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REVIEW

New and future perspectives in Behçet's syndrome

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ABSTRACT

Behçet's syndrome is a variable vessel vasculitis characterized by a diverse range of clinical manifestations resulting from inflammation involving several organs and systems. While significant progress has been made in understanding the pathogenesis and treatment of Behçet's syndrome, challenges remain in achieving optimal disease control and preventing long-term complications. This review explores recent advances in the management of Behçet's syndrome, with a focus on emerging therapies and future directions. Apremilast, a phosphodiesterase-4 inhibitor, has shown promise in managing mucocutaneous manifestations, particularly oral ulcers. Tocilizumab, an interleukin (IL)-6 receptor inhibitor, has demonstrated efficacy in certain patient populations, especially those with ocular involvement. However, its use in vascular Behçet's syndrome requires careful consideration. Relapses of oral and genital ulcers can be challenging during tocilizumab treatment. Other emerging therapies, such as IL-17 inhibitors, including secukinumab and ixekizumab, IL-12/23 inhibitor ustekinumab, and Janus kinase (JAK) inhibitors, including tofacitinib and baricitinib, are being investigated for their potential to target specific inflammatory pathways. Future research directions include the development of novel therapeutic targets, better use of existing agents by identifying patient populations that would benefit from these, developing better instruments for disease assessment, and a treat-to-target approach in order to improve outcomes and quality of life for patients with Behçet's syndrome.

Keywords: Behçet's disease, Behçet's syndrome, TNF inhibitors, treatment, treat-to-target.

Behçet's syndrome is a unique vasculitis associated with inflammation of arteries and veins of various size. Patients may present with active disease in one or more domains including mucocutaneous lesions, arthritis, uveitis, arterial aneurysms or thrombosis, venous thrombosis, gastrointestinal ulcers, and central nervous system disease. Disease course is heterogeneous with more frequent uveitis, vascular, and central nervous system involvement and a more severe course among men.[1] Manifestations show a relapsing and remitting course with usually more frequent relapses during the initial years after disease onset. In the majority of patients, disease activity tends to wane after a few decades. All of these features are important when planning management in patients with Behçet's syndrome, and the treatment modalities can be quite different across patients based on these factors.[2]

For patients with only skin and mucosa involvement, patients' preferences determine whether systemic treatment is required or not. Some patients with infrequent relapses of skin and mucosa manifestations may prefer to use only topical glucocorticoids during these exacerbations. Some may also benefit from a short course of low dose oral prednisolone. On the other hand, long-term systemic treatment modalities may be required to prevent recurrences when relapses are more frequent or bothersome. The initial systemic treatment for skin, mucosa, and joint involvement is usually colchicine due to its favorable efficacy profile and tolerability in a good proportion of the patients, and its relatively low cost. Options that were recommended for refractory patients included apremilast, azathioprine, interferon-alpha, thalidomide, and tumor necrosis factor (TNF) inhibitors.[2] Patients who present with active major organ involvement

require treatment with immunosuppressants in addition to glucocorticoids. Glucocorticoid use may vary from a moderate dose of oral prednisolone to intravenous methylprednisolone pulses for up to 10 days depending on the severity of the exacerbation.[2] Whether conventional immunosuppressants such as azathioprine, cyclosporine-A, or mycophenolate mofetil, or biologic agents such as TNF inhibitors should be preferred as the first-line treatment of major organ involvement is an ongoing discussion.

Despite advances in the management of patients with Behçet's syndrome, there is still need for improvement. A recent study showed that 19% of the patients developed at least one damage item during their five-year follow-up in a dedicated multidisciplinary Behçet's syndrome clinic.[3] Developing better management strategies with new agents and more effective use of existing treatment modalities is key to better outcomes in this chronic, organ and life-threatening condition that most commonly affects young adults.

In this review we aim to summarize the new trends in the management of patients with Behçet's syndrome with special emphasis on emerging treatment modalities, novel data on predictors of severe disease requiring more aggressive treatment, and disease assessment. We also aim to elaborate on future perspectives including efforts for developing a treat-to-target strategy for Behçet's syndrome.

