

A comprehensive review of therapeutic agents used in the treatment of recurrent aphthous ulcer and oral ulcers in Behcet's syndrome

Sheshaprasad R.^{1,*}, Anuradha Pai²

¹Senior Lecturer, ²Professor & HOD, Dept. of Oral Medicine and Radiology, The Oxford Dental College an Hospital, Bengaluru, Karnataka, India

***Corresponding Author:**

Email: drsheshaprasad@gmail.com

Abstract

Introduction: Recurrent aphthous ulcer (RAU) is a common oral disease characterized by ulcers with an erythematous halo, affecting 5–25% of the general population. The underlying etiology is not clear, but several factors are believed to be responsible for the pathogenesis of the disease including stress, hormones, genetic factors etc. Behcet's syndrome is a multisystem disorder involving vasculitis of small and medium-sized vessels and inflammation of the epithelium, characterized by recurring oral and genital ulcers with eye lesions.

Aim: The objectives of this paper were to compare different treatment options available for the patients suffering from RAU and major refractory oral aphthae without any systemic disease or any syndromes except Behcet's, associated with RAU published in the review of RAU, point out drugs and therapies along with their dosages that may be used in the first line of treatment (topical) and second line of treatment (systemic).

Materials and Methods: Pub Med search (full text and abstracts) with drugs belonging to several categories like anesthetics; antibiotics and antiseptics, corticosteroids, anti-inflammatory and antiallergic drugs hemorrheologic agents, zinc substitutes, immunomodulatory agents and chemical cauterizing agents was done. Pub Med search term "Behcet's oral" was used and only those publications that described clinical trial with drugs on patients with Behcet's disease involving oral lesions were selected.

Result: Total 62 articles were analyzed to extract the data regarding different therapeutic agents used in the treatment of Recurrent aphthous ulcer and oral ulcers in Behcet's syndrome. The drugs most commonly used were lidocaine, benzocaine, tetracycline, chlorhexidine amlexenox and dexamethasone topically and prednisolone, levamisole and thalidomide systemically as a single therapy or in combination. The impact of immunomodulators and LASER in comparison with topical drugs also was assessed.

Conclusion: Novel research strategies should be designed to clinically test combination therapies in the treatment of aphthous ulcers.

Keywords: RAU, aphthous ulcers, Behcet's syndrome.

Introduction

Recurrent aphthous ulcer (RAU) is a common oral disease characterized by ulcers with an erythematous halo, affecting 5–25% of the general population.¹⁻⁴ The underlying etiology is not clear, but several factors are believed to be responsible for the pathogenesis of the disease, which include genetic factors, food allergens, local trauma, hormonal changes (menstrual cycle), stress, anxiety, smoking cessation, chemical products, and microorganism such as *H. pylori*.^{1-3,5,6} Tumor necrosis factor (TNF) is also believed to play an important role in the formation of RAU lesions.² An increase in the expression of vascular and keratinocyte adhesion molecules is observed in the lesion. Accumulation of lymphocytes and lymphocyte infiltration of the epithelium is a common occurrence, which results in ulcer formation.^{1,2,7}

Based on size, RAU is classified into three types: small ulcers or Mikulicz aphthous ulcers, large ulcers or Suttons disease, and herpetiform ulcers. Small ulcers of the minor type (Mikulicz) are less than 1 cm in diameter and represent 80–90% of all recurrent oral aphthous ulcers.^{8,9} Large ulcers of the major type (Suttons disease) are usually 1–3 cm in diameter and

account for approximately 10% of recurrent benign oral ulcers.^{8,10} Herpetiform aphthous ulcers are very small (1–2 mm), which account for 5% of RAU and are very painful.^{8,11}

