**Management of Skin, Mucosa and Joint Involvement of Behçet’s Syndrome: A Systematic Review for Update of the EULAR Recommendations for the Management of Behçet’s Syndrome**

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This paper is dedicated to the memory of Ignazio Olivieri.

**Abstract**

**Objectives:** The aim of this systematic review was to inform the update of European League Against Rheumatism (EULAR) Recommendations for the management of Behçet’s syndrome (BS), on the evidence for the treatment of skin, mucosa and joint involvement of BS.

**Methods:** A systematic literature search, data extraction, statistical analyses and assessment of the quality of evidence were performed according to a pre-specified protocol using the PRISMA guidelines. Studies that assessed the efficacy of an intervention in comparison to an active comparator or placebo for oral ulcers, genital ulcers, papulopustular lesions, nodular lesions or arthritis were included. Where possible, risk ratios were calculated for binary outcomes and mean difference for continuous outcomes.

**Results:** Among the 3,927 references that were screened, 37 were included in the analyses. Twenty-seven of these assessed mucocutaneous and 17 assessed joint involvement.  Twenty-one of these studies were randomised controlled trials (RCTs). RCTs with colchicine, azathioprine, interferon-alpha, thalidomide, etanercept and apremilast showed beneficial results with some differences according to lesion type and gender. These agents were generally well tolerated with few adverse events causing withdrawal from the study.

**Conclusions:**   RCTs comprised more than a half (21/37, 57%) of the sources included in the evidence synthesis related to skin, mucosa and joint involvement applicable for the EULAR Recommendations for the management of BS. Differences in the outcome measures that were used across the included studies often made it difficult to combine and compare the results.

**Keywords:** Behçet’s disease, treatment, anti-TNF, systematic review

**1.Introduction**

Behçet’s syndrome (BS) is a primary systemic vasculitis that can involve arteries of all sizes as well as veins [[1](#_ENREF_1)]. The clinical hallmarks of BS that occur in almost all of the patients are mucocutaneous manifestations which include oral apthous ulcers, genital ulcers, papulopustular lesions and erythema nodosum. Other manifestations of BS include arthritis, eye, central nervous system, gastrointestinal and vascular involvement that can cause significant morbidity and mortality [[2](#_ENREF_2)]. Mucocutaneous and articular manifestations typically have a relapsing and remitting, self-limited course. Although these are not life threatening manifestations they can have an important (negative) impact on quality of life [[3](#_ENREF_3)]. The treatment goals are reducing the inflammatory process, improving quality of life and preventing relapses.

The 2008 EULAR Recommendations for the management of Behçet’s disease, now termed BS for reasons explained in the Recommendations manuscript, are updated under the auspices of the EULAR Standing Committe for Clinical Affairs (ESCCA) [[4](#_ENREF_4)]. The aim of this systematic review was to provide the evidence synthesis needed to inform the task force for updating the Recommendations, about the evidence for the treatment of skin, mucosa and joint involvement of BS. Major organ involvement is addressed in a separate systematic review. The scope of this work was to expand knowledge on agents already present in the previous review and on newer biological and non-biological agents available so far.

**2.Methods**

The systematic literature search, data extraction and statistical analyses were performed according to a pre-specified protocol according to the principles stated in the PRISMA guidelines [[5](#_ENREF_5)]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42015027033.

**2.1 Search strategy**

Specific research questions were identified through a Delphi process among the task force members and reformulated according to the PICO format (Patients, Interventions, Comparison and Outcomes) [[6](#_ENREF_6)]. The research questions, keywords, databases that were searched, details of study selection and data extraction are provided in the online supplement.

**2.2 Data analysis**

We calculated the mean difference (MD) with 95% confidence interval (CI) for continuous outcomes [[7](#_ENREF_7)] and the risk ratio (RR) with 95% CI for dichotomous outcomes [[8](#_ENREF_8)]. When the MD equals zero, this means that there is no difference between the treatment groups. When the mean difference is greater than 0 and the 95% CI does not contain 0, this indicates that the “Intervention is better than the Comparator”. When the risk ratio equals 1, this means that there is no difference in the probability of an outcome occurring across the treatment groups. When RR is greater than 1 and the 95% CI does not include the null value (RR=1), this indicates that the “Intervention is better than the Comparator”. The assessment of risk of bias in included studies was done using the Cochrane Collaboration’s Risk of Bias Tool.