PHOSPHODIESTERASE 4 INHIBITORS

Apremilast has been the first oral phosphodiesterase-4 (PDE4) inhibitor used for Behçet's syndrome and has emerged as a promising therapy. By increasing intracellular cyclic adenosine monophosphate (cAMP) levels, it downregulates pro-inflammatory cytokines such as TNF-α, interleukin (IL)-17, and IL-8 while enhancing the anti-inflammatory cytokine IL-10. Its efficacy was initially established in psoriasis and psoriatic arthritis, where it demonstrated a favorable safety profile.[4] Recent trials and real-world studies have extended its application to Behçet's syndrome, particularly for refractory oral ulcers.

Two pivotal clinical trials evaluated apremilast in Behçet's syndrome patients.[5,6] A Phase 2 randomized controlled trial (RCT) included 111 patients with active oral ulcers.[5] Participants received either apremilast 30 mg twice daily or placebo for 12 weeks, followed by an active treatment phase until week 24. Apremilast significantly reduced the number and pain of oral ulcers by week 12 compared to placebo. At week 12, 71% of apremilast-treated patients achieved complete ulcer resolution versus 29% in the placebo group.

A larger Phase 3 RCT further confirmed these findings.[6] In this trial, 207 patients with persistent oral ulcers despite prior therapies were randomized to apremilast or placebo for 12 weeks. Apremilast showed a significant reduction in ulcer number and associated pain, with sustained benefits through the study's extension phase. The drug also demonstrated improvements in overall disease activity assessed using Behçet's Disease Current Activity Form (BDCAF) and Behçet's Syndrome Activity Scale (BSAS) scores, as well as health-related quality of life assessed using Behçet's Disease Quality of Life scale, highlighting its broader efficacy beyond oral lesions.

Real-world evidence corroborates the trial data. In one multicenter study, 51 Behçet's syndrome patients with refractory mucocutaneous lesions received apremilast.[7] Rapid and sustained improvements in oral and genital ulcers, skin lesions, and arthritis were reported. A recent retrospective study compared TNF inhibitors and apremilast in patients with refractory ulcers. There were similar rates of improvement in the number of oral ulcers at month 3 and month 6 and similar response rates in genital ulcers, whereas TNF inhibitors were more effective for arthritis.[8]

Apremilast is well-tolerated, with a safety profile consistent across Behçet's syndrome, psoriasis, and psoriatic arthritis studies.[9] Common adverse events include gastrointestinal symptoms such as diarrhea and nausea, headache, and upper respiratory infections. No deaths were associated with apremilast in Behçet's syndrome trials.

Apremilast represents a valuable addition to the Behçet's syndrome treatment arsenal,

particularly for patients with refractory oral ulcers. It offers a favorable balance of efficacy and safety compared to traditional immunosuppressants and biologics. However, challenges remain, including under-recognition of oral ulcers' impact on quality of life and the lack of standardized criteria for clinically meaningful improvements in trials. Potential benefit of apremilast in combination with other treatment modalities needs to be further explored.

A more recent study with another PDE4 inhibitor, roflumilast, suggests that this is another promising agent for Behçet's syndrome.[10] An observational study including Behçet's syndrome patients with mucocutaneous involvement showed that during the 12-week roflumilast treatment period, patients had a significantly lower number of oral ulcers and significantly fewer flare-ups defined as presence of oral or genital ulcers after a period of remission compared to their previous periods not receiving any treatment or receiving other treatment modalities including apremilast, colchicine, dapsone, and adalimumab.[11] Future controlled studies are needed to explore the role of roflumilast reliably and in broader Behçet's syndrome manifestations.

