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Original Research Article

Efficacy and safety of apremilast versus dapsone versus colchicine in recurrent aphthous stomatitis: a three arm double blinded comparative study

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is often considered as an incurable ailment. Therefore, an effective management option is required for controlling the symptoms and severity of RAS. We aimed to conduct a study to compare the effectiveness and safety profile of apremilast, dapsone and colchicine in management of RAS.
Methods: This three-arm double blinded comparative study included 60 cases of recurrent aphthous stomatitis (RAS). Twenty patients each were randomly allocated in three groups: group A (apremilast), group B (dapsone) and group C (colchicine).
Results: At the end of 6 weeks, the complete response was seen in 6 (30%) patients in group A as compared to 2 (10%) and 4 (20%) patients in group B and C ($p > 0.05$). At the end of 12 weeks, response rate became statistically significant ($p=0.003$) with complete response in 14 (70%) of patients. Median time to recurrence, defined as oral ulcer after loss of complete response, was significantly increased to 4.3 weeks in group A as compared to group B and C. The most commonly encountered side effects were gastrointestinal in all three groups. None of the adverse effects resulted in discontinuation of treatment, hospitalization or death in any patient.
Conclusions: Although, traditional therapies like dapsone and colchicine have been commonly used in clinical practice, apremilast yielded a rapid and maintained improvement of RAS.

Keywords: Aphthous ulcer, Apremilast, Colchicine, Dapsone

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disease of the oral mucosa. Factors like local trauma, anemia, stress, smoking etc may predispose to RAS.[1,2] Chronic conditions such as Crohn disease, ulcerative colitis, malabsorption diseases like celiac disease, neutrophilic disorders like Behçet disease and HIV are also linked to the development of oral aphthous ulcers. Diagnosis of RAS is made based on the history, presentation, and morphology of lesions. Although, oral aphthosis has numerous potential causes with an extensive differential of possible underlying diseases. However, if no distinct underlying disease is found, diagnosis of primary or idiopathic RAS is made. This condition poses a significant challenge to healthcare professionals due to its uncertain etiology. Topical corticosteroids are the first line of treatment for managing RAS.[3,4] A short course of systemic steroids is reserved for more severe cases. Immunosuppressants are sometimes indicated to prevent the formation of new RAS lesions and decrease the prevalence of adverse effects experienced with systemic steroids. It is often considered as an incurable ailment. Therefore, an

effective management option is required for controlling the symptoms and severity of RAS.[4]

We aimed to conduct a study to compare the effectiveness and safety profile of apremilast, dapsone and colchicine in management of RAS.

METHODS

This three-arm double blinded comparative study was conducted in Al Falah school of medical sciences and research centre, Faridabad, India comprising a group of 60 cases of recurrent aphthous stomatitis (RAS) from January 2023 to September 2023.

All patients who were 18 years of age or older with chronic aphthous stomatitis and presenting with active oral ulcers at the time of screening visit and who have not been exposed to any immunomodulator or biological (except topical or oral steroids) in past for RAS were included in the study.

Exclusion criteria included patients with history of any form of cancer or blood dyscrasia and its treatment, any chronic drug intake, presence of any systemic or autoimmune disease or any other vesiculobullous disorder, presence of any other form of oral or genital mucosal diseases, nutritional deficiencies like iron, vitamin B_{12} or folic acid, history of smoking or alcohol intake, patients with immunocompromised status, and pregnant and lactating females were excluded from the study. Patients with any hematologic disease, Behcet's syndrome, Crohn's disease, HIV infection or Reiter's syndrome, either initially or as a later development, oral ulcerations associated with a drug reaction. An informed written consent form was signed by the patients. Ethical approval was obtained from the ethical committee.

Assessment of patients and baseline work up

A case of RAS was characterized by at least 3 recurrent bouts in last six months of solitary or multiple small, round, or ovoid shallow painful ulcers, with circumscribed margins, having yellow or gray floors and surrounded by erythematous halos, at intervals of few months to few days in patients who were otherwise well and had been free of symptoms in between the two episodes. The eligible subjects should have been off the treatment in past three months.

Patients were evaluated for an underlying cause of oral aphthae (e.g., connective tissue disease, vasculitis, vitamin deficiency, medication-induced aphthae, and celiac disease), with testing for levels of antinuclear antibody and antineutrophil cytoplasmic antibody; levels of iron, ferritin, folate, thiamine (vitamin B_1), riboflavin (vitamin B_2), vitamin B_6, vitamin B_{12}, and zinc; and levels of IgA endomysial antibody and IgA or IgG tissue transglutaminase antibody.

Baseline blood work before the initiation of colchicine or dapsone therapy included a complete blood cell count with a differential count and testing for levels of creatinine levels, liver enzymes and glucose 6 phosphate dehydrogenase levels.

