Announcement

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Evaluation of the Efficacy of Topically Applied Tacrolimus in the Treatment of Oral Ulcers in Behcet's Disease

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Abstract

Objectives: Compare the clinical efficacy of topical oral Tacrolimus versus oral colchicine based on disease activity, pain and ulcer severity score in oral ulcer associated with BD.

Methodology: 40 BD cases (> 3 months underwent traditional treatment with persistent active oral ulceration). They were equally randomized into either group I (Colchicine and topically applied Tacrolimus), or whereas group II (Colchicine only). All participants were evaluated through based on Behcet's Disease Current Activity Form (BDCAF), Ulcer Severity Score (USS) and visual analog scale (VAS) pre-injection, and then re-evaluated post-injection at four-time points (15 days, 1st, 2nd, and 3rd months). Registered in clinicaltrials.gov under the number of (NCT05032248)

Results: VAS was significantly lower in group I after 2 weeks and 3 months than in group II. USS was significantly lower in group I after 3 months of follow up. BDCAF showed significant improvement in 3 months follow up within each group, while there was insignificant difference between both.

Conclusion: Topical Tacrolimus has been proved as to be a safe and effective adjunctive therapy in the management of oral ulcerations in BD.

Keywords: Bechet's • Behcet's disease • Aphthous ulcer • Colchicine • Topical tacrolimus

Introduction

Behcet's disease (BD) is a chronic multisystem organ disease affecting the variable-sized blood vessels of the body. Primarily, the condition was characterized by recurrent oral genital ulcerations and relapsing iritis [1]. The exact cause of BD is still undetermined;, therefore, various hypotheses have been formulated in an attempt to investigate its etiology including innate and adaptive immunity factors as well as genetic and environmental factors [2]. Major symptoms of BD including recurrent aphthous like ulceration of the oral mucous membrane, skin lesions, eye lesions and genital ulcers in addition to minor symptoms including arthritis without deformity or ankylosis, gastrointestinal lesions. Epididymitis, vascular lesions and central nervous system symptoms [3]. Recurrent aphthous like ulcer is the most frequent manifestation, detected in more than 95% of patients, and; it is usually the earliest sign of the disease (47-86% of patients) and may precede by the onset of other symptoms by many years [4,5]. Ttreatment protocols for muco-cutaneous manifestations remain unclear in cases of BD and total remission of mucocutaneous lesions usually cannot be achieved with the current approaches [6,7]. Colchicine is the most common anti-inflammatory drug used in treatment of oral ulceration of Behçet's disease, particularly for mucocutaneous disease. The working mechanism of colchicine is mainly based on both anti-inflammatory and anti-fibrotic activities [7,8]. Tacrolimus (also FK-506 or Fujimycin) is an immunosuppressive drug used primarily after organ transplant to reduce the activity of patient's immune system, and

thus the risk of organ rejection. It is also used in a topical preparation in the treatment of oral lichen planus resist to traditional treatment with corticosteroids [9]. Tacrolimus ointment 0.1% has been safe and effective in treating the cutaneous manifestations of Crohn's disease, particularly perineal disease and pyoderma gangrenosum; nevertheless, it is rarely effective in treating this condition [10]. Topical Tacrolimus may be a well-tolerated and effective therapy for controlling mucous membrane pemphigoid (MMP), which does not respond to corticosteroid therapy [11]. The aim of this study was to optimize the treatment protocols of oral ulceration in BD by evaluating the efficacy of topical Tacrolimus in the treatment of oral ulcers in Behcet's disease. Our primary outcome was the effect of topical Tacrolimus in treatment ulcer pain visual analog scale (VAS) in the two groups and over 3 months of follow up. Secondary outcomes included changes in the Ulcer severity scale (USS) between the two groups and over 3 months follow up.