RAU is also one of the most common diseases associated with Behcet's syndrome, characterized by recurring oral and genital ulcers with eye lesions.¹² Behcet's syndrome is a multisystem disorder involving vasculitis of small and medium-sized vessels and inflammation of the epithelium. The abnormal inflammatory response in Behcet's syndrome is caused by the T-lymphocytes and plasma cells. Although Behcet's syndrome generally affects adults, it is not uncommon in children.¹³⁻¹⁵ Distinguishing RAU and Behcet's disease clinically is challenging. However, an effective test is developed in which a high titer of anti-*Saccharomyces cerevisiae* antibodies (ASCA) has been detected in patients with Behcet's syndrome compared with that of RAS and healthy individuals.¹⁶ Although ASCA test can be used to distinguish between patients with RAU and Behcet's; however, it may not be accurate, as 70% of patients with Crohn's disease and 15% of patients with ulcerative colitis are ASCA

positive and both of the diseases are associated with recurring oral ulcers.

Apart from Behcet's syndrome, many other ulcerative conditions may be confused with RAU, including primary herpetic gingivostomatitis, cyclic neutropenia, pemphigus vulgaris, benign mucous membrane pemphigoid, herpangina, mouth and genital ulcers with inflamed cartilage (MAGIC syndrome), periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). These conditions should be considered before starting the treatment of RAU. Oral ulceration may also indicate underlying or developing systemic disease; the definitive diagnosis of which may not be possible until later in the disease process. Therefore a dental surgeon should continually monitor the patient and collaborate with the medical colleagues to distinguish between RAU, ulcerative colitis, and Crohn's disease. Treatment of RAU involves a list of drugs and combined use of therapies. Several drugs such as antiseptics, anesthetics, anti-inflammatory, corticosteroids, and laser therapies are common recommendations. Both topical and systemic therapies are employed to treat the disease. There are the drugs, which are used to treat RAU without any systemic abnormalities and RAU in Behcet's syndrome. In this article, we performed a systematic review of clinical trials involving several therapeutic approaches to treat RAU without any other systemic abnormalities and oral aphthous ulcers in Behcet's syndrome. Similar analysis was performed and reported by a study done by Andreas et al.¹⁷ using Pub Med and Cochrane Central Register of Controlled Trials database. A literature review was also performed by Irene et al.¹⁸ who searched Pub Med, Cochrane, and Scopus databases by using the keywords such as recurrent aphthous stomatitis, treatment and clinical management, combined and related by means of the Boolean operator—AND. In our systematic review, we used search terms in an effective manner and performed several analysis strategies to present comprehensive information on RAU.

The objectives of this paper were to compare different treatment options available for the patients suffering from RAU and major refractory oral aphthae without any systemic disease or syndrome other than Behcet's syndrome, enlist the suggestions published in the review of RAU, point out drugs and therapies along with their dosages that may be used in the first line of treatment (topical) and second line of treatment(systemic), and enlist medications that have been successfully tested in the treatment of oral ulcers in Behcet's disease.

Materials and Methods

We began our search in Pub Med with a list of drugs used in the treatment of RAU including anesthetics such as lidocaine, benzocaine; antibiotics and antiseptics such as tetracycline, chlorhexidine,

triclosan; corticosteroids such as triamcinolone, prednisolone, and dexamethosone; anti-inflammatory and antiallergic drugs such as amlexanox, 5-aminosalicylic acid, colchicines, hyaluronic acid; hemorrhheologic agents such as pentoxifylline; zinc substitutes such as oral and systemic zinc sulphate; immunomodulatory agents such as cyclosporine, thalidomide, and interferon alpha; chemical cauterizing agent such as silver nitrate; and finally laser therapy. For retrieving the literature for each drug, we typed the name of the drug followed by the term aphthous, for example tetracycline aphthous, zinc sulphate aphthous, triamcinoloneaphthous. From the obtained list of publications, we selected only those publications that involved clinical trial of drugs related to RAU.

We also searched Pub Med using the term "Behcet's trial oral" and selected only those publications that described clinical trial with drugs on patients with Behcet's disease involving oral lesions. We reported the drug used, size of the patients sample, patient benefits, control for every drug, and the publication associated with the trial in a tabular form. Our search with the terms "lidocaine aphthous" retrieved 19 publications, of which we selected two articles. Similarly, with the term "benzocaine aphthous", total six publications were retrieved, of which we selected one article. We did not consider other articles, as they did not involve clinical trials on the drugs used for the treatment of aphthous ulcer.

