or the recurrence of symptoms and signs. If recurrence was noted, patients were treated with oral steroids.

https://doi.org/10.1017/S0022215116009658 Published online by Cambridge University Press

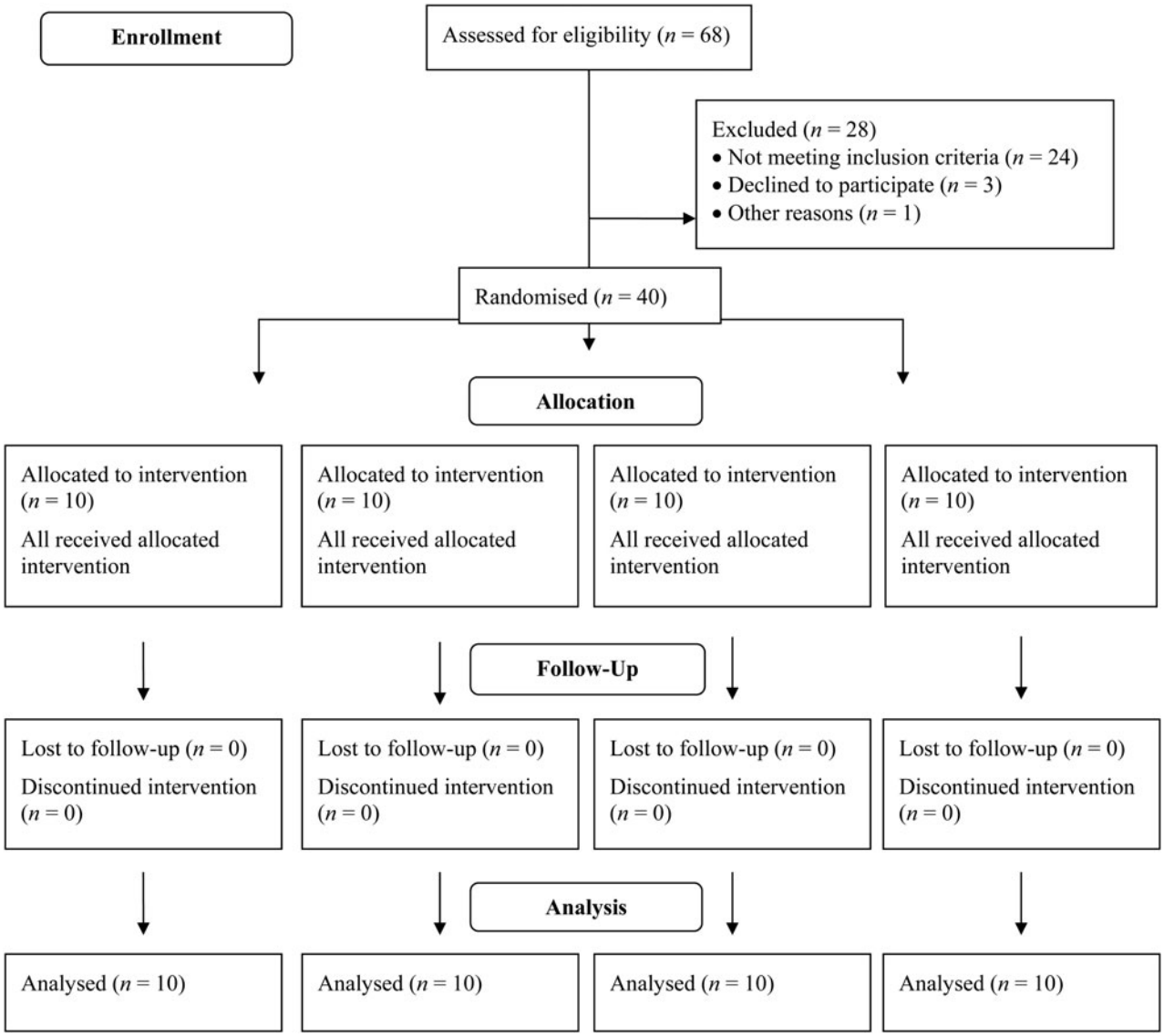

FIG. 1

Consolidated Standards of Reporting Trials ('CONSORT') 2010 flow diagram showing patient numbers for enrollment, allocation, treatment and inclusion in the final analysis.

