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IM - REVIEW

Update on the treatment of Behçet's syndrome

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Abstract
Behçet's syndrome (BS) is a complex disease that shows important heterogeneity in clinical findings and physiopathology. Its treatment can be problematic as BS manifestations in different organs may respond differently to the same drug. The cornerstone of therapy for inducing remission is corticosteroids whereas immunomodulatory and immunosuppressive agents such as colchicine, azathioprine, cyclosporine-A, interferon-alpha, and cyclophosphamide are used as steroid-sparing agents and to prevent further relapses. However, a considerable number of patients continue to have mucocutaneous lesions despite therapy, and some patients require more aggressive treatment for refractory major organ involvement. Tumor necrosis factor alpha inhibitors, especially infliximab and adalimumab, are increasingly used for various refractory BS manifestations despite the lack of controlled studies. In this review, we aim to focus on both the traditional and new treatment modalities for BS, with more emphasis on recent data on newer agents.

Keywords Behçet's syndrome · Treatment · Management · TNF inhibitors · Biologic agents

Introduction

Behçet's syndrome (BS) is a multisystem vasculitis with a relapsing and remitting course. When planning management in BS, a multidisciplinary approach is essential due to its multisystem involvement. The main goals of management are to suppress exacerbations rapidly to prevent damage and to prevent further inflammatory attacks. However, BS manifestations and their severity may vary among patients and may change over time in the same patient. Therefore, age, gender, type and severity of organ involvement, disease duration, patients' preferences, and organ specific prognostic factors should be taken into account when considering treatment options. Treatment options may vary from the solo use of topical measures or colchicine for a patient with only mild mucocutaneous lesions to a combination of glucocorticoids and immunosuppressives including biologics for a patient with severe major organ involvement. Immunosuppressive agents are crucial to prevent organ damage and decrease mortality in patients with major organ involvement. On the other hand, they may also be given to patients with refractory mucocutaneous lesions to improve quality of life [1].

In this review, we aimed to focus on both the traditional and new treatment modalities for BS, with more emphasis on recent data on newer agents such as apremilast, golimumab, certolizumab, interleukin (IL)-1 antagonists, tocilizumab, intravenous immunoglobulin (IVIG), ustekinumab, secukinumab, rituximab, and mycophenolate mofetil. We planned this review based on the type of organ involvement with the purpose of facilitating its use in clinical practice.

Mucocutaneous involvement

The majority of the randomized controlled trials (RCTs) that were conducted in BS have aimed to assess the efficacy of drugs on mucocutaneous lesions. However, these trials have been very heterogeneous regarding the patient population, study duration, study design, and especially outcome measures. Most of the studies had a small number of patients and were not powered for a specific mucocutaneous lesion, leading to lower quality of studies. Moreover, the relapsing and remitting course of BS renders disease assessment even more difficult. These factors lead to difficulties in interpretation of the results and comparison of different treatment modalities.

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In 1980, the first double-blind, placebo-controlled trial with colchicine in BS was conducted in our center among 35 patients with only mucocutaneous involvement. This small trial showed beneficial results for only erythema nodosum and arthralgia [2]. In 2001, a second RCT was conducted with colchicine in a large cohort with a study duration of 24 months. This trial also failed to show a beneficial effect on oral ulcers. On the other hand, the number of genital ulcers and erythema nodosum among women and arthritis among both men and women showed greater improvement with colchicine compared to placebo [3]. The third placebo-controlled study with colchicine used Iranian Behçet's Disease Dynamic Activity Measure (IBDDAM) score that evaluates BS symptoms up to 12 months prior to the date of assessment. Baseline IBDDAM scores were calculated dividing by 12 to get mean score per month. Five oral ulcers, one genital ulcer, ten papulopustular lesions, and five erythema nodosum get 1 point in this activity index, making it more reliable for assessing overall disease activity. IBDDAM scores for oral and genital ulcers, papulopustular lesions and erythema nodosum significantly improved after colchicine treatment. A significant difference between colchicine and placebo for oral and genital ulcers was reported [4]. However, when the mean difference (MD) and relative risk (RR) were calculated for these studies during the systematic review for the 2018 update of the EULAR recommendations (Table 1), colchicine did not show any benefit on oral ulcers and papulopustular lesions in all the three studies [5]. Colchicine shows a significant benefit over placebo for erythema nodosum only in Davatchi's study and genital ulcers only in Yurdakul's study and only among women. Despite these conflicting results, colchicine seems to be beneficial in some patients; however, subpopulations of patients who are likely to respond to colchicine cannot yet be defined.

Azathioprine is found to be effective for oral and genital ulcers and arthritis [6]. A number of patients with oral ulcers and genital ulcers at month 24 are significantly lower in the azathioprine arm (RR 0.04, 95% CI 0.12–0.99 for oral ulcers and RR 0.08, 95% CI 0.01–0.63 for genital ulcers). In a 24-week RCT, complete remission rate of oral and genital ulcers during 24 weeks at visits is significantly higher among patients treated with two different doses of thalidomide (RR 21, 95% CI 1.28–343 for 100 mg and RR 19.6, 95% CI 1.19–322 for 300 mg) [7]. A rapid response is observed at week 4 for oral ulcers and at week 8 for genital ulcers. There were more nodular lesions in the thalidomide arm than in the placebo arm, but it is not clear whether these were erythema nodosum or superficial thrombophlebitis lesions. Four patients were withdrawn, due to severe sedation in three and polyneuropathy in one. There were three additional patients who developed polyneuropathy after the trial had ended.