Material and Methods

Participants and study design

Study design definition (100% agreement): A TES is a study that follows all patients beyond a pre-specified trial period whether the trial was (a) a placebo-controlled RCT with the possibility to cross over to an open-label experimental drug A prospective randomized double blind controlled trial was conducted in Rheumatology clinic, Assiut University Hospital and Faculty of Dental Medicine, Al-Azhar University, Assiut branch outpatient's clinic. It was evaluated and approved by the ethical committee, Faculty of Dental Medicine, Al-Azhar University, Assiut branch and Faculty of Medicine, Assiut University (AUAREC201048-11) and registered in clinicaltrials.gov (registration date: 08/27/2021) under the number of (NCT05032248// https: //www.clinicaltrials.gov/). The study was run with adherence to the Declaration Helsinki [12]. 40 adult patients with BD their ages ranged between 18-50 years, who had active oral ulcers were enrolled in this study. Eligible patients were 18 years of age or older, had received a diagnosis of Behçet's syndrome according to International Study Group criteria BD diagnosis was confirmed through the modified International Criteria for Behcet's Disease [13] and had active oral ulcers that had occurred at least three times in the previous 12-month period (including the screening visit) despite the previous use of at least no biologic medication, such as (but not limited to) topical or systemic glucocorticoids, nonsteroidal anti-inflammatory drugs, colchicine, immunosuppressant's, or thalidomide. Active oral ulcers were defined as two or more oral ulcers at the screening visit and two or more oral ulcers at randomization, when randomization occurred at least 14 days after screening, or two or more oral ulcers at the screening visit and three or more oral ulcers at randomization, when randomization occurred at any time between 1 and 42 days after screening. Patients were excluded if they had Behçet's syndrome-related active major organ involvement that had led to systemic treatment, such as uveitis (except for mild uveitis treated with topical agents) or vascular or central nervous system involvement during the 12 months before trial entry, had previously used biologic agents for oral ulcers, or had any clinically significant medical condition (infection, cancer, laboratory abnormality, or psychiatric illness) that would prevent them from participating. Rather than those who previously developed allergy to Tarcolimus drug. A written informed consent was obtained from all participants who were then randomized through a computer-based randomization table into two groups in a ratio of 1: 1 [Figure 1]. Group I included BD patients who received topical Tarcolimus oral gel and Colchicine, and group II included BD patients who received topical local placebo oral gel and Colchicine. Scoring the severity of ulcer was assessed by, characteristics of the ulcer attacks in the preceding 3 months were recorded on a standardized form, patients were questioned to ascertain the average size of the ulcers, the number of ulcer within an attack, the duration of the ulcer, the frequency of the ulcer attacks, the sites affected and the intensity of the pain caused by the ulcers. The patient's description of the ulcers was verified clinically whenever possible. A separate form was completed on each subsequent clinical visit, and the ulcers scored independently and without referring to the score of previous visits. ulcer characteristics were converted into numbers to give a numerical score to facilitate the objective comparison of

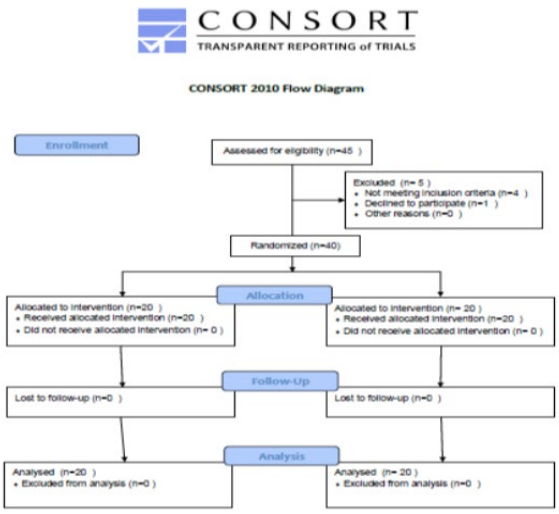

Figure 1: Consort flow chart of the participants.

the severity of the condition especially before and after treatment.

The calculation of the scores was as follows

Number: The score corresponds to the average number of ulcers per crop the patient has been having in the last 3 months, that is, a patient having on average four ulcers would score 4 for this parameter.

