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Recommendations

EULAR recommendations for the management of Behçet's syndrome: 2025 update

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A R T I C L E I N F O

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A B S T R A C T

Objectives: This study aims to update the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of Behçet's syndrome according to the updated EULAR standard operating procedures.
Methods: The task force comprised 29 members from 11 countries, including 19 rheumatologists, 2 ophthalmologists, 1 dermatologist, 1 gastroenterologist, 1 neurologist, 1 health professional, 2 patient research partners, and 2 Emerging EUlar NETwork members. Research questions were proposed by the task force through a Delphi survey and formulated into patients, interventions, comparison, and outcomes (PICO) questions for the systematic literature review. The results of the systematic literature review were discussed among the task force members. Previous recommendations and overarching principles were modified, and new recommendations were developed as needed. The updated recommendations were voted, and the levels of evidence and levels of agreement were determined.
Results: The updated recommendations consist of 5 overarching principles and 12 recommendations that were tabulated according to organ involvement. Among the 12 recommendations, 1 was a new recommendation, 7 recommendations were modified, and only the wording was changed in 4 recommendations. The overarching principles focus on the importance of recognising the relapsing and remitting disease course and individualising treatment according to disease activity and prognostic risk factors, and emphasise the importance of a multidisciplinary approach, patient education, and shared decision making for optimal care. For mucocutaneous and joint involvement, colchicine is recommended as the first-line treatment modality. Apremilast and immunosuppressives such as tumour necrosis factor alpha (TNFα) inhibitors are recommended for refractory patients. For patients with organ involvement, more aggressive treatment with glucocorticoids and immunosuppressives is recommended for rapid induction of remission. Early use of monoclonal antibodies against TNFα is encouraged in patients with organ or life-threatening manifestations.
Conclusions: These recommendations, which were updated based on new evidence and expert opinion, provide guidance for all stakeholders involved in the management of patients with Behçet's syndrome to improve the quality of care of these patients.

INTRODUCTION

Behçet's syndrome (BS) is a systemic vasculitis that affects large, medium, and small-sized arteries and veins. This wide range of vascular inflammation, which has resulted in classifying BS as a variable vessel vasculitis, causes various organ manifestations, including uveitis, arterial aneurysms, thrombosis affecting arteries, veins, cerebral venous sinuses, and the right

heart, gastrointestinal ulcers, and parenchymal nervous system lesions, in addition to inflammatory skin, mucosa, and musculoskeletal manifestations. The heterogeneity in the type and severity of manifestations that are active in an individual patient mandates individualised treatment strategies to preserve organ function and quality of life [1−4].

Management of BS has substantially changed over the last decades. In the recent past, glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including immunosuppressives such as azathioprine, cyclosporine-A, cyclophosphamide, and methotrexate, have been the mainstay of treatment for organ involvement and refractory mucocutaneous and joint involvement. The first biologic disease-modifying antirheumatic drug (bDMARD) that was successfully used in BS was interferon-alpha, followed by tumour necrosis factor alpha inhibitors (TNFαi). However, interferon-alpha, which was an important treatment option especially for patients with eye, mucocutaneous, and joint involvement, is no longer available in Europe and many other parts of the world. More recently, other anticytokine bDMARDs, including interleukin (IL)-1, IL-6, IL-17, and IL12/23 inhibitors, and targeted synthetic disease-modifying antirheumatic drugs, including apremilast and Janus kinase (JAK) inhibitors, have started to be used with different levels of evidence [5].

The first European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of BS were published in 2008 [6], and these were updated in 2018 [7]. New evidence has become available since the 2018 update, including randomised placebo-controlled trials, randomised controlled trials (RCTs) comparing csDMARDs with bDMARDs, and head-to-head RCTs comparing 2 different bDMARDs. Moreover, observational studies are available that tackle questions like the benefit of using concomitant csDMARDs with TNFαi in active patients, relapse rates in long-term follow-up with different agents used for maintenance, and withdrawal of these agents in patients who achieve sustained remission. These new studies prompted an update of the EULAR recommendations for the management of BS.

In this recommendation set, we aimed to bring together the most recent evidence with expert opinion from different disciplines, including rheumatology, dermatology, ophthalmology, gastroenterology, and neurology, together with health professionals and patient research partners. The target population of these recommendations includes physicians from all disciplines and health care professionals taking care of patients with BS, physicians in training, patients with BS and patient organisations, private and public reimbursement agencies, policy makers, and the pharmaceutical industry.

METHODS

A proposal was submitted to the EULAR Quality of Care committee for updating the EULAR recommendations for the management of BS. After approval, a task force was formed comprising the steering committee which included the 2 convenors (GH and HY), a methodologist (SR), a comethodologist (GT), and 2 fellows (YO and SNE) who conducted the systematic literature reviews (SLRs), in addition to 13 rheumatologists (5 of them recruited among those who applied to an open call by EULAR for these recommendations), 2 ophthalmologists, 1 dermatologist, 1 gastroenterologist, 1 neurologist, 1 health professional, 2 patient research partners, and 2 Emerging EUlar NETwork members. Among the 29 task force members from 11 countries, 16 (55%) were new members. Task force members disclosed their potential conflicts of interest at the beginning of the project. Updated EULAR standard operating procedures (SOPs) were followed throughout the process [8].

Research questions that would address areas not covered by the previous recommendations or that were previously included but needed updating were proposed by the task force members through a Delphi survey and formulated into patients, interventions, comparison, and outcomes (PICO) questions by the steering committee. The SLR protocol was recorded in International Prospective Register of Systematic Reviews (CRD42025637593) for the 2 SLRs, 1 on major organ involvement and the other on mucocutaneous and joint involvement, similar to what was done during the 2018 recommendations [9,10]. These SLRs, including studies published between October 2015 and November 2024, were performed by the fellows under the guidance of the methodologist, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Medical Literature Analysis and Retrieval System Online (Ovid), Embase, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database, Epistemonikos, and clinicaltrials.gov databases and abstract archives of International Conference on Behçet's Disease, the American College of Rheumatology, and EULAR congresses during 2023 and 2024 were used for the literature search. Data extraction was performed separately for major organ involvement comprising eye, vascular, gastrointestinal, and nervous system involvement, and for mucocutaneous and joint involvement. Quality of evidence was assessed using the Cochrane Risk of Bias (RoB) tool [11] for RCTs and Newcastle-Ottawa scale [12] for cohort and case-control studies. Details of the SLRs are presented in 2 separate manuscripts, 1 on major organ involvement and the other on mucocutaneous and joint involvement, as well as overall disease activity and health-related quality of life (HRQoL) [13,14]. These 2 manuscripts present an essential part of the recommendation development process and are intended to be read together with this recommendation manuscript.

The results of the SLR were tabulated into standardised tables that summarised the study characteristics, population, interventions, outcomes, and RoB of each study. These were initially discussed among the steering committee, and suggestions for updating the recommendations were drafted to facilitate the discussions during the face-to-face meeting with the whole task force. The SLRs were presented to the task force members together with a summary of the previous evidence and the suggestions for modification of the previous recommendations, in a one-and-a-half-day face-to-face meeting. During this meeting, the previous recommendations and overarching principles (OAPs) were modified based on the new evidence and expert opinion, and 1 new recommendation was formed. In some of the recommendations, only the wording was changed for the purposes of brevity and clarity, in line with the updated EULAR SOP. The updated recommendations were voted and a minimum of 75% of the votes were required to change a recommendation or to develop a new one. If there was a consensus on changing the recommendation or formulating a new one, discussions took place on the exact wording. Consensus was reached if $\geq$75% of the members voted in favour of the recommendations in the first (or $\geq$67% and $\geq$50% in a second and third) round. If multiple rounds of voting were necessary, discussion took place in between voting rounds to refine the drafted statements.

