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Management of Oro-Cutaneous Manifestations in Behçet disease and Recurrent Oral Aphthosis, review article

Khalifa E. Sharquie[1], Fatema A. Al-Jaralla[2]

[1]Department of Dermatology, College of Medicine, University of Baghdad. Iraqi and Arab Board for Dermatology & Venereology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq.
[2]Department of Dermatology, College of Medicine, University of Baghdad, Baghdad, Iraq.

ABSTRACT

Recurrent oral aphthosis is a major health problem affecting 20% of population. Its pathogenesis is not well elucidated, however, it's considered as part of major criteria of Behçet disease. Many therapies adviced to manage these ulcerations in both diseases and most of them are symptomatic, however, in the last decades; some of them have shown therapeutic as well as prophylactic roles. Herein, we review the different aspects of these threapies with emphasis on Iraqi experience.

Keywords: Recurrent oral aphthosis, Behçet disease, Management

***Correspondence to Author:**
Khalifa E. Sharquie
Department of Dermatology, College of Medicine, University of Baghdad. Iraqi and Arab Board for Dermatology & Venereology, Baghdad Teaching Hospital

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Introduction

Behçet disease (BD) is a rare vasculitic disorder that is characterized by a triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis.[1] The disease is named after the Turkish dermatologist Hulusi Behçet, who identified it in a patient in 1924 and published a description of the disease in 1937.[2]

BD is very prevalent from the Mediterranean to Japan, in countries alongside the ancient Silk Road, extending from the Middle East to China. The highest BD prevalence ratios were found in Turkey, with 420 cases per 100,000 populations.[3] Its incidence is rare in the West (0.64/100,000 population in the United Kingdom and 0.12-0.33/100,000 in the United States). The estimated prevalence of 1.7 BD patients for 10,000 Iraqi populations is more or less similar to the prevalence in other Mediterranean and Far East countries, excluding Turkey.[4] Careful neurological assessment of Iraqi patients with Behcet's disease may show a relatively high prevalence of neuro-Behcet features, and though the clinical patterns of presentation are characteristic a mixed pattern may occur.[5] There is a close correlation between the geographical distribution of the human leukocyte antigen (HLA) B51 and the prevalence of BD. The frequency of HLA-B51 in the Silk Road area is 20-25% among the general population and 50-80% among patients. In Northeastern Europe and the United States, this frequency is 2-8% and 15%, respectively.[6-8] While in Iraqi population was 20%.[9] In another Iraqi study; HLA-B51 was present in (62%) patients with BD compared with (29%) unrelated normal controls.[10]

Etiopathogenesis:

Although several theories exist behind the pathogenesis of Behçet disease, the specific etiology of Behçet disease remains elusive. It is thought that in genetically predisposed individuals, exposure to an infectious agent or an environmental antigen triggers the autoimmune response. The most probable hypothesis is that of an inflammatory reaction set off by infectious agents such as herpes simplex virus (HSV)-1 or Streptococcus species such as Streptococcus sanguinis or by an autoantigen such as heat shock proteins (HSP) in genetically predisposed individuals.[11] A possible assocation between HSV-1 with BD has been the subject of several investigations. Hybridization between HSV-1 DNA and complementary RNA in mononuclear cells was found to be higher in BD patients than the control patients. Results indicated the presence of at least a part of the HSV-1 genome in mononuclear cells of patients with BD.[12]

The study of heat shock proteins (HSPs) has provided some insight into possible mechanisms that contribute to the development of BD. Streptococcal 65-kDa HSP from an uncommon serotype (KTH-1, strain BD113-20) of oral S. sanguinis have been noted to be important extrinsic factors in the pathogenesis of BD.[13]

The human HSP-60 and HSP-65 share greater than 50% homology with mycobacterial HSP enhanced T-cell response has been elicited with exposure to both bacterial and human homogenates in BD patients compared with controls in United Kingdom, Japanese, and Turkish populations. HSP-65, found in high concentrations in oral ulcers and active skin lesions in patients with BD, has also been demonstrated to stimulate production of antibodies that exhibit cross-reactivity with streptococcal species present in the mouth.[14-16]

BD has been considered to be a Th1 mediated inflammatory disease, with high levels of Th1 cytokines. Recently, studies reported increased Th17-associated cytokines as well.[17] The specific role of neutrophils in BD has been difficult to characterize. Some studies have found that cytokine release in BD may, by an unknown mechanism, place neutrophils in a static pre-excitatory “primed” state, eventually triggered into hyperactivity by environmental stimuli at a lower threshold than in individuals who do not have BD.[18-21]

An environmentally triggered hyperactive primed state of autoimmunity ensues, resulting in

vasculitic lesions that may be widespread. However, studies have demonstrated excessive thrombin formation and the potential role of impaired fibrinolytic kinetics in the generation of the hypercoagulable/prothrombotic state. There are several clinical clues suggesting the inflammatory nature of thrombosis in BD, especially of the venous involvement, thus BD is considered a model of inflammation - induced thrombosis.[22-23]

Diagnostic criteria

The diagnosis of BD is mainly clinical and many diagnostic criteria have been applied like Mason and Barns 1969, O'Duffy 1974, and Dilsen 1986. More commonly the International Study Group criteria in 1990 gained acceptance, which required the presence of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test.[24]