Treatment groups and outcome measures

A total of 60 cases of RAS were randomly divided into three groups with 20 patients in each group. In group A, patients were treated with apremilast 30 mg twice a day after initial 7 days of titration schedule. In group B, patients were given dapsone 100 mg once a day after initial trial dose of 50 mg for first 7 days. In group C, colchicine 1 mg once a day was given after 7 days of testing digestive tolerance with 0.5 mg/day.

Statistical analysis

The primary measure of efficacy was decrease in mean number of ulcers. Other secondary measures of efficacy were decrease in the pain, episodes of recurrence, median time to recurrence and complete clearance of ulcers etc. Complete response was defined as complete clearance of oral ulcers. The data was analyzed with the help of frequencies, figures, percentages and measures of central tendency with standard deviation. Statistical analysis was done using unpaired t test and chi-square test. P values less than 0.05 were considered significant.

RESULTS

The baseline clinical and demographic data was recorded (Table 1). Statistically significant reduction in mean number of oral ulcers was in apremilast group as compared to other two groups (Figure 1).

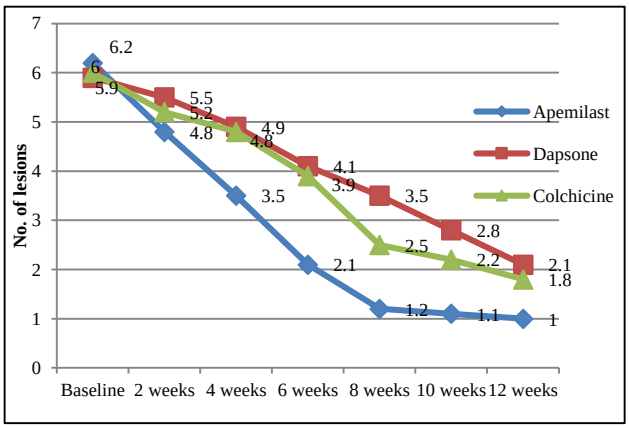

Figure 1: Reduction in mean number of oral ulcers in three groups.

Table 1: Baseline characteristics of study participants in each arm of the study.

	Group A	Group B	Group C
Age (mean age)	37.75±11.59	36.15±12.52	35.7±11.58
Gender			
Male	11	8	7
Female	9	12	13
Mean duration of lesions (months)	10.2±4.2	9.2.1±3.5	11.1±4.8
Type of lesions			
Major aphthous ulcer	4	3	4
Minor aphthous ulcer	11	13	12
Herpetiform aphthous ulcer	5	4	4
Mean episodes of relapse in last 3 months	3.6±1.4	3.7±1.6	3.5±1.2
Mean duration between two episodes of relapse (days)	18±4.3	17.65±5.6	18.23±3.2
Number of lesions per episode			
<3	4	4	4
3 to 6	7	8	8
>6	9	8	8

Table 2: Response to treatment in three groups.

	Group A (Apremilast)	Group B (Dapsone)	Group C (Colchicine)
Complete response of oral ulcers at 12 weeks (% of patients)	14	8	10
Median time to complete response (weeks)	6.5	8.7	7.1
Median time to recurrence, defined as oral ulcer after loss of complete response (weeks)	4.3	2.1	3.5
Change from baseline in pain associated with oral ulcer as measured by VAS at 12 weeks	-46.3±3.7	-30.7±2.5	-37.4±3.1

Table 3: Adverse effects.

Side effects	Group A (Apremilast) n=20	Group B (Dapsone) n=20	Group C (Colchicine) n=20
Dyspepsia	10	6	9
Diarrhea	3	1	4
Nausea	11	3	10
Abdominal pain	8	4	6
Loss of appetite	9	5	5
Fatigue	1	4	4
Myotoxicity	0	1	3
Raised transaminase levels	0	1	4
Upper respiratory tract infection	3	0	1
Headache	4	1	2
Fever	2	0	0
Skin rash	0	0	1
Neurotoxicity	0	0	0

At the end of 6 weeks, the complete response was seen in 6 (30%) patients in group A as compared to 2 (10%) and 4 (20%) patients in group B and C (p>0.05). At the end of 12 weeks, response rate became statistically significant (p=0.003) with complete response in 14 (70%) of patients.

The mean healing time was lower for group A, however, statistically insignificant (p=0.3). Although, minor and herpetiform aphthous ulcers showed faster rate of healing in all the three groups, there was no significant correlation between the type of aphthous ulcers and rate of clearance in the three groups (p>0.05).

Median time to recurrence, defined as oral ulcer after loss of complete response, was significantly increased to 4.3 weeks in group A as compared to group B and C (Table 2).