Search with the term "tetracycline aphthous" retrieved 45 publications from which three articles discussing clinical trials of tetracycline were selected. Search with chlorhexidine aphthous retrieved 29 articles from which we chose five articles.

Similar searches were performed in Pub Med using the terms triclosan aphthous, triamcinolone aphthous, prednisolone aphthous, dexamethasone aphthous, amlexanox aphthous, 5-aminosalicylic acid, colchicines aphthous, hyaluronic acid, and pentoxifylline aphthous. The searches produced 3, 43, 95, 22, 20, 6, 86, 5, and 28 articles, respectively, for each drug of which 1, 4, 3, 2, 8, 1, 5, 4, and 2 articles were selected, respectively.

We also searched for the terms "zinc sulphate aphthous" in Pub Med and obtained 6 articles, of which we selected four publications relevant to our systematic review. Search using the term "cyclosporine aphthous" produced 40 publications, but we could not find any publication that narrates clinical trials of cyclosporine on aphthous ulcer patients. However, search with the term "thalidomide aphthous" produced 178 publications, out of which we selected three publications. Search for immunomodulator interferon alpha aphthous resulted in 41 publications, out of which we selected two publications describing clinical trial.

Pub Med search on "silver nitrate aphthous" and "laser aphthous" produced 15 and 66 publications,

respectively, of which 1 and 10 articles were chosen, respectively.

We searched the Pub Med using the term “Behcet’s trial oral “and retrieved 86 publications, out of which we selected 20 publications.

Results and Discussion

Search results using the term aphthous with selected drugs and therapies belonging to different categories of drugs are described in Figs. 1a, b, and 2.

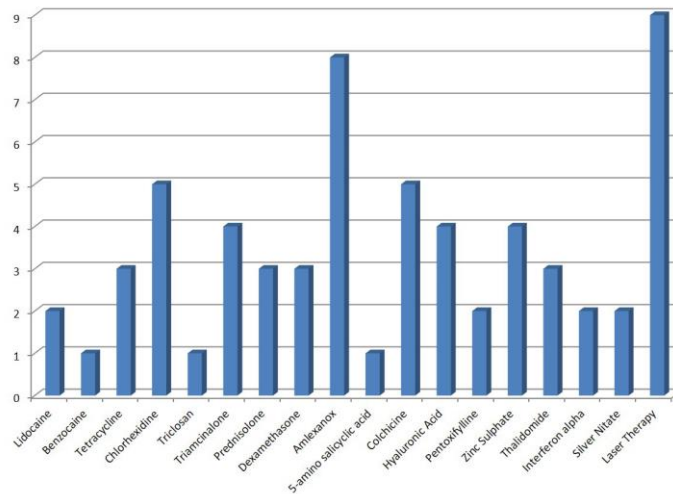


Fig. 1a: Number of clinical trials obtained by Pubmed searching for each drug category

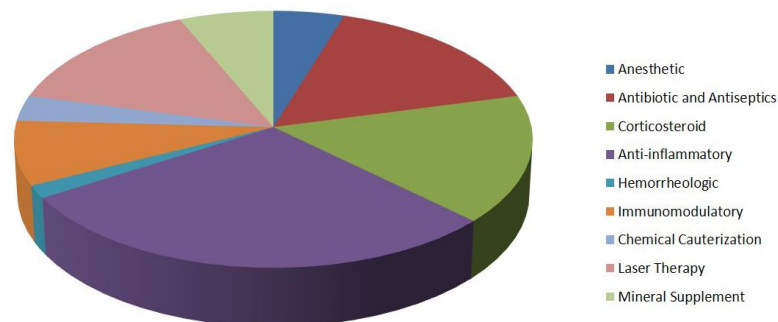


Fig. 1b: Representing largest and smallest number of drug clinical trials, obtained by searching Pubmed for drug categories