Size: The score corresponds to the average diameter of the ulcers in millimetres, that is, a patient having ulcers of average size of 5 mm would score 5.

Duration: The score corresponds to the average ulcer duration calculated in ½ week units, that is, ulcers lasting 10-11 days (1½ weeks) will score 3 and an ulcer lasting 5 weeks or more will score the maximum of 10.

Ulcer-free period: The score for this parameter is 10 minus the average ulcer-free period in weeks, that is, somebody who is never free from ulcers will score the maximum 10, but somebody who is ulcer free for 4 weeks at a time will score 6.

Site: The sites that are usually affected by the ulcers are recorded.

Pain: The pain associated with a crop of ulcers was estimated subjectively by the patient on a scale of 0 to 10. The total score is the summation of the six parameters scores [21].

On the first visit, patients were asked to keep a diary of subsequent ulcer attacks to increase accuracy. The regime they were on was the tacrolimus (0.1% w/w) was incorporated into (2.5 % w/w) hydroxyl propyl methyl cellulose (HPMC) gel base. HPMC gel were prepared by dispersing the required quantity of polymer in small quantity of distilled water to prepare an aqueous dispersion. The aqueous dispersion was allowed to hydrate for 4-5 hours, Tacrolimus (0.1% w/w) was added and properly dispersed then the final weight of the gel was adjusted to 20g with distilled water [20], mouth gel administered twice daily when ulcers are present and once a day in between ulcer attacks).

End points: The primary efficacy end point was the area under the curve (AUC) for the total number of oral ulcers during the 12-week placebo-controlled period. This measure reflects the number of oral ulcers over time and accounts for the remitting and relapsing course of oral ulcers in Behçet's syndrome. Oral ulcers were assessed by the investigator at weeks 0, 2, 4, 8, and 12 during the placebo-controlled period. The number of oral ulcers that was counted for the analysis of the primary end point included current and recurrent ulcers at each time point; a single oral ulcer could be recounted multiple times if it persisted or recurred at subsequent visits. The primary efficacy end point was also analyzed in prespecified subgroups defined according to baseline demographic and disease characteristics. Data collection and assessment were done by two physicians who were blinded to the grouping and previous follow up data, also patients were blinded to their medications. The following well validated scales were used to evaluate the patients, the initial pain visual analog scale (VAS) [14], Ulcer Severity Scale (USS) [15] and Behçet's Disease Current Activity Form (BDCAF) [16], and then re-evaluated post-treatment at four-time points (2w, 4w, 8w, and 12ws). The secondary efficacy end points: the change from baseline in pain associated with oral ulcers (on a 100-mm visual-analogue scale, with higher scores indicating more pain); the change from baseline in the patient-reported Behçet's Syndrome Activity Scale score (scores range from 0 to 100, with higher scores indicating more disease activity); the Behçet's Disease Current Activity Form, which comprised three components (the Behçet's Disease Current Activity Index [on a scale from 0 to 12, with higher scores indicating more activity], the patient's perception of disease activity [on a scale from 1 to 7, with higher scores indicating more activity], and the physician's overall perception of disease activity [on a scale from 1 to 7, with higher scores indicating more activity]); the percentage of patients free from oral ulcers by week 6 who remained oral ulcer-free for at least 6 weeks; the time to resolution of oral ulcers (complete response); the percentage of patients free from oral ulcers at week 12; the change from baseline in the Behçet's Disease Quality of Life score (scores range 0 to 30, with higher scores indicating greater impairment in quality of life. To ensure no worsening of new, recurrent, or other manifestations of Behçet's syndrome, patients reported activity related to skin lesions, arthritis, and uveitis as well as gastrointestinal, central nervous system, and vascular symptoms at each visit; these were compared with baseline reports of symptoms. Patients had ophthalmologic examinations at baseline and at week 12. At each trial visit, all medications and therapies (e.g., prescription and over-the-counter drugs), including the dose, unit, frequency, route of administration, and start and stop dates, were recorded. Glucocorticoid eyedrops and oral and topical analgesic agents (withheld 24 hours before trial visits) were not permitted during the placebo-controlled period.