**3.Results**

The search identified 3,927 potentially eligible articles; 395 were selected for full-text review and finally 21 randomised controlled trials (RCTs) and 16 observational studies were included. Figure describes the study selection process and Table 1 describes the characteristics of the eligible RCTs. The quality assessment and risk of bias assessment of these RCTs are provided in the online supplement (Figure 1 and 2). The results of the systematic review are sorted by type of clinical manifestation.

**3.1. Oral ulcers**

**3.1.1. Systemic treatment**

Among the 17 RCTs that reported on outcomes assessing the response of oral ulcers to different drugs, 12 evaluated systemic treatment modalities (Table 2). Three RCTs assessed the efficacy of colchicine in managing oral ulcers [[9-11](#_ENREF_9)]. The first study was a double-blind, placebo controlled study involving 28 patients. Colchicine 1.5 mg/day used for 6 months was ineffective for oral ulcers (RR 0.75, 95%CI 0.48 to 1.17). The second study was a 2-year, double-blind, placebo controlled study conducted among a larger cohort of BS patients and the results of treatment with colchicine (1-2 mg/day, adjusted according to body weight) were separately evaluated for men and women. Colchicine did not statistically significantly improve the number of oral ulcers in women (MD -5.73, 95%CI -12.6 to 1.16 ulcers) or men (MD 0.80, 95%CI -7.83 to 9.47 ulcers). The third study was a randomised, placebo controlled, double-blind, crossover trial conducted among 169 patients. The primary endpoint was disease activity evaluated using the Iranian Behçet’s Disease Dynamic Activity Measure (IBDDAM) score. There was a trend for improvement in mean IBDDAM score for oral ulcers in the colchicine group compared to placebo (MD -0.55, 95%CI -0.99 to 0.10). Colchicine was generally well tolerated. Only one patient had to stop treatment due to nausea and vomiting in one of the RCTs.

There was one double-blind, placebo-controlled study with azathioprine (2.5 mg/kg/day) that involved only men with and without eye disease [[12](#_ENREF_12)]. After 24 months the number of patients with active oral ulcers was lower in the azathioprine group (RR 0.34, 95%CI 0.12 to 0.99). There were no serious adverse events.

One RCT evaluated the efficacy of interferon-alpha-2a (6x106 IU 3 times per week) compared to placebo for the treatment of mucocutaneous manifestations [[13](#_ENREF_13)]. Complete remission was obtained in 2 of 23 patients in the interferon-alpha-2a group and in none of the 21 patients in the placebo group (RR 4.58, 95%CI 0.23 to 90.3). No patients were withdrawn due to toxicity.

The only RCT with a tumor necrosis factor alpha inhibitor (TNFi) was the 4 week, double-blind, placebo-controlled trial with etanercept (25 mg twice a week) that involved 40 men without major organ involvement [[14](#_ENREF_14)]. Complete remission of oral ulcers was achieved in 9 of 20 patients (45%) in the etanercept arm and in 1 of 20 patients (5%) in the placebo arm (RR 9, 95%CI 1.25 to 64.6). One patient in the etanercept arm discontinued the study because of diarrhoea.

In a 24 week, double-blind, placebo-controlled trial, 96 men with BS were randomised to receive thalidomide (100 mg/day or 300 mg/day) or placebo [[15](#_ENREF_15)]. Remission of oral and genital ulcers during 24 weeks was achieved with the dose of 100 mg/day at and between visits (RR 5, 95%CI: 0.25 to 100) and at visits only (RR 21, 95%CI 1.28 to 343). Four patients were withdrawn due to toxicity (3 for severe sedation and 1 for polyneuropathy).

Rebamipide (300 mg/day) showed a trend for being more effective compared to placebo for improving oral ulcers at 6 months (RR 1.85, 95%CI 0.81 to 4.21) in a RCT [[16](#_ENREF_16)]. No serious adverse events were reported.