The RCT with interferon-alpha including 50 patients demonstrates a significant decrease in the duration and pain of oral ulcers, and the frequency of genital ulcers and papulopustular lesions during 3 months of treatment [8]. However, the rate of complete remission of oral ulcers is similar among the interferon-alpha and placebo arms (RR 4.58, 95% CI 0.23–90.3). Open-label trials with a small number of patients report conflicting results (Table 2). Regarding adverse events, almost all the patients experienced flu-like

Table 1 The effect sizes of three randomized control studies with colchicine

Author/year	Number of patients	Outcome	Risk ratio (RR) or mean difference (MD)
Aktulga [2], 1980	28	Improvement in OU score at month 6	RR 0.75 (95% CI 0.48 to 1.17)
		Improvement in GU score at month 6	RR 1 (95% CI 0.37 to 2.70)
		Improvement in PP lesions at month 6	RR 0.07 (%95 CI 0.24 to 1.86)
		Improvement in EN at month 6	RR 2 (95% CI: 0.20 to 19.6)
Yurdakul [3], 2001	116	Number of OU during 2 years (women)	MD −5.73 (95% CI −12.6 to 1.16)
		Number of OU during 2 years (men)	MD 0.80 (95% CI −7.83 to 9.47)
		Number of GU during 2 years (women)	MD −2.50 (95% CI −4.24 to −0.75)
		Number of GU during 2 years (men)	MD −1.10 (95% CI −4.10 to 1.90)
		Number of PP during 2 years (women)	MD −1.80 (95% CI −4.15 to 0.55)
		Number of PP during 2 years (men)	MD 2.60 (95% CI −1.6 5 to 6.85)
		Number of EN during 2 years (women)	MD −4.60 (95% CI −10 to 1.20)
		Number of EN during 2 years (men)	MD −1.30 (95% CI −3.70 to 1.12)
Davatchi [4], 2009	169	IBDDAM score for OU at week 16	MD −0.55 (95% CI −0.99 to 0.10)
		IBDDAM score for GU at week 16	MD −0.22 (95% CI −0.4 to 0.003)
		IBDDAM score for PP at week 16	MD −0.06 (95% CI −0.23 to 0.11)
		IBDDAM score for EN at week 16	MD −0.35 (95% CI −0.57 to −0.12)

OU oral ulcer, *GU* genital ulcer, *PP* papulopustular lesion, *EN* erythema nodosum, *IBDDAM* Iranian Behçet's Disease Dynamic Activity Measure

Table 2 The characteristics of open-label studies of interferon-alpha on the efficacy of mucocutaneous lesions

Author	Year	Duration	Dose	Number of patients (W/M)	Outcome
Hamuryudan [9]	1994	16 weeks	5 MU/3 times per week for 6 weeks 5 MU/week for 10 weeks	20 (12/8)	No significant decrease in the mean number of OU, GU and EN
Azizlerli [8]	1996	12 weeks	3 MU/3 times per week in the first week, 6 MU/3 times per week in the second week, 9 MU/3 times per week in for 14 weeks	18 (13/5)	Reduction in pain, healing time or number of lesions and resolution of at least one symptom ($n=7$) Reduction in pain, healing time or number of lesions ($n=9$) No change ($n=2$)
Alpsoy [11]	1994	8 weeks	3 MU/3 times per week gradually increased to 12 MU/3 times per week	14 (8/6)	Reduction in the frequency of OU, GU and PP No decrease in EN
Boyvat [10]	2000	12 weeks	3 MU/every other day in the first week, 6 MU/every other day in the second week, 9 MU/every other day for 10 weeks	20 (9/11)	Reduction in the frequency and pain of OU, size, pain and duration of GU and number and duration of EN No decrease in PP
O'Duffy [12]	1998	24 weeks	3 MU/day	11 (9/2)	Reduction in the number of OA, GU and cutaneous lesions
Georgiou [13]	1998	8 weeks	6 MU/3 times per week	12 (4/8)	Complete remission ($n=9$) Partial remission ($m=2$) No response ($n=1$)

OU oral ulcer, *GU* genital ulcer, *EN* erythema nodosum, *PP* papulopustular lesion, *MU* million unit

symptoms. Leukopenia, alopecia and transient elevation of liver enzymes are some of the commonly reported adverse events [9–14]. Apart from these adverse events, interferon-alpha therapy may lead to psychiatric symptoms as shown in a prospective 12-week study in our center [15]. In 19 BS patients treated with interferon-alpha, depression scales increased significantly compared to 24 patients treated with other agents. Suicidal ideation developed only among patients receiving interferon-alpha.

Among the tumor necrosis factor alpha inhibitors (TNFis), only etanercept was studied in a 4-week RCT and oral ulcers and erythema nodosum are significantly lower in the etanercept arm ($n=20$) than in the placebo arm ($n=20$) [16]. Small sample size, short duration of trial and a high placebo response rate (17/20 for etanercept and 14/20 for placebo) may have led to an underestimation of the treatment effect of etanercept on genital ulcers. One patient was withdrawn due to infectious colitis, and another patient developed gastrointestinal involvement. Although there are no RCTs with other TNFi, several observational studies and case series suggest beneficial results with infliximab and adalimumab, even in patients who are refractory to traditional immunosuppressives [17]. Despite the beneficial results reported with these agents, their potential adverse events limit their use in BS patients with only mucocutaneous lesions.

Apremilast is a phosphodiesterase-4 inhibitor immunomodulatory agent that seems to have a favorable safety profile with good efficacy for oral ulcers. Both the phase 2 and phase 3 studies show significant improvement in the number and pain of oral ulcers, complete response rates, overall disease activity and quality of life in the apremilast group compared to placebo. There is also a trend for improvement in genital ulcers, but there were only a small number of patients with genital ulcers at baseline [18, 19].