TUMOR NECROSIS FACTOR INHIBITORS

Tumor necrosis factor inhibitors have been used successfully in patients with Behçet's syndrome for more than two decades. Their effective use has been relatively more established in Behçet's syndrome patients with uveitis. A recent randomized controlled study compared cyclosporine-A, interferon-alpha, and adalimumab in 270 Behçet's syndrome patients with uveitis.[11] All of the patients received concomitant glucocorticoids which were gradually tapered. Annual relapse rate was significantly lower in the adalimumab group compared to the cyclosporine-A group, while a significant difference was not observed between adalimumab and interferon-alpha, or interferon-alpha and cyclosporine-A. Another recent head-to-head trial randomized Behçet's syndrome patients to receive infliximab or interferon-alpha.[12] The primary efficacy endpoint which was BDCAF score at week 12 was similar between the two groups with a mean difference of 0.13 (80% CI: –0.19, 0.46). The secondary endpoints were also similar. The corticosteroid sparing effect was somewhat better in the interferon-alpha group, where 44% of the patients stopped glucocorticoids compared with 20% of the patients in the interferon-alpha group. Tolerability was slightly better in the infliximab group.

Evidence is growing on the use of TNF inhibitors for other organ domains. A randomized controlled trial compared cyclophosphamide with infliximab among 37 patients with vascular and 15 with nervous system involvement.[13] The primary endpoint was complete response at week 22, a composite of resolution of all clinical symptoms, a normal CRP level, radiologic remission, and a prednisone dose of ≤0.1 mg/kg/day. Although the number of patients was quite small, a significant difference was observed between the two groups favoring infliximab in terms of both safety and efficacy. A vascular complete response was observed in 56% of patients who received cyclophosphamide and 94% of patients who received infliximab. Among the 15 patients with nervous system involvement, the complete response rate was 57% in the cyclophosphamide group and 71% in the infliximab group. This beneficial response observed with infliximab in patients with vascular involvement in this study was somewhat better than previous real-world data. A retrospective study that reported on a cohort of 127 patients with vascular involvement treated with infliximab showed an overall remission rate of 73% at month 6 and 63% at month 12.[14] The overall relapse rate was 13% over a mean follow-up of 28 months. The remission rates were higher and relapse rates were lower among patients with pulmonary artery involvement and venous thrombosis, compared to patients with peripheral artery involvement.

Tumor necrosis factor inhibitors may also be changing the disease course of Behçet's syndrome, by preventing the development of new organ involvement. A study evaluating the development of new major organ involvement during adalimumab treatment showed that only 14 of 335 patients (4%) treated with adalimumab experienced a de novo organ manifestation.[15] The rates were also low for infliximab in a previous study which showed that 19 of 282 (7%) Behçet's syndrome patients treated with infliximab had

a new major organ involvement over a median follow-up of 30 months.[16]

TOCILIZUMAB

A multicenter retrospective observational study from France evaluated the outcomes in a cohort of 204 patients with refractory non-infectious uveitis complicated by macular edema, treated with adalimumab (39.2%), infliximab (33.4%), and tocilizumab (26.9%).[17] The median follow-up duration was 74.5 months (37-137), and the median age of the cohort was 40 years (28-58). Patients in the tocilizumab group were significantly older (p=0.03), with 76% having previously received TNF inhibitors. Concomitant corticosteroid or disease-modifying antirheumatic drug (DMARD) use was required in 40% of the tocilizumab group, compared to 89.7% in the TNF inhibitor group. At six months of treatment, a complete response was achieved in 24.5% of patients, with rates of 21.8% in the TNF inhibitor group and 35.8% in the tocilizumab group. Efficacy did not differ between adalimumab and infliximab, nor within tocilizumab, based on its route of administration. Tocilizumab was independently associated with achieving a complete response, with an odds ratio of 2.10 (95% CI: 1.06-4.06; p=0.03). The corticosteroid-sparing effect was similar among treatment groups, with tocilizumab reducing the median daily dose from 15 mg (8-20) to 10 mg (0-40) over six months (p=0.006). Relapses were observed in 44.6% of patients, with a median time to relapse of 41 months. The median duration of disease control was 12 months (6.8-28.5) in the TNF inhibitor group and 11 months (6-15.3) in the tocilizumab group.

It is important to note that the cohort was heterogeneous, and there were significant differences in the underlying etiologies between the TNF inhibitor and tocilizumab groups. Patients with Behçet's disease accounted for only 17.2% of the cohort, with 91.4% predominantly treated with TNF inhibitors. Poor visual prognosis was three times more likely in patients with Behçet's disease compared to those with idiopathic uveitis, highlighting the severity of ocular involvement in this group. However, Behçet's disease was inversely associated with relapse risk (HR: 0.40; 95% CI: 0.21-0.77; p=0.007).