In 2013, proposed criteria was published based on the training set data and agreed upon by the research team included oral aphthosis, genital aphthosis, ocular lesions (anterior uveitis, posterior uveitis, or retinal vasculitis), neurological manifestations, skin lesions (pseudofolliculitis, skin aphthosis, erythema nodosum) and vascular manifestations (arterial thrombosis, large vein thrombosis, phlebitis or superficial phlebitis). Oral aphthosis, genital aphthosis and ocular lesions were each given 2 points, whereas 1 point was assigned to each of skin lesions, vascular manifestations and neurological manifestations. A patient scoring 4 points or above was classified as having BD (Table 1). With the training data set, this scheme exhibited an estimated 93.9% sensitivity and 92.1% specificity. [25]

Table 1. International Criteria for Behcet's Disease – point score system: scoring 4 indicates Behcet's diagnosis

Sign/symptom Points
Ocular lesions 2
Genital aphthosis 2
Oral aphthosis 2
Skin lesions 1
Neurological manifestations 1
Vascular manifestations 1
Positive pathergy test* 1*

*Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.

Treatment

Past decades

Several treatment modalities with different mechanisms of action have been studied in patients with BD. The relapsing and remitting nature of BD and the differences in natural course of different types of organ and system involvement, as well as differences in the disease course between men and women, mandate that the treatment should be individualized accordingly. In patients with BD, skin, mucosa and joint involvement can cause impairment of quality of life but do not cause permanent damage whereas untreated eye, vascular, nervous system and gastrointestinal system involvement can cause serious damage

and even death. When there is only skin, mucosa and joint involvement, treatment can be tailored according to the patient's need and how much the symptoms impact on their quality of life compared with the risks associated with adverse effects of any medication used. The European League against Rheumatism (EULAR) recommendations for the management of BD, which were developed in 2008 and updated in 2018, aid in the management of different aspects of BD. [26]

In mild forms of the mucocutaneous ulcerations, initial treatment consists of mild diet, and avoidance of hard, spicy, or salty nutrients and chemicals, topical corticosteroids or sucralfate solution are first-line therapy for mild isolated ulcerations. Topical sucralfate for 3 months durations as mouthwash. Other topical treatment of oral ulcers includes caustic solutions (silver nitrate, tinctura myrrhae, hydrogen peroxides, and methyl violet, topical antiseptic and anti-inflammatory drugs (amlexanox, rebamipine, hexetidin, chlorhexidine, benzydamine, camomile extracts, and tetracycline mouth-wash), topical anaesthetics , topical aminosalicylic acid. [27-31]

Topical treatment of genital ulcers and cutaneous ulcers includes corticosteroid, topical anaesthetic in cream. [32] Sucralfate [30], and topical granulocyte colony-stimulating factor.[33]

In severe forms of the mucocutaneous ulcerations, additional systemic treatment is required. In the past decades, traditional immunosuppressive agents were largely used to reduce the ulcers disability, but some contrasting results were observed, particularly in terms of maintaining remission effectiveness. The following drugs have proven beneficial: Corticosteroids (prednisolone, initial dose 30–60 mg/day p.o. for at least 4 weeks) as monotherapy or in combination with colchicine 1.0–2.0 mg/ day or azathioprine 2.5 mg/kg/day; interferon-2a subcutaneously 6 MU three times a week, and pentoxifylline.[34-38]

Colchicine is an anti-inflammatory plant alkaloid and inhibits neutrophil chemotaxis by inhibiting the microtubule function. It is useful only for erythema nodosum and arthralgia. In a more recent, 2-year placebo- controlled, trial in a greater number of patients, colchicine was beneficial only for genital ulcers, erythema nodosum and arthritis in women, and only for arthritis in men.[39, 40] It has effectively been used in placebo-controlled study for the treatment of active mucocutaneous and joint manifestations of Behçet' s disease without ocular or major organ involvement, because it is well tolerated at a dosage of 1.0–2.0 mg/ day with the least risk and side effects, especially among women.[41]

Cyclosporine-A is a calcineurin inhibitor and naturally occurring product of fungi with more specific effect on the immune system than corticosteroid and cytotoxic drugs. The primary effect of cyclosporine-A is the inhibition of T lymphocyte activation and recruitment, which is safer than cytotoxic agents because it does not induce permanent immunosuppression.[42] Cyclosporin A (3 mg/kg/day p.o.) is capable of markedly ameliorating mucocutaneous ulcers. But, it should be reserved for the most severe patients because of its significant long-term adverse effects.[43]

Azathioprine (2.5 mg/kg/day) seems to be effective in controlling the progression of BD, especially in most critical manifestations, such as eye diseases. Favorable effect on mucocutaneous lesions is proven by statistically significant reductions in the frequency of oral and genital ulcerations.[44]

Methotrexate (7.5–20 mg/1× weekly p.o. over 1 month) is able to induce an improvement of severe mucocutaneous ulcers.[45]

Mycophenolate mofetil (MMF) was found to be safe and effective in controlling cystoid macular oedema and in reducing the uveitis relapse rate in patients not responding to traditional immunosuppressants.[46]

Several studies have demonstrated thalidomide (300mg/day) effectiveness in the treatment of oral and genital ulcers, in addition to papulopustular lesions. However, its use is

limited due to its association with severe adverse events and birth defects, besides its failing in the treatment of eye involvement.[47-51]