The 2018 update of the EULAR recommendations for the management of Behçet's syndrome advises the use of topical measures such as low or moderate oral glucocorticoids for rapid healing of oral and genital ulcers, and trying colchicine as first-line systemic treatment for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer, based on the safety and easy tolerability of colchicine. Topical antibiotics may be preferred for preventing secondary infections in genital ulcers, and oral antibiotics in addition to topical measures may be used for papulopustular lesions, similar to the treatment of acne vulgaris. Drugs such as azathioprine, thalidomide, interferon-alpha, TNFis or apremilast can be used in refractory patients. Lactobacillus lozenges, dapsone and azithromycin have also shown beneficial results in RCTs [1].

Biologic and non-biologic agents with other mechanisms of action such as anakinra, canakinumab, ustekinumab, secukinumab, and mycophenolate mofetil have been tried for mucocutaneous lesions of BS, but controlled evidence is not available for these agents [20].

Based on the proposed role of autoinflammation in BS pathogenesis, different IL-1 blockers have been tried in BS [21]. In 2015, Cantarini et al. reported the first case series of nine refractory BS patients treated with anakinra. All the patients had active mucocutaneous lesions in addition to major organ involvement [22]. Eight of them improved promptly within 1–2 weeks; however, all experienced one or more clinical manifestations during a mean follow-up of 29 weeks. Four had to switch to another agent (one canakinumab, one adalimumab and two cyclophosphamides). The same group evaluated the efficacy and safety of IL-1 antagonists in a multicenter retrospective study [23]. Overall, 41% (11/27) of the patients treated with anakinra could not maintain the therapy. Reasons for discontinuation were adverse events in four patients, inefficacy in three, loss of efficacy in two, and low compliance in two patients. Cumulative treatment survival at 24 months was only 26.3% for anakinra and 40.6% for canakinumab. These findings suggest that anakinra does not seem to be a sustainable treatment for most of the patients.

A prospective open-label study recruited 6 BS patients with mucocutaneous involvement who were refractory to standard therapy [24]. The dose of anakinra had to be increased from 100 mg to 200 mg/day due to inadequate response at month 1 in all the patients. Two patients achieved the primary endpoint defined as no oral ulcers for two consecutive months between 3 and 6 months. Two patients had partial response defined as a decrease in the number of oral and genital ulcers. The remaining two were considered as treatment failures.

Ustekinumab is a humanized monoclonal antibody against IL-12 and IL-23. Mirouse et al. conducted an open-label study and included 14 patients with active oral ulcers who were refractory to colchicine [25]. Seventy percent of the patients had received another immunosuppressive therapy before the inclusion. The primary endpoint of the study was the proportion of patients with complete remission, defined as no oral ulcers, at week 12. The primary endpoint was achieved in nine (64.3%) patients. Three (21.4%) had a partial response and two (14.3%) had no response. After a median follow-up of 7 months, four patients had relapses other than oral ulcers. An open-label study with ustekinumab (STELABEC 1/2) is ongoing for patients with active oral/genital ulcers and for those with eye involvement (ClinicalTrials. gov Identifier: NCT02648581).

Tocilizumab was also tried among BS patients. Up to now, 21 BS patients were reported with conflicting findings regarding its efficacy on mucocutaneous lesions. Of these 21 patients, 4 were treated for refractory mucocutaneous lesions and the indication of tocilizumab was refractory uveitis in 15 patients and parenchymal neurologic involvement in the remaining 2. Among these 21 patients in whom the course of mucocutaneous lesions was reported during tocilizumab therapy, 9 had improvement whereas 12 had no response or even paradoxical exacerbation [26–32].

Golimumab and certolizumab, another two monoclonal anti-TNF antibodies, have been reported in one case series, each. All but two receiving certolizumab were refractory to at least one biologic agent. In the first study with golimumab by Vitale et al., 16/17 patients went into complete remission of the manifestation requiring golimumab [33]. Almost 50% of these patients had mucocutaneous or articular involvement. There were three patients with uveitis and six patients with gastrointestinal involvement. BDCAF significantly decreased at the end of follow-up (mean 18.47 ± 20.8 months). The response was significantly better in patients receiving concomitant immunosuppressive agent than in those receiving golimumab alone. The same group also described their certolizumab experience in patients with different organ involvement [34]. All the patients received certolizumab due to two active BS manifestations. These were mucocutaneous lesions in six, gastrointestinal involvement in five, arthritis in seven, central nervous system involvement in two, and uveitis in five patients. All but two patients had been treated with at least one biologic agent previously. Although 7/13 patients had a good response, the remaining 6 experienced disease exacerbations within a mean duration of 4 months and had to be switched to another biologic drug. Two of these six failed patients had refractory mucocutaneous lesions at baseline; however, the manuscript did not provide which manifestations exacerbated under golimumab therapy.

Secukinumab, an IL-17 inhibitor, was studied in five patients in whom mucocutaneous and joint involvements were refractory to at least one TNF inhibitor [35]. Four patients also had ankylosing spondylitis and one patient psoriatic arthritis. Secukinumab dose was 300 mg in the patient with psoriatic arthritis and 150 mg in the others. The patient with psoriatic arthritis and two-fourth of the patients with ankylosing spondylitis achieved complete remission at month 6. One relapsed patient and the remaining two patients had to increase the dose to 300 mg, resulting in complete remission, partial remission and no response in one patient each.

After the success of mycophenolate mofetil in the field of transplantation, it has also been studied in rheumatologic diseases. It has been found to be non-inferior to CYC in proliferative lupus nephritis [36], and is now recommended as a first-line agent for scleroderma patients with interstitial lung disease [37]. However, it failed to be an alternative to azathioprine in anti-neutrophil cytoplasmic antibody-associated vasculitis [38]. In 2001, Adler et al. evaluated the efficacy of mycophenolate mofetil on mucocutaneous lesions but had to terminate the study due to deterioration of disease in all the six patients [39]. However, another open-label study with mycophenolate sodium reports significant improvement on

mucocutaneous lesions in all the ten patients after 6 months [40].