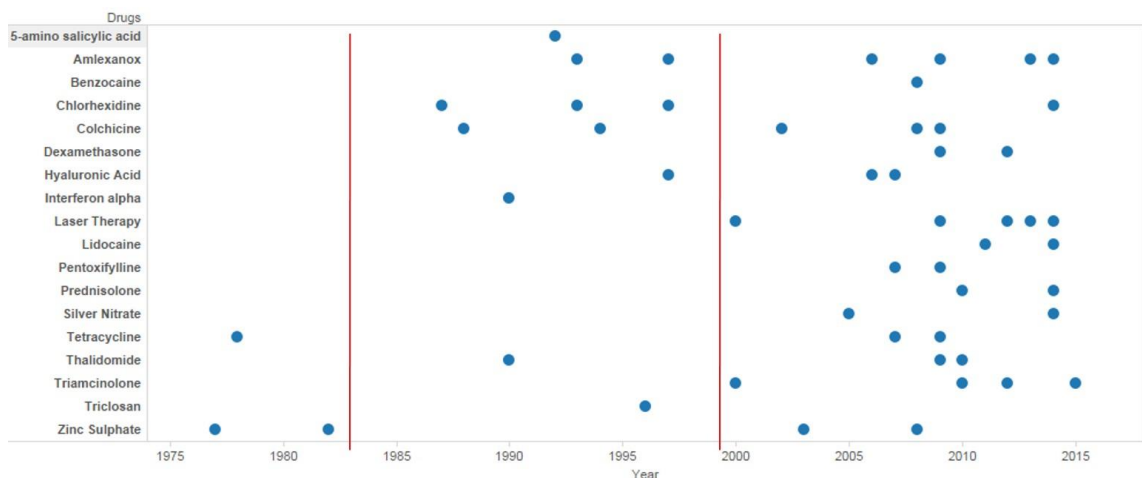


Fig. 2: Number of clinical trials conducted between 1975 and 2015 as enlisted by our search strategies

Our results indicate that a large number of studies that we selected using the keywords aphthous followed by the name of the drug were conducted between 2000

and 2015 (Fig. 2). Some of the clinical trials were conducted without using a placebo whereas some of the research trials had compared the efficacy of one drug with another. Some researchers had used combined therapies to treat recurrent aphthous ulcers.

Drug-drug comparison/combined therapy

Out of 62 studies, 16 had performed comparative clinical trial and compared the effect of one drug with the other (**Table 1**). Also, few studies had used combined therapies to treat aphthous ulcers (**Table 2**). For example, study conducted by Sharda et al.³⁵ compared the combined effect of levamisole and prednisolone with levamisole alone in treating aphthous ulcer; and the study by Saxen et al.⁵⁴ compared the efficacy of hyaluronic acid and diclofenac combined with only hyaluronic acid.

Table 1: Drug-Drug Comparison

Drug-Trial	No of Patients	Patient Benefits	Placebo/Other Drugs as Control	Publication
Tetracycline	17	More pain reduction and less healing time with minocycline	Minocycline	Gorsky M et al. ²²
Chlorhexidine	70	More patients got healed with Sucralfate	Sucralfate	SoyluÖzler G et al. ²⁵
Chlorhexidine	30	No difference between chlorhexidine and triamcinolone treatment	Triamcinolone	Miles DA et al. ²⁶
Chlorhexidine	18	No difference between chlorhexidine and benzydamine treatment	Benzydamine	Matthews RW et al. ²⁹
Triamcinolone	60	More people using the Eupatorium paste got healed after 5 days.	Eupatorium laevigatum paste	Paulo Filho W et al. ³¹
Triamcinolone	56	The healing time was less in the Ageratinapichinchensis	Extract of Ageratinapichinchensis	Romero-Cerecero O et al. ³²
Triamcinolone	180	Reduction in ulcer size and pain was more in triamcinolone group	0.5% Acemannan	Bhalang K et al. ³³
Triamcinolone	20	Regression of lesion happened earlier in the laser group	Low-level laser therapy	De Souza TO et al. ³⁴
Prednisolone plus Levamisole	50	No difference between prednisolone plus levamisole treatment and only levamisole treatment	Levamisole	Sharda N et al. ³⁵
Prednisolone	30	There was no difference between prednisolone treatment and colchicine treatment	Colchicine	Pakfetrat A et al. ³⁶
Prednisolone	60	Predisolone was more effective than montelukast in reducing number of lesions and pain.	Montelukast	Femiano F et al. ⁵
Dexamethasone	90	Ulcer healing significantly faster and adverse effects reduced as compared to triamcinolone	Triamcinolone	Al-Na'mah ZM et al. ³⁸