Statistical analysis

Data entry and data analysis were done using SPSS version 22 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation, median and range. Chi-square test and Fisher Exact test were used to compare between qualitative variables. Mann-Whitney test and the independent

samples t-test were used to compare quantitative variables between groups. Wilcoxon Signed Rank test was done to compare quantitative variables between before and after treatment, Pearson correlation was done to measure correlation between quantitative variables. P-value considered was statistically significant when P = 0.05.

Results

Both groups were comparable in terms of their demographic data Clinical data of the patients are summarized in Table 1. Regarding the clinical manifestations of the group I patients, 20% of the patients had fever, 95% had genital ulcers, 40% had erythema, 55% had skin pustules, 60% had arthralgia, 50% had arthritis, 70% of patients had eye manifestation, 30% had vascular manifestation, 25% had GIT manifestation and 40% had CNS manifestation. In group II patients, 35% of the patients had fever, 100% had genital ulcers, 55% had erythema, 50% had skin pustules, 65% had arthralgia, 35% had arthritis, 75% of patients had eye manifestation, 25% had vascular manifestation, 10% had GIT manifestation and 30% had CNS manifestation. Clinical presentation and treatment strategies with insignificant differences between the two groups. Regarding the primary outcome (VAS scale), it was significantly lower in topical applied Tacrolimus combined with the colchicine group (Group I) after the 2nd week than colchicine alone group (Group II), then there was insignificant difference between both group after the 1st month. At the 2nd and 3rd months follow-up, Group I showed a significant decreases in VAS more than Group II. Additionally, there was a significant improvement in VAS during the whole study period within each group in comparison to its baseline value [Table 1]. Regarding BDCAF score [Table 2], there was no significant difference between both group at baseline assessment and after 2 weeks. There was a significant decrease in BDCAF during the 1st, 2nd and 3rd months follow up within each group in comparison to its baseline value [Table 3]. Table 3 shows the score of BDCAF that each patient taken in all periods of study: At baseline in group I Mean ± SD 2.35 ± 1.27 but in group II 2.55 ± 1.32 with no significant difference. After 2weeks in group I Mean ± SD 2.30 ± 1.26 but in group II 2.45 ± 1.28 with no significant difference. After 1month in group I Mean ± SD 1.10 ± 1.21 but in group II 1.70 ± 1.26 with no significant difference between 2 groups but with significant difference in same group from baseline and after 1month in group I (P-Value2 0.002), in group II (P Value2 0.007). After 2monthes in group I Mean ± SD 0.70 ± 0.98, in group II 0.75 ± 0.64 with no significant difference between 2 groups but with significant difference in same group from baseline and after 2monthes in group I (P-Value2 0.000), in group II (P-Value2 0.000). After 3monthes in group I Mean ± SD 0.55 ± 0.76, in group II 0.75 ± 0.79 with no significant difference between 2 groups but with significant difference in same group from baseline and after 3monthes in group I (P-Value2 0.000), in group II (P-Value2 0.000). The results of USS revealed no significant difference between both groups in baseline assessment apart from number of ulcer and VAS were higher in group I than group II. All USS data showed a significant improvement in comparison to the baseline value in each group. Moreover, ulcer number, size, duration and ulcer free period were significantly lower in Tacrolimus group at 12 weeks of follow up Table 3 shows the score of USS that each patient taken in all periods of study:

At baseline in group I Mean ± SD 24.56 ± 3.13 but in group II 22.65 ± 4.13 with no significant difference. At

Table 1: Illustrating mean ± SD, median of VAS score and P-value in studied groups at different intervals.