Statistical analysis

As the sample size was small, data distribution was analysed using the Kolmogorov-Smirnov normality test and found to be asymmetric and abnormal. Hence, a non-parametric analysis was performed. Changes in symptom and sign scores for each treatment group were compared using the Wilcoxon signed rank test. Pre- and post-treatment scores were also compared among the four treatment groups using Mann–Whitney rank sum test. A confidence level of 95 per cent was adopted; hence, a p value of less than 0.05 indicated a statistically significant change.

Results

The mean age at presentation was 32 ± 10.5 years and the mean symptom duration was 9 months ± 9.5 months. The commonest sites of involvement were the bilateral buccal mucosa (55 per cent) followed by the tongue (30 per cent).

Of the six different types of oral lichen planus, only four were identified in this patient cohort. The reticular type was the most common (found in 72 per cent of patients) and the erosive type the second most common (found in 18 per cent of patients). The atrophic and plaque types were each found in 5 per cent of patients. No patient had papular or bullous disease.

Most patients (65 per cent) presented with a pre-treatment symptom score of 3, while 20 per cent and 15 per cent of patients had pre-treatment symptom scores of 2 and 4, respectively (Table I). The most common pre-treatment sign score was 2 (Table II). Tables III and IV show improvements in the symptom and sign scores, respectively, for each group after three months of treatment.

Post-treatment scores for all groups were compared to determine which drug was the most efficacious (Table V). Oral dapsone had the best efficacy, and all other treatments had equal efficacy. However, only

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TABLE I
DISTRIBUTION OF PRE-TREATMENT SYMPTOM SCORE

Pre-treatment symptom score	Patients* (*n* (%))	Percentage of total (%)		Percentage of male patients (%)	Percentage of female patients (%)
		Men	Women		
0	0 (0)	0	0	0	0
1	0 (0)	0	0	0	0
2	8 (20)	15	5	30	10
3	26 (65)	28	38	60	70
4	6 (15)	5	10	10	20

*$n = 40$.

TABLE II
DISTRIBUTION OF PRE-TREATMENT SIGN SCORES

Pre-treatment sign score	Patients* (*n* (%))	Percentage of total (%)		Percentage of male patients (%)	Percentage of female patients (%)
		Men	Women		
0	0 (0)	0	0	0	0
1	5 (12)	0	12	0	25
2	17 (42)	28	15	55	30
3	16 (40)	22	18	45	35
4	1 (2)	0	2	0	5
5	1 (2)	0	2	0	5

*$n = 40$.

TABLE III
SYMPTOM SCORE IMPROVEMENT AFTER TREATMENT

Treatment group	Pre-T SySc	Post-T SySc	Percentage improvement (%)	Pre-T SySc*	Post-T SySc*	*p* value
Oral dapsone	30	1	97	3.0 ± 0.47	0.1 ± 0.31	<0.05
Topical retinoid	29	7	76	2.9 ± 0.73	0.7 ± 0.48	<0.05
Topical tacrolimus	29	6	79	2.9 ± 0.56	0.6 ± 0.51	<0.05
Topical steroid	30	4	87	3.0 ± 0.66	0.4 ± 0.48	<0.05

*Mean ± standard deviation. Pre-T = pre-treatment; post-T = post-treatment; SySc = symptom score

the differences between post-treatment symptom and sign scores for oral dapsone and topical retinoid were significant.

Changes in disease stage following treatment were compared among groups (Table VI). In all patients who initially had severe disease, the stage was reduced to mild irrespective of treatment. In patients who initially had moderate disease, downstaging to mild was seen in all those in the topical tacrolimus and topical retinoid groups, 75 per cent of those in the topical tacrolimus group and 44 per cent of those in the oral dapsone group. However, the small sample size precluded statistical analysis to establish the best treatment for disease downstaging.

Table VII shows disease recurrence following treatment. After recurrence, all lesions were of the same disease subtype as the original lesion. Notably, no major side effects were seen in any group, except for mild tingling in the oral cavity in patients treated with topical agents.