Interferon-2a has been successfully used in the treatment of BD. Its immunomodulatory effect, ability to augment the decreased activity of the patient's natural killer cells, capacity to intibit neovascular proliferation, and antiviral activity have been suggested to explain its action in BD. It was shown to markedly inhibits IL-8 synthesis and secretion form endothelial cells. Interferon--2a treatment at dose of 6 million IU/3× week s.c. for 3 months, is an effective alternative treatment, particularly for management of mucocutaneous ulcerations.[52]

Infliximab (3-5 mg/kg infusion repeated in intervals of 4 weeks) seems to produce good and long-lasting remission of mucocutaneous lesion, after its discontinuation at the 13th infusion as described in two clinical cases in which the patients were treated with infliximab, respectively, in association with azathioprine and cyclosporine.[53, 54]

In a randomized controlled trial the effectiveness of etanercept 25mg subcutaneously twice a week in suppressing most of the mucocutaneous manifestations, such as the oral ulcers, the papulopustular lesions and nodular lesions has been demonstrated, and a lower probability of recurrence of oral ulcers has been described; the genital ulcers do not seem to improve after the treatment.[55]

Interleukin-1 Inhibitors have been recently described as a mediator of BD. This innovative concept introduces the identification of new potential targets for biological therapy.[56] The recombinant human IL-1 receptor antagonist (anakinra), the human immunoglobulin G1 (IgG1) anti-IL-1 beta monoclonal antibody (canakinumab150-300 mg every 6 weeks), and the recombinant humanized anti-IL-1 beta antibody (gevokizumab) are proven to be partially useful in the treatment of BD, while appearing to be more effective in ocular involvement.[57]

Two case series[58, 59] described the effectiveness of azithromycin 500 mg/day for four weeks in decreasing folliculitis and in fastening the healing time of oral ulcers. Minocycline for three months is described to decrease the frequency of the OA, erythema nodosum lesions, and papulopustular lesions in an open study [59]. Rebamipide (300 mg/day for 3 to 6 months) , used to treat gastritis and gastric ulcer in Japan, is observed to improve the aphthae count and to relieve the pain secondary to oral ulcers in a double placebo-controlled study.[61]

Apremilast (30 mg twice-daily) an inhibitor of phosphodiesterase 4 (PDE), a drug approved for psoriasis and psoriatic arthritis, seems to be a good alternative treatment in BD. In a phase II randomized, placebo-controlled, double-blind study, the apremilast is observed to be effective in the treatment of oral ulcers and in treating genital ulcers.[62]

Alemtuzumab (60- 134 mg) is a humanized immunoglobulin G1 monoclonal antibody that targets CD 52. Its main effect is T-cell depletion; has shown to be effective in an open trial of 18 patients with orogenital ulcerations, ocular involvement, and neurological involvement.[63]

Lactobacilli, which have anti-inflammatory activity, may be useful in inflammatory bowel disease. In a study aimed at evaluating the efficacy of lactobacilli lozenges in the management of oral ulcers of BD, a significant decrease in the mean number of ulcers was found following treatment.[64]

Current experience

Patients who fulfilled the International Study Group criteria for the diagnosis of BD were included in Sharquie et al studies. The International Study Group criteria [64] require the presence of oral aphthae plus two of the following:

1. Recurrent genital aphthae
2. Eye lesions
3. Skin lesions
4. A positive pathergy test

Dapsone; dapsone was first introduced by Sharquie et al in 1984 to treat BD [66], and later was confirmed by a double blind/placebo controlled clinical trial in 2002 [67], dapsone was effective in the treatment of twenty patients with mucocutaneous manifestations of Behçet's disease and possibly in prophylaxis against systemic manifestations of the disease. Dapsone significantly controlled oral ulcers by decreasing their number, duration, and frequency when compared with pretreatment data. Although dapsone controlled the size of oral ulcers, the effects did not reach statistical sigificance, so dapsone has a suppressive effect on oral ulcers. Although episodes of ulcers still occur, they are less frequent and of shorter duration. Ulcers in some patients are smaller in size and less in number than before treatment. Dapsone also significantly controlled the number of genital ulcers, but the suppressive effects of dapsone on their size, duration, and frequency did not reach statistical significance.

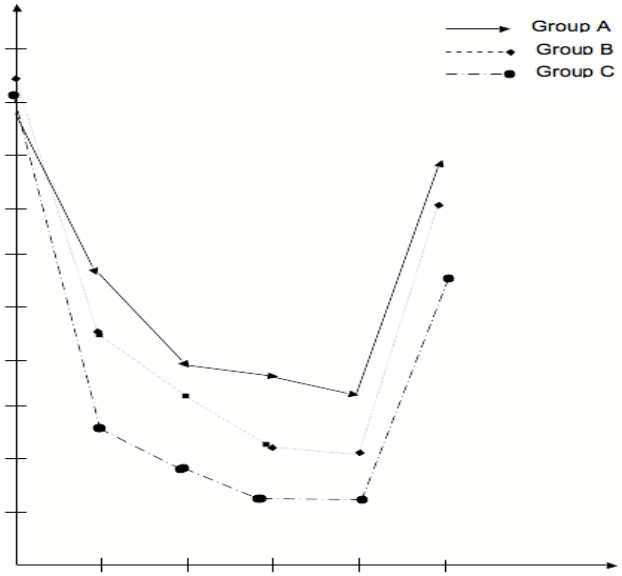

Fig. 1. Effect of dapsone on clinical manifestations index. Data expressed as mean rank. Compared to values before treatment P<0.001.