Joint involvement

Arthritis in BS is usually monoarticular, non-erosive and self-limiting with attacks that usually last for a few weeks. Intra-articular corticosteroid injections, non-steroidal anti-inflammatory drugs or low-to-moderate dose oral glucocorticoids may be used during acute exacerbations. In patients with recurrent arthritis episodes, long-term systemic treatment may be necessary. Significantly more patients achieve complete response of arthritis at month 24 with colchicine in one of three RCTs (RR 1.53, 95% CI 1.16–2.02 for men and RR 1.47, 95% CI 1.11–1.97 for women) [3]. In the other colchicine trial by Aktulga et al., there were only five patients with arthritis in each arm [2]. The third colchicine trial by Davatchi et al. used IBDDAM scores as mentioned previously [4]. In this activity index, arthralgia is scored as 1 point, monoarthritis as 2 points and polyarthritis as 3 points. They report a significant difference in the improvement in IBDDAM scores for overall joint manifestations between colchicine and placebo, but IBDDAM scores do not significantly improve compared to baseline in the colchicine arm. Mean difference in IBDDAM scores for joint manifestations is also not different between the colchicine and placebo arms (MD −0.21, 95% CI −0.49 to 0.07) [5].

Azathioprine is beneficial for preventing new arthritis attacks in a RCT (RR 1.25, 95% CI 1.03–1.53). [6]. RCTs of etanercept, thalidomide, intramuscular methylprednisolone acetate, and azapropazone do not show any benefit in reducing arthritis attacks [5]. However, the study duration was only 4 weeks in the etanercept trial and there was a high placebo response rate [16].

Three observational studies of interferon-alpha report a complete remission rate of 100% for 42 patients with arthritis [12, 41, 42]. In another observational study, interferon is found to be effective in reducing the frequency and duration of arthritis in nine patients [10].

Four observational studies of infliximab report successful results in mostly refractory patients. Among them, the indication for infliximab was arthritis in only 1 study and 32 (94%) of the 34 patients achieved complete remission. Adalimumab, the other monoclonal anti-TNF antibody, is beneficial in six of the ten reported patients [5].

Secukinumab was evaluated in five refractory patients and provided complete remission in three patients, partial remission and no response in one patient each as mentioned above [35].

The first-line use of colchicine for preventing arthritis episodes, and azathioprine, interferon-alpha or TNFi in refractory and chronic cases is advised in the updated EULAR recommendations.

Eye involvement

Eye involvement is one of the most disabling complications of BS, since it can be seen in around half of the patients and in up to 70% of young men with BS, and runs a recurrent course with progressive impairment in vision leading to blindness in around 50% if not adequately treated [43]. Isolated anterior uveitis can be treated with topical agents such as mydriatics and topical corticosteroids. However, some of these patients may progress to panuveitis. Since young men are at a higher risk for severe eye involvement than women [44], some authors prefer to use immunosuppressive agents to prevent the complications due to anterior uveitis and the development of a probable posterior uveitis in such patients. In this setting, azathioprine is a reasonable option as it was shown to prevent uveitis among male patients without eye involvement.

Different from other types of non-infectious uveitis where corticosteroids are the mainstay of therapy [45], immunosuppressive agents along with high-dose corticosteroids should be initiated in all the BS patients with posterior uveitis to prevent damage. Azathioprine and cyclosporine-A are the preferred drugs for the initial use. Azathioprine shows efficacy in reducing hypopyon uveitis (RR 0.06, 95% CI 0.01–0.43) and the development of new eye disease (RR 0.14, 95% CI 0.02–0.93) in a RCT [6]. Cyclosporine-A was studied in three RCTs. In the first study, it is effective in decreasing the frequency and severity of ocular attacks when compared to colchicine [46]. In the second study, cyclosporine-A is superior to cyclophosphamide in the improvement of visual acuity at month 6 [47]. In the third RCT, ocular inflammation shows less worsening in the cyclosporine-A group ($n=20$) than in the conventional treatment group (17 corticosteroid and 3 chlorambucil) but the difference is not significant (RR 0.25, 95% CI 0.06–1.02) [48].

For refractory patients, interferon-alpha or monoclonal anti-TNF antibodies are recommended. These agents may be given to patients presenting with sight-threatening uveitis at their first attack. Interferon-alpha was compared with cyclosporine-A in a RCT and infliximab was compared with cyclosporine in a non-randomized observational study. In the RCT by Kötter et al., all the 13 patients assigned to interferon-alpha and 9 of the 13 patients assigned to cyclosporine-A achieve remission [49]. However, 7/13 patients in the cyclosporine-A arm had to switch to interferon-alpha due to adverse events in 3 and loss of efficacy in 4. In the uncontrolled observational study, infliximab is significantly better in decreasing the number of ocular attacks compared to cyclosporine-A [50]. Additionally, there are more patients who achieve complete remission at month 6. However, there are no studies that compare infliximab and interferon-alpha. Several open-label and retrospective studies report favorable results with both agents. Pooling the results of these