In a 3-month, double-blind, placebo-controlled, cross-over trial dapsone (100 mg/day) provided a significant decrease in the number (MD -2.70, 95%CI -3.75 to -1.65 ulcers) and frequency of oral ulcers (MD -1.0, 95%CI -1.72 to -0.27 ulcers per month) [[17](#_ENREF_17)]. No patients were withdrawn due to serious adverse events.

In the only RCT with a corticosteroid (40 mg methylprednisolone acetate i.m. every 3 weeks) no beneficial effect on reducing the number of oral ulcers was obtained (MD 0, 95%CI -0.46 to 0.46 ulcers during 27 weeks) [[18](#_ENREF_18)].

There was one RCT with apremilast (30 mg BID) in 111 BS patients without major organ involvement [[19](#_ENREF_19)]. Apremilast was effective in reducing the number (MD -1.60, 95%CI -2.33 to 0.86 ulcers) and pain of oral ulcers (MD -28.7, 95%CI -39.3 to -18 mm VAS) at week 12. Complete remission rate of oral ulcers was also higher with apremilast (RR 2.48, 95%CI 1.59 to 3.88). Two serious adverse events, 1 diplegia and 1 anal fissure and hemorrhoids were observed in patients receiving apremilast.

Benzathine penicillin showed a trend for reducing the frequency (MD -0.29, 95%CI -0.86 to 0.26 ulcer), and duration (MD -0.20, 95%CI -1.29 to 0.89 days) of oral ulcers [[20](#_ENREF_20)].

**3.1.2. Topical treatment**

There were 5 RCTs evaluating topical treatment. Topical sucralfate applied 4 times a day for 12 weeks was not effective in reducing the frequency of oral ulcers (MD -0.80, 95%CI -2.12 to 0.52 ulcers) [[21](#_ENREF_21)]. Topical interferon-alpha-2c hydrogel (1x106 U/g) applied 3 times a day for 24 weeks was also not effective in the treatment of oral ulcers [[22](#_ENREF_22)]. In the other RCT evaluating topical interferon-alpha at a dose of 1000 IU/day and 2000 IU/day for oral ulcers, neither of the two compounds were effective in reducing the total ulcer burden [[23](#_ENREF_23)]. Phenytoin syrup was more effective than triamcinolone acetonide ointment for oral ulcers [[24](#_ENREF_24)]. The last RCT with topical cyclosporine-A failed to show an effect on the number, size and healing time of oral ulcers [[25](#_ENREF_25)].

**3.1.3. Observational studies**

Observational studies with mycophenolate mofetil, azithromycin and anakinra showed response in some of the patients whereas tocilizumab caused a paradoxic increase in mucocutaneous lesion as summarized in the online supplement [[26-33](#_ENREF_26)].

**3.2. Genital ulcers**

**3.2.1. Systemic treatment**

Among the 3 RCTs with colchicine (Table 3), the drug was effective in reducing the number of genital ulcers only in one study and only among women (MD -2.50, 95%CI -4.24 to -0.75 ulcers) [[10](#_ENREF_10)]. Azathioprine was effective in reducing the frequency of genital ulcers after 2 years of treatment (RR 0.08, 95%CI 0.01 to 0.63 ulcers) [[12](#_ENREF_12)]. Benzathine penicillin was also effective in reducing the frequency (MD -0.30, 95%CI -0.53 to -0.07 ulcers) [[20](#_ENREF_20)]. There was a trend for inducing remission of genital ulcers with etanercept compared to placebo (RR 0.82, 95%CI 0.59 to 1.16) [[14](#_ENREF_14)]. In one RCT dapsone was effective in reducing the number of genital ulcers (MD -0.50, 95%CI -1.02 to -0.03 ulcers) [[17](#_ENREF_17)]. No improvement in genital ulcers was observed with methylprednisolone acetate 40 mg every 3 weeks for 27 weeks [[18](#_ENREF_18)]. In the apremilast trial all of the 10 patients with genital ulcers in the apremilast group were free of genital ulcers at week 12 compared to 3 of 6 patients in the placebo group (RR 2, 95%CI 0.90 to 4.45) [[19](#_ENREF_19)].