Cutaneous manifestations were apparently suppressed by dapsone fig 1, and no noticeable cutaneous manifestations were reported in dapsone-treated patients during the trial. In the placebo-treated group, new manifestations were reported. This might indicate that dapsone has a therapeutic as well as prophylactic role in BD. No patient in the dapsone-treated group showed further systemic manifestations, while three placebo-treated patients developed systemic affects (one patient with uevitis, two with phlebitis). These findings are in favor of a prophylactic role of dapsone in BD. Sharquie [67, 68] ; reported the suppressive effects of dapsone on pathergy test. Dapsone significantly suppressed the pathergy test in comparison with pretreatment data, although fluctuations occurred during the follow-up period. Placebo caused only a small insignificant difference (positive trend) in the degree of the pathergy test positiviy, especially in those pretreated with dapsone. The results of this study show that both ESR and WBC counts were significantly lowered by dapsone. The clinical manifestations index (table 2) was also found to be positively correlated with ESR and WBC count. This index was reduced by dapsone, and the reduction was highly significant. The mechanism of the action of dapsone in BD as well as in other dermatoses in which PMNs play a major role might be explained by inhibition of lysosomal activity and interference with the myeloperoxidase H2O2-halide mediated cytotoxic system in PMNs.[69]

It has also been reported that dapsone exerts some of its anti-inflammatory effects by interfering with PMN-dependent production of

oxygen intermediates, thus conferring protection from auto-oxidative tissue injury.[70] Other studies have suggested that dapsone inhibits leukotrine B4 binding to neutrophils,[71] ،and inhibits the neutrophil response to some chemotactic stimuli [72] such as inhibiting inter- leukin 1-stimulated neutrophil adhesion to endothelial cells. [73] The fact that dapsone is retained in the skin and that trace concentrations of the drug may present in the skin up to 3 weeks after discontinuation of dapsone therapy may account for the observation that parameters tended to reach pretreatment values only at about one month after discontinuation of the drug. The frequency of dapsone side effects are much low than what has been reported if is used in ordinary 100mg daily dose.

Table 2. Clinical manifestations index

***mucocutaneous:**
— oral ulcers
0 No ulcers
1 1–3 minor ulcers (minor: 2–4 mm in diameter)
2 1–3 major ulcers or more than 3minor ulcers (major: up to 10mm in diameter or larger)
3 More than 3 major ulcers
— Genital ulcers
0 No ulcers
1 1–3 minor ulcers
2 1–3 major ulcers or more than 3 minor ulcers
3 More than 3 major ulcers
— Frequency (episodes/month)
0 No episodes
1 1–2 episodes/month
2 More than 2 episodes/month
3 Continuous (status aphthaticus)
1-Erythema nodosum like-lesions
1-Papulopustular lesions
1-Acneiform lesions
***Rheumatological**
1 Arthritis of each joint
1 Arthralgia (irrespective of number of joints)
***Orchitis**
1 Involvement of one side
2 Involvement of both sides
***Vascular**
1 Unilateral limb deep venous thrombosis/or superficial vein thrombosis
2 Bilateral venous thrombosis
3 Vein thrombosi requiring bed rest
4 Thrombosis of both superior/inferior vena cava
5 Thrombosis of both superior vena cava and inferior vena cava or arterial occlusion
***Eye (for each eye)**
0 Normal
1 Cell in vitreous/or anterior chamber only
2 Vision 50%
3 Vision 30%
4 Able to see a few feet
5 Blind
***Neurological**
2 Intracranial hypertension
4 Multiple sclerosis-like syndrome
5 Pyramidal and/or cerebellar involvement

Oral zinc sulfate; In a randomized, controlled, double-blind trial for 30 patients with BD [74]; zinc was found to be low in the serum of patients with BD compared to healthy subjects, thus zinc was found to be a good option in the treatment of BD. An inverse correlation between clinical manifestations index (CMI) and serum zinc level was found. The CMI readings decreased with the elevation of serum zinc in patients with BD illustration 1.

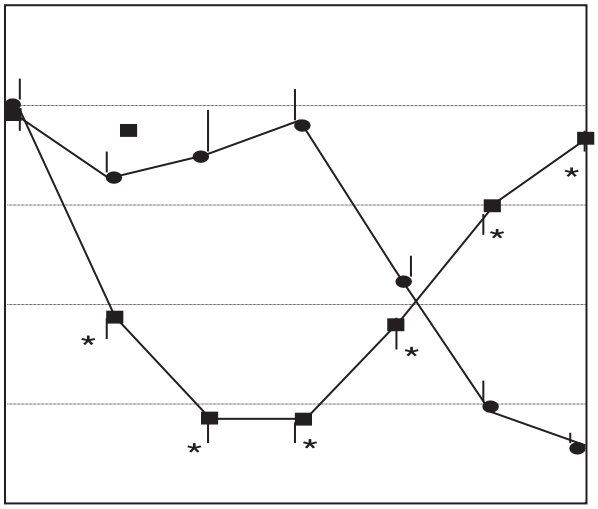

Illustration 1. Mean clinical manifestations index (CMI) score ± SEM in group A (■, first 3 months with zinc sulfate then placebo) and group B (●, first 3 months placebo then zinc sulfate) during the 6-month study period. *, *P* < 0.05 when compared with group B for the corresponding month.