Amlexanox 5%	100	Reduction in ulcer number, size and frequency of ulcer as compared to antiseptic, analgesic and anesthetic paste	Benzalkonium chloride, choline salicylate and lidocaine hydrochloride	Darshan DD et al. ³⁹
Hyaluronic acid	60	There was more pain reduction in the diclofenac plus hyaluronan compared to only hyaluronan	Hyaluronan plus diclofenac	Saxen MA et al. ⁵⁴
Zinc Sulphate	45	Rapid and sustained action of zinc sulphate was observed	Dapsone, Glucose	Sharquie KE et al. ⁵⁸
Laser Therapy	180	There were reduction in pain intensity, erythema and epithelization time	Granofurin and Solcoseryl	Lalabonova H and Daskalov H. ⁶⁹

Table 2: Combination therapy in aphthous ulcer

Prednisolone plus Levamisole	50	No difference between prednisolone plus levamisole treatment and only levamisole treatment	Levamisole	Sharda N et al. ³⁵
Amlexanox 5%	100	Reduction in ulcer number, size and frequency of ulcer as compared to antiseptic, analgesic and anesthetic paste	Benzalkonium chloride, choline salicylate and lidocaine hydrochloride	Darshan DD et al. ³⁹
Hyaluronic acid	60	There was more pain reduction in the diclofenac plus hyaluronan compared to only hyaluronan	Hyaluronan plus diclofenac	Saxen MA et al. ⁵⁴
Laser Therapy	180	There were reduction in pain intensity, erythema and epithelization time	Granofurin and Solcoseryl	Lalabonova H and Daskalov H. ⁶⁹
Levamisole plus colchicine	118	Significant Reduction in the level of IL-6,IL-8 and TNF-alpha	Placebo	Sun A et al. ⁸²

Studies with large sample size

In the selected list of publications, several cases involved a considerably large sample of patients. Study on the effect of laser therapy by Lalabonova⁶⁹ involved 180 patients, study on the effect of hyaluronic acid involved 180 patients, and a clinical trial performed by Liu C et al.³⁷ to check the efficacy of dexamethasone involved a total of 240 patients. To know the effectiveness of amlexanox in healing aphthous ulcers, Binnie et al.⁴⁴ and Khandwala et al.⁴⁵ recruited more than 1000 patients.

Measuring end points

Many studies among the selected list of publications had used pain scale measurement as one of the endpoints in their clinical trial. Two types of pain

scales were used: (a) one-dimensional pain scales such as visual analog scale (VAS) and numerical rating scale (NRS) and (b) multidimensional pain scale such as brief pain inventory (BPI). Most of the studies reported decrease in the severity of pain as a result of their selected interventions. Some studies including that of Alidaee et al.⁶⁷ reported decrease in pain level but not in shortening of healing time as a result of application of silver nitrate.

Several studies had measured ulcer size as one of the endpoints. Study by Darshan et al.³⁹ reported the frequency of ulcer development; however, Liu et al.⁴², Bhat et al.⁴⁰, Greer et al.⁴⁶ and Lalabonova⁶⁹ reported reduction of erythema. Interestingly, some of the selected clinical studies reported complete remission or no reappearance of aphthous ulcers. Studies belonging

to this group are the clinical trials performed by Mimura et al.⁴⁸ with pentoxifylline, study by Orbak et al.⁵⁹ with zinc sulphate, Hello et al.⁶² with thalidomide, Hutchinson et al.⁶⁵ with interferon alpha, and Aggarwal et al.⁷¹ with laser therapy.