**3.2.2. Topical treatment**

Sucralfate suspension applied topically 4 times a day for 3 months did not significantly reduce the healing time (MD -3.92, 95%CI -9.02 to 1.18 days), or frequency of genital ulcers (MD 0.02, 95%CI -0.63 to 0.67 ulcers) [[21](#_ENREF_21)]. In one RCT pimecrolimus cream was effective in shortening the healing time of genital ulcers (MD -10, 95%CI -14.68 to -5.32 days) [[34](#_ENREF_34)]. However in the other RCT, pimecrolimus was beneficial for shortening the duration of pain but not the healing time of genital ulcers [[35](#_ENREF_35)].

**3.3. Skin lesions**

There was a trend for decrease in the number of nodular lesions only among women (MD -4.60, 95%CI -10 to 1.20 lesions) in one of the colchicine trials [[10](#_ENREF_10)] and there was a significant decrease with colchicine compared to placebo among the whole group (MD -0.35 95%CI -0.57 to -0.12 lesions) in the other colchicine trial (Table 4) [[11](#_ENREF_11)]. There were significantly more patients with remission in erythema nodosum at week 4 in the etanercept group compared to placebo (RR 3.40, 95%CI 1.56 to 7.43) [[14](#_ENREF_14)]. Methylprednisolone acetate (40 mg every 3 weeks) decreased the number of nodular lesions compared to placebo (MD -0.20, 95%CI: -0.37 to -0.02 lesions) [[18](#_ENREF_18)]. The number of nodular lesions increased during the first 2 months of thalidomide use compared to placebo [[15](#_ENREF_15)]. The authors considered that these nodular lesions may have been superficial thrombophlebitis lesions, which are difficult to differentiate from erythema nodosum clinically. Benzathine penicillin was effective in reducing the frequency (MD -0.0, 95%CI -0.49 to -0.30 lesions), duration (MD -1.00, 95%CI -1.55 to -0.44 days) and severity (MD -0.10, 95%CI -0.18 to -0.01) but not the number (MD -0.10, 95%CI -0.51 to 0.31 lesions) of nodular lesions [[20](#_ENREF_20)].

None of the systemic treatment modalities were proven to be effective for papulopustular lesions in the RCTs with colchicine [[9-11](#_ENREF_9)], azathioprine [[12](#_ENREF_12)], etanercept [[14](#_ENREF_14)] or depot corticosteroid [[18](#_ENREF_18)].

**3.4. Arthritis**

Nine RCTs reported on the efficacy of 7 different agents in managing arthritis (Table 5). The first study with colchicine reported no difference from placebo, but this may have been due to the small sample size (5 patients in each arm). There were significantly more patients with complete response of arthritis in one of the colchicine trials at month 24 among both men (RR 1.53, 95%CI 1.16 to 2.02) and women (RR 1.47, 95%CI 1.11 to 1.97) [[10](#_ENREF_10)]. There was a trend for improvement in the mean IBDDAM joint score at week 16 in the third colchicine trial (MD -0.21, 95%CI -0.49 to 0.07) **.** The RCT with azathioprine also showed a trend for preventing new arthritis attacks in the azathioprine group (RR 0.13, 95%CI 0.02 to 1.00) [[12](#_ENREF_12)]. Benzathine penicillin showed efficacy in reducing the mean number of arthritis attacks during 24 months (MD -0.60, 95%CI -0.92 to -0.28 attacks), and in preventing new attacks among patients with no prior history of arthritis (RR 0.16, 95%CI 0.02 to 1.17) [[36](#_ENREF_36)]. Etanercept did not provide a statistically significant difference from placebo in the number of patients with complete response of arthritis (RR 1.06, 95%CI 0.88 to 1.26) and the number of swollen joints (MD -0.10, 95%CI -0.43 to 0.23 joints) [[14](#_ENREF_14)]. However, in this 4-week trial there was a high response rate in the placebo group, reflecting the relapsing and remitting nature of arthritis in BS. Intramuscular methylprednisolone acetate 40 mg every 3 weeks did not decrease the mean number of arthritis attacks during 27 weeks (MD: 0, 95%CI -0.15 to 0.15 attacks) [[18](#_ENREF_18)]. Thalidomide 100 mg/day showed no improvement in the number of patients with arthritis (RR 1.25, 95%CI 0.37 to 4.23) and in the number of arthritis episodes during 24 weeks (RR 0.64, 95%CI 0.28 to 1.43) [[15](#_ENREF_15)]. Thalidomide 300 mg/day was also ineffective for both outcomes (RR 0.52, 95%CI 0.10 to 2.62 and RR 0.38, 95%CI 0.13 to 1.05, respectively) [[15](#_ENREF_15)]. In the only RCT with a non-steroidal anti-inflammatory drug, azapropazone 900 mg/day was not effective in reducing the number of patients with persistence of arthritis (RR 1.29, 95%CI 0.74 to 2.25), number of patients with new arthritis attacks (RR 0.69, 95%CI 0.28 to 1.69), and mean duration of arthritis attacks (MD: 2.90, 95%CI -1.11 to 6.91 days) [[37](#_ENREF_37)].