Barroso-Garcia et al.[18] found no significant differences between adalimumab, infliximab, and tocilizumab in a more homogeneous group of patients with isolated Behçet's uveitis and macular edema, where treatment distribution was more balanced. Further studies are needed for the group that could benefit from tocilizumab, as three cases of refractory pan-uveitis have been reported to fail treatment with tocilizumab.[19]

Liu et al.[20] evaluated 11 patients with neuro-Behçet's syndrome, 54.5% of whom were from a historic cohort with poor clinical response to previous conventional and/or biological treatments. All patients had parenchymal lesions and oral ulceration, and 72.7% had skin lesions. A history of multiple immunosuppressants was present in 72.7% of cases. Among the patients, seven were treated with pulse therapy, eight received cyclophosphamide and five patients were treated with infliximab. The mean follow-up duration was 13.1±10.2 months. Two patients had a complete response, and all showed some improvement, with four achieving radiological remission. The treatment resulted in corticosteroid and immunosuppressant-sparing effects and a significant decrease in activity and disability/quality of life scores, as reflected by the BDCAF score (p=0.004) and Rankin scores (p=0.005), respectively. After a median of two doses of tocilizumab, cerebrospinal fluid (CSF) IL-6 levels decreased significantly in five patients (p=0.048), and these levels were linked to BDCAF scores (p=0.017). Longer follow-up studies are recommended to better evaluate the efficacy of tocilizumab in neurological involvement, as it has a traceable activity marker.

A rare manifestation of AA amyloidosis has been reported in two inactive Behçet's syndrome patients with previous ocular and/or mucocutaneous involvement in which proteinuria, an indicator of the end organ damage caused by amyloidosis was resolved with tocilizumab.[21,22]

There are controversial reports on the efficacy of tocilizumab for vascular Behçet's syndrome.[23] A case series involving seven patients, all with a history of at least one biologic agent, reported vascular relapses after a median of six months on tocilizumab treatment. None of the patients experienced a severe vascular event in the recent period prior to starting tocilizumab, which was

initiated due to elevated acute phase reactants, indicating systemic inflammation without evidence of vascular relapse. The median age at the start of tocilizumab was approximately 47 years, with a median disease duration of 20 years. The outcomes included new thrombosis, de novo pulmonary artery aneurysms, and mucocutaneous flares with negative acute phase reactants because of the anti-IL-6 effect. However, aortitis responded well to treatment. This response was supported by 17 cases in the literature that demonstrated aortic and branch involvement, distinct from pulmonary and venous involvement.[24,25]

A challenging complication that may occur during tocilizumab treatment is mucocutaneous flares.[23,26] These may be severe enough to require discontinuation of the drug. Tocilizumab may also induce deep ulcers in the terminal ileum resembling Behçet's intestinal ulcers.[27] These differences in treatment response between different organs may be attributed to the differences in disease mechanisms between different types of organ involvement in Behçet's syndrome.

SECUKINUMAB

The SHIELD study, which evaluated the efficacy of secukinumab in treating pan- and posterior Behçet's uveitis, failed to achieve its primary endpoint of effectively controlling uveitis. As a result, the study was terminated early, along with two other randomized controlled trials investigating secukinumab for non-Behçet uveitis: the INSURE and ENDURE studies. The most common serious adverse events associated with secukinumab in the SHIELD study were non-ocular Behçet's syndrome exacerbations, uveitis, and papulopustular lesions.[28]

Fagni et al.[29] investigated the efficacy of secukinumab in 15 active patients with mucocutaneous and articular involvement who had failed at least one TNF inhibitor. The study cohort's gender distribution and involvement differed from the typical Behçet population. Out of 15 patients, 13 were female. Oral aphthosis and peripheral joint involvement were present in all patients, while axial joint and intestinal involvement occurred in 60% (9/15). Additionally, the median age for starting secukinumab was relatively high at 51.4 (45.9-61.7). By month three, overall BDCAF scores decreased, along with significant reductions in oral-genital ulcers and improvements in articular and intestinal involvement. By month six, 13 (86.7%) patients had a complete or partial response. Of the 11 (84.6%) patients who achieved sustained clinical remission with a follow-up longer than six months, 54.5% were not on corticosteroid treatment, while the remaining patients were receiving 5 mg of prednisone daily. A total of nine relapses occurred, with two patients on 150 mg/month and seven on 300 mg/month. However, in patients with follow-up longer than one year, mucosal and articular relapses increased, although no systemic relapses were reported. A complete response was achieved in all cases with an available follow-up, either spontaneously, through an increased secukinumab dose, or with methotrexate combination therapy.