Differences observed in the studies

Among the comparative studies on aphthous ulcer from the selected list of publications, some studies did

not find any significant difference between the interventions used (**Table 3**). For example, Miles et al.²⁶ did not find any significant difference between chlorhexidine and triamcinolone treatment, Matthews et al.²⁹ did not report any difference between chlorhexidine and benzydamine treatment, and Sharda et al.³⁵ did not find any difference between levamisole and levamisole plus prednisolone treatment. Lastly, no difference was observed between colchicine and prednisolone treatment in a study by Pakftrat et al.³⁶

Table 3: Differences observed between two therapies

Drug-Trial	No of Patients	Patient Benefits	Placebo/Other Drugs as Control	Publication
Chlorhexidine	30	No difference between chlorhexidine and triamcinolone treatment	Triamcinolone	Miles DA et al. ²⁶
Chlorhexidine	18	No difference between chlorhexidine and benzydamine treatment	Benzydamine	Matthews RW et al. ²⁹
Prednisolone plus Levamisole	50	No difference between prednisolone plus levamisole treatment and only levamisole treatment	Levamisole	Sharda N et al. ³⁵
Prednisolone	30	There was no difference between prednisolone treatment and colchicine treatment	Colchicine	Pakftrat A et al. ³⁶

Superiority of one treatment over others

Several studies among the selected list of publications showed superiority of one intervention to another (**Table 4**). For example, mucoadhesive patch was superior to benzocaine,²¹ minocycline was superior

to tetracycline,²² sucralfate was superior to chlorhexidine²⁵, triamcinolone was superior to 5% acemannan,³³ and laser therapy was better than triamcinolone.³⁴

Table 4: Comparison of superiority of one treatment over another

Drug-Trial	No of Patients	Patient Benefits	Placebo/Other Drugs as Control	Publication
Benzocaine	48	More pain reduction and less healing time with mucoadhesive patch.	Mucoadhesive Patch	Shemer A et al. ²¹
Tetracycline	17	More pain reduction and less healing time with minocycline	Minocycline	Gorsky M et al. ²²
Chlorhexidine	70	More patients got healed with Sucralfate	Sucralfate	SoyluÖzler G et al. ²⁵
Triamcinolone	180	Reduction in ulcer size and pain was more in triamcinolone group	0.5% Acemannan	Bhalang K et al. ³³
Triamcinolone	20	Regression of lesion happened earlier in the laser group	Low-level laser therapy	De Souza TO et al. ³⁴

Retrospective and prospective studies

A few retrospective studies had been enlisted in our study. Studies by Lynde et al.,⁴⁹ Hello et al.,⁶² and

Gil et al.⁶³ were retrospective in nature. Prospective and retrospective studies had both strength and weaknesses. The major strength of a prospective cohort study was

the accuracy of data collection with regard to exposures, confounders, and endpoints. This approach was both expensive and time consuming because of long follow-up period. The retrospective design was very time efficient and new questions were answered with the existing data. However, one has no choice other than to work with what has been measured in the past.

Immunomodulators/phosphodiesterase inhibitors in treating oral lesions associated with Behcet's disease

Behcet's syndrome is associated with lesions in multiple organs including the skin, mouth, intestine, and eye. The first line of therapy is corticosteroid and immunomodulatory agents followed by TNF-blocking agents. In our review, we report several clinical trials involving various therapeutic agents. The outcome measures of the clinical trials may involve measurements associated with genital ulcers, skin lesions, or uveitis; however, we have solely reported outcomes associated with oral lesions. One of the interesting finding was the clinical trial by Kotter et

