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Management of Behcet's syndrome

Omer Karadag [1,2] **and Ertugrul Cagri Bolek** [1,2]

Abstract

Behcet's syndrome (BS) is a variable vessel vasculitis with heterogeneous clinical features. Skin, mucosa and joint involvement can cause impairment of quality of life but do not cause permanent damage whereas untreated eye, vascular, nervous system and gastrointestinal system involvement can cause serious damage and even death. Management of BS as a multidisciplinary team enables a faster and more accurate diagnosis and well-integrated treatment strategies. Corticosteroids are the mainstay of therapy. Colchicine, AZA, ciclosporin-A, cyclophosphamide, IFN alpha, and tumour necrosis factor alpha inhibitors are other agents used as induction and/or maintenance therapy. Although biologic agents have been increasingly used, there are still unmet needs. Head-to-head comparison studies of some therapeutic options (e.g. TNF inhibitors *vs* IFN alpha in uveitis) are required. Novel therapeutic agents in the pipeline could change the standard of care for BS in the future

Key words: Behcet's syndrome, Behcet's disease, uveitis, biologic agents, anti-TNF agents, interferon alpha, vascular Behcet's syndrome, Neurobehcet's syndrome

Rheumatology key messages:

- Management of a patient with Behcet's syndrome requires a multidisciplinary collaboration.
- Corticosteroids are the mainstay; immunomodulatory and immunosuppressive drugs are used for sustainability of remission.
- Despite increasingly usage of biologics, there are still unmet needs.

SUPPLEMENT

Introduction

Behcet's syndrome (BS) is a variable vessel vasculitis that often follows a relapsing and remitting course. Although classical clinical manifestations are mucocutaneous lesions (i.e. oral and genital ulcers, erythema nodosum and papulopustular lesions), arthritis and uveitis, it can also affect the vessels, nervous system and gastrointestinal tract.

The evidence on management of BS mostly comes from randomized controlled trials (RCTs) for mucocutaneous lesions, arthritis and uveitis. On the other hand, treatment strategies of vascular, neurologic and gastrointestinal involvement are mostly based on uncontrolled studies and sometimes limited to case reports and series. Even though biologic agents such as IFN-α, TNFi and other biologics have been increasingly used, there are still unmet needs in BS. In this article, authors aimed to create a mini-review for disease management, treatment choice and their implications in BS. Knowledge and literature in clinical rheumatology are constantly changing. That is why it is the responsibility of clinicians to choose the best treatment options and to determine dosages for each individual patient, and to take all appropriate safety precautions.

Treatment of Behcet's syndrome according to clinical features

Skin, mucosa and joint involvement can cause impairment of quality of life but do not cause permanent damage whereas untreated eye, vascular, nervous system and gastrointestinal system involvement can cause serious damage and even death [1].

Because BS is a multisystemic disease and each discipline requires specialty, a multidisciplinary collaboration is rational for an optimum care [2]. The main goal of management is preventing relapses and suppressing inflammation rapidly for major organ involvement that may cause damage and even be fatal [1]. Therefore, age, gender, type and severity of organ involvement(s), disease duration, patients' preferences, and organ-

[1]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey and [2]Hacettepe University Vasculitis Centre (HUVAC), Ankara, Turkey

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Correspondence to: Omer Karadag, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Gevher Nesibe Street, 06100 Sıhhiye, Ankara, Turkey.
E-mail: omerk@hacettepe.edu.tr or omerkaradag@ymail.com

specific prognostic factors should be taken into account while treatment options are considered. Evidence from literature about treatment choices and management of BS are summarized below under each feature. Also, the discussed drugs' dosing range in RCTs and side effects were shown all together at Table 1.

Mucocutaneous involvement

Maintaining oral hygiene, avoiding irritating behaviours and food should be recommended to all patients because repetitive microtraumas and poor hygiene may increase the occurrence of oral ulcers. Also, wound care is advised to reduce the secondary bacterial infections for genital ulcers.

Colchicine is one of the trailblazer treatments in BS. Since 1980, a few placebo-controlled trials investigating the beneficial roles of colchicine on mucocutaneous features of BS have been done. However, most of the studies had a small number of patients and were not powered for a specific mucocutaneous lesion and the relapsing and remitting course of BS renders disease assessment even more difficult [60]. Although efficacy of colchicine on oral ulcers and papulopustular lesions is controversial, it was shown that is effective for genital ulcers and nodular lesions, especially in female patients [1, 13–15]. Despite these conflicting results, colchicine seems to be beneficial in some patients; however, subpopulations who are likely to respond to colchicine cannot yet be defined.

There are limited data from RCTs to recommend the routine usage of local therapeutics such as corticosteroids, NSAIDs, anti-microbials (i.e. tetracycline, minocycline, penicillin, chlorhexidine and Listerine®), immunosuppressives (i.e. pimecrolimus and ciclosporin-A) and surface agents (i.e. sucralfate) for treatment of oral ulcers and genital ulcers [3, 61–68]. Study of topical pentoxifylline gel on oral ulcers is still ongoing [10]. On the other hand, many experts have their own clinical experiences on topical corticosteroids that contribute to faster healing of oral ulcers and topical antibiotics that can be useful for papulopustular lesions. Besides, a prospective study with addition of systemic (i.m.) benzathine penicillin to colchicine in BS was performed in our centre [11]. According to this study, frequency of genital ulcers, frequency and duration of oral ulcers and erythema nodosum was decreased in the benzathine penicillin + colchicine group in comparison with the colchicine group. Addition of benzathine penicillin to colchicine may be a useful alternative for refractory patients [69].