TABLE IV
IMPROVEMENT IN SIGN SCORES AFTER TREATMENT

Treatment group	Pre-T SiSc	Post-T SiSc	Percentage improvement (%)	Pre-T SiSc	Post-T SiSc	*p* value
Oral dapsone	25	4	84	2.5 ± 0.707	0.4 ± 0.516	<0.05
Topical retinoid	26	10	62	2.6 ± 0.737	1.0 ± 0.0	<0.05
Topical tacrolimus	19	7	63	1.9 ± 0.737	0.7 ± 0.483	<0.05
Topical steroid	25	7	72	2.6 ± 1.173	0.7 ± 0.483	<0.05

*Mean ± standard deviation. Pre-T = pre-treatment; post-T = post-treatment; SiSc = sign score

https://doi.org/10.1017/S0022215116009658 Published online by Cambridge University Press

TABLE V
COMPARISON OF POST-TREATMENT SCORES AMONG GROUPS

Treatment groups	*p* value for SySc	*p* value for SiSc
Oral dapsone *vs* topical retinoid	<0.05	<0.05
Oral dapsone *vs* topical tacrolimus	>0.05	>0.05
Oral dapsone *vs* topical steroid	>0.05	>0.05
Topical retinoid *vs* topical tacrolimus	>0.05	>0.05
Topical retinoid *vs* topical steroid	>0.05	>0.05
Topical tacrolimus *vs* topical steroid	>0.05	>0.05

SySc = symptom score; SiSc = sign score

Discussion

There is no standard protocol for treating oral lichen planus. The present prospective, randomised, open-labelled study compared the efficacy of topical steroid and three non-steroidal agents (oral dapsone, topical retinoid and topical tacrolimus) in a cohort of 40 patients. Most previous studies have compared only two or three drugs.[7,16,18,19,20,21]

After three months of continuous treatment, patients in all groups showed a significant reduction in symptoms, with 55 per cent experiencing no burning (symptom score 0) and 45 per cent experiencing only occasional symptoms (symptom score 1). This suggests that all treatment modalities were effective in relieving oral lichen planus symptoms. Following drug treatment, lesions had completely resolved in 30 per cent of patients (sign score 0), while 70 per cent had white striae only (sign score 1). Hence, all drug treatments effectively cleared oral lichen planus lesions.

The possibility that improvements resulted from a placebo effect has been ruled out because each treatment group showed significant improvements in both symptoms and signs (i.e. an objective outcome measure). In addition, only 12 per cent of patients experienced disease recurrence (and of lesser severity) following treatment completion; higher recurrence rates would have been expected for a placebo. However, a potential placebo effect can only be excluded in a placebo-controlled trial.

The present study found an 87 per cent improvement in symptoms and a 72 per cent improvement in signs in patients treated with a topical steroid (0.1 per cent triamcinolone acetonide). In an open trial, Lozada-Nur *et al*. treated 24 patients with persistent oral vesiculoerosive disease of at least 1 month duration with clobetasol propionate: 15 patients had complete remission of signs and symptoms, 7 had an excellent response for signs and complete remission of symptoms, and 2 failed to respond.[7] The present study had comparable results. Azizi and Lawaf treated erosive lichen planus with topical tacrolimus and triamcinolone and reported a 57.3 per cent improvement in symptom scores (using a visual analogue scale (VAS)) and a 55.8 per cent improvement in sign scores.[22] These less comparable outcomes may be the result of including only patients with erosive lesions, the shorter study period (four weeks) and use of a different symptom scoring system.

TABLE VI
EFFECT OF DRUGS ON DISEASE DOWNSTAGING

Disease downgrading	Treatment (*n* (%))*			
	Topical steroid	Oral dapsone	Topical tacrolimus	Topical retinoid
From severe to moderate	0/2 (0)	0/1 (0)	0/0 (–)	0/2 (0)
From severe to mild	2/2 (100)	1/1 (100)	0/0 (–)	2/2 (100)
From severe to no disease	0/2 (0)	0/1 (0)	0/0 (–)	0/2 (0)
From moderate to mild	6/8 (75)	4/9 (44)	8/8 (100)	8/8 (100)
From moderate to no disease	2/8 (25)	5/9 (56)	0/8 (0)	0/0 (–)
From mild to no disease	–	–	2/2 (100)	–

*Denominator = number of patients at each stage before treatment.