The level of evidence (LoE) for each recommendation was determined using the 2011 version of the Oxford Centre of Evidence-Based Medicine levels of evidence, following the EULAR

SOP [15]. As for the 2018 recommendations, the 2009 version of the Oxford Center of Evidence-Based Medicine levels of evidence had been used. The main differences between the 2011 and 2009 Oxford LoE versions are that the 2011 update removed the a/b/c sublevels, simplifying the hierarchy; reorganised the table by clinical question type; added categories for screening and treatment harms; emphasised n-of-1 and large-effect observational studies; introduced mechanism-based reasoning at level 5; and adopted explicit rules for grading up or down the LoE. The differences between grading systems led to a decrease in the LoE of some of the recommendations, although the content was not changed.

Finally, the recommendations were sent to the task force members for rating their level of agreement (LoA) on a scale of 0 to 10, where 0 meant no agreement and 10 meant full agreement. Task force members were also asked how they rated the feasibility of implementation and potential impact on quality of care of each recommendation on a scale of 0 to 10, as well as their suggestions for future research. The recommendations with the highest scores for implementability and impact on quality of care were selected for determining quality indicators. Two quality indicators were proposed by the steering committee and discussed within the task force. The final manuscript was reviewed and approved by all task force members, followed by the EULAR Quality of Care committee.

RESULTS

The updated recommendations for the management of BS consist of 5 OAPs and 12 recommendations. The OAPs and recommendations are presented in Table 1 together with their LoE and LoA. Similar to the previous versions, these recommendations were developed according to organ involvement [6,7]. Among the 12 recommendations, 1 was a new recommendation, 7 recommendations were modified, and only the wording was changed in 4 recommendations. None of the recommendations was exactly the same as the previous version.

The SLRs yielded a total of 7128 articles, and 83 of them were selected after full-text review. There were 3 articles that reported different outcomes of a single study [16–18]. Overall, 81 studies were included. These comprised 9 RCTs, 34 observational comparative studies, and 38 observational noncomparative studies that were analysed to inform the task force. Among these, mucocutaneous involvement was addressed by 13 studies, joint involvement by 6, leg ulcers by 2, eye involvement by 24, vascular involvement by 22, gastrointestinal involvement by 14, nervous system involvement by 7, overall disease activity by 5, HRQoL by 4. Twelve studies included data pertaining to more than 1 PICO.

Overarching principles

A. BS has a relapsing and remitting course that may be organ- or life-threatening, while disease manifestations may ameliorate over time.
B. The goal of treatment is to prevent irreversible organ damage and to maximise HRQoL.
C. Organ involvement should be evaluated throughout the disease course, and mimickers should be ruled out with appropriate modalities.
D. Treatment should be individualised according to age, sex, type, and severity of organ involvement, disease duration, and patient preferences.
E. A multidisciplinary approach, patient education, shared decision making, adherence to treatment, and lifestyle changes are necessary for optimal care.

It is important to recognise the variable disease course of BS for successful management. The relapsing and remitting course mandates a strategy that aims at both prompt suppression of inflammatory attacks and prevention of new ones. The relapses can be frequent for skin, mucosa, and joint manifestations, and somewhat for uveitis, whereas relapses of other organ manifestations tend to be sparse. Relapses of organ involvement need to be treated immediately and aggressively due to the potential damage that can be caused. On the other hand, management of mucocutaneous and joint manifestations depends mainly on the level of impact on the patient's quality of life. Treatment should be individualised to cover all types of organ involvement that are active. The fact that in many patients, disease manifestations tend to diminish as the disease evolves is also important, meaning that tapering and withdrawal of immunosuppressives should be aimed at in the long run. However, even if the patient achieves drug-free remission, caution is still needed for organ relapses and new organ involvement [19]. It is also important to differentiate relapses from comorbidities or complications, such as infections, because these can mimic organ manifestations of BS, where immunosuppressives may be harmful. A patient with BS can develop syphilitic uveitis, lymphoma, or central nervous system, or gastrointestinal tuberculosis that can be detrimental if misdiagnosed. Especially, tuberculosis should not be overlooked in patients who use TNFαi [20]. Diagnostic modalities such as cranial magnetic resonance imaging and magnetic resonance venography, fundus fluorescein angiography, or gastrointestinal endoscopy should be used to confirm the diagnosis and to rule out mimickers. Genetic testing may be necessary in selected patients, such as those with a strong family history and onset of symptoms during early childhood, to rule out monogenic mimickers such as A20 haploinsufficiency, especially in parts of the world with a low prevalence of BS and other conditions like trisomy 8-associated autoinflammatory disease [21].

The heterogeneity of clinical manifestations makes it impossible to develop a standard strategy for the management of BS. The choice of treatment modalities relies on demographic factors such as sex, age, and disease duration, as well as the type and severity of organ involvement. Demographic factors that are associated with a more severe disease course with more frequent organ involvement are being male, having a young age at disease onset, and being in the early years of the disease course [22]. These patients may require more aggressive treatment and more frequent follow-up to prevent long-term damage. The presence of organ involvement in addition to mucocutaneous and joint involvement is an important indicator of disease severity that necessitates the use of immunosuppressives. There are additional clinical features with prognostic importance that need to be considered when planning the treatment. These are discussed separately under each organ involvement.

The involvement of several organs and systems, including the eyes, central nervous system, gastrointestinal system, musculoskeletal system, arteries, and veins, in addition to the skin and mucosa lesions, requires a close collaboration between disciplines. A multidisciplinary approach, including rheumatologists, dermatologists, ophthalmologists, neurologists, gastroenterologists, and vascular surgeons, is crucial for the diagnosis, severity assessment, treatment, and follow-up of each manifestation.

Patient education is important for the patients' active participation in developing individualised treatment strategies, shared

decision making, and optimising treatment adherence. Lifestyle changes, including good oral hygiene, a healthy diet, and exercise, are also important. Patients should be informed about the association between poor oral hygiene and an increased number of oral ulcers. Quitting smoking should be encouraged, but patients must be warned about the possibility of a transient increase in the number of oral ulcers.

Recommendations

Mucocutaneous involvement

- Recommendation 1: colchicine should be the first-line treatment for recurrent mucocutaneous lesions. In patients refractory or intolerant to colchicine, apremilast or TNFαi should be considered (LoE 2).
- Recommendation 2: topical measures such as glucocorticoids can be used for the management of oral and genital ulcers (LoE 2); chronic use of systemic glucocorticoids should be avoided (LoE 5).

Management of mucocutaneous involvement depends on the frequency and severity of lesions and how much they bother the patient. Preserving quality of life is the main goal of treatment, because mucocutaneous lesions do not cause damage except for genital ulcers, which may leave whitish, superficial scars on the skin. It is important to balance the adverse event risk with the potential benefit of therapeutic agents. Some patients may prefer to have occasional mucocutaneous lesions and manage them with topical agents instead of using systemic treatment, especially immunosuppressive. On the other hand, some experts prefer using systemic therapies that are well-tolerated to control the disease and avoid the risk of progressing to a more severe form.

Colchicine remains the first-line treatment modality for patients with active mucocutaneous manifestations who do not have major organ involvement, based on its efficacy, especially for genital ulcers and nodular lesions, its tolerability, and low cost (Fig 1). Topical measures, including glucocorticoids applied to the ulcer and good oral hygiene, are recommended for oral ulcers [23]. Topical glucocorticoids with high potency can be preferred, but should not be used for a prolonged duration. Topical glucocorticoids together with topical antibiotics may be preferred for active genital ulcers, since these lesions may become infected. Papulopustular lesions may be treated with topical measures that are used in acne vulgaris and with retinoids in severe cases. In patients who have active major organ involvement, immunosuppressives that are used for organ involvement are usually sufficient to suppress mucocutaneous lesions. These patients may additionally use topical agents if they experience occasional ulcers. Systemic glucocorticoid use is not recommended for patients with only mucocutaneous lesions, to avoid long-term adverse events. A short course of low-dose glucocorticoids may be tried during severe genital ulcers to accelerate the healing.