**3.4.1. Observational studies**

Interferon-alpha was beneficial for the treatment of arthritis in 4 observational studies. Three of these reported complete response in all of 11, 24 and 8 patients respectively and one showed a significant decrease in the mean duration and the frequency of arthritis in 9 patients as explained in more detail in the online supplement [[38-41](#_ENREF_38)] . Four studies reported favourable results with infliximab for joint involvement. Among them, the indication for infliximab was uveitis in 2, gastrointestinal involvement in 1 and arthritis in 1 study [[42-45](#_ENREF_42)]. Infliximab provided complete response in 30 of 32 patients (94%). Improvement in arthritis was observed in 6 of 10 patients treated with adalimumab [[45](#_ENREF_45)].

**4. Discussion**

Several immunomodulatory and immunosuppressive agents have shown beneficial results in decreasing the frequency of mucocutaneous lesions and arthritis episodes. Around one half of patients with BS have one or more type of major organ involvement such as eye, vascular, nervous system and gastrointestinal involvement in addition to skin, mucosa and joint lesions. In such patients the systemic immunosuppressives that are used for major organ involvement are usually enough to prevent mucocutaneous and joint lesions and topical agents may be used for shortening the duration and decreasing the pain of occasional lesions.

In contrast to major organ involvement of BS, skin, mucosa and joint lesions do not cause damage and are not organ or life threatening apart from rare instances of major oral/pharyngeal ulcerations. However they cause pain and can be disabling due to difficulty in performing daily activities such as eating, talking, and moving. Thus, when treating patients with only skin, mucosa and joint involvement, the major concern is to improve the quality of life without causing harm. Few serious adverse events were reported in the RCTs included in this review. However some of these studies had a short duration and the frequency of adverse events may increase with long term use. Moreover some of the therapeutic modalities may cause an impairment in quality of life without causing serious adverse events. A good example to this is interferon-alpha that causes flu-like symptoms in the majority of patients and depression in about one fourth [[46](#_ENREF_46)]. Trials that assess the overall effect of treatment modalities on patient important outcomes are necessary to help making treatment decisions for mucocutaneous and joint involvement of BS.

The main limitation of this systematic review was the heterogeneity in the outcome measures that were used across the included studies. This made it impossible to bring together the results of trials in a meta-analysis, which would especially be desirable for evaluating the efficacy of colchicine for oral ulcers where conflicting results were reported in RCTs. Moreover, no head-to-head trials directly comparing the efficacy of treatment modalities were available. The lack of standard outcome measures made it very difficult to make even an indirect comparison of the efficacy of different agents.

In conclusion, this systematic review formed the basis for the recommendations related to skin, mucosa and joint involvement in the updated EULAR Recommendations for the management of BS. Randomised controlled trials comprised slightly more than half (21/37, 57%) of the sources informing these Recommendations.

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**Figure legends:**

**Table 1.** Characteristics of RCTs for mucocutaneous and joint involvement of Behçet’s syndrome

**Table 2**. Efficacy of interventions for oral ulcers

**Table 3.** Efficacy of interventions for genital ulcers

**Table 4.** Efficacy of interventions for skin lesions

**Table 5.** Efficacy of interventions for arthritis

**Figure.** Flowchart of study selection

\*Some trials assessed more than one type of involvement.

 Obs: observational study