**Management of Major Organ Involvement of Behçet’s Syndrome: A Systematic Review for Update of the EULAR Recommendations**

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This paper is dedicated to the memory of Ignazio Olivieri.

**ABSTRACT**

**Objectives:** To assess the efficacy and safety of treatment modalities for major organ involvement of Behçet’s syndrome (BS), in order to inform the update of the European League Against Rheumatism (EULAR) Recommendations for the Management of BS.

**Methods:** A systematic literature review of all randomised controlled trials (RCTs), controlled clinical trials, or open label trials assessing eye, vascular, nervous system or gastrointestinal system involvement of BS was performed. If controlled trials were not available for answering a specific research question, uncontrolled studies or case series were also included.

**Results:** We reviewed the titles and abstracts of 3927 references and 161 studies met our inclusion criteria. There were only 9 RCTs. Observational studies with interferon-alpha and monoclonal anti-TNF antibodies showed beneficial results for refractory uveitis. Meta-analysis of case control studies showed that immunosuppressives decreased the recurrence rate of deep vein thrombosis significantly whereas anticoagulants did not. Cyclophosphamide and high dose glucocorticoids decreased mortality in pulmonary arterial aneurysms and postoperative complications in peripheral artery aneurysms. Beneficial results for gastrointestinal involvement were obtained with 5-ASA derivatives and azathioprine as first line treatment and with thalidomide and/or monoclonal anti-TNF antibodies in refractory cases. Observational studies for nervous system involvement showed improved outcome with immunosuppressives and glucocorticoids. Meta-analysis of case-control studies showed an increased risk of developing nervous system involvement with cyclosporine-A.

**Conclusion:** The majority of studies related to major organ involvement that informed the updated EULAR recommendations for the management of BS were observational studies.

**Keywords:** Behçet’s syndrome, treatment, eye involvement, uveitis, vascular involvement, nervous system involvement, gastrointestinal involvement

**INTRODUCTION**

Behçet’s syndrome (BS) is a multisystem vasculitis that has a relapsing and remitting course. The main goal of management is to prevent relapses and to suppress inflammation rapidly for major organ involvement that may cause damage and even be fatal.

Substantial amount of new data were published on the management of BS, especially with biologics over the last years. This led to the update project of the EULAR Recommendations for the management of Behçet’s disease, now termed BS as explained in the Recommendations manuscript [1]. This article reports the results of the systematic review (SR) and meta-analyses when possible, that formed the base for updating the Recommendations on major organ involvement including eye, vascular, nervous system and gastrointestinal involvement.

**METHODS**

The protocol for this SR was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42015027033. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [2]. The electronic databases that were searched, the keyword combinations that were used, eligibility criteria, study selection and data collection process are provided in supplementary data, section Methods of Systematic Literature Review, available at *Rheumatology* online.

Risk of bias (RoB) was assessed using the Cochrane RoB assessment tool [3] for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for cohort and case–control studies [4].

**Data analysis**

A meta-analysis was performed whenever more than one study was available for a specific PICO (Patients, Interventions, Comparison and Outcomes) question. A random effects model was applied to pool overall effect estimate by using Review Manager 5.3. For continuous outcomes, we summarized data using the mean difference (MD) with 95% confidence interval (CI) [5]. For dichotomous outcomes, we presented the risk ratio (RR) and its 95% CI.[6] A 2-sided p value 0.05 was considered as the threshold for statistical significance.

**RESULTS**

The initial electronic database search yielded 3927 articles and 161 studies met the inclusion criteria (Figure 1). Study characteristics of the 9 RCTs are summarized in Table-1 and the main outcomes are summarized in Table-2. The quality assessment and risk of bias assessment of these RCTs are provided in supplementary data, section Treatment for eye involvement, available at *Rheumatology* online (supplementary Figure S1 and S2)

**Eye involvement**

*Non-biologic agents*

Among the 83 studies that reported on outcomes assessing eye involvement, 9 were RCTs. Azathioprine (2.5 mg/kg/day) was effective in decreasing the number of patients with hypopyon uveitis (RR 0.06, 95% CI 0.01 to 0.43) and the development of new eye disease (RR 0.14, 95% CI 0.02 to 0.93) [7]. None of the patients in the azathioprine group experienced serious adverse events whereas one patient died due to ruptured pulmonary artery aneurysm in the placebo group.