Interval	VAS	Group I (n= 20)	Group II (n= 20)	P-value1
Baseline	Mean ± SD	7.10 ± 1.55	5.25 ± 1.83	0.002*
	Median (Range)	7.0 (4.0-10.0)	5.0 (2.0-9.0)	
2 week	Mean ± SD	0.65 ± 1.73	2.35 ± 2.85	0.037*
	Median (Range)	0.0 (0.0-6.0)	0.0 (0.0-8.0)	
	P-value2	0.000*	0.001*	
I month	Mean ± SD	3.15 ± 3.59	3.65 ± 3.22	0.547
	Median (Range)	0.5 (0.0-9.0)	3.5 (0.0-9.0)	
	P-value2	0.001*	0.091	
2 month	Mean ± SD	1.10 ± 2.36	3.10 ± 3.39	0.037*
	Median (Range)	0.0 (0.0-8.0)	2.0 (0.0-9.0)	
	P-value2	0.000*	0.026*	
3 month	Mean ± SD	1.15 ± 2.85	3.40 ± 3.27	0.025*
	Median (Range)	0.0 (0.0-9.0)	5.0 (0.0-9.0)	
	P-value2	0.000*	0.057	

Table 2: Illustrating BDCAF score, mean ± SD, median and P-value1, P-value2 between and within both groups in all periods of study.

	BDCAF	Group I (n= 20)	Group II (n= 20)	P-value1
Base line	Mean ± SD	2.35 ± 1.27	2.55 ± 1.32	0.643
	Median (Range)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	
After 2 weeks:	Mean ± SD	2.30 ± 1.26	2.45 ± 1.28	0.681
	Median (Range)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	
	P-value2	0.317	0.317	
After 1 month:	Mean ± SD	1.10 ± 1.21	1.70 ± 1.26	0.065
	Median (Range)	1.0 (0.0-4.0)	2.0 (0.0-5.0)	
	P-value2	0.002*	0.007*	
After 2 months:	Mean ± SD	0.70 ± 0.98	0.75 ± 0.64	0.471
	Median (Range)	0.0 (0.0-3.0)	1.0 (0.0-2.0)	
	P-value2	0.000*	0.000*	
After 3 months:	Mean ± SD	0.55 ± 0.76	0.75 ± 0.79	0.347
	Median (Range)	0.0 (0.0-2.0)	1.0 (0.0-3.0)	
	P-value2	0.000*	0.000*	

Table 3: Comparison of mean scores of individual characteristics of USS before and after treatment.

		Group I(n= 20)	Group II (n=20)	P-value
No. of ulcers	Mean ± SD	2.65 ± 1.14	1.65 ± 0.75	0.004*
	Median (Range)	2.5 (1.0-5.0)	1.5 (1.0-3.0)	
No. of ulcers 3m;	Mean ± SD	0.25 ± 0.64	0.80 ± 0.83	0.014*
	Median (Range)	0.0 (0.0-2.0)	1.0 (0.0-2.0)	
	P-value2	0.000*	0.009*	
Size score baseline;	Mean ± SD	4.14 ± 0.99	4.23 ± 0.97	0.803
	Median (Range)	4.0 (2.5-6.0)	4.0 (3.0-7.0)	
Size score 3m;	Mean ± SD	0.65 ± 1.61	2.03 ± 2.04	0.022*
	Median (Range)	0.0 (0.0-5.0)	3.0 (0.0-6.0)	
	P-value2	0.000*	0.001*	
Site score baseline;	Mean ± SD	1.00 ± 0.00	1.00 ± 0.00	1
	Median (Range)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
Site score 3m;	Mean ± SD	0.15 ± 0.37	0.55 ± 0.51	0.009*
	Median (Range)	0.0 (0.0-1.0)	1.0 (0.0-1.0)	
	P-value2	0.000*	0.003*	
Duration score baseline;	Mean ± SD	2.68 ± 1.71	2.75 ± 1.68	0.837
	Median (Range)	2.3 (1.0-7.0)	2.3 (1.0-7.0)	
Duration score 3m:	Mean ± SD	0.35 ± 0.99	1.27 ± 1.27	0.009*
	Median (Range)	0.0 (0.0-4.0)	1.5 (0.0-3.0)	
	P-value2	0.000*	0.002*	
UFP score baseline:	Mean ± SD	7.11 ± 2.56	7.64 ± 1.86	0.645
	Median (Range)	7.9 (1.4-9.6)	8.3 (3.0-9.6)	
UFP score 3m:	Mean ± SD	1.06 ± 2.67	4.36 ± 4.21	0.008*
	Median (Range)	0.0 (0.0-9.2)	5.3 (0.0-9.0)	
	P-value2	0.000*	0.005*	
VAS baseline:	Mean ± SD	7.10 ± 1.55	5.25 ± 1.83	0.002*
	Median (Range)	7.0 (4.0-10.0)	5.0 (2.0-9.0)	
VAS 3m:	Mean ± SD	1.15 ± 2.85	3.40 ± 3.27	0.025*
	Median (Range)	0.0 (0.0-9.0)	5.0 (0.0-9.0)	
	P-value2	0.000*	0.057	