De novo Behçet-like syndrome or gastrointestinal flares have been reported with secukinumab.[30-34] Whether secukinumab's effect is paradoxical or predisposing remains controversial due to symptom resolution upon withdrawal and the HLA burden among patients.[33] The most common presenting symptoms in newly emerging Behçet's-like syndrome are fever, as well as oral and genital ulcers,[30-32] while gastrointestinal flares are more common in patients with pre-existing Behçet's syndrome.[31,34]

USTEKINUMAB

Ustekinumab is a humanized monoclonal antibody that targets the p40 subunit of IL-12 and IL-23, inhibiting their binding to their receptors on T cells, BK cells, and antigen-presenting cells.[35] Ustekinumab's proven effectiveness and safety in Crohn's disease highlight its potential as a promising treatment for Behçet's syndrome. However, data on its use in Behçet's syndrome remains limited. Three studies have shown significant improvements in colchicine-resistant oral ulcers and accompanying joint involvement, which are often part of the same clinical cluster with a favorable safety profile.

Mirouse et al.[36] investigated 30 active patients with orogenital ulcers, having a median BSAS

of 70 (IQR 50-70) at the time of inclusion. The median number of oral ulcers was 2 (IQR 2-3), and the median number of tender joints was 6 (IQR 4-8), with joint involvement present in 53% of patients at the time of inclusion. The median age at the initiation of ustekinumab was 39 years (IQR 33-45). Along with ustekinumab, 50% of patients were using colchicine, and 53% were using steroids with a median dose of 11 mg/day (IQR 10-16). The study showed a significant corticosteroid-sparing effect, with 25% of patients discontinuing steroids by week 12, which increased to 38% by the end of the 12-month follow-up. Additionally, the complete response rate increased from 60% to 76.7% after 12 months, with BSAS showing a sevenfold decrease.

The STELABEC trial, a prospective, open-label Phase 2 study, included patients with colchicine-resistant recurrent oral and/or genital ulcers.[37] The study enrolled 15 patients, nine of whom were male, with a mean age of 35.5±9.5 years. At week 24, the number of oral ulcers decreased by an average of 85%, and 73.3% of patients showed a clinical response, with complete responses seen in 60% of cases. The number of oral ulcers ($p=0.0017$) and the mean pain score for oral ulcers on VAS ($p=0.0005$) decreased significantly, accompanied by improvements in disease activity and quality of life scores ($p<0.05$). By week 52, disease activity and quality of life improvements were maintained, along with a sustained complete response rate. Three out of four patients who had elevated serum CRP levels (median 13 mg/L) associated with poor response switched therapy.

In 2017, Mirouse et al.[38] conducted a pilot study demonstrating that ustekinumab effectively reduced serum IL-12 and IL-17 levels in patients with colchicine-resistant oral ulcers ($p=0.008$). The study included 14 patients with both oral and genital ulcers, 60% of whom were male, with a median age of 39. By week 12, 69.2% of patients achieved complete remission. Disease activity, measured by the BSAS decreased significantly ($p=0.01$). A corticosteroid-sparing effect was observed, with the median daily steroid dose reduced by 41% ($p=0.02$). However, 29% of patients experienced relapses as early as five months (IQR 2-9.8) after treatment initiation.