studies shows a similar rate of complete remission among both agents (64% for interferon-alpha vs 57% for infliximab) [51]. However, sustained remission is more common among patients treated with interferon-alpha (71% for interferon-alpha vs 44% for infliximab). The main advantage of infliximab is its rapid action with effects visible within 24 h [52]. Although there are no studies looking specifically at the time of onset of action of interferon-alpha, observational studies suggest that ocular inflammation resolves within 2–4 weeks [51]. Two RCTs with adalimumab report beneficial results in patients with non-infectious uveitis, and thereafter adalimumab was approved by EMA and FDA for this indication [53, 54]. The main concern is that few BS patients have been recruited in two RCTs, and the data on BS patients was not reported separately. However, there is growing evidence of adalimumab in uveitis due to BS. An observational study from Italy finds a similar efficacy between adalimumab ($n=26$) and infliximab ($n=22$) in treating refractory retinal vasculitis during a follow-up of 12 months [55]. Retinal vasculitis due to BS accounted for 73% of the 48 patients; however, a separate analysis of BS patients was not provided. The same group also reports a similar cumulative retention rate of adalimumab and infliximab in 80 BS patients [56] and the cumulative retention rate of adalimumab in 54 BS patients (82 eyes) as 76.9% and 63.5% at 12 and 48 months, respectively [57]. Another study evaluated the efficacy, safety, and cost-effectiveness of increasing the dosing interval of adalimumab and shows that tapering is similarly efficient, cost effective and safe [58]. There is no difference between adalimumab monotherapy and co-treatment with disease-modifying antirheumatic drugs regarding efficacy, time to response, relapses, and adalimumab discontinuation in a 24-month study [59]. As there is no evidence for superiority of the overall efficacy of interferon-alpha or monoclonal anti-TNF antibodies, several factors such as clinician's experience, adverse events, patients' preferences, comorbidities, and reimbursement policies play role in making a treatment decision.

Other agents that were studied in BS uveitis are IL-1 inhibitors (anakinra, canakinumab, and gevokizumab), IL-6 inhibitor tocilizumab, golimumab, secukinumab, rituximab, and pegylated interferon-alpha. The RCTs with secukinumab [60], gevokizumab [61] and pegylated interferon-alpha [62] fail to meet their primary endpoints. In a 6-month RCT, rituximab 2 courses of 1 gr, 2 weeks apart with concomitant methotrexate 15 mg/week was compared with combination therapy of cyclophosphamide (1 gr/monthly) and azathioprine (2–3 mg/kg/day) [63]. Both the groups received prednisolone (0.5 mg/kg/day). The primary endpoint was the improvement in the Total Adjusted Disease Activity Index (TADAI). Nine of the 10 patients in the rituximab group improved compared to seven-tenth patients in the other group ($p=0.27$). The effect size of the primary and secondary endpoints was not significantly in favor of rituximab (MD −5.10, 95% CI −21.01 to 10.81 for TADAI; RR 0.67, 95% CI 0.14 to 3.17 for visual acuity; RR 0.86, 95% CI 0.45 to 1.64 for posterior uveitis; RR: 1.17, 95% CI 0.61 to 2.23 for retinal vasculitis).

The only case series including 19 patients that specifically evaluated the role of IL-1 inhibitors in the management of refractory uveitis came from Italy [64]. Ocular inflammatory flares and frequency of retinal vasculitis significantly decrease at month 12. Notably, the same group reports their experience with adalimumab in 40 patients. Ocular inflammatory flares drop from 200/100 patient-years to 47.5/100 patient-years with IL-1 inhibitors and 200 flares/100 patient-years to 8.5 flares/100 patient-years with adalimumab. A significant improvement in best corrected visual acuity and macular thickness at month 12 is only observed in the adalimumab study [65]. These findings suggest that adalimumab may be more effective than IL-1 blockers for BS uveitis. No tuberculosis reactivation is reported with IL-1 blockers in the Italian retrospective case series, in contrast to what is known for TNF inhibitors [66]. Thus IL-1 inhibitors may be an alternative for BS patients who require biologic agents and who have a high risk of tuberculosis. However, caution is still required for patients living in regions with a high-background tuberculosis rate, since one of our ten BS patients treated with IL-1 inhibitors developed tuberculosis during this treatment [67].

Tocilizumab, a humanized anti-IL-6 receptor antagonist, is reported in 7 papers including 24 patients who were refractory to standard therapy. Almost all of them had been treated with TNFi previously and all responded well to tocilizumab [27, 29, 32, 68–71].

One case series from Italy report their experience with golimumab in patients with retinal vasculitis who received at least one biologic. During a follow-up of 12 months, retinal vasculitis completely resolved with golimumab in eight eyes of five patients and golimumab could control the disease in seven-eighth eyes [72].

Vascular involvement

Venous thrombosis

Venous thrombosis most commonly affects men, and can present as superficial thrombophlebitis, deep-vein thrombosis of upper and lower extremities, vena cava inferior and superior thrombosis, and Budd–Chiari syndrome. Recurrences are common, and are reported as 29, 37 and 45% at 6, 12 and 24 months, respectively [73]. Post-thrombotic syndrome is an important complication resulting from recurrent thrombotic events in the lower extremities. Venous insufficiency leading to ulcers that are very difficult to heal may result. Although the mainstay of treatment for an acute

episode of deep-vein thrombosis is moderate-to-high-dose glucocorticoids, immunosuppressives are required to prevent relapses. A meta-analysis of three retrospective studies shows that immunosuppressives and anticoagulants are superior to anticoagulants alone (RR 0.17, 95% CI 0.08–0.35), and adding anticoagulants to immunosuppressives provides no benefit (RR 0.75, 95% CI 0.48–1.17) [1]. Regarding the role of anticoagulants in the post-thrombotic complications, there are two studies reporting conflicting results [74, 75]. Thus, the issue of adding anticoagulants remains to be studied.