2weeks in group I Mean ± SD 3.00 ± 7.35 but in group II 9.38 ± 10.88 with significant difference between both groups in same period (P-Value1 0.037) and significant difference in same group from baseline and after 2weeks in group I and group II (p-value2 0.000). At 4weeks in group I Mean ± SD 11.43 ± 11.89 but in group II 15.26 ± 10.51 with no significant difference between 2 groups but with significant difference in same group from baseline and 4weeks in group I (P-Value2 0.001), in group II (P-Value2 0.023). At 8weeks in group I Mean ± SD 4.22 ± 8.71 but in group II 10.83 ± 11.22 with significant difference between both groups in same period (P-Value1 0.049) and significant difference in same group from baseline and 8 weeks in group I (p-value2 0.000) and in group II (P-value2 0.001). No. of ulcers score at baseline; in group I Mean ± SD 2.65 ± 1.14, in group II 1.65 ± 0.75 with significant difference between both groups (P-Value1 0.004) and 12 weeks; in group I Mean ± SD 0.25 ± 0.64, in group II 0.80 ± 0.83 with significant difference between both groups (P-Value1 0.014) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.009). Size of ulcers score at baseline; in group I Mean ± SD 4.14 ± 0.99, in group II 4.23 ± 0.97 with no significant difference between both groups and 12 weeks; in group I Mean ± SD 0.65 ± 1.61, in group II 2.03 ± 2.04 with significant difference between both groups (P-Value1 0.022) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.001). Site of ulcers score at baseline; in group I and II Mean ± SD 1.00 ± 0.00 with no significant difference between both groups and after 3monthes; in group I Mean ± SD 0.15 ± 0.37, in group II 0.55 ± 0.51 with significant difference between both groups (P-Value1 0.009) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.003). Duration of ulcers score at baseline; in group I Mean ± SD 2.68 ± 1.71, in group II 2.75 ± 1.68 with no significant difference between both groups and after 3monthes; in group I Mean ± SD 0.35 ± 0.99, in group II 1.27 ± 1.27 with significant difference between both groups (P-Value1 0.009) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.002). Ulcer free period score at baseline; in group I Mean ± SD 7.11 ± 2.56, in group II 7.64 ± 1.86 with no significant difference between both groups and after 3monthes; in group I Mean ± SD 1.06 ± 2.67, in group II 4.36 ± 4.21 with significant difference between both groups (P-Value1 0.008) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.005). VAS score at baseline; in group I Mean ± SD 7.10 ± 1.55, in group II 5.25 ± 1.83 with significant difference between both groups (P-Value1 0.002) and 12 weeks; in group I Mean ± SD 1.15 ± 2.85, in group II 3.40 ± 3.27 with significant difference between both groups (P-Value1 0.025) and significant difference in same group before and after treatment in group I (P-value2 0.000), in group II (p-value2 0.057). At 12 weeks in group I Mean ± SD 3.62 ± 8.91 but in group II 12.41 ± 11.66 with significant difference between both groups in same period (P-Value1 0.018) and significant difference in same group from baseline and after 3monthes in group I (p-value2 0.000) and in group II (P-value2 0.004). Figure 2 shows Clinical photograph of with oral ulceration treated by tacrolimus and colchicine in group I (A, B) pre-treatment and (C, D) post-treatment and Figure 3 shows Clinical photograph of patient with oral ulceration treated by colchicine only in group II (A) pre-treatment and (B) post-treatment.