This study proved that such inverse correlation is also found after treatment with zinc sulfate. The ESR was also decreased after treatment with oral zinc sulfate, but tended to increase when patients were crossed over to placebo. The mechanism of action of zinc sulfate in treatment of BD could involve the antioxidant effect of zinc. Therefore, increased serum zinc levels enhanced the antioxidant capacity of the patients and protected against damage caused by the reactive oxygen species, which were generated by the immunological events that are part of BD. Another possible mechanism of the action of zinc in treatment of BD might be through immunomodulatory effect. In the dose used of 100 mg three times daily, the response of patients with BD to zinc sulfate was very much comparable to the effectiveness of dapsone using a similar double-blind crossover study. However, side-effects recorded with zinc are much less common and less serious than those with dapsone. Therefore, this study proposed that zinc may prove superior to dapsone as a treatment for BD.

Retinoids

Oral isotretinoin; In order to evaluate the long-term remission efficacy and safety of isotretinoin in the treatment of BD, a single-blind, controlled therapeutic study was conducted on a thirty patients with BD.[75]

Each patient received isotretinoin 20 mg orally once daily for 3 months. They were assessed at week 2 and then monthly depending on the Clinical Manifestation Index (CMI) and to record any side effects. At week 12, isotretinoin was stopped and patients were given placebo therapy in a form of glucose capsules for another 3 months.

During the first 3 months of therapy, the ordinary pathergy test, oral pathergy test, and C-reactive protein were significantly minimized. The CMI before isotretinoin therapy ranged between 2 and 8 (mean +/- SD, 4.933 +/- 1.91). After therapy, within the first 14 days, the mean CMI

started to decline to a lower level, and it continued to decline significantly until week 12. It then started to increase through week 4 of placebo therapy, but remained statistically significant until the second month of placebo therapy. Isotretinoin therapy also had a statistically significant effect in reducing oral ulcers and skin manifestations. Therefore, this study had proved that isotretinoin is an effective therapeutic and prophylactic drug in the management of BD. This drug has many side effects but mainly hyperlipedemia, dry skin and cheilitis and has teratogenicity action in pregnancy.

Oral acitretin 25mg/day; In a comparative cross-over therapeutic study [76] ; oral acitretin versus oral zinc gluconate 25 mg/ twice daily were used in controlling BD. CMI was dramarically reduced after three months of acitretin use and the effect continued one month after stopping the therapy. Therefore, it had proved both therapeutic and prophylactic action.

Zinc gluconate was used in the next three months of therapy and was also effective at the end of three months with statistically significant results. However, acitretin was more effective than zinc gluconate. Oral acitretin was shown to be inferior in reducing the number of oral and genital ulcers when compared with isotretinoin from previous study (Sharquie et al., 2013). The effect of oral acitretin in reducing pathergy test was comparable to zinc gluconate and isotretinoin, but the later was superior in reducing oral pathergy test.

In contrast to isotretinoin, acitretin had no effect on C-reactive protein. On comparing the mean reduction of CMI, zinc sulfate proved to be superior to zinc gluconate, isotretinoin and acitretin

Colchicine and benzathine pencillin; Multiple drug regimens are often used in medicine to enhance action and decrease side effects. A case-comparative study to evaluate efficacy of combined colchicine and benzathine penicillin in the treatment and prophylaxis of BD was conducted on 66 patients. [77]

The patients were divided into three groups: group 1 (20 patients) received 1.2 Mu benzathine penicillin injections monthly; group 2 (21 patients) received two tablets of colchicine daily (each tablet contained 0.5 mg); and group 3 (25 patients) received both 1.2 Mu benzathine penicillin injection monthly and two tablets of colchicine daily. Each patient was followed up monthly for 5 months; 4 months on treatment and 1 additional month follow up. The CMI was reduced by colchicine and benzathine penicillin treatment, and the reduction was highly significant fig 2. The reduction in the CMI remains satisfactory and good for 1 month after stopping the treatment. This means that the combination of colchicine and BP has therapeutic and prophylactic roles in BD.

When each colchicine and benzathine Penicillin are used alone the index is also reduced significantly, but this reduction is much less than when both drugs are used together and there is also rapid and earlier relapse. Based on this study, the combination of colchicine and benzathine penicillin appears to be of greater efficacy in the treatment of Behçet disease than the use of either drug alone.

According to this study, the previously reported serious side effects seen with colchicine, such as polyneuropathy, pancytopenia, and renal failure were not observed in this study. There was hair loss in one patient and mild gastrointestinal disturbance in five patients. The small dose of colchicine (0.5mg twice daily) used might explain the low incidence of side effects. The mechanism of action of colchicine in BD may be attributed to inhibition of PMN chemotaxis and lysosomal degranulation. [77] Benzathine penicillin acts mainly on *Streptococcus sanguis*, which is present in the oral flora of high proportion patients with BD.[78] Decreasing this flora may prevent abnormal immune reaction and response to the heat-shock protein normally present in tissue and microbial agents; this in turn prevents tissue injury.