There is no consensus on which immunosuppressive should be used as first line for prevention of deep-vein thrombosis relapses. A prospective study from our center shows that 45% of the 29 patients with deep-vein thrombosis relapse under azathioprine treatment during a mean follow-up of 40.7 ± 13.4 months, indicating a need for better options [73]. In this study, 13/14 of the patients treated with interferon-alpha had good recanalization, which was found to predict further relapses, and only 2 (11%) had a relapse during a mean follow-up of 29 ± 20 months. Recently, a study including 70 patients with deep-vein thrombosis or superficial thrombophlebitis retrospectively compared a biologic agent with conventional immunosuppressive therapies including azathioprine, cyclosporine-A, and cyclophosphamide [76]. During a mean follow-up of 25.7 ± 23.2 months, adalimumab-based regimens provide a better vascular response (34/35; 97%) compared to conventional immunosuppressive therapies (23/35; 66%). Vascular response is achieved earlier in patients treated with adalimumab-based regimens, allowing less exposure to systemic corticosteroids. Vascular relapse is observed in 3 (9%) of 35 patients treated with adalimumab-based regimens and in 14 (40%) of 35 patients treated with conventional therapies. For both groups, the rates of vascular response are similar among patients treated with and without concomitant anticoagulants.

Deep-vein thrombosis of lower extremities, which is the most common manifestation of vascular involvement of BS, is generally managed with corticosteroids and azathioprine. On the other hand, vena cava inferior thrombosis and Budd–Chiari syndrome require more aggressive therapy due to their poor prognosis and tend to occur together. Apart from case reports, the most comprehensive analysis of Budd–Chiari syndrome due to BS includes 43 patients [77]. Patients were divided into groups according to their liver symptoms at the time of Budd–Chiari syndrome diagnosis. There were 33 symptomatic patients in Group 1 and 10 asymptomatic patients in Group 2. Mortality rate is higher in Group 1 (58% vs 10%). Overall, 36/43 patients were initially treated with immunosuppressive agents including cyclophosphamide in 31 patients, azathioprine in 4, and interferon in 1 patient. Five patients had to switch TNFi (four infliximab and one etanercept). Two of them had died, one treated with etanercept had a relapse of cerebral venous thrombosis and the remaining two responded well to infliximab. Mortality rate is 39% among patients treated with immunosuppressives, and 86% among those who receive only diuretics or anticoagulants. Recently, a French group describes their experience with TNFi (15 infliximab and 3 adalimumab) in patients with major vessel involvement who were refractory to standard therapy including cyclophosphamide [78]. There were 23 vascular lesions (9 aneurysms and 14 venous thromboses) in 18 patients. Among the 14 venous thromboses, there were 7 pulmonary artery thromboses, 5 inferior vena cava thromboses and 2 Budd–Chiari syndromes. Sixteen of these 18 patients achieved vascular remission defined as the resolution of clinical symptoms and normalization of acute phase reactants and the absence of new vascular lesions or no progression of affected vessels. One patient had a new peripheral aneurysm 24 months after TNFi initiation, and another had a relapse of pulmonary artery thrombosis after 8 months.

Arterial involvement

The most lethal complication of BS is pulmonary artery involvement that can manifest as aneurysms, thrombosis or both. No controlled studies were conducted in patients with pulmonary artery involvement, mainly due to its rarity with a frequency of less than 5% [79]. The usual practice is to treat such patients with monthly 1 gr cyclophosphamide for 6–12 months along with pulse methylprednisolone (1 gr/day) for 3 days. Patients who obtain remission are switched to AZA for maintenance therapy. In refractory cases, cyclophosphamide may be replaced with infliximab. Open surgical procedures are not promising in earlier cohorts including ours [80–82]. However, we recently reported nine BS patients with refractory arterial involvement who underwent lung surgery [83]. The surgical interventions were lobectomy in six patients, and decortications and pleural interventions in the remaining three. The reasons for lobectomies were giant pulmonary arterial aneurysms with diameters ranging from 2.5 to 8 cm in four patients, pneumothorax due to large cavities, and bronchiectasis in one patient each. Decortications and pleural interventions were done due to a bronchopleural fistula after pulmonary artery coil embolization, and pneumothorax due to large cavities in one patient each. Only one patient experienced a perioperative complication (transient foot drop). Two patients had died after lobectomy. One died 3 months after surgery due to massive hemoptysis and the second died 12 months after surgery due to Budd–Chiari syndrome. After a median follow-up of 8 years (IQR 4–11), the remaining seven patients were

still alive. We think that lobectomy may be less feared in patients with life-threatening refractory giant pulmonary artery aneurysms by experienced surgeons.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a less frequently recognized, but potentially lethal complication in BS patients with pulmonary artery thrombosis. One cohort reports endarterectomy results of nine BS patients with CTEPH [84]. There were two postoperative complications that resulted in death of one patient. One of them died a month after surgery due to massive hemoptysis. Another one manifested with bilateral vocal cord paralysis on the second day of surgery. His symptoms resolved with immunosuppressive therapy within 6 weeks. After 3 months, he underwent right pneumonectomy due to a cavity in the right upper lobe, giant bullous lesion in the middle lobe and right main pulmonary artery thrombosis that were refractory to immunosuppressive and antifungal treatments. Overall, endarterectomy provided a symptomatic improvement in eight-ninth patients during a median follow-up of 24 months. However, caution is required during patient selection for this procedure. The risk of right heart failure and hemoptysis due to CTEPH should be weighed against the potential complications of endarterectomy in such a group of patients with vessel wall inflammation. Another unresolved issue in the management of such patients is whether anticoagulation should be performed, as is the usual practice after endarterectomy for CTEPH. Different from other diseases resulting in CTEPH, the thrombosis of pulmonary arteries in BS is thought to result from in situ thrombosis of the artery due to inflammation, rather than embolization from a venous thrombosis. Disappointing results with anticoagulation in BS as explained above, and the potential risk of bleeding from an already present or newly developing aneurysm cause some experts to avoid anticoagulation in such patients.