Discussion

Oral ulceration is the most common manifestation of BD with a high recurrence rate with traditional treatment. The present study was aimed to evaluate the efficacy of topical applied Tacrolimus in the management of recurrent oral ulceration. In this study,

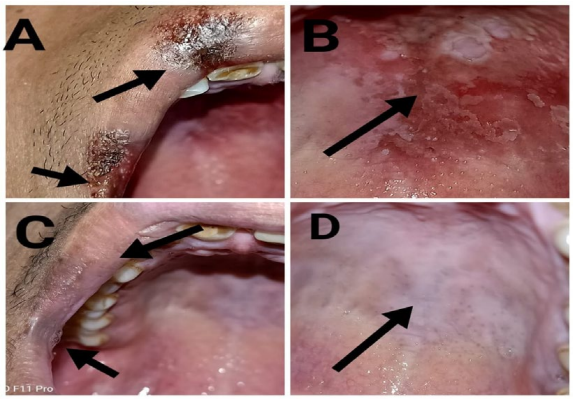

Figure 2: Clinical photograph of with oral ulceration treated by tacrolimus and colchicine in group I (A, B) pre-treatment and (C, D) post-treatment.

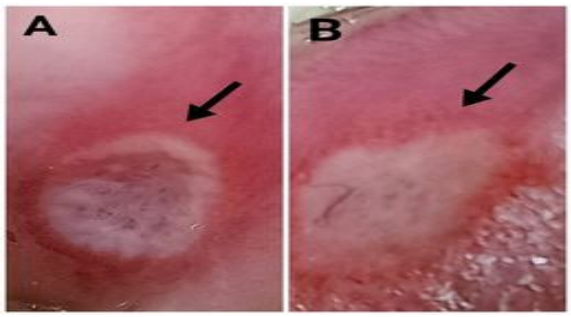

Figure 3: Clinical photograph of patient with oral ulceration treated by colchicine only in group II (A) pre-treatment and (B) post-treatment.

oral ulceration in Behcet's disease patients was treated with topical Tacrolimus combined with oral colchicine or oral colchicine alone. To our knowledge, this is the first trial to compare the efficacy of both drugs in such a group of patients. The results demonstrated a significant improvement in BDCAF, VAS score, ulcer number, size, duration and an increase in ulcer free period in patients treated with Tacrolimus and colchicine group after 15 days of treatment and through the 3rd month more significantly than the colchicine group. However, both groups showed a significant improvement with regard to the previous clinical parameters in comparison to the baseline value. BDCAF was chosen for the present study because of its validity and reliability, which have already been established in the international literature [16]. BDCAF, showed a decrease in the score of both groups indicating improved patient statues. After one month, there was a significant difference between both groups with a substantial improvement in Group I than Group II, but there was no significant difference in mean score after 2 and 3 months. According to awareness, there have been no other studies used using BDCAF to assess the improvement of oral ulceration after treatment by topical tacrolimus. Regarding Ulcer Severity Score (USS),; it has been used to assess and monitor the severity of other ulcerative lesions. The USS was indicative of the disease activity in recurrent oral ulceration. It contributed to assess the efficacy of therapy, as change in the numerical score reflected a change in ulcer severity in response to treatment [15]. The present study demonstrates statistically significant differences in the USS average. The results showed that the group taking Tacrolimus have significantly lower scores in on all individual characteristics including (number of ulcers, site of ulcer, size of ulcer, duration, ulcer free period and finally pain) than those who only took colchicine . These findings are consistent with the results of other study [17] which showd that 50% of patients with erosive lichen planus treated with 0.1% topical Tacrolimus displayed a suboptimal response at a 12-months follow-up period. They postulated that it is not highly effective in treatment of erosive oral lichen planus. This can be explained by the different tools used to assess clinical improvement used to white-erosive-atrophic-modify (WEA-MOD) scoring system and the longer follow-up duration. Furthermore, VAS was significantly lower in the Tacrolimus group at 3 months follow-up than in the colchicine group. However, we detected a significant improvement in VAS during the whole study period within each group in comparison to its baseline value. VAS was validated in measuring symptoms of oral lichen planus [18]. Moreover, Hatemi G et al 2015, used visual-analogue scale in assessment and follow-up of oral ulceration in BD patients after treatment with Apremilast [19]. Finally, from the result of present study, USS may be considered a higher indicator for improvement of oral ulceration than BDCAF especially when indicate topically applied oral treatment,; so it may be used as a clinical marker to evaluate the severity and improvement of this condition. This may interpreted by the constitution of each variable, since BDCAF consisted of assessment of oral statues and other systemic manifestation while the USS formed oral statues only. The limitation in this study was the inability to stop a patient's treatment during the research, which may affect our result, and the follow-up period could be extended further.