JANUS KINASE (JAK) INHIBITORS

The Chinese pilot studies on tofacitinib and baricitinib demonstrated successful remission in Behçet's vascular involvement; however, tofacitinib failed to achieve remission in intestinal involvement.[39-41] The study on the specific JAK 1-2 inhibitor baricitinib for refractory vascular involvement included 17 patients, with venous, arterial, and cardiac involvement observed in 23.5%, 35.3%, and 47.1% of cases, respectively.[39] Thirteen patients had previously received cyclophosphamide, and seven had undergone TNF inhibitor therapy. After 10.7±5.3 months of treatment with 2 mg/day baricitinib, acute phase reactants decreased, and BDCAF scores resolved. The complete response rate was 88.2%, with seven patients (53.8%) on ≤5 mg/day of glucocorticoids. Among the seven patients who underwent repeat imaging, five showed radiological improvement in vascular lesions.

The pilot study investigated the JAK 1/3 inhibitor tofacitinib in refractory patients, including 13 individuals.[40] Six patients had gastrointestinal involvement, five had vascular or cardiac involvement, and two had joint involvement. Ten patients had previously been treated with cyclophosphamide, and six had received biologic DMARDs. The median BDCAF score was 5 (IQR 4-5). After a median of eight months (IQR 5.5-19), patients with vascular or articular involvement achieved both clinical and radiological remission. Among three patients with uncomplicated gastrointestinal involvement refractory to cyclophosphamide and thalidomide, one showed improvement. However, the outcome in another patient with perforation and fistula formation, refractory to a biological DMARD, worsened. Tofacitinib's role in complicated intestinal involvement of Behçet's syndrome appears unfavorable, similar to its effect in Crohn's disease. Four TNF inhibitor naive patients with uncomplicated intestinal Behçet's syndrome reported achieving remission with tofacitinib.[42] Another case report involved a patient with intestinal Behçet's syndrome who had a history of perforation.[43]

The pilot study of baricitinib for refractory intestinal Behçet included 13 patients with active ulcerative lesions and/or fistulas.[41] Baricitinib was initiated at doses of 2 to 4 mg, depending

on disease activity, which was assessed using the Disease Activity Index for Behçet's Disease (DAIBD), a 4-point global gastrointestinal symptom score, and endoscopy scores. During a median follow-up of 11 months (IQR 9-14), the dose was increased to 4 mg for four patients who had an inadequate response to 2 mg, while those in complete remission tapered the dose. The complete remission rate was 76.92% (10/13), and mucosal healing occurred in 66.67% (6/9) of patients. DAIBD scores significantly decreased after a median of five months of treatment. In 10 patients on glucocorticoids, the median dose was reduced from 15 mg/day to 8.75 mg/day (p=0.016). Inflammatory markers also improved, with a significant reduction in C-reactive protein levels (p=0.017).

One case report describes upadacitinib providing remission, while another demonstrates its potential for maintaining remission previously achieved with baricitinib in TNF inhibitor refractory intestinal Behçet's syndrome.[44,45] Upadacitinib also achieved remission in a patient with spondyloarthritis and Behçet's syndrome, involving mucocutaneous, articular, and ocular symptoms, although its effect on ocular involvement was not specified.[46] The only prospective study of upadacitinib for ocular involvement could not demonstrate glucocorticoid-sparing effects due to its heterogeneous cohort, which included just one case (8.3%) of Behçet's uveitis (anterior).[47] Tofacitinib has also been shown to spare glucocorticoids and achieve remission in refractory ocular involvement.[48,49]

The use of JAK inhibitors in adolescents remains uncertain, as highlighted by a case report in which one of two adalimumab-refractory macular edema patients treated with upadacitinib, an adolescent, developed mild side effects.[50] The side effects seen in pilot studies of baricitinib, including anemia, hepatic impairment, peripheral neuropathy, premature ovarian failure, and osteoporosis, may limit its use in the pediatric population.[39-41]