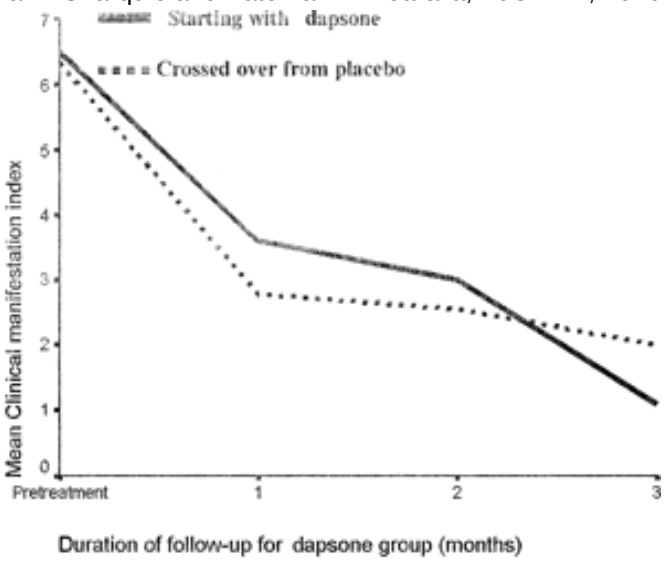

Figure 2. CMI score in all groups (groups A, B and C) during the five months study period.

Table 3. Randomized controlled trials in Behçet's disease, Iraq experience.

Intervention	Duration	Outcome	Result
Dapson 100 mg/day	3 months	Mucocutaneous manifestations especially oral ulcers	improvement
Zinc sulfate 100 mg three times daily	3 months	Mucocutaneous manifestations especially oral ulcers	improvement
Colchicine and benzathine pencillin: group 1 (20 patients) received 1.2 Mu benzathine penicillin injections monthly; group 2 (21 patients) received two tablets of colchicine daily (each tablet contained 0.5 mg); and group 3 (25 patients) received both 1.2 Mu benzathine penicillin injection monthly and two tablets of colchicine daily	4 months	CMI score	improvement
isotretinoin 20 mg orally once daily	3 months	Mucocutaneous manifestations especially oral ulcers	improvement
Oral acitretin 25mg/day; In a comparative cross-over therapeutic study versus oral zinc gluconate 25 mg/ twice daily	3 months	CMI score	Acitretin was more effective than zinc gluconate

CMI, clinical manifestations index

Multiple drug therapy; multiple drugs use in Behcets disease is strongly recommended as these combinations increase the effectiveness of these therapies and minimize their side effects like using combination of dapsone and oral zinc sulfate or zinc sulfate in combination with oral isotretinoin with topical therapy of oral ,genital uclcers and skin manefestations or for eye complaints.

Similarly, topical therapies (will be discussed thoroughly under the management of recurrent oral aphthosis); like nigella sativa, 5% zinc sulfate mouth wash, honey, pumpkin seed oil, BCG and sesame seed oil have been advocated singly or in combination with other systemic therapies, may induce a long lasting therapeutic and prophylactic actions lasting for months.

Recurrent oral aphthosis

This disease presents as recurrent, multiple, small, round or ovoid ulcers, with circumscribed margins, having yellow or gray floors and surrounded by erythematous haloes, present first in childhood or adolescence, table 4.-[80]

Table 4. Clinical feature of minor, major, and herpetiform recurrent oral aphthosis

	Minor RAS	**Major RAS**	**Herpetiform RAS**
Gender predilection	equal	equal	female
Morphology	Round or oval lesions Gray–white pseudo-membranes erythematous halo	Round or oval lesions Gray–white pseudo-membranes erythematous halo	small, deep ulcer that commonly converge irregular contour
Distribution	Lips, cheeks, togue, floor of mouth	Lips, soft palate, pharynx	Lips, cheeks, togue, floor of mouth, gingiva
Number of ulcer	1 - 5	1 - 10	10 -100
Size of ulcer	< 10 mm	>10 mm	2 -3 mm
Prognosis	Lesions resolve in 4-14 days No scarring	Lesions persist >6weeks High risk of scarring	Lesion resolve in <30 days Scaring uncommon

(Adapted from walace afogers SC.et al. management of recurrent aphthous stomatitis in children. oral medicine. 2015; 42(6); 564-572).

They are located in decreasing frequency on the buccal and labial mucosa, edges of the tongue, buccal and lingual sulci, and soft palate.[81]

Multifactorial etiopathogenesis has been suggested to explain the cause of ROA but the exact etiology and pathogenesis still not well elucidated. Similar to other chronic inflammatory conditions, DNA damage secondary to oxidative stress is thought to play a large role in recurrent ulcerations. A recent study strongly suggested that ROA patients have a systemic imbalance in the oxidant-to-antioxidant ratio favoring oxidative damage [81]. The potential triggering factors include local trauma, genetic predisposition, nutritional deficiency, immunological abnormalities, microbial and hormonal factors.

Treatment

Despite numerous clinical trials, no medication gives completely reliable cure. Predisposing factors should be corrected, if there is an obvious relationship to certain foods, the causal food should be excluded from the diet [82]. The primary goals of therapy for ROA are relief of pain, reduction of ulcer duration and restoration of normal oral function. Secondary goals include reduction in the frequency and severity of recurrences and maintenance of remission.