Conclusion

Both Tacrolimus and colchicine had favourable effects on the symptoms of oral ulceration in patients with BD.; However, topical applied Tacrolimus much further decrease disease activity, alleviates pain, declines the size of ulceration, decreases the duration and frequency of oral ulceration, and improves the ulcer-free period. In addition, Ulcer severity score was referred a higher beneficial guidance than BDCAF in evaluation of topical treatment oral ulceration. Therefore, it can be used as a clinical marker for evaluating topical oral therapy.

Key messages

Recurrent oral ulcer is the most frequent manifestation, detected in more than 95% of patients; recurrent relapsing and remitting oral ulcers are often the first manifestations of Behçet's syndrome.

• Oral ulcers cause pain; difficulty in eating, drinking, and talking; and decreased participation in routine daily activities and quality of life,1 out of 3 patient doesn't achieve total remission of muco-cutaneous lesions with the current treatment approaches

• Topical corticosteroids suppress the inflammation associated with the formation of aphthae, and they are effective on both OU and GU especially when they are used in the early stage of these lesions.

• Tacrolimus ointment 0.1% was has been safe and effective in treating the cutaneous manifestations of Crohn's disease, particularly perineal disease and pyoderma gangrenosum and Genital ulcers in BD,

• Topical Tacrolimus may be a well-tolerated and effective therapy for controlling mucous membrane pemphigoid (MMP), which does not respond to corticosteroid therapy.

• To-date there is No Local immunosuppressive agent used for treating OU in Behcet disease.

• This study designed to optimize treatment protocols

of oral ulceration by evaluating the efficacy of topical Tacrolimus in the treatment of oral ulcers in Behcet's disease.

• Topical tacrolimus oral gel is effective with no need for other systemic immunosuppressive in the treatment course.

Here is a clear unmet need for a reliable approach to the reporting of TES to maximize our understanding of drug effects in chronic conditions. This initiative, its principles and resulting recommendations apply to TES for a drug in Behcet as well as for drugs used to treat other chronic rheumatological conditions. This document provides much needed first recommendations to ensure a transparent and standardized approach to the reporting of future TES.

Conflict of interest

Nothing to report.

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Competing interests

Nothing to report.

Contributor ship

All authors contributed substantially to the design, implementation and data collection of the Delphi exercises. Analysed the DELPHI data reviewed the DELPHI data analysis before dissemination to the task force. All authors wrote the paper and the supplementary materials. All authors discussed the summaries presented in the Delphi exercises, results and implications and commented on the manuscript at all stages.

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Ethical approval information, institution(s) and number(s)

Was conducted in Rheumatology clinic, Assiut University Hospital and Faculty of Dental Medicine, Al-Azhar University, Assiut branch outpatient's clinic. It was evaluated and approved by the ethical committee, Faculty of Dental Medicine, Al-Azhar University, Assiut branch and Faculty of Medicine, Assiut University (AUAREC201048-11) and registered in clinicaltrials.gov under the number of (NCT05032248). The study was run with adherence to the Declaration Helsinki [12].

Data sharing statement

Approved free online sharing.

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