"STEP-UP" OR "STEP-DOWN" TREATMENT FOR ACTIVE MAJOR ORGAN INVOLVEMENT

The typical strategy for immunosuppressant use in patients with major organ involvement had been to start with a conventional agent such as azathioprine. In case of relapses or failure to obtain remission, one would switch to a biologic agent such as interferon-alpha or a TNF inhibitor or add another conventional agent such as cyclosporine-A in patients with uveitis.[51] An exception to this was arterial and large vein involvement, in which case cyclophosphamide would be the first choice. This "step-up" approach has changed over the years with more patients being treated with first-line biologics. The reasoning behind a "step-up" approach is that more than half of the patients respond well to conventional immunosuppressants. Real-world data from a cohort of Behçet's uveitis patients showed that 59% of the patients performed well on conventional immunosuppressants including azathioprine and cyclosporine-A.[52] A prospective study of Behçet's syndrome patients who had their first deep vein thrombosis episode showed that 55% of the patients were free of relapses over a mean follow-up of 41 months under treatment with azathioprine.[53] A retrospective study of Behçet's syndrome patients with gastrointestinal involvement showed that around two-thirds of the patients showed a good response to 5-ASA derivatives with or without azathioprine.[54] Based on these studies one may argue that if all patients with organ involvement are given first-line biologic treatment, more than one-half would have used biologic agents unnecessarily. On the other hand, a retrospective study among Behçet's syndrome patients with uveitis showed that patients who were prescribed adalimumab in addition to conventional immunosuppressants as initial treatment had a better visual outcome when compared to patients who were prescribed only conventional immunosuppressants.[55] In our opinion, the decision between a step-up or step-down strategy depends on individual factors that would predict the outcome. Current observations suggest that patients with Behçet's uveitis who have severe vitreous haze, inflammatory lesions within the arcades, extensive leakage on fluorescein angiography, and active inflammation in addition to reduced visual acuity due to structural damage from previous episodes are candidates for initial aggressive therapy.[56] Patients with arterial aneurysms or thrombosis, large vein thrombosis, and intracardiac thrombosis were already being treated with cyclophosphamide for induction therapy. Recent data discussed

above shows that infliximab can be a good alternative for such patients for both induction and maintenance treatment.[13,14] Future studies are needed to accurately identify patients who carry a higher risk of severe disease course with more damage, in order to select those who would benefit from initial biologic therapy.

DISEASE ASSESSMENT

Reliable disease assessment is crucial for a good management strategy. Challenges in disease assessment in patients with Behçet's syndrome include heterogeneity of outcomes and outcome measures that are being used, and lack of standard definitions for disease states such as relapse, remission, or response. In order to overcome these challenges, the OMERACT Behçet's syndrome working group has undertaken a multistep process that comprised a systematic review, focus group meetings among patients, physicians, and researchers, and a 3-step Delphi exercise.[57-59] As a result, a Core Set of Domains was established.[60] Efforts are continuing to identify instruments that match the domains, in order to develop a Core Set of Outcome Measures for Behçet's syndrome. Although the main aim in developing such a core set is harmonizing clinical studies, it would also help to optimize disease assessment in daily practice.

DEVELOPING A "TREAT-TO-TARGET" STRATEGY

Treat-to-target strategies were developed for several rheumatic diseases starting with rheumatoid arthritis. These entail determining treatment targets that would predict good long-term outcomes, determining the time intervals and instruments for monitoring the achievement of these targets, and developing predefined strategies for treatment modification when the target is not met. Such a strategy that would ensure preserved quality of life in the short term and prevent damage in the long term is also desirable for Behçet's syndrome. However, there are certain challenges. The heterogeneous nature of Behçet's syndrome renders it impossible to define a single target that would be applicable to all patients who have different types of organ involvement and different levels of severity. Moreover, the frequency of monitoring and the vigilance in treatment modifications when the target is not met would be different for each domain. Currently, ongoing efforts aim to identify the outcomes and outcome measures that are candidates for use as feasible targets. Data-driven validation of these targets will require multinational and multidisciplinary work to ensure that these targets are feasible, reliable, and predict long-term outcomes. Subsequently, studies that compare long-term outcomes among patients treated according to these treat-to-target strategies with patients who received standard care will be needed.

In conclusion, while significant progress has been made in the management of Behçet's syndrome, there is still a need for more effective and safer therapies. In addition to emerging treatments, improving the use of currently available treatment modalities through better risk assessment and better monitoring of the patients by developing novel outcome measure instruments may improve patient outcomes and quality of life. Continued research and clinical trials are essential to advance our understanding of this complex disease and develop novel therapeutic strategies.

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