al.⁸⁸ which describes significant reduction in genital and skin lesions, and oral ulcers by interferon-alpha. Cyclosporine has been stated to be more effective than colchicines in reducing oral apthae as reported by Masuda et al.⁹⁵ Interestingly, azithromycin has been shown to reduce oral lesions in Behcet's syndrome by Mumcu et al.,⁸⁴ however, antiviral agent acyclovir has no effect on Behcet's disease as reported by Davies et al.⁹⁶ Tanida et al.⁸⁵ reported complete remission of oral ulcers by adalimumab, which is a TNF-inhibiting anti-inflammatory agent. Apart from the immunomodulatory agents, phosphodiesterase inhibitors have also shown promise in reducing apthous ulcer in patients with Behcet's syndrome. Clinical trials conducted by Nanke et al.⁸⁶ onirsogladineand Hatemi et al.⁷⁸ on apremilast provide evidence on the efficiency of phosphodiesterase inhibitors.

Based on the results of our systematic review we have enlisted certain drugs, which may be used in the first- and the second-line therapy for RAU (**Tables 5 and 6**).

Table 5: List of drugs and dosages to be used in first line of therapy for minor RAU

First Line of Treatment	Class of Drug	Dosage	Duration
Sucralfate	Oral-Local	Topical 10% sucralfate solution	3 months
Minocycline	Antibiotic	0.2% minocycline mouthwash	10 days
Hyaluronic Acid plus Diclofenac	Anti-inflammatory	3% Diclofenac in 2.5% Hyaluronan	8 hours
Dexamethasone	Corticosteroid	Oral Paste 0.1%	14 days
Amlexanox	Anti-Inflammatory	5% Amlexanox oral paste	4 days
Low level Laser	Light Therapy	Output power of 0.5 W and a Wavelength of 810 nm	7 days

Table 6: List of drugs and dosages to be used in second line of therapy for major refractory apthae

Second Line of Treatment (For major refractory apthous ulcer)	Class of Drug	Systemic Dosage	Duration
Colchicine	Secondary Metabolite/Natural Product	1.5 mg/day	1 year
Prednisolone	Synthetic Glucocorticoid	25mg/day	15 days
Interferon alpha	Biological therapy	6 million IU-3 times weekly	3 months
Adalimumab	Therapeutic monoclonal antibody (TNF alpha inhibitor)	160mg on the first day, 80mg two weeks later and 40mg alternate weeks for 52 weeks.	54 weeks
Ethancercept	Biopharmaceutical (TNF alpha inhibitor)	25mg twice a week	4 weeks
Apremilast	Phosphodiesterase 4 inhibitor	30mg Apremilast twice daily	12 weeks
Irsogladine	Phosphodiesterase inhibitor	2-4 mg/day	3 months

Comparison of several drugs used in first line of treatment

Use of sucralfate

Topical medication is definitely the first-line of treatment in oral aphthous ulcer followed by systemic therapy. Belenguer-Guallar et al.,¹⁸ suggested that several drugs including chlorhexidine, triclosan, hyaluronic acid, benzydamine, doxycycline, and amlexanox. sucralfate healed more number of patients with aphthous ulcer than chlorhexidine (SoyluOzler et al.²⁵). It should be noted that sucralfate is routinely used in the treatment of gastrointestinal ulcers, duodenal ulcers, stress-related ulcers, and aphthous ulcers resulting from chemotherapy and radiotherapy.

Use of minocycline

A study by Alpsy et al.⁹¹ showed the efficacy of sucralfate in reducing oral ulcers in Behcet's disease. Belenguer-Guallar et al.,¹⁸ suggested the use of doxycycline. However, minocycline can be more effective than doxycycline²² as it has broader spectrum of action as compared to other tetracycline drugs.