During the follow-up of patients with pulmonary artery involvement, bronchial artery enlargement may be a potential cause of hemoptysis refractory to immunosuppressive treatment [85]. Embolization of the bronchial arteries have been tried with some success in stopping hemoptysis in the short term, but is not definitive since the persistent high pressure in the pulmonary vascular bed usually causes new bronchial arteries to enlarge in due course.

The medical treatment of peripheral artery and aortic involvement is similar to that of pulmonary artery involvement. However, surgery is usually required depending on the type and size of aneurysm, and should be accompanied with immunosuppressive therapy. Immunosuppressive therapy decreases relapse risk and should be initiated in the perioperative setting. Although there is no consensus on the preference of endovascular or open surgical interventions in BS, synthetic grafts should be preferred over autologous grafts due to a lower relapse risk [1, 51].

Central nervous system involvement

Parenchymal central nervous system involvement

Parenchymal central nervous system (CNS) involvement is another cause of morbidity and mortality in BS. CNS attacks tend to cause damage leading to serious physical and mental disability, and relapses are seen in 30–50% of the patients [86]. Thus, it is essential to rapidly suppress the attack and to prevent further relapses to reduce disability. Treatment recommendations are mainly based on observational studies as there are no RCTs. Pulse steroids (1 gr/day) up to 7 days followed by oral prednisolone 1 mg/kg/day is initiated to control the acute attack, prednisolone is gradually tapered over 3–6 months and azathioprine is used for maintenance of remission. Observational data show that infliximab is effective in preventing further relapses, stabilizes the level of disability and has a steroid-sparing effect [51]. These advantages led to increased use of infliximab. Infliximab is currently recommended for patients whose attack cannot be controlled with conventional treatment modalities, experience relapses under azathioprine treatment or upfront during the first attack in patients presenting with severe disease and poor prognostic factors. Its optimal use is unknown; however, one of the larger series reported from our center shows that 15 patients receiving infliximab do not experience relapses during a median follow-up of 39 months [87]. Adalimumab may be another option for patients who are refractory or intolerant to infliximab [51].

Different from primary CNS angiitis, cyclophosphamide has limited benefit in the induction treatment of parenchymal CNS involvement of BS. Noel et al. from France observe no difference regarding event-free survival among three treatment arms, which were cyclophosphamide ($n=53$), azathioprine ($n=40$), and corticosteroid alone ($n=19$) [88]. A subgroup analysis of patients with a baseline Rankin score ≥ 3 shows that event-free survival rates at 1, 5, 7, and 10 years are somewhat higher among patients treated with cyclophosphamide ($n=31$) compared to those treated with azathioprine ($n=12$); however, the difference is not significant (93% vs 75% at 1 year, 56% vs 44% at 5 years, 56% vs 15% at 7 and 10 years, and $p=0.06$; log rank test). Another study from Korea reports the outcome of their 22 patients with parenchymal CNS involvement [89]. Relapse rates are similar among patients treated with cyclophosphamide in addition to corticosteroids (2/7; 29%) and those treated with only corticosteroids (5/14; 35%).

Cyclosporine-A should be avoided as it is associated with an eightfold increased risk of development of neurologic involvement [51].

Mycophenolate mofetil has been proposed as an alternative to azathioprine for patients with parenchymal CNS involvement [90]. The reason for mycophenolate mofetil

initiation was gastrointestinal intolerance to azathioprine in three patients. The fourth patient developed parenchymal CNS involvement under azathioprine treatment and then switched to mycophenolate mofetil during remission induction with high-dose corticosteroid treatment. Three of them had relapses after the cessation of mycophenolate mofetil and remained in remission after re-introduction of mycophenolate mofetil. The last patient did not experience a relapse during 1 year. Mycophenolate mofetil or mycophenolate sodium may be an alternative option for patients with major organ involvement who are intolerant to azathioprine or for those who use warfarin.

Favorable results with tocilizumab have been reported in five patients with neurologic involvement who were refractory to TNFi [26, 91, 92].

Extra-parenchymal central nervous system involvement

High-dose glucocorticoid therapy is usually effective in the acute stage of extra-parenchymal involvement that presents with cerebral venous thrombosis. Adding anticoagulants is a controversial issue as its benefit has not been shown. If a decision has been made to start anticoagulants, it is crucial to exclude the presence of arterial aneurysms. This is especially important since a significant correlation is observed between pulmonary artery involvement and cerebral venous thrombosis [93]. Although cerebral venous thrombosis has a good prognosis in most of the patients, a prolonged increase in intracranial pressure causing visual loss due to optic atrophy may be observed. Saadoun et al. report this severe complication in 15% of their patients [94]. To prevent this complication, lumboperitoneal shunt or optic nerve decompression may be considered in patients with persistent papilledema despite aggressive medical treatment. Different from parenchymal involvement, recurrences are rare and immunosuppressive treatment may not be necessary for maintenance of remission. However, cerebral venous thrombosis is found to be associated with other types of venous thrombosis, which may be a reason for adding immunosuppressive treatment to prevent further thrombosis. Saadoun et al. report that six of their seven relapsed patients with cerebral venous thrombosis experienced new thrombosis after the cessation of anticoagulants despite ongoing corticosteroid and immunosuppressive therapies [94]. One patient relapsed within 1 year, two within 2 years, three within 3 years, and one within 10 years. Recently, another group from France evaluated the need of long-term anticoagulant, and only one of their seven patients had a relapse 5 months after the cessation of anticoagulant and this patient was not using corticosteroid or immunosuppressives [95]. Among the remaining six patients without relapse, five were using both corticosteroid and azathioprine, and one was using corticosteroid alone. The follow-up time after the cessation of anticoagulants of these patients was 10, 12, 24, 26, 120 and 144 months. They suggest that the difference between their results and the previous report may be related to the relatively short duration of follow-up. However, they also point out to the importance of immunosuppressive therapy in the prevention of relapse.