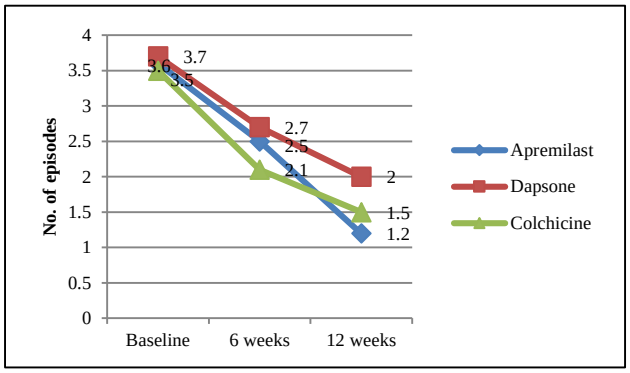

Figure 2: Reduction in mean episodes of recurrence in three groups.

Mean episodes of recurrence on 3 months follow up reduced to 1.2, 2.0 and 1.5 episodes in group A, B and C ($p<0.05$) (Figure 2). Apremilast and colchicine resulted in significant decrease in number of episodes of recurrence as compared to dapsone.

At week 12, the mean reduction from baseline in the pain associated with oral ulcers as assessed on a 100-mm visual-analogue scale was −46.3 in the apremilast group, as compared with −30.7 and −37.4 in dapsone and colchicines group respectively. The reduction in oral ulcer pain paralleled the reduction in the number of oral ulcers from week 1 to week 12.

The most commonly encountered side effects were gastrointestinal in all three groups (Table 3). None of the adverse effects resulted in discontinuation of treatment, hospitalization or death in any patient.

DISCUSSION

Treatment for RAS is difficult. These extremely painful lesions with frequent recurrences accompanied by functional symptoms and has a major psycho-social impact. Numerous topical and systemic therapies have been tried over time in an effort to treat pain, shorten the length of recurrent episodes, distance them in time, and improve the quality of life for these patients, in the absence of a clear etiopathogenesis.[5] The need for appropriate and effective systemic therapy is necessary for management of RAS. There has been armamentarium of systemic drugs available like prednisolone, azathioprine, thalidomide, cyclosporine, methotrexate, dapsone, pentoxifylline and colchicine.[6] Apremilast is the new addition to this spectrum. Till date, there are no studies which conducted a head on comparison between apremilast and other conventional drugs like colchicine and dapsone.

Our study is first of its kind to compare the efficacy and safety of traditional drugs like colchicine and dapsone with newer drug like apremilast in primary RAS. Although apremilast has been approved for aphthous ulcer in Behcet disease, its role in primary RAS has not been described yet in the literature.[7]

Hatemi et al conducted a study on the efficacy of apremilast in management of oral ulcers in Behcet disease.[8] They concluded significant reduction in mean number of oral ulcers per patient at week 12 in the apremilast group than in the placebo group ($p<0.001$). Nausea, vomiting, and diarrhea were more common in the apremilast group than in the placebo group.

A study by Mimura et al conducted an open clinical trial on severe patients of RAS.[9] The study showed that only 5 and 4 cases showed complete remission in dapsone and colchicine group respectively.

Dapsone is an often-cited systemic treatment for RAS; however, few studies have evaluated its effectiveness in patients with RAS.[10] Sharquie et al found that dapsone was effective at decreasing the number, duration, and frequency of oral ulcers with Behçet syndrome.[11]

Our study showed a greater reduction in the number of oral ulcers in patients with RAS treated with apremilast as compared to dapsone and colchicine. A decrease in the number of oral ulcers and the pain associated with oral ulcers started as early as 2 weeks and the results became statistically significant by the end 12 weeks. The reduction in oral ulcer pain paralleled the reduction in the number of oral ulcers from week 2 to week 12, therefore, reduction in oral pain was most significant in apremilast group.

Most common side effects associated with apremilast and colchicine were gastrointestinal side effects like nausea and dyspepsia. Rarer acute adverse effects like rhabdomyolysis and myelosuppression associated with colchicine were not encountered in our study. Dapsone induced rare severe side effects like haemolysis, neutropenia, methemoglobinaemia, agranulocytosis, peripheral neuropathies were not noted in the study. Therefore, all the three drugs are safer treatment modalities with respect to adverse effects.[12,13]

CONCLUSION

Recurrent aphthous stomatitis is a very common, recurrent painful ulceration occurring in the oral cavity. The etiopathogenesis of this disease is yet unclear. Apremilast is a promising drug in management of primary RAS in terms of complete clearance and decrease in number and duration of recurrence. Although, traditional therapies like dapsone and colchicine have been commonly used in clinical practice, apremilast yielded a rapid and maintained improvement of RAS.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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