Some patients may continue to have bothersome mucocutaneous lesions despite colchicine and topical measures. Apremilast may be preferred in such refractory patients. Two RCTs showed that apremilast is an effective treatment modality for oral and genital ulcers, improves quality of life, and has a good safety profile [16,24]. Apremilast may be used in combination with csDMARDs, if necessary. TNFαi may also be used as an alternative. In a small RCT comparing adalimumab (n = 22) and infliximab (n = 18), the mucocutaneous remission rate at month 6 was 100% for adalimumab and 86% for infliximab [25]. The median time to response was shorter with adalimumab (42 days) compared to infliximab (152 days, P = .002). There were significant improvements in quality of life and overall disease activity in both groups, and the scores were similar for adalimumab and infliximab at the end of follow-up. A retrospective study showed similar response rates between apremilast and TNFαi for oral and genital ulcers [26]. Screening for latent tuberculosis and viral hepatitis, as well as vaccination according to local recommendations, is crucial before starting a TNFαi. Azathioprine and interferon-alpha are other agents that have been shown to provide benefit for mucocutaneous lesions [27,28]. There are severe shortages and instability in the availability of interferon-alpha, including the pegylated form, in many parts of the world. Thus, interferon-alpha was removed from the wording of the recommendations, but still emphasised in the text for each organ manifestation that it was shown to be beneficial. The task force considers interferon-alpha to be an important therapeutic agent that many patients with BS would benefit from if its manufacture were restarted.

Although there are no RCTs with the IL12/23 inhibitor ustekinumab, 2 prospective noncomparative observational studies with high RoB have shown significant improvement in the number of all mucocutaneous manifestations and pain of oral ulcers at week 24 compared with baseline, in addition to glucocorticoid tapering [29,30].

Previous studies had also shown benefit with thalidomide and dapsone [31,32], but these are currently not preferred due

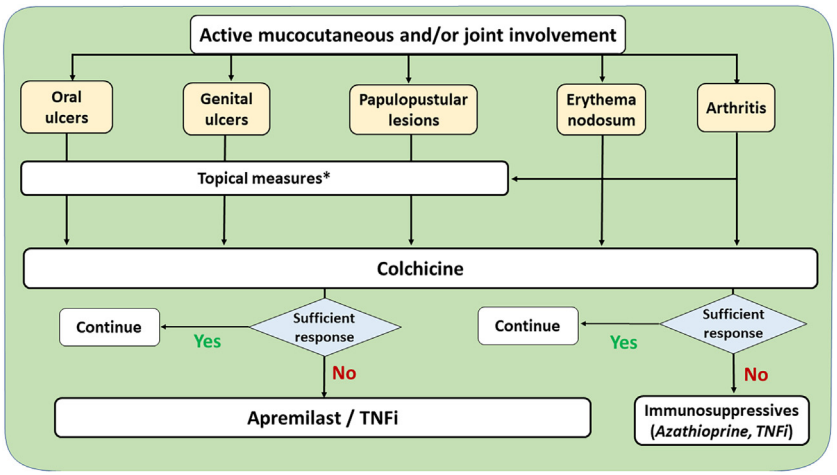

Figure 1. Management of mucocutaneous and joint involvement. *Topical glucocorticoids can be used for oral and genital ulcers. Topical antibiotics may be used in combination with topical glucocorticoids when necessary. Topical measures that are used in acne vulgaris may be used for papulopustular lesions. Consider intra-articular glucocorticoids for patients with monoarthritis. TNFαi, tumour necrosis factor alpha inhibitors.

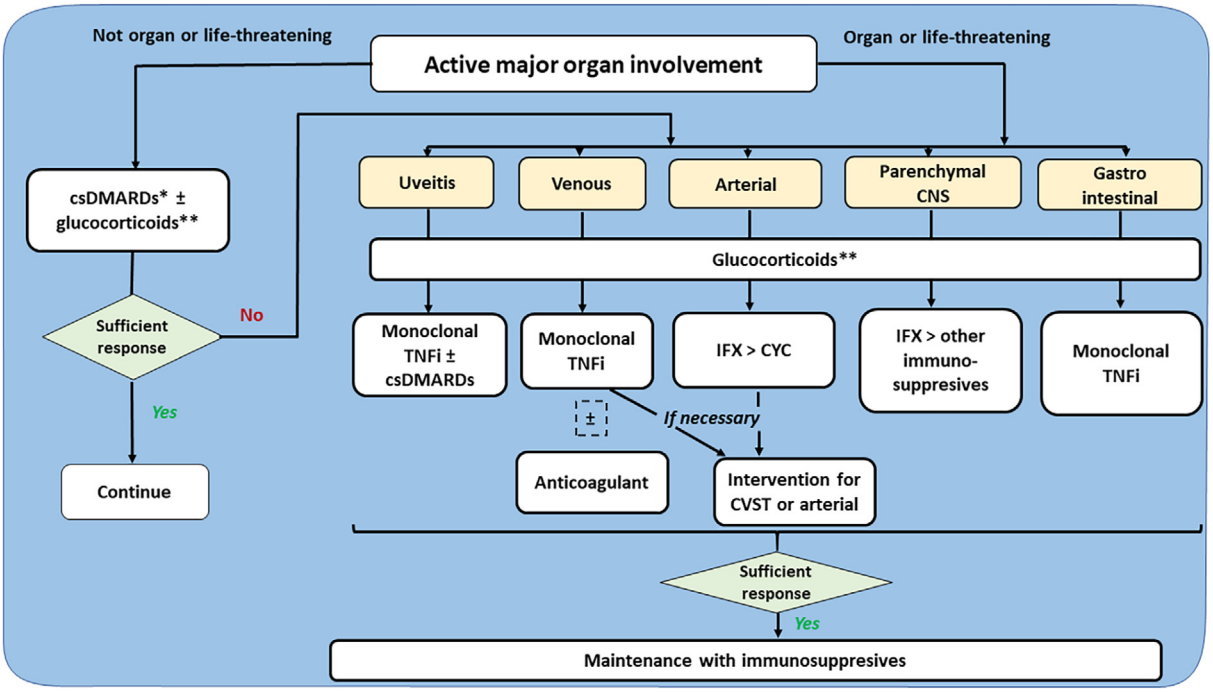

Figure 2. Management of major organ involvement. *csDMARDs include azathioprine and/or cyclosporine-A for uveitis, azathioprine for lower extremity venous thrombosis and nervous system involvement, and azathioprine and/or 5-ASA for gastrointestinal involvement. **High-dose glucocorticoids are recommended for organ or life-threatening major organ involvement; intravenous pulse methylprednisolone may be preferred for major venous thrombosis, arterial, and parenchymal nervous system involvement. CNS, central nervous system; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CVST, cerebral venous sinus thrombosis; CYC, cyclophosphamide; 5-ASA, 5-aminosalicylic acid; IFX, infliximab; TNFαi, tumour necrosis factor alpha inhibitors.

to potential adverse events. These agents are not recommended for mucocutaneous involvement since their risk-benefit ratio does not support their use in the majority of patients. If they are required due to a lack of other options, especially in resource-limited settings, they would have been used by experienced specialists with appropriate monitoring.