Topical agents:

Topical Corticosteroids: Most widely used drugs in immune-mediated oral mucosal diseases. The aim of such treatment is to eliminate the symptoms, thereby allowing the patient to eat, speak and perform normal oral hygiene, topical corticosteroids reduce or even suppress the pain and shorten the healing time.[84]

Triamcinolone acetonide is used at concentrations ranging from 0.05-0.5%, applied 3 times a day. It is particularly indicated in patients with small and mild erosive lesions. Some authors consider the most effective concentration to be 0.1%. [85] A mixture

of equal parts fluocinonide ointment and orabase applied to the ulcers three to four times daily is effective in aiding the healing of existing ulcers, however, it does not prevent new ulcers.[81] Clobetasol 0.05% in aqueous solution mouth wash is a safe and efficacious option for the treatment of severe chronic oral ulcers.[86]

Antibacterial agents: Such as chlortetracycline, and oxytetracycline rinses have been tested clinically with good responses.[87] Tetracycline and their derivatives (doxycycline and minocycline), in gel or rinse format, have also been found to lessen the pain and outbreaks of ROA. These drugs act through the local inhibition of collagenases and metalloproteinases (MPs) that form part of the inflammatory response and contribute to tissue destruction and ulcer formation, and more over exert immune modulating effects.[88] Of the commercially available tetracyclines, doxycycline has shown the best inhibition of MP.[89] The administration of fixed- dose doxycycline in mucoadhesive gel formate has shown to be effective in treating ROA. Other authors recommend its application at a dose of 100 mg in 10 ml of water, performing rinses for 2-3 minutes (without swallowing), four time daily.[90]

Amlexanox 5% oral paste: is a newly investigated, anti-inflammatory agent, potentially useful topical therapy to induce healing and relieve pain with minimal irritation.[81] Its mechanism of action is not known, though it is a topical agent with established anti-inflammatory and anti-allergic properties.[88]

Irsogladin maleate: accelerate the wound healing process in oral mucosa by reinforcing gap junctional intercellular communication (connexin 26, 32) among oral mucosal cells and therefore, it's effective for treatment of ROA.[91]

Triclosan; an anti-microbial agent has been shown to have anti-inflammatory and analgesic properties, can be used in gel or rinse formate three time a day, as long as the lesion persist. [92] 0.2% chlorhexidine in rinse or gel, used three time daily (without swallowing), for as long as the lesion persist. Topical 3% diclofenac with 2.5% hyaluronic acid can applied to lessen the pain.[93]

Oral rinses with benzidamine hydrochloride, result in temporary pain relief. [88] An Iraqi study showed that Topical honey with or without steroids has a good healing and antibacterial effects.[94, 95]

Iraqi study also showed that Lactic acid 5% mouthwash 3 times daily before meals is an effective therapy for patients with ROA and had significantly reduced the signs and symptoms of the disease, especially when compared with placebo, with response rate 90.8%. The mechanism of action may be related to increasing spontaneous secretion of endothelial growth factor from keratinocytes, An oral clinical manifestation index was used to assess response (table 5).[96]

In other study 5% lactic acid mouth wash showed response rate of 69.16%, also showed significant prophylactic effect, with no side effect apart from mild irritation in some patients.[97]

Nigella sativa oil 100% and 5% zinc sulfate mouth wash also, can be used as a safe and effective topical treatment for ROA, with response rate 60.60% and 66.33% respectively.[98]

A very recent Iraqi study had shown that 100% pumpkin seed oil is a new effective therapeutic and prophylactic agent in management of ROA.[99]

Amylogulucosidase and glucose oxidase enzymes: have been used and show significant reduction in the number and pain of the ulcer.[100]

Low-intensity ultrasound: its effect is through stimulation of fibroblast, increased angiogenesis and promotion of granulation tissue formation.[101]
Sucralfate suspension, alone or in compounded with topical corticosteroid, may be useful.[81]

Topical anesthesics: These agents help relieve pain of ROA locally. Lidocaine (xylocaine viscous) 2% solution, keeping 1 teaspoonful in the mouth for several minutes is helpful in

allaying pain.[81] Natural substances such as myrtle (Myrtuscommunis), a bush from northern Iran that possesses blood glucose-lowering, antibacterial, analgesic and antioxidant properties, thus suggesting potential usefulness in application to diseases characterized by inflammation and allergy. [102]

Quercetin, a flavonol found in fruits and vegetables, with antioxidant properties and which may prove useful in shortening aphthae healing time when applied as daily topical treatment. [103]

Bioadhesive patches containing licorice hydrogel, which reduce the diameter of the inflammatory halo and the necrotic center of the aphthae, and the pain they produce [104], or oral rinses containing an aqueous extract of Damask rose, which possesses anti-inflammatory and anti-nociceptive properties.[105]

In a recent single blind clinical therapeutic trial, sesame oil was proved to be effective owing to its anti-inflammatory and anti-oxidant effects, in addition to its analgesic and wound healing properties.[106]

Table 5. Oral Clinical Manifestation index

Type	Scoring
Minor ulcer	1
Herpetiform	2
Major ulcer	3
Number of ulcers/ attack	
1-3	1
4-6	2
7-9	3
9-12	4
More than 12	5
Duration of the attack	
1-4 day	1
5-8 days	2
9-12 days	3
More than 12 days	4
Frequency (attack/date)	
0-2 weeks	5
3-4 weeks	4
5-6 weeks	3
7-8 weeks	2
More than 8 weeks	1
Associated symptoms	
Uncomfortable	1
Painful, but not interfere with eating or swallowing	2
Interfere with solid feeding	3
Interfere with liquid eating	4