TABLE VII
PROFILE OF DISEASE RECURRENCE

Age (yr)	Sex	Add	Type of lesion	Treatment	Lag* (wk)	SySc		SiSc	
						Pre-T	Post-T	Pre-T	Post-T
45	F	Y	Erosive	Topical retinoid	6	3	3	3	2
25	F	N	Reticular	Topical tacrolimus	4	3	3	2	2
20	F	N	Reticular	Topical tacrolimus	3	4	3	1	1
25	F	N	Reticular	Topical tacrolimus	4	3	2	2	2
30	M	Y	Reticular	Topical steroid	4	3	3	3	2

*Time between end of treatment and symptom recurrence. Yr = years; Add = addiction; pre-T = pre-treatment; post-T = post-treatment; wk = weeks; SySc = symptom score; SiSc = sign score; F = female; Y = yes; N = no; M = male

https://doi.org/10.1017/S0022215116009658 Published online by Cambridge University Press

The present study recorded a 76 per cent improvement in symptom score and a 62 per cent improvement in sign score in the topical retinoid group. All patients reported symptom improvement at the end of treatment, but only 30 per cent reported complete resolution. Ten per cent of patients experienced disease recurrence (although follow up was limited). Giustina *et al.* reported that twice daily application of 0.1 per cent isotretinoin gel for eight weeks was effective in improving symptoms in 90 per cent of oral lichen planus patients.[23] Tretinoin monotherapy has limited value in oral lichen planus but when combined with topical corticosteroids, modest benefits may be achieved with high doses and frequent applications, especially for reticular lesions.[24] Piattelli *et al.* performed a double-blind study to compare 0.1 per cent isotretinoin with placebo in 20 patients: there were 10 complete and 10 partial responses.[18] In another study by Petruzzi *et al.*, tazarotene significantly reduced lesion size compared with placebo.[19]

The present study found oral dapsone to be highly effective for treating oral lichen planus: there was a 97 per cent improvement in symptom score and an 84 per cent reduction in sign score. In a comparative study of steroid and dapsone in 75 patients, Chopra *et al.* found dapsone to be superior to local corticosteroids alone for treating cutaneous lichen planus.[25] The disparity between these results and those of the present study may be attributable to differences in the site affected by lichen planus. Raj *et al.* reported that after dapsone treatment 54.54 per cent of patients with resistant erosive oral lichen planus had an improved symptom score of 0, 45.45 per cent had an improved symptom score of 1 and 83.36 per cent had an improved sign score of 0.[16] Differences in the level of improvement may be explained by the different lesion types included in the study.

Topical corticosteroids appear to be safe when applied to mucous membranes. In 1969, Lehner and Lyne measured plasma cortisol levels before and after topical application of corticosteroids in patients with oral diseases. No adrenal suppression was reported after daily application of 0.4 mg betamethasone valerate to oral lesions in 17 patients for several months. Kutcher *et al.* reported no adverse effects of triamcinolone acetonide in doses up to 480 mg for several months, although plasma cortisol levels were not measured.[26] However, dapsone has significant adverse effects such as haemolysis and headache, which preclude its use.[20]

In the present study, a 79 per cent improvement in symptom score was seen after topical tacrolimus treatment for 3 months. A major drawback of topical tacrolimus was the recurrence of disease symptoms and signs after stopping treatment: 30 per cent of patients reported recurrence within three to four weeks, although with less severe symptoms and signs. Byrd *et al.* reported that 89 per cent of patients using topical tacrolimus experienced symptom improvement and 84 per cent had partial to complete lesion clearance.[27] Their slightly inferior results may be due to differences in the drug concentration (0.03 per cent or 0.1 per cent) used by patients. In all, 32 per cent of patients reported minimal adverse effects (such as burning, irritation and tingling) and 50 per cent experienced recurrence. Azizi and Lawaf reported improvements of 58.9 per cent and 62.5 per cent, respectively, in symptom (using a VAS) and sign scores in patients after tacrolimus treatment.[22] The present study found a better response in symptom scores (79 per cent improvement), which might be due to differences in symptom scoring systems between studies. However, both studies reported a comparable improvement in sign score. After evaluating several reports of the outcomes of treating lichen planus with calcineurin inhibitors, Samycia *et al.* concluded that there was strong evidence (double-blind and open studies) to support the use of topical tacrolimus ointment for treating oral lichen planus; it had equal efficacy to topical 0.05 per cent clobetasol propionate ointment.[21]