Cyclosporine-A was studied in 3 RCTs ( see supplementary data, section Treatment for eye involvement, available at *Rheumatology* online) [8-10]. Cyclosporine-A decreased the frequency (RR 2.47, 95% CI 1.68 to 3.64) [8] and severity of ocular attacks (RR 2.11, 95% CI 1.44 to 3.10) [8]. There was also a trend for a decrease in worsening of ocular condition with cyclosporine-A (RR 0.25, 95% CI 0.06 to 1.02) [10]. Visual acuity at month 6 improved significantly more in the cyclosporin-A group (MD 2.99, 95% CI 0.58 to 5.39 lines on Snellen chart) [9]. Renal dysfunction was more frequent in the cyclosporine-A group (RR 5.50, 95% CI 1.29 to 23.45), but withdrawal of cyclosporine-A was required in only 1 patient [8].

In a small observational study methotrexate improved visual acuity in 68% of patients [11]. However the same group reported that this rate decreased to 46.5% in long term follow-up [12].

*Biologic agents*

The only prospective head to head RCT with a biologic agent was the single-blind INCYTOB study which compared interferon-alpha 3 to 9 MU 3 times per week with cyclosporine-A 3-5 mg/kg ( see supplementary data, section Treatment for eye involvement, available at *Rheumatology* online) [13]. Interferon-alpha was superior to cyclosporine-A in the number of patients who achieved ocular remission (RR 1.44, 95% CI 1.01 to 2.08), visual acuity and posterior uveitis score.

The only other controlled study with a biologic was a non-randomised observational study that compared infliximab (5-10 mg/kg) with cyclosporine-A (3-5 mg/kg) [14]. The number of ocular attacks was significantly lower (MD -0.80, 95% CI -1.50 to -0.91 attacks during 6 months) and the number of patients achieving complete remission was significantly higher in the infliximab arm (RR 1.83, 95% CI 1.07 to 3.12). There were no differences between infliximab and cyclosporine-A in improvement of visual acuity (RR 1.05, 95% CI 0.94 to 1.17).

There were no studies comparing infliximab and interferon-alpha. However several open label uncontrolled studies and retrospective case series had studied the efficacy of both agents ( see supplementary data, section Treatment for eye involvement, available at *Rheumatology* online) [15-51]. Remission rates were similar for infliximab and interferon-alpha, but the sustained remission rate was higher with interferon-alpha (71%) compared to infliximab (43%) among the 7 studies with interferon-alpha [20, 26, 27, 31, 33, 36, 40] and 6 studies with infliximab [25, 29, 32, 47, 48, 50] that addressed this question (Table 3). The success rate for improving visual acuity was 76% for infliximab [22-24, 43] and 46% for interferon-alpha [20, 27, 35, 40]. However, it should be noted that there was heterogeneity in the reporting of visual acuity. Most of the infliximab studies reported the patient as the unit of measure whereas most of the interferon-alpha studies reported the involved eye as the unit of measure. Corticosteroid cessation rate was higher in interferon-alpha group (66%)[20, 26, 31, 40] when compared to infliximab (33%) [29, 42, 49].

A prospective observational study showed that infliximab is a rapidly acting agent when compared to methylprednisolone in suppressing ocular inflammation [39]. The effect of infliximab started within the first 24 hours for suppressing ocular inflammation, as well as in decreasing anterior chamber cells, clearing retinal vasculitis and resolution of retinitis and cystoid macular edema [17, 23, 32, 39]. There were no studies that specifically explored the time of onset of action with interferon-alpha but three open studies indicated that retinal infiltrates resolved within 2 weeks and infiltration of anterior chamber, vasculitis, and macular edema resolved within 4 weeks with interferon-alpha treatment [15, 20, 27].

Most frequent adverse events were infections including tuberculosis with infliximab and flu-like symptoms, depression, leukopenia, thrombocytopenia, alopecia and transaminase elevations with interferon-alpha.

Adalimumab was evaluated in patients with non-infectious uveitis in a RCT [52]. This study included BS patients but their results were not reported separately and were not provided by the study sponsor with the explanation that the study was not powered to detect the effect in uveitis of differing etiologies and it would be difficult and inaccurate to make any inferences from these data. Based on few case series and reports adalimumab seems to improve visual acuity [51, 53-55].

Pegylated interferon-alpha, secukinumab, daclizumab and gevokizumab did not meet the primary endpoints for uveitis compared to placebo in 4 RCTs (see supplementary data, section Treatment for eye involvement, available at *Rheumatology* online) [56-59].

Rituximab (RTX) in combination with methotrexate and prednisolone was compared with cytotoxic combination group using cyclophosphamide, azathioprine and prednisolone in a single-blind trial in 20 patients [60]. Although there was a significant difference in “Total Adjusted Disease Activity Index” score favoring RTX in the t-test conducted by the authors, when we calculated the RR and MD, the difference was not statistically significant for primary (MD -5.10, 95% CI -21.01 to 10.81) and secondary endpoints (RR, 95% CI; visual acuity 0.67, 0.14 to 3.17; posterior uveitis 0.86, 0.45 to 1.64; retinal vasculitis 1.17, 0.61 to 2.23). In the RTX group, one patient had pneumonia, one patient had herpes zoster and one patient dropped out due to a severe infusion reaction. In cytotoxic combination group, none of the patients experienced severe adverse events.

Tocilizumab was reported in 3 case reports including 4 patients [61-63]. Visual acuity improved in 2 patients, macular edema improved in 2 patients and 1 patient did not benefit from tocilizumab.

Intravitreal triamcinolone treatment which may be used in addition to systemic immunosuppressives in severe patients, was assessed in 5 studies that included 86 patients (96 eyes) [64-68]. Improvement in visual acuity was observed in 54%. However complications were frequent (49%), with cataracts in 36%, increased intraocular pressure in 43% and glaucoma in 9% of the patients.

**Vascular involvement**

*Venous thrombosis*

There were 3 retrospective studies that reported on the efficacy of immunosuppressives and anticoagulants for preventing relapses of deep vein thrombosis in BS patients (see supplementary data, section Treatment for vascular involvement, available at *Rheumatology* online) [69-71]. We pooled these 3 studies to obtain an estimate of the efficacy of immunosuppressives and anticoagulants in preventing relapses. Meta-analysis of these studies showed that immunosuppressives significantly reduced the relapse risk (RR 0.17, 95%CI 0.08 to 0.35) whereas anticoagulants did not (RR 0.75, 95%CI 0.48 to 1.17) (Figure 2). Bleeding occurred in 2.4% and 4.5% of the anticoagulated patients in 2 of these studies [70, 71].

One retrospective study looked at the risk of post-thrombotic syndrome among BS patients who experienced deep vein thrombosis and suggested that not having used anticoagulants in addition to immunosuppressives seem to increase the risk of post-thrombotic syndrome (PTS) (OR 3.8, 95%CI 1.04 to 14.1) [72]. However this finding was not supported by a more recent study that did not report a significant effect of anticoagulation for preventing PTS[73].

*Intracardiac thrombosis*

A small study that compared the use of immunosuppressives together with anticoagulants (n=9) to immunosuppressives alone (n=12) for intracardiac thrombosis showed no difference (RR 1.29, 95% CI 0.91 to 1.82) [74].

*Pulmonary artery aneurysms and thrombosis*

Two retrospective studies evaluated the mortality rate in BS patients with pulmonary artery involvement treated with cyclophosphamide compared to other interventions (surgery or azathioprine and corticosteroids) ( supplementary table S1, available at *Rheumatology* online) [75, 76]. In the first study 6 out of 17 patients in the cyclophosphamide group and all patients (n=5) with other interventions group died (RR 0.35, 95% CI 0.19 to 0.67). In the second study, 1 patient (25%) in the cyclophosphamide group and all patients (n=5) in the other intervention group died (RR 0.25, 95% CI 0.05 to 1.36).

Mortality rate with embolization and open surgery during emergency pulmonary hemorrhage was reported in retrospective series. Three studies including a total of 78 patients reported on emergency embolization in 7 (9%) BS patients with pulmonary hemorrhage and 4 of them died [77-79]. Mortality rate with open surgery was reported in 3 other studies including 79 patients with pulmonary artery aneurysms [75, 76, 79]. Eight (10%) patients had open surgery and 6 of them died within the first month after surgery.



Infliximab was tried in 13 BS patients who were refractory to cyclophosphamide and 11 had a good response [80]. In 4 patients infliximab was stopped due to remission but 2 of them relapsed after cessation. In 2 patients infliximab had to be stopped due to tuberculosis and aspergillosis.

*Peripheral artery aneurysms*

Unlike pulmonary arteries, surgical intervention is usually required for peripheral artery aneurysms. Perioperative use of immunosuppressives with or without corticosteroids is an important issue that was assessed in retrospective studies (see supplementary data, section Treatment for vascular involvement, and supplementary table S1, available at *Rheumatology* online) [78, 81, 82]. Immunosuppressives and corticosteroids decreased postoperative complication rate significantly when compared to no medical treatment (RR, 95% CI; 0.08, 0.01 to 0.55 and 0.30, 0.12 to 0.77 respectively) [78, 82].

The possible types of interventions in such patients are endovascular graft, bypass surgery, ligation and graft interposition. Peripheral arterial ligation was reported in 4 retrospective series [78, 83-85]. Among a total of 20 patients, relapses occurred in 5 patients and death in 1 patient. Bypass was performed in overall 32 patients [78, 83, 85-87]. Relapses occurred in 11 (34%), occlusion in 5 (16%) and death in 6 (14%) patients. Graft interposition was performed in overall 48 patients.[83-85, 87, 88] Fourteen (29%) patients experienced graft occlusion, 13 (27%) patients relapsed and 7 (15%) died.



**Nervous system involvement**

*Parenchymal involvement*

No RCTs were available for the treatment of nervous system involvement in BS. In one retrospective study patients who used cyclophosphamide had a trend for a lower relapse rate compared to azathioprine during the first year (RR 0.62, 95% CI 0.38 to 1.01). However, this difference was not observed at 5th,7th and 10th years (see supplementary data, section section Treatment for neurologic involvement, available at *Rheumatology* online) [89]. In another retrospective study adding cyclophosphamide to corticosteroids did not provide additional benefit to corticosteroids alone [90]. This is interesting since cyclophosphamide is used as first line in other CNS vasculitides.

Case series reported the efficacy of infliximab in the management of patients with parenchymal involvement. In a large published case series, it was shown that in patients with NBS who had ongoing clinical relapses on single or multiple immunosuppressives, a switch to infliximab was beneficial in preventing further relapses and stabilizes disability [91]. It is of interest that in the same center among 74 BS patients without nervous system involvement, who were put on infliximab for either arterial or eye involvement because of failure of other immunosuppressives, none had developed nervous system involvement at the time of last follow-up. The efficacy of infliximab for patients with severe nervous system involvement and resistant to standard immunosuppressive regimens was also shown in another recent case series. Collectedly, 56 out of 60 patients had a good clinical response [37, 51, 91-94]. Furthermore, infliximab showed a corticosteroid sparing effect and a rapid onset of action. Two patients (3.3%) stopped infliximab due to adverse events and in 2 patients serious adverse events were reported. Beneficial results were reported in case reports and case series with interferon-alpha, mycophenolate mofetil, tocilizumab, anakinra and methotrexate ( see supplementary data, section Treatment for neurologic involvement, available at *Rheumatology* online) [95-101].

There were 4 studies that evaluated the risk of developing nervous system involvement among BS patients who use cyclosporine-A ( see supplementary data, section Treatment for neurologic involvement, available at *Rheumatology* online) [102-105]. A meta-analysis of these studies showed that the risk of developing nervous system involvement was significantly higher among BS patients who used cyclosporine-A compared to those who did not (RR 8.26, 95% CI 4.45 to 15.32) (Figure 3).

*Cerebral venous thrombosis*

There were 3 retrospective studies evaluating the efficacy of corticosteroids plus anticoagulants in the treatment of cerebral venous thrombosis [106-108]. Among a total of 80 patients, 74 (92.5%) showed a good response. Bleeding complications were reported in 4 patients (6.4%), but they recovered without sequelae. In a retrospective study involving 36 patients with cerebral venous thrombosis treated with corticosteroids alone, a good response was observed in all [109].

**Gastrointestinal system involvement**

*Non-biologic agents*

Three retrospective studies reported on the efficacy of azathioprine and 5-ASA derivatives in the treatment of gastrointestinal involvement [110-112]. In the first study, the treatment outcome was evaluated in 16 patients with mild gastrointestinal involvement who initially received 5-ASA derivatives (3-4 gr/day) and in 37 patients with active moderate-severe gastrointestinal involvement who initially received azathioprine (2-2.5 mg/kg/day). Ten patients (62.5%) in the 5-ASA group and 24 patients in the azathioprine group (65%) achieved complete clinical and endoscopic remission without relapse during a mean follow-up of 89.3±64.5 months and 68.6±43.6 months, respectively. No withdrawals due to adverse events were reported. In the second study, the cumulative relapse rates at 1, 3, 5 and 10 years among 143 patients who achieved remission with 5-ASA compounds (3-4 gr/day) for at least 6 months were 8.1%, 22.6%, 31.2% and 46.7% respectively. In the third study among 39 patients who achieved remission with first line azathioprine, the cumulative relapse rates were 5.8%, 28.7%, 43.7% and 51.7% at 1, 2, 3 and 5 years respectively.

A systematic review and case series reported on thalidomide use in a total of 19 BS patients with refractory gastrointestinal involvement [113]. Clinical remission was achieved in 84%.

Postoperative corticosteroid use was found to be associated with higher re-operation rates in a retrospective study (HR 2.85 95% CI, 1.21 to 6.75) [114]. Thiopurine decreased post-operative recurrences compared to 5-ASA (RR 0.56 95% CI 0.33 to 0.95), but not the rates of reoperation, readmission, and death [115]. Whether this is associated with thiopurine being prescribed to more severe patients was not assessed.

*Biologic agents*

Five case series reported on the use of infliximab (5 mg/kg at week 0, 2, 6 and then every 6-8 weeks) for gastrointestinal involvement refractory to conventional therapy [113, 116-119]. Among the total of 63 patients treated with infliximab, 34 patients (54%) obtained clinical remission. Safety data was available for 49 patients and 1 had stopped treatment due to an adverse event.

Adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg every other week thereafter) was evaluated in an open-label study in 20 BS patients with active gastrointestinal involvement refractory to corticosteroids and/or standard immunosuppressive therapy [120]. After 24 weeks of treatment clinical and endoscopic improvement was observed in 9 patients (45%) and complete remission in 4 (20%). There were 2 withdrawals due to adverse events.

Etanercept (25 mg twice a week) was compared to conventional treatment (MTX 15 mg/wk or prednisolone) in an open study [121]. Higher clinical remission rate (RR 1.74, 95% CI 1.22 to 2.49) and healing of intestinal ulcers (RR 1.66, 95% CI 1.22 to 2.25) was observed with etanercept. No withdrawals due to toxicity were reported.

**DISCUSSION**

Major new findings of this systematic review compared to the one performed during the previous EULAR Recommendations for BS were increased evidence for the use of biologics and especially TNF inhibitors in patients with all types of major organ involvement refractory to conventional treatment modalities, review of surgical intervention types for arterial aneurysms and the meta-analysis showing that immunosuppressives rather than anticoagulants decreased the recurrence rate of deep vein thrombosis.

Although there are no RCTs comparing interferon-alpha and TNF inhibitors in BS patients with eye involvement, there were 2 studies that compared and showed superiority of these agents to cyclosporine-A. There were several observational studies that assessed these 2 agents for eye involvement. Methodologic differences in studies such as the unit of measure hamper the comparability of these findings. Moreover, the higher corticosteroid cessation rate may be related to the old contention that corticosteroids may decrease the efficacy of interferon-alpha. An important issue that is operative in choosing one of these 2 agents is the difference in the adverse event profile. Increased risk of tuberculosis and other infections with infliximab and difficulty in tolerating interferon-alpha due to flu-like symptoms and depression are the major concerns.

Unfortunately, the 3 recent RCTs with promising biologic agents, pegylated interferon-alpha, secukinumab and gevokizumab failed to meet their primary endpoints. Whether these agents are completely ineffective for BS patients or these disappointing results are related to trial design or the choice of outcomes is not clear.

Anticoagulation for the treatment of venous thrombosis in BS is a controversial issue. Our meta-analysis showed that there was no beneficial effect of adding anticoagulation to immunosuppressives when compared to immunosuppressives alone for preventing relapses. Two retrospective studies assessed whether anticoagulation may decrease post-thrombotic syndrome in BS patients who experienced venous thrombosis and showed conflicting results [72, 73]. Prospective studies are needed to ascertain the role of anticoagulation in preventing venous thrombosis relapses and post-thrombotic syndrome in patients with BS.

CSs are frequently used during the perioperative period in BS patients with the aim of decreasing postoperative complication risk related to pathergy phenomenon induced by surgical intervention. It was previously observed that immunosuppressive and corticosteroid use decreased postoperative complication rate in BS patients undergoing surgery for peripheral artery aneurysms. Surprisingly one retrospective study suggested that CS use may increase recurrence risk in the post-operative period in BS patients with gastrointestinal involvement [114]. We think that this finding may be confounded by indication since those patients who required steroids in the postoperative period were probably those with more severe gastrointestinal involvement.

The main limitation of this systematic review was the rarity of RCTs and the lack of head-to-head trials with biologic agents. Another limitation was the heterogeneity in the methodology of studies including patient selection, unit of measure and the outcomes and outcome measures that were used.

In conclusion, we have updated the evidence on efficacy and safety of pharmacological and surgical treatment modalities for major organ involvement of BS. Majority of the studies were observational studies.

**Key Messages**

* Major organ studies in BS included in the updated EULAR Recommendations were mostly observational.
* Biologic treatments, mostly TNF-inhibitors, have started to gain importance in the treatment of BS.

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**Supplementary data**

**Supplementary data are available at *Rheumatology* online.**

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**Figure legends:**

**Table-1.** Characteristics of Randomised Controlled Trials for Major Organ Involvement in Behçet’s Syndrome

**Table-2.** Efficacy of Randomised Controlled Trials for Eye Involvement in Behçet’s Syndrome

**Table-3.** Comparisons of observational studies of IFN-alpha and IFX in BS uveitis

**Figure-1.** Flow-chart of study selection process

**Figure-2.** Relapse risk of DVT with immunosuppressives and anticoagulants compared to anticoagulants alone (A) Relapse risk of DVT with immunosuppressives and anticoagulants compared to immunosuppressives alone (B)

**Figure-3** Risk of nervous system involvement among BS patients using cyclosporine-A