Systemic therapy

Colchicine 0.6 mg two or three times daily, is an efficient preventive treatment of severe ROA. In a large open study of Fontes et al, colchicine produced clear improvement in 63% of cases over a period of 3 months. 22% of the patients were free of disease, while 41% had at least a 50% reduction in number and duration of aphthous ulcers [107] , the aphthous ulcers frequently recurred when the treatment was stopped. Up to 45% of patients experienced gastrointestinal side effect.[108]

Thalidomide in dose ranging from 100-300 mg daily is an effective treatment of severe ROA, used for patients with HIV disease but caution regarding teratogenicity and neurotoxicity is necessary[80] , when it is discontinued, recurrences may develop rapidly.[109]

Systemic corticosteroids are usually used in patients with acute severe ROA outbreaks [110], oral prednisone has been used at a starting dose of 25 mg/day, followed by stepwise dose reduction, during two months, with disappearance of the pain and re-epithelization of the lesions in the first month of therapy.[111]

The drug can produce long-term adverse effects; as a result, its efficacy has been compared with that of other drugs, in search of an alternative treatment. In this context, Femiano et al. compared the efficacy of prednisone prescribed at a dose of 25 mg/day via the oral route during 15 days, 12.5 mg/day during 15 days, 6.25 mg/day during 15 days, and then 6.25 mg on alternate days during 15 days, in comparison with montelukast (a leukotriene receptor antagonist used as antiasthma drug) 10 mg via the oral route each night, followed by administration on alternate days during the second month. The authors found both treatment modalities to be effective in reducing the number of lesions, affording pain relief and accelerating healing of the ulcers. As regards adverse effects, montelukast was found to be safer, and therefore should be taken into account as an option when systemic corticosteroids are contraindicated.[112]

In another comparative study, pakfetrat et al. compared prednisolone 5 mg/day versus colchicine 0.5 mg/day. Both treatments were seen to be equally effective and significantly reduced the lesion outbreaks, though colchicine produced more side effects. Thus, 5mg/day of prednisolone seems to be a better option in reducing the signs and symptoms of the disease.[113]

Dapsone has anti-inflammatory effect by inhibit the chemotactic activity of neutrophils. In double-blind cross over study of 20 patients, Sharquie et al, reported significant reductions in the number, duration and frequency of oral aphthous ulcer in patients treated with dapsone 100mg one daily for three months, hemolytic anemia and methemoglobinemia are the main side effect but with low frequency which may limit their use.[67]

In an Iraqi study, Oral Zinc sulfate has been investigated as a possible treatment for ROA at a dose of 150 mg twice daily, compared with dapsone at a dose of 50 mg twice daily, assessment of each patient was carried out by the Oral Clinical Manifestation Index and diameter of ulcer at day 0, day 4, and at the second, fourth, sixth, eighth, tenth and twelfth weeks, Both treatments found to have significant therapeutic and prophylactic effects in controlling ROA, however, zinc sulfate had much more rapid and sustained action.[114]

BCG vaccine had been used as immunomodulator in patients with ROA, it has an effective therapeutic and prophylactic action.[115]

Calculated by Kruskal-Wallis test. Model-1assesses the statistical significance of differences observed between the 4 groups (before treatment, 1, 2 and 3 months of treatment). Model 2 assesses the statistical significance of differences between the three treatment groups (1, 2 and 3 months after treatment).

Oral Levamisole also have been used in treatment of ROA through its immunomodulatory effect and showed controlling effect on the

incidence or recurrence of ROA, there is also significant improvement in clinical symptoms and normalization of the decreased CD4+/CD8+ ratio in RAS patients after levamisole Treatment.[116]

An Iraqi study, showed that oral Isotretinoinin a dose of 20 mg once daily after meal for three months was an effective therapeutic and prophylactic drug in ROA, but unfortunately this drug has many unwanted side effects, the mechanism of action of isotretinoin in ROA is difficult to explained but it might work through its multiple actions like increase differentiation of epithelial cell, anti-inflammatory effect, immunomodulator effect, indirect anti-bacterial effect, inhibition of Toll-like receptor 2 (TLR2) and antiestrogenic effect.[117]

Most recently, oral acitretin 25mg once daily for three months showed to be effective therapeutic and prophylactic drug in ROA, but unfortunately this drug has many unwanted side effects.[79]

Oral clofazimine is an antimicrobial used for the treatment of leprosy in combination with other drugs such as rifampicin and dapsone. When administered at a dose of 100 mg/day during 6 months, the drug was found to avoid the appearance of new lesions during the mentioned treatment period.[109]

Oral Rebamipide 300 mg/day useful in the treatment and prevention of ROA, with no significant adverse effect, the mechanism of action in ROA is by replacement of lost tissue by increasing the expression of epidermal growth factor (EGF) and EGF receptor, these EGF causes angiogenesis, increased production of granulation tissue and epithelization of ulcer, it's also act by preservation of existing cells by increase mucosal blood flow through enhance nitric oxide synthase activity, decrease in expression of neutrophils adhesion molecules (CD11b/CD18), inhibition of secretion ofTNF-α by inhibiting the synthesis of inflammatory E-selectin and has free radical scavenging effect on reactive oxygen species.[62]

TNF-α inhibitors are an effective and safe treatment option for patients with severe complex aphthosis who do not respond sufficiently to standard therapy.[118]

Multiple drug therapies of ROA is also encouraged to decrease the dose of these agents and minimize their side and adverse effects like combination of oral zinc sulfate with dapsone or isotertinoin.

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