Malik *et al.* reported that topical tacrolimus produced complete resolution in 61.1 per cent of patients with erosive, ulcerated and reticular forms of oral lichen planus; in contrast, only 30 per cent of patients in the present study showed complete lesion clearance.[28] This difference may be explained by the shorter treatment duration in the present study: 3 months *vs* a mean of 81 ± 44 days) in the former study.

- **Oral lichen planus is a chronic autoimmune disease and tends to be persistent and treatment resistant**
- **Non-steroidal drugs such as dapsone, tacrolimus and retinoid have equal efficacy to steroidal drugs**
- **No major side effects were noted in any treatment group**
- **Disease recurrence was more common with topical tacrolimus, but generally less severe**
- **Severe disease had the best treatment response**

By comparing the effects of non-steroidal drug treatments, the present study showed that oral dapsone had a significantly greater efficacy than topical retinoid, but there was no significant difference in results for oral dapsone *vs* topical tacrolimus or topical retinoid *vs* topical tacrolimus. Chopra *et al.* reported that dapsone is superior to local corticosteroids alone for treating cutaneous lichen planus. These results contradict those of the present study (i.e. that both treatments had equal efficacy).[25] This difference may be attributable to differences in the lesion site (cutaneous and mucosal). Sahebjamee *et al.* found significant differences in efficacy for 0.05 per cent retinoic acid *vs* 0.1 per cent triamcinolone acetonide for treating atrophic and erosive oral lichen planus ($p \leq 0.003$ and $p \leq 0.0001$, respectively).[29] In

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contrast, the present study found that both drugs had equal efficacy, possibly because of the longer treatment duration. However, similar to the present findings, Azizi *et al*. found no significant differences in score improvement when comparing the efficacy of triamcinolone and topical 0.1 per cent tacrolimus for treating erosive oral lichen planus.[22]

The present study classified the disease stage as mild, moderate and severe by combining symptom and sign scores. Efficacy in downstaging disease was compared among drug treatments. All patients with severe disease experienced downstaging to mild disease, irrespective of treatment (although no patients in the topical tacrolimus group initially had severe disease). This finding suggests that severe disease has the best treatment response. Downstaging to mild was achieved in all patients with moderate disease in the topical tacrolimus and topical retinoid groups, in 75 per cent of those in the topical steroid group and in 44 per cent of those in the oral dapsone group. Downstaging from moderate to no disease was achieved in 25 per cent of patients in the topical steroid group and 56 per cent in the oral dapsone group, but none in the topical tacrolimus and topical retinoid groups. However, the differences were not significant because of the small sample size. In contrast, Kaliakatsou *et al*. found 0.1 per cent tacrolimus to be effective for treating erosive and ulcerative oral lichen planus.[17] Moreover, in a double-blind study of 28 severe oral lichen planus patients treated with an oral retinoid (75 mg etretinate daily) or placebo for two months, by Hersle *et al*. found that the drug had a marked beneficial effect.[30] No previous trials have compared drug efficacy for different disease stages.

Conclusion

The present study was limited by cohort size and follow-up duration. Hence, although the data support the use of these agents for treating oral lichen planus, further randomised controlled trials with larger cohorts and longer follow up are warranted.

Acknowledgements

I express my sincere gratitude to all my teachers, Dr M Singh, Dr S Jain, Dr A Rai and Dr M Aftab for guiding me through this study. I also thank Dr K G Singh of the Department of Skin and Venereal Diseases, Dr V Misra of the Department of Pathology and Dr K Verma of the Department of Pathology for their valuable contribution to the study. I thank my patients for being a source of constant motivation to continue the hard work. I also wish to thank Dr V Singh for proofreading the manuscript.

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Dr A R Singh takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215116009658 Published online by Cambridge University Press