Gastrointestinal involvement

Gastrointestinal involvement is a much less frequent manifestation of BS around the Mediterranean, whereas it is reported in up to 30% of patients from the Far East. Recommendations rely on observational studies and extrapolations from trials on inflammatory bowel diseases, as there are no RCTs for gastrointestinal involvement of BS. Infliximab and adalimumab have been studied in prospective open-label studies, whereas there is only retrospective data on the other treatment options. [96]. Different from other types of major organ involvement, the use of high-dose glucocorticoids during acute exacerbations is controversial for gastrointestinal involvement. This is based on the contention that high-dose glucocorticoid use may be associated with intestinal perforation. However, this may have resulted from the use of high-dose glucocorticoids in patients with large and deep ulcers that already carry a high perforation risk. 5-aminosalicylate derivatives are preferred in mild cases with colonic involvement whereas azathioprine is the recommended agent for severe cases or for those with ileal involvement. [97]. Azathioprine is also found to reduce relapse risk after surgical procedures. [98] Methotrexate that is used in Crohn's disease has been studied in a small number of patients with BS and most of them were also receiving infliximab or adalimumab [99], suggesting that it may be an option in intolerant/refractory cases to azathioprine. Infliximab and adalimumab provide promising results in open-label and retrospective studies [96]. Interestingly, etanercept that is not considered useful for inflammatory bowel disease has been reported to be beneficial in a retrospective study [100]. Thalidomide used to be an alternative for refractory patients before TNFis were available, and can still be used in addition to TNFi in severe cases. [101]. Caution is required for neurotoxicity and birth defects.

Among the newer agents in BS treatment, there is one case report with tocilizumab. This patient with refractory gastrointestinal disease achieved complete remission with tocilizumab [102].

Myelodysplastic (MDS) syndrome should be considered in refractory cases with unexplained cytopenias as it has been shown to be associated with gastrointestinal involvement of BS [103]. These patients tend to have a more refractory disease, and may benefit from treatment modalities such as 5-azacytidine or allogeneic stem cell transplantation that are used for MDS [104].

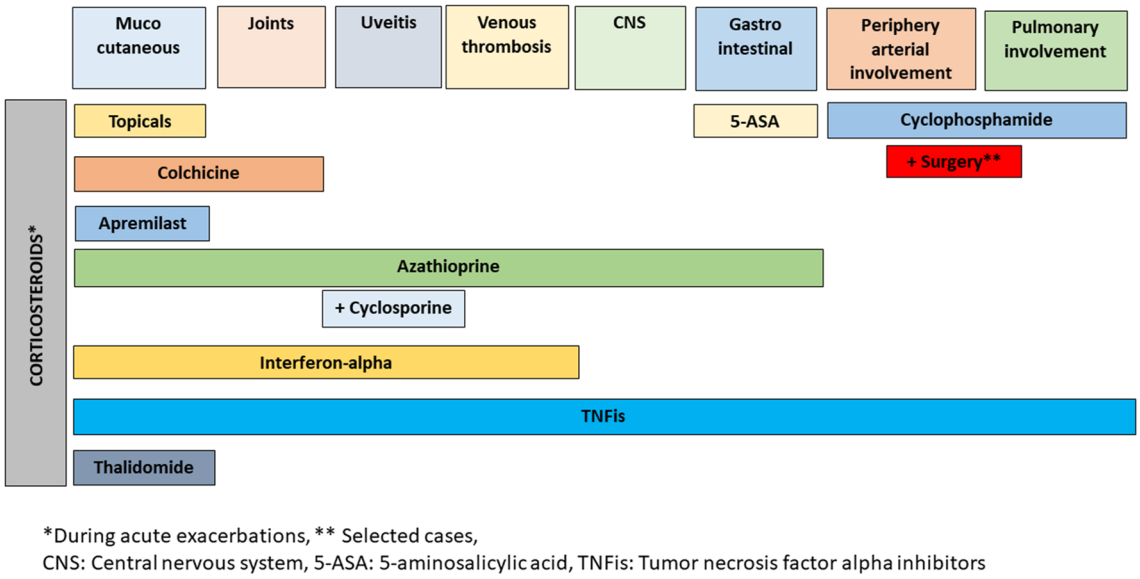

Fig. 1 A proposed algorithm for the management of Behçet's syndrome

Other therapies that are tried for BS patients

Thirteen BS patients have been reported to be treated with intravenous immunoglobulin (IVIG) due to refractory disease in 12 patients [105–110], and due to recurrent severe varicella zoster reactivation in 1 patient [111]. The indications of IVIG were eye involvement in five patients, mucocutaneous and articular involvement in two patients, leg ulcer, mucocutaneous, peripheral nervous system, central nervous system, gastrointestinal, and both central nervous system and gastrointestinal involvement in one patient each. All but one BS patient with refractory eye disease responded to IVIG.

Conclusions

A proposed algorithm for the management of different BS manifestations is presented in Fig. 1. The evidence on the management of BS mostly comes from RCTs for mucocutaneous lesions, arthritis, and uveitis. On the other hand, treatment strategies of vascular, neurologic and gastrointestinal involvement are mostly based on uncontrolled studies. Colchicine is still the first choice for most of the patients with mucocutaneous lesions. Apremilast is another promising and safe agent for oral ulcers. Monoclonal anti-TNF antibodies may be used for refractory manifestations of BS, but they may not be beneficial for all the refractory cases, suggesting that new treatment modalities are needed. Further studies are needed for determining the ideal duration of immunosuppressive treatment, whether concomitant use of conventional immunosuppressives is necessary during treatment with TNF inhibitors, the role of anticoagulants for venous thrombosis, potential benefit of early immunosuppressive treatment in patients with high risk of major organ involvement and early use of biologics in patients with major organ involvement.

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