Joint involvement

- Recommendation 3: colchicine should be the first-line treatment for acute arthritis (LoE 2). Immunosuppressives should be considered in recurrent and chronic cases (LoE 3).

Previous RCTs have shown favourable results with colchicine [33–35], and based on its efficacy, tolerability, and cost, the task force did not change the recommendation for the first-line use of colchicine (Fig 1). In patients with recurrent episodes of arthritis despite colchicine, immunosuppressive agents such as azathioprine and TNFαi may be tried [26,28,36]. Apremilast may be an option when immunosuppressives are not preferred. There were very few patients with arthritis in the apremilast RCTs [16,24]. An observational comparative study showed similar arthritis rates at month 3 and month 6 with apremilast and TNFαi, but the proportion of patients with arthritis in the apremilast group was already small (15%) compared with the TNFαi group, in which 45% of the patients had arthritis [26]. Low-dose oral glucocorticoids or intra-articular glucocorticoid injections, and nonsteroidal anti-inflammatory drugs can also be tried during arthritis episodes. Continuous low-dose glucocorticoids may be preferred to immunosuppressives in selected patients who are refractory to colchicine. Prospective single-arm studies with ustekinumab with high RoB showed a significant reduction in the occurrence of arthritis at week 24 compared with baseline [29,30].

Eye involvement

- Recommendation 4: immunosuppressive treatment must be given in all patients with Behçet's uveitis with the aim of inducing and maintaining clinical and angiographic remission (LoE 2). Monoclonal anti-TNFα antibodies (LoE 2), preferably infliximab in combination with other immunosuppressives, should be used in those with sight-threatening inflammation involving the posterior segment (LoE 5). Glucocorticoids should not be given as monotherapy (LoE 2).

Glucocorticoids help to provide rapid control of inflammation in Behçet's uveitis and can be started with a dose of 0.5 to 1 mg/kg/d (Fig 2). Intravenous (IV) methylprednisolone pulses in addition to immunosuppressives provided better visual acuity compared with no IV pulses in an RCT [37]. On the other hand, infliximab showed superior efficacy compared to IV methylprednisolone pulses in a previous study [38]. Topical glucocorticoids and intravitreal injections may also be used during acute exacerbations in addition to immunosuppressives [9,39,40].

In addition to glucocorticoids, immunosuppressives are crucial for all patients with BS with active uveitis, and the choice of immunosuppressives depends on severity and prognostic factors. Sight-threatening posterior uveitis with findings such as severe vitreous haze and extensive capillary leakage on fundus fluorescein angiography requires early use of monoclonal TNFαi. First-line use of bDMARDs for patients with sight-threatening posterior uveitis was already included in the previous version of the recommendations, and now there is some controlled evidence to support this [41]. Adalimumab was previously approved for the treatment of noninfectious inflammatory uveitis based on 2 RCTs [42,43]. A recent RCT comparing adalimumab, interferon-alpha, and cyclosporine-A in Behçet's uveitis showed that adalimumab was superior to cyclosporine-A for

controlling uveitis with a significantly lower annual relapse rate, whereas the annual relapse rate was similar between adalimumab and interferon-alpha [44]. Secondary outcomes, including visual acuity, cystoid macular oedema, anterior chamber cell score, vitreous haze score, and retinal vascular lesions, were similar across the 3 groups. It should be noted that this study was criticised due to its limited external validity, because the patient population had a long history of inadequately treated uveitis and patients continued to use moderate to high doses of prednisone for a long time during the trial. Another RCT that compared infliximab with interferon-alpha included 10 patients in the infliximab group and 7 in the interferon-alpha group who had active uveitis at baseline [45]. The visual acuity was similar between the 2 groups at week 12. Another small RCT compared interferon-alpha with cyclosporine-A and showed a shorter time to complete remission and better 'Behçet's disease ocular attack score-24' scores with interferon-alpha, despite no difference in complete remission rates between the groups [46]. Interferon-alpha is an effective agent for Behçet's uveitis, which provides sustained remission, but, as mentioned above, it is not available in European countries.

Although monoclonal TNFαi are more effective than conventional agents in controlling uveitis in BS, some physicians consider that there may be patients with mild uveitis who can be started treatment with a conventional immunosuppressive such as azathioprine, cyclosporine-A, or mycophenolate mofetil. These patients can be switched to a bDMARD or a bDMARD may be added if remission cannot be obtained with conventional immunosuppressives or in case of relapse. There is an unmet need for prospective studies comparing long-term outcomes of patients treated with first-line bDMARDs to patients who are started with conventional immunosuppressives and switched to a bDMARD in case of relapse.

There were no RCTs comparing 2 TNFαi in uveitis. Observational comparative studies reported inconsistent results regarding the difference between infliximab and adalimumab [47–51]. However, there was a general consensus that IV infliximab may have a more rapid onset of action compared with adalimumab, whereas long-term compliance and drug survival may be better with adalimumab. In patients who have relapses despite being on a monoclonal TNFαi, escalating the current TNFαi by decreasing the dose intervals or increasing the applied dose may be tried before switching to another monoclonal TNFαi. A small retrospective comparative study with high RoB reported similar visual acuity, cystoid macular oedema improvement, and vitritis score with tocilizumab compared with infliximab and adalimumab [48]. The majority of the patients who used tocilizumab were refractory to TNFαi.

The question of whether csDMARDs should be added to TNFαi has not been addressed by any RCTs. Observational studies comparing patients who used csDMARDs together with TNFαi to patients who used TNFαi alone reported conflicting results [52–54]. The task force thought that adding csDMARDs to TNFαi may provide benefit by preventing immunogenicity and by not leaving the patient without treatment in case of a delay in obtaining the bDMARD. It was considered that csDMARDs and bDMARDs may be used concomitantly when the potential benefit outweighs the risk of adverse events for that patient.

Some patients with BS may initially present only with anterior uveitis, but the majority of those patients later develop posterior involvement. Only a small proportion of patients in Behçet's uveitis cohorts have isolated anterior uveitis during follow-up. In a retrospective cohort of 94 patients who presented with Behçet's uveitis during the 1990s, 18.6% had only anterior uveitis at 3 years, whereas this frequency increased to 25.4% among 115 patients who presented during the 2000s, suggesting a change towards a milder disease course over decades [55]. There is no consensus on whether these patients can be treated with only topical glucocorticoids during anterior uveitis attacks or if a systemic immunosuppressive is needed. Some experts think that systemic immunosuppressives are necessary for effective control of the disease and for preventing progression to a more severe form. Azathioprine may be preferred in young men with anterior uveitis because there is a high risk of developing posterior involvement in these patients [28]. The presence of vitreous cells at baseline was also suggested as a risk factor for developing posterior uveitis in patients with anterior uveitis [56]. Immunosuppressives should always be used in patients with hypopyon uveitis, which is, as a rule, associated with retinal vasculitis [57].

The aim of treatment for all types of major organ involvement is to provide complete remission rapidly, and this is very important for patients with uveitis, for preserving vision. Wider availability of imaging modalities has expanded the definition of remission to include angiographic remission, since leakage on angiography was shown to be associated with relapses in the long term [58]. The management should be planned and monitored together with an ophthalmologist. Monitoring with fundus fluorescein angiography to detect ongoing inflammation that may be present despite a normal fundus examination has been proposed. There are currently no studies that compare the outcome of patients whose treatment is modified based on fundus fluorescein angiography findings to those monitored without fundus fluorescein angiography. This is an important item in the research agenda. There is also no evidence to determine the optimal frequency of performing fundus fluorescein angiography for monitoring uveitis, but the task force considered that it is necessary at least when treatment changes are planned, including tapering of immunosuppressives.