Thalidomide and dapsone can be used for oral ulcers and genital ulcers [5, 6]. However, thalidomide may cause a flare in erythema nodosum lesions [6]. AZA is another alternative drug for mucocutaneous lesions of BS [16]. Although its effect on other BS features is unknown, apremilast, with its phase III trial having just been completed without important side effects, seems to be another promising and safe novel choice for oral ulcers [8, 9]. Furthermore, data from RCTs for using IFN-α and etanercept (TNFi) shows them to also be effective agents for mucocutaneous features [25, 43]. Nevertheless, clinicians must oversee the benefit/harm balance and cost-effectiveness while they are managing the refractory mucocutaneous symptoms.

Literature knowledge about interleukin-1 inhibitors (IL-1i) such as anakinra and canakinumab is being collected and they seem effective for mucocutaneous complaints (oral ulcers and genital ulcers) [56–59]. Similarly, an interleukin-17 inhibitor (IL-17i) secukinumab and an interleukin-12/23 inhibitor (IL-12/23i) ustekinumab may be alternatives in management of mucocutaneous features of BS [52–55]. There is a report of two cases with tocilizumab (TCZ; interleukin-6 inhibitor: IL-6i) irresponsive mucocutaneous features [44].

Joint involvement

A typical feature of BS is usually monoarticular, nonerosive and self-limiting with attacks lasting for a few weeks. Colchicine, which is shown as effective in RCTs, is mostly used as an initial treatment of acute arthritis in BS [15]. Depot-form and/or low-dose-systemic corticosteroids can be effective and they are considered as additives to colchicine treatment in resistant cases by experienced clinicians [1, 4]. Depending on the case, intra-articular glucocorticoids might be an option for monoarticular diseases. NSAID can be used during acute exacerbations. Data from RCTs shows that AZA is beneficial for preventing new arthritis attacks in patients with recurrent arthritis [16]. For resistant patients, IFN-α or etanercept should be considered [25, 43]. Data from some observational studies illustrates the efficacy of other TNFi (adalimumab and infliximab) on arthritis even though there are no RCTs [70]. Accumulating knowledge and experience with other chronic inflammatory rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis indicates that TNFi may be effective and tolerable. Benzathine penicillin may be considered for controlling the joint manifestations of patients who have recurrent arthritis attacks despite effective treatment [12].

Some resistant patients with lower extremity oligoarthritis might have a chronic course mimicking seronegative spondyloarthropathies. Conventional disease-modifying antirheumatic drugs (csDMARDs; i.e. sulfasalazine, methotrexate and leflunomide) may be considered as a possible alternative mono- or combination therapies in these patients, especially refractory ones. However, these drugs have not yet been supported with data from RCTs in BS. Also, preliminary study of secukinumab in BS is promising in terms of articular manifestations [52].

Eye involvement

Ocular involvement is the most common major organ manifestation in BS. Considering that ocular involvement can cause irreversible vision loss if left untreated, screening for ocular involvement at diagnosis is essential. Induction and maintenance treatment is

Table 1 Table summarizing drugs (dose, indication, side effects. . .) that are useful in managing Behcet's syndrome

Drugs	Clinical trial ref.	Route of administration	Recommended dose range	Indications	Possible side effects and precautions
Corticosteroids	[3]	Topical (0.1% triamcinolone acetonide)	T.I.D	Oral ulcers	—
	[4]	Systemic	Depot 40 mg methylprednisolone acetate	Erythema nodosum	Fatigue, weight gain, abdominal pain, hypertrichosis, other possible steroid side effects (cataract, osteoporosis etc.)
	[1]	Systemic (p.o. or i.v.)	Low to high dose AND / OR Pulse corticosteroids	Oral ulcers, genital ulcers, erythema nodosum, arthritis, vascular, neurological, gastrointestinal	
	Intravitreal (for uveitis) and intra-articular (for arthritis) corticosteroids may be used for selected cases depending on clinicians experience and indications.				
Dapsone	[5]	p.o.	100 mg daily	Oral ulcers, genital ulcers	Diarrhea, nausea / vomiting, headache, hemolysis, methemoglobinemia, cholestatic hepatitis
Thalidomide	[6, 7]	p.o.	100–300 mg/day	Oral ulcers, genital ulcers, arthritis, gastrointestinal	Increase in erythema nodosum [6], skin rash, dizziness, sedation, fatigue, thrombo-embolism, peripheral neuropathy, teratogenicity (phocomelia)
Apremilast	[8, 9]	p.o.	30 mg B.I.D	Oral ulcers	Diarrhea, nausea / vomiting, headache
Pentoxifylline	[10]	5% gel (topical)	Q.I.D	Oral ulcers[a]	—
Benzathine Penicillin	[11, 12]	i.m.	1.2 million units/3 weeks	Oral ulcers[a], genital ulcers