Use of hyaluronic acid plus diclofenac

If the medical practitioner wishes to prescribe hyaluronic acid, a combination of hyaluronic acid and diclofenac is suggested.⁵⁴ Belenguer-Guallar et al. has described the use of anti-inflammatory drug amlexanox in the early phase of the disease, as several clinical trials have confirmed the effectiveness of amlexanox in treating recurrent aphthous ulcer.⁴¹⁻⁴⁵

Use of laser therapy

In the first-line of therapy, involving topical corticosteroids, Belenguer-Guallar et al. suggested the use of three drugs triamcinolone acetonide, fluocinolone acetonide or clobetasol propionate. Clinical trials have shown low level laser therapy to be more effective as compared to triamcinolone.³⁴

Comparison of several drugs used in second line of treatment

Use of colchicine

Second line of therapy involving systemic corticosteroids and immunomodulators are prescribed very severe and are refractory recurrent oral ulcers. Belenguer-Guallar et al.,¹⁸ mentioned the use of drugs such as pentoxifylline, colchicine, dapsone, and thalidomide in treating severe aphthous ulcer. Use of corticosteroid prednisolone was also suggested as one of the treatment options in severe aphthosis. However, according to Pakfetrat et al.³⁶ no difference was

observed between prednisolone and colchicines in treatment of aphthous ulcer. Lynde et al.⁴⁹ and Fontes et al.⁵⁰ recommended colchicine treatment in patients with severe and complex aphthous. According to Lynde et al. colchicine is safe and effective without any serious side effect supported by the data of more than 50 patients treated at Mayo Clinic, USA between 1998 and 2007. Apart from this article, a study by Fontes et al., in a follow up study with colchicine for more than 4 years, also recommended colchicine as preventive therapy in severe recurrent stomatitis.

Use of interferon alpha

Hutchinson et al.⁶⁶ reported complete remission of major aphthae in two patients when interferon-alpha was administered. Alpsy et al.,⁹⁰ Hamuryudan et al.,⁹⁴ and O'Duffy et al.⁹² observed effectiveness of interferon-alpha in the treatment of oral ulcers in Behcet's disease. Although thalidomide is an effective treatment for severe aphthous ulcer (Hello M et al.⁶²), Belenguer-Guallar et al. has mentioned about its potential side effects.

Use of adalimumab, etanercept, aprelimast, and irsogladine in treatment of oral lesions in Behcet's disease

Clinical trials involving adalimumab, an inhibitor of TNF-alpha, performed on patients with Behcet's disease showed its effectiveness in completely eradicating oral aphthous ulcer in two-third of the total patients (Tanida et al.⁸⁵). Although there are case reports on effectiveness of adalimumab in treating major recalcitrant oral aphthous ulcers, there is no report of clinical trial with the drug in patients with major aphthae. Adalimumab may be a potential therapy in patients with major aphthous ulcer. Another inhibitor of TNF-alpha, etanercept, has also been effective in suppressing oral ulcers in Behcet's disease.⁸⁷ There are a few case reports on the drug in recalcitrant major aphthae, but no comprehensive clinical trial has been reported. There is another class of drug called phosphodiesterase inhibitors type 4 (PDE4), which inhibits the activities of TNF. Clinical trials with PDE4 inhibitors—aprelimast and irsogladine performed by Hatemi et al.⁷⁸ and Nanke et al.⁸⁶ reported effective treatment of oral ulcers in patients with Behcet's. A well-designed clinical trial is recommended for these drugs in major oral refractory aphthous ulcer patients.

To summarise, we have compared different treatment options for patients suffering from RAU and major refractory oral aphthae, and discussed the suggestions by Belenguer-Guallar et al.¹⁸ about the drugs and therapies along with their dosages, which may be used in the first-line of treatment (topical) and second-line of treatment (systemic). Also, the selected medications, which have been successfully tested in oral ulcer in Behcet's disease, are discussed. The

limitations of this study is we have not considered other systemic conditions and syndromes which has RAU as its component except Behcet's syndrome. An extensive review with the above inclusions would be better in understanding the efficacy of drugs (both topical and systemic) in treating RAU and RAU associated conditions.

Conclusion

Novel research strategies should be designed to clinically test combination therapies in the treatment of aphthous ulcer. Drugs that are clinically effective and have cured aphthous ulcers in large number of patients may be used. Further research may be carried out to understand the effectiveness of immunomodulators and phosphodiesterase inhibitors in the treatment of major recalcitrant aphthous ulcer and oral lesions associated with Behcet's disease.

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