There are no prospective studies that address drug cessation, and data from retrospective studies of patients who were able to discontinue TNFαi were not considered reliable enough to make a recommendation on withdrawal of immunosuppressives in patients with uveitis. The task force agreed that bDMARDs should be used for a long time to prevent relapses of uveitis. Angiographic remission should be ensured when discontinuation is attempted, and it should be done by gradual tapering. Many experts prefer continuing conventional immunosuppressives for even a longer duration.

Arterial involvement

- Recommendation 5: for the management of pulmonary and peripheral artery aneurysms, high-dose glucocorticoids and infliximab are recommended; cyclophosphamide may be an alternative (LoE 2). Glucocorticoids should be slowly tapered (LoE 5) and immunosuppressives, preferably monoclonal anti-TNFα antibodies, should be continued as maintenance (LoE 4).
- Recommendation 6: vascular procedures, if necessary, should not be delayed following the prompt initiation of medical treatment (LoE 4). For patients with pulmonary artery aneurysms at high risk of major bleeding, embolisation should be preferred to open surgery (LoE 5).

Glucocorticoids should be started immediately in patients with arterial involvement, typically with IV pulses of 1 g methylprednisolone for 3 consecutive days (Fig 2), followed by oral

prednisolone, equivalent to 1 mg/kg/d, which would be slowly tapered and discontinued over 6 to 12 months.

One of the important changes in these recommendations compared with 2018 was that infliximab was recommended as the first-line treatment in addition to high-dose glucocorticoids in patients with arterial involvement. This approach has been preferred over the recent years due to the high adverse event rates with cyclophosphamide and good experience with monoclonal TNFαi in patients with arterial involvement who were refractory to or did not agree to using cyclophosphamide [59–63]. Retrospective studies that reported on the long-term outcomes of TNFαi for vascular involvement showed high remission and low relapse rates. The majority of these patients were treated with infliximab and a smaller number with adalimumab. A recent RCT comparing IV infliximab and cyclophosphamide in patients with vascular and nervous system involvement supports this approach [64]. The study included patients with arterial aneurysms and/or thrombosis as well as patients with major venous thrombosis. Although there were only 18 patients with vascular involvement in the cyclophosphamide group and 19 in the infliximab group, infliximab provided higher remission rates compared to cyclophosphamide at week 24. The frequency of mild and moderate adverse events was lower with infliximab, while the frequency of severe adverse events was similar between the groups. Apart from the small number of patients, an additional shortcoming of this study was that it did not differentiate between the venous, pulmonary, and peripheral arterial forms of vascular disease in drug response. It should be noted that a cohort study reported higher remission rates in patients with pulmonary artery and venous involvement compared to patients with peripheral artery involvement [60]. Based on these studies, the task force decided that infliximab may be preferred to cyclophosphamide for remission induction in patients with arterial involvement. Cyclophosphamide is still an alternative to infliximab, especially in patients who are refractory, intolerant, or do not have access to TNFαi. Increasing the dose of infliximab, switching to another TNFαi or adding cyclophosphamide to infliximab has been reported in refractory cases with life-threatening arterial involvement [60]. However, caution regarding toxicity is required in such cases.

Another important difference from the 2018 recommendations was that monoclonal TNFαi were preferred to conventional immunosuppressives such as azathioprine for maintenance treatment. This change was based on low relapse rates with infliximab, both in the RCT [64] and in retrospective studies [60–63] with long-term follow-up that are mentioned above. There are no data to guide when and how immunosuppressives should be tapered and discontinued in patients with arterial involvement. The task force proposed that treatment should be continued for at least 5 years.

The recommendation on vascular procedures was not changed, and the importance of performing these procedures under adequate immunosuppression to reduce the risk of perioperative and postoperative complications was emphasised [65,66]. Emergency vascular procedures may be required for large and symptomatic peripheral artery and aortic aneurysms. The choice of vascular procedure, such as graft insertion, ligation, or bypass surgery, depends on the size and location of the aneurysm and the centre's experience. Synthetic grafts should be preferred to venous grafts due to a higher risk of thrombosis [66,67]. In patients with pulmonary artery aneurysms, endovascular procedures should only be considered if there is a high risk of life-threatening major bleeding, because high complication rates have been reported with these procedures [68–70].

Venous thrombosis

- Recommendation 7: for the management of acute thrombosis of deep veins, including cerebral venous sinuses, glucocorticoids and immunosuppressives, preferably monoclonal anti-TNFα antibodies should be considered (LoE 2). Immunosuppressives should be continued as maintenance (LoE 3).
- Recommendation 8: anticoagulants may be added, provided the risk of bleeding is low and coexistent pulmonary artery aneurysms are ruled out (LoE 5).
- Recommendation 9: in cerebral venous sinus thrombosis with vision-threatening intracranial hypertension, surgical interventions should be given prompt consideration (LoE 5).

Venous involvement is usually a less severe form of vascular involvement compared with arterial involvement. However, it still has significant morbidity. Venous thrombosis can result in postthrombotic syndrome with venous ulcers in the lower extremities, portal hypertension in Budd-Chiari syndrome, endomyocardial fibrosis when persistent intracardiac thrombosis is present, and intracranial hypertension that can lead to blindness when cerebral sinuses are involved extensively. Thus, prompt treatment with glucocorticoids and immunosuppressives is mandatory (Fig 2). A high-dose regimen starting with IV methylprednisolone pulses, similar to arterial involvement, may be preferred in acute thrombosis of large veins, intracardiac thrombosis, and vision-threatening cerebral venous sinus thrombosis. A moderate initial dose may be adequate for patients with lower extremity deep vein thrombosis.

Immunosuppressives, preferably monoclonal TNFαi, should be started immediately, together with glucocorticoids. In addition to the RCT favouring infliximab over cyclophosphamide for vascular involvement [64], there are 2 observational comparative studies that show better outcomes with bDMARDs compared with conventional immunosuppressives. One of these was a prospective study of patients who experienced their first lower extremity deep vein thrombosis [71]. This study showed that 45% of the patients experienced relapses with azathioprine as the initial immunosuppressive and that the relapse rate was lower and thrombus recanalisation rate was higher with interferon-alpha compared with azathioprine, even among patients who relapsed under azathioprine treatment. It should be noted that, similar to eye involvement, interferon-alpha was not recommended as a preferred treatment for venous involvement due to the lack of availability. The second study was a retrospective study that showed higher response rates with adalimumab compared with conventional immunosuppressives [72]. There are no studies that report long-term outcomes of patients with venous involvement who are initially given csDMARDs and switched to bDMARDs in case of refractory or relapsing disease, compared to patients who are started with first-line bDMARDs. The task force recommends that first-line bDMARDs with TNFαi may be preferred due to the serious morbidities that may result in refractory or relapsing cases.

Although cerebral venous sinus thrombosis follows a mild course with no recurrences in the majority of cases, there may be patients who experience vision-threatening intracranial hypertension despite medical treatment with high-dose glucocorticoids and immunosuppressives [73]. Irreversible vision loss can develop rapidly in such patients, and surgical interventions such as lumboperitoneal shunts or fenestration should be considered promptly.

There is still no controlled evidence for the use of anticoagulants in patients with BS with thrombosis. In addition to the 2

retrospective studies published before 2018 showing that anticoagulants did not decrease the risk of relapse of venous thrombosis [74,75], the study mentioned above, which compared adalimumab with conventional immunosuppressives, showed that additional anticoagulants did not improve outcomes in either group [72]. Other retrospective studies showed conflicting results regarding the benefit of adding anticoagulants to immunosuppressives on relapse rates and on preventing postthrombotic syndrome [62,76–83]. The task force did not recommend against anticoagulation due to the lack of controlled data, but advised caution against the risk of bleeding since arterial aneurysms are accompanied or preceded by venous thrombosis in the majority of patients and may become fatal with anticoagulation [84]. The optimal duration of anticoagulation in Behçet-related thrombosis remains unknown.

An important complication experienced by patients with postthrombotic syndrome is recurrent leg ulcers. These ulcers are usually refractory to treatment and require close collaboration with dermatologists and vascular surgeons. Bed rest and compression stockings, and bandages are important components of management. Antibiotics and debridement may be needed [85]. Maggot (*Lucilia sericata*) application was found useful for debridement with a good healing rate when used in addition to immunosuppressives [86]. Immunosuppressives have been used for leg ulcers because obliterative vasculitis, causing ischaemia, is suspected to contribute to the formation of ulcers in addition to venous stasis. However, a retrospective study showed that TNFαi do not seem to enhance the healing [60].

Gastrointestinal involvement

- Recommendation 10: diagnosis, assessment of severity, and management of gastrointestinal involvement should be based on endoscopy (LoE 5).
- Recommendation 11: in patients with gastrointestinal involvement, 5-aminosalicylic acid (5-ASA) or azathioprine should be used with or without glucocorticoids. In severe or refractory patients, monoclonal anti-TNFα antibodies should be considered (LoE 3).

Endoscopy is required for diagnosing patients with BS with gastrointestinal involvement, for differential diagnosis of mimickers such as Crohn's disease, ulcerative colitis, nonsteroidal anti-inflammatory drug-related ulcers, and tuberculosis, for determining severe disease requiring aggressive treatment, and for monitoring of patients to ensure complete remission [87].

Azathioprine or 5-ASA derivatives may be adequate to control mild to moderate gastrointestinal involvement (Fig 2) [9]. Prednisone at a dose of 0.5 to 1 mg/kg can be initiated during acute exacerbations. Glucocorticoids may be beneficial due to their rapid onset of action in patients with disturbing gastrointestinal symptoms and risk of potential complications such as bleeding and perforation. However, the possibility of masking signs of perforation with high-dose glucocorticoids should not be overlooked. Certain ulcer morphology features, such as volcano-type ulcers, deep ulcers, and ulcers larger than 2 cm, prompt treatment with monoclonal TNFαi due to a higher risk of bleeding and perforation [88]. There are no data that compare the efficacy of infliximab and adalimumab in patients with gastrointestinal involvement, but infliximab may be preferred due to its fast attainment of high therapeutic serum concentrations, a key consideration when rapid disease control is required in gastrointestinal ulcers at high risk for complications. Increasing the dose of TNFαi or switching to another monoclonal TNFαi may be considered in refractory patients. Adding thalidomide to TNFαi may be an option in rare cases that cannot be controlled with these measures [89]. Small case series with JAK inhibitors that show promising results for gastrointestinal involvement have been reported, but the results must be interpreted with caution due to the noncomparative design of these studies and their high RoB [90,91].

Surgery may be required due to severe bleeding, perforation, or obstruction [92,93]. It is important to provide effective immunosuppression to prevent perioperative complications [9].

Parenchymal nervous system involvement

- Recommendation 12: for active parenchymal involvement, high-dose glucocorticoids and immunosuppressives, preferably infliximab, should be initiated (LoE 2). Glucocorticoids should be slowly tapered (LoE 5) and immunosuppressives continued as maintenance (LoE 4).

Parenchymal nervous system involvement is an important cause of morbidity and mortality that requires immediate and effective immunosuppression to effectively control the inflammation and prevent damage. IV 1 g methylprednisolone pulses may be given in patients who present with a severe flare, followed by 1 mg/kg/d oral prednisolone (Fig 2). The pulses may be repeated up to 7 to 10 times in patients who show poor recovery from the relapse over the days. Observational studies have shown good response rates with infliximab [94–99]. In the RCT comparing infliximab with cyclophosphamide, among the very small number of patients, also with a heterogeneous type of disease, as was the case for vascular disease in this study, remission was obtained in 4 of 7 patients treated with cyclophosphamide and 5 of 8 patients treated with infliximab [64]. Infliximab is considered a good option for both inducing remission of flares and for long-term maintenance, aiming to prevent relapses. Adalimumab may be an alternative. The previous approach of starting with azathioprine and switching to a TNFαi in refractory cases has changed towards starting a TNFαi as first-line, since patients with acute nervous system involvement of BS carry a high risk of disability. Moreover, TNFαi may allow more rapid glucocorticoid tapering compared with azathioprine. Concomitant use of azathioprine with TNFαi may be considered for the same reasons discussed above for eye involvement. There are limited, uncontrolled noncomparative data with high RoB showing that tocilizumab may be beneficial in some patients with nervous system involvement who are refractory to other treatment modalities [100–103]. It should be noted that mucocutaneous flares have been observed in some patients with BS treated with tocilizumab [104].

Monoclonal TNFαi may be preferred for maintenance based on the low relapse rates that were reported [94–98]. There are no data to guide the tapering of immunosuppressives in patients who achieve sustained remission. The general approach is to continue maintenance treatment for at least 5 years, especially in younger patients who carry a higher relapse risk.

A meta-analysis showed an increased risk of nervous system involvement among patients with BS who use cyclosporine-A [9]. Thus, the task force advises against the use of cyclosporine-A in patients with nervous system involvement. This was a separate recommendation in the 2018 version. The task force considered that it would be adequate to mention it only in the text due to the decreased use of cyclosporine-A in patients with BS.

Quality indicators

Two recommendations were identified based on the highest scores among the task force members for the feasibility of implementation and impact on the quality of care of each recommendation. These recommendations were those involving joint involvement and arterial involvement. The quality indicators for these domains are provided in Table 2. These quality indicators are intended to give a measurable construct to assess the gap in providing healthcare.

Research agenda

The SLRs conducted to inform these recommendations highlighted existing gaps in the literature, which, together with key discussion points raised during the task force meeting, resulted in our proposed research agenda (Box).

DISCUSSION

The updated EULAR recommendations for the management of BS were developed based on studies with new treatment modalities, head-to-head trials with bDMARDs, and studies of csDMARDs and bDMARDs in patients with different types of organ involvement. Similar to the previous versions, the updated recommendations were developed based on organ involvement [6,7]. This is important because management of BS shows variability depending on organ involvement, since treatment response to pharmaceuticals showed differences across organ domains. Moreover, prognostic differences between organ domains mandate differences in management approaches. A life-threatening pulmonary artery aneurysm needs to be treated aggressively upfront, whereas a step-up approach may be more appropriate for mucocutaneous and joint involvement based on patients' preferences [1].

We formulated the recommendations, as much as possible, based on controlled evidence. For some treatment options, such as tocilizumab, ustekinumab, and JAK inhibitors, only small studies or studies at high RoB had been conducted. Nevertheless, they were mentioned in the text, in order to guide the treatment of patients who are refractory to the treatment modalities mentioned in the recommendations and have run out of evidence-based options. This was a challenging task since caution is required when mentioning the possibility of using a drug based on noncomparative—and especially retrospective—studies due to the well-known potential biases. On the other hand, not mentioning these drugs may mean overlooking up to one-third of patients with BS who have primary or secondary failure with, or intolerance to TNFαi, as observed in long-term real-life data with TNFαi [49,60,72,105–107]. We mentioned the alternative treatment options that have been used in patients who were refractory or intolerant to the treatment as recommended in this 2025 update, by indicating that there are only noncomparative studies with high RoB with these agents that require caution. Results of these studies and their shortcomings can be found in detail in the SLRs.

The most important changes from the 2018 recommendations are the preference of monoclonal TNFαi in patients with eye, vascular, or nervous system involvement for both induction of remission of the current attack and for maintenance treatment for preventing relapses. This is especially important for patients with poor prognostic features as described for each organ involvement. In the previous versions, TNFαi were recommended mainly for patients who were refractory to csDMARDs such as azathioprine. However, due to the importance of rapid and effective suppression of inflammation to prevent organ damage and based on studies showing their superiority to csDMARDs, earlier use of bDMARDs is recommended in patients with eye, vascular, and nervous system involvement. bDMARDs may be used in combination with csDMARDs, after weighing the risks and benefits. The wider availability of biosimilars has made this approach more feasible in terms of cost, but it should be noted that there are no comparative studies with biosimilars in BS. There is an unmet need for prospective trials comparing strategies involving a step-up approach with upfront use of TNFαi in patients with BS with organ involvement. Another unmet need is a data-driven strategy for monitoring patients with organ involvement. Absence of capillary leakage on fundus fluorescein angiography for uveitis, remission of clinical, laboratory, and radiologic findings for vascular and nervous system involvement, and endoscopic remission for gastrointestinal involvement were discussed as treatment targets based on the experience of the task force members and uncontrolled evidence. The frequency of monitoring could vary from every week for a patient with active uveitis who just started treatment to every 3 to 6 months for patients with no active organ involvement. Studies testing the benefit of these monitoring approaches are also needed. Moreover, prospective studies testing the benefit of concomitant use of csDMARDs with TNFαi and use of anticoagulation together with immunosuppressives are required for making strong recommendations on these aspects of treatment. These studies that are listed in the research agenda (Box) would enable the development of a more structured treat-to-target approach for BS.

The task force continued to support the step-up strategy for mucocutaneous and joint involvement, where colchicine was recommended as the initial systemic treatment modality. Colchicine may not be adequate in some patients, especially for oral ulcers, as shown by previous RCTs. However, it is preferred as first-line in patients who do not have organ involvement, due to its relatively low cost and safety. The main change from the 2018 mucocutaneous involvement recommendation was the positioning of treatment modalities for colchicine-refractory mucocutaneous involvement. In the current revised version, apremilast and TNFαi are recommended based on new data on their efficacy and safety. There is no standard definition of being refractory, and the decision to escalate treatment depends on patients' preferences. There may be differences between patients regarding the level of mucocutaneous and musculoskeletal disease activity that they are willing to tolerate without switching to another agent that may be associated with potential adverse events.

An important strength of these recommendations is the multidisciplinary composition of the task force. A close collaboration between disciplines is crucial at each step, including diagnosis, determining the organs that are involved, determining level of disease activity and severity for each organ involvement, planning the management to cover all necessary disease domains without overtreatment, monitoring treatment response of each organ involvement, monitoring for development of new organ involvement and modifying treatment accordingly, and differentiating disease activity from mimickers of each organ involvement that may develop throughout the disease course. A multidisciplinary team can importantly improve the quality of care of patients with BS.

Another strength is the presence of task force members from 11 countries. BS is very interesting regarding the variability in clinical manifestations across different countries, such as the

Box
Research agenda

Theme	Research agenda
Overall	• Biomarkers for diagnosis and monitoring disease activity • Better definition of disease endotypes and their mimickers • Studies comparing long-term outcomes of a step-up approach starting with csDMARDs and switching to a bDMARD in refractory patients with upfront bDMARD use in patients with organ involvement • Determining the benefit and risk of using concomitant csDMARDs with bDMARDs • Developing strategies for tapering and stopping glucocorticoids, csDMARDs, and bDMARDs • Developing data-driven strategies for monitoring patients with organ involvement • Defining remission, relapse, and refractoriness for each type of organ involvement • RCTs with newer biologics and JAKi for organ involvement • Optimal treatment during pregnancy and lactation • Standardisation of outcome measures used in trials by developing a core set • Studying patient-important outcomes such as fatigue, and work disability in drug trials
Mucocutaneous involvement	• Studies with high-potency topical glucocorticoids for oral and genital ulcers • An index for determining the minimal mucocutaneous activity level that is acceptable for the patients without requiring treatment escalation
Joint involvement	• RCTs with apremilast, bDMARDs, and JAKi for patients with joint involvement refractory to colchicine
Uveitis	• RCT comparing infliximab and adalimumab in patients with uveitis • RCT to test the efficacy and safety of interferon-beta • Comparing the outcome of patients whose treatment is modified based on fundus fluorescein angiography findings to those monitored without fundus fluorescein angiography.
Vascular involvement	• RCT to assess the efficacy and safety of anticoagulation for preventing relapses of venous thrombosis, postthrombotic syndrome, and recurrent arterial occlusive events • Determining the optimal dose and duration of immunosuppressives after surgical intervention for peripheral artery aneurysms
Nervous system involvement	• Controlled studies for determining the optimal management of initial, refractory, and recurrent parenchymal nervous system involvement • Determining the role of MRI and other laboratory tests in making treatment decisions and follow-up of patients with nervous system involvement
Gastrointestinal involvement	• Controlled studies for determining the optimal management of initial, refractory, and recurrent gastrointestinal system involvement • Determining whether a control colonoscopy is needed in patients with clinical remission and the optimal timing for control colonoscopy

bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor; MRI, magnetic resonance imaging; RCT, randomised controlled trial.

Table 1
2025 Update of EULAR recommendations for the management of Behçet's syndrome

OVERARCHING PRINCIPLES		LoA	
		Mean (SD)	% with score ≥8
A	Behçet's syndrome has a relapsing and remitting course that may be organ or life threatening, while disease manifestations may ameliorate over time.	9.7 ± 0.8	96
B	The goal of treatment is to prevent irreversible organ damage and to maximize health-related quality of life.	9.8 ± 0.5	100
C	Organ involvement should be evaluated throughout the disease course and mimickers should be ruled out with appropriate modalities.	9.7 ± 0.8	96
D	Treatment should be individualized according to age, sex, type, and severity of organ involvement, disease duration, and patient preferences.	9.8 ± 0.4	100
E	A multidisciplinary approach, patient education, shared decision making, adherence to treatment, and lifestyle changes are necessary for optimal care.	9.8 ± 0.4	100

RECOMMENDATIONS		**LoE**	**LoA**		**Feasibility***	**Impact****
			Mean (SD)	**% with score ≥8**		
Mucocutaneous involvement						
1	Colchicine should be the first-line treatment for recurrent mucocutaneous lesions. In patients refractory or intolerant to colchicine, apremilast or TNFα inhibitors should be considered.	2	9.5 ± 0.8	96	9.1 ± 1.1	9.2 ± 0.7
2	Topical measures such as glucocorticoids can be used for the management of oral and genital ulcers; chronic use of systemic glucocorticoids should be avoided.	2 (topical measures) 5 (systemic glucocorticoids)	9.0 ± 1.2	89	9.0 ± 1.3	8.3 ± 2.1
Joint involvement						
3	Colchicine should be the first-line treatment for acute arthritis. Immunosuppressives should be considered in recurrent and chronic cases.	2 (colchicine) 3 (immunosuppressives)	9.4 ± 1.0	93	9.4 ± 0.9	8.9 ± 1.2
Eye involvement						
4	Immunosuppressive treatment must be given in all patients with Behçet's uveitis with the aim of inducing and maintaining clinical and angiographic remission. Monoclonal anti-TNFα antibodies, preferably infliximab in combination with other immunosuppressives should be used in those with sight-threatening inflammation involving the posterior segment. Glucocorticoids should not be given as monotherapy.	2 (aim and TNFαi) 5 (preference of infliximab) 5 (combination with immunosuppressives) 2 (no glucocorticoid monotherapy)	9.7 ± 0.7	96	9.1 ± 1.1	9.4 ± 1.1

(*continued*)

Table 1 (*Continued*)

RECOMMENDATIONS		LoE	LoA		Feasibility*	Impact**
			Mean (SD)	% with score ≥8		
Arterial involvement						
5	For the management of pulmonary and peripheral artery aneurysms, high-dose glucocorticoids and infliximab are recommended; cyclophosphamide may be an alternative. Glucocorticoids should be slowly tapered and immunosuppressives, preferably monoclonal anti-TNFα antibodies continued as maintenance.	2 (infliximab over cyclophosphamide) 5 (slow tapering) 4 (maintenance)	9.8 ± 0.6	96	9.2 ± 1.0	9.4 ± 1.2
6	Vascular procedures, if necessary, should not be delayed following the prompt initiation of medical treatment. For patients with pulmonary aneurysms at high risk of major bleeding, embolization should be preferred to open surgery.	4 (medical treatment) 5 (embolization)	9.7 ± 0.5	100	8.8 ± 1.4	9.1 ± 1.6
Venous involvement						
7	For the management of acute thrombosis of deep veins, including cerebral venous sinuses, glucocorticoids and immunosuppressives preferably monoclonal anti-TNFα antibodies should be considered. Immunosuppressives should be continued as maintenance.	2 (monoclonal anti-TNFαs) 3 (maintenance)	9.7 ± 0.7	96	9.1 ± 0.9	9.4 ± 0.9
8	Anticoagulants may be added, provided the risk of bleeding is low and coexistent pulmonary artery aneurysms are ruled out.	5	8.7 ± 1.2	82	8.8 ± 1.2	8.4 ± 1.8
9	In cerebral venous sinus thrombosis with vision threatening intracranial hypertension, surgical interventions should be given prompt consideration.	5	9.0 ± 1.5	96	8.2 ± 1.8	8.5 ± 1.8
Gastrointestinal involvement						
10	Diagnosis, assessment of severity, and management of gastrointestinal involvement should be based on endoscopy.	5	9.5 ± 0.9	96	9.0 ± 1.2	9.1 ± 1.4
11	In patients with gastrointestinal involvement, 5-ASA or azathioprine should be used with or without glucocorticoids. In severe or refractory patients monoclonal anti-TNFα antibodies should be considered.	3	9.6 ± 0.7	100	9.4 ± 0.9	9.3 ± 1.1
Parenchymal nervous system involvement						
12	For active parenchymal involvement high dose glucocorticoids and immunosuppressives, preferably infliximab, should be initiated. Glucocorticoids should be slowly tapered and immunosuppressives continued as maintenance.	2 (infliximab) 5 (slow tapering) 4 (maintenance)	9.8 ± 0.4	100	9.3 ± 0.8	9.5 ± 0.6

LoA: level of agreement, LoE: level of evidence, TNFα: tumor necrosis factor alpha, TNFαi: tumor necrosis factor alpha inhibitors; 5-ASA: aminosalicylic acid

* Feasibility was asked as follows: "Please rate the recommendation on its feasibility to be implemented (0-10)".

** Impact was asked as follows: "Please rate the recommendation on its impact on quality of care (0-10)".

Table 2
Quality indicators

Recommendation number	Proposed quality indicator, domain	Proposed quality indicator, phrase	Numerator	Denominator
3	Joint involvement	Colchicine should be first-line treatment for acute arthritis. Immunosuppressives should be considered in recurrent and chronic cases.	The number of patients with Behçet's syndrome and acute arthritis in whom colchicine has been initiated as first-line treatment	The number of patients with Behçet's syndrome who presented with acute arthritis
			The number of patients with Behçet's syndrome and recurrent or chronic arthritis (≥3 mo) in whom immunosuppressives have been initiated.	The number of patients with Behçet's syndrome and recurrent or chronic (≥3 mo) arthritis
5	Arterial involvement	For the management of pulmonary and peripheral artery aneurysms, high-dose glucocorticoids and infliximab are recommended; cyclophosphamide may be an alternative. Glucocorticoids should be slowly tapered and immunosuppressives, preferably monoclonal anti-TNFα antibodies continued as maintenance.	The number of patients with Behçet's syndrome and pulmonary or peripheral artery aneurysms in whom high-dose glucocorticoids and infliximab or alternatively cyclophosphamide have been initiated.	The number of patients with Behçet's syndrome and pulmonary or peripheral artery aneurysms.
			The number of patients with Behçet's syndrome and pulmonary or peripheral artery aneurysms in whom immunosuppressives have been initiated for maintenance treatment, while slowly tapering the glucocorticoids.	The number of patients with Behçet's syndrome and pulmonary or peripheral artery aneurysms who received induction treatment with high-dose glucocorticoids and infliximab or cyclophosphamide

TNFα, tumour necrosis factor.

high prevalence of gastrointestinal involvement in the Far East and vascular involvement in the Middle East, and the low prevalence of pathergy reaction in European countries. Other differences that need to be taken into account are differences in healthcare systems, availability of newer agents, reimbursement policies, differences in patients' perceptions, and background risk of certain complications, such as latent tuberculosis that may reactivate during treatment with TNFαi. The multinational composition of our task force enabled us to recognise and address these differences. We tried to provide options for different situations, because these recommendations aim to guide the management of patients with BS from all over the world.

An important challenge when developing these recommendations was the heterogeneity of the trial populations and outcome measures that made it impossible to bring together the results in a meta-analysis or make comparisons between different therapeutic modalities. A core set of domains for BS was developed by the Outcome Measures in Rheumatology BS working group, and work is continuing towards developing a core set of instruments that would cover each organ domain and overall disease assessment [108]. Another limitation was the small sample size of the RCTs, which made it difficult to interpret the results. Separate analyses for men and women are important in BS studies due to the known differences in disease severity and possibly drug response. However, this was not available in most of the studies. Moreover, patient-important domains such as fatigue and work disability were not addressed in any of the drug trials.

In this update, we aimed to provide guidance on the positioning of the therapeutic agents by forming an algorithm based on organ involvement, in a stepwise approach, and covering patients with different severity and extent of disease. We also identified 2 quality indicators that can help to understand the impact of following these recommendations on the outcomes of patients with BS. These recommendations reflect the best available evidence and the experience of experts from different disciplines, and are planned to be updated when new evidence is available to better guide the management of patients with BS.

Competing interests

GH received research grants, speaker fees and/or consulting fees from AbbVie, Amgen, Johnson & Johnson, MSD, Novartis, Soligenix and UCB Pharma. SR received research grants or consulting fees from AbbVie, Alfasigma, Eli Lilly, Johnson & Johnson, MSD, Novartis, Pfizer, UCB. BB received consultant fees from AbbVie, Alimera, Bausch and Lomb, Novartis, Roche and Horus Pharma. LC received research support from Recordati and Novartis and speaker honoraria from Argenx and Novartis. AG received research grants, speaker fees and/or consulting fees from AbbVie, Pfizer, Johnson & Johnson, and Novartis. IK received speaker honoraria from AbbVie, Amgen, Boehringer, GSK, Janssen, Lilly, Medac, Novartis, Sobi. GL received research support from AbbVie and Novartis and speaker honoraria from AbbVie, Novartis, Eli Lilly, and UCB. RT received research support from Argenx. All other authors declare they have no competing interests.

Contributors

GH contributed to writing the original draft, methodology, formal analysis, data curation, supervision, conceptualisation, and funding acquisition. SR contributed to reviewing & editing, methodology, formal analysis, data curation, supervision, and conceptualisation of data. YO and SNE contributed to reviewing & editing, formal analysis, and data curation. GT contributed to reviewing & editing and methodology of data. HY contributed to reviewing & editing, methodology, formal analysis, data curation, supervision, and conceptualisation of data. All other authors reviewed and edited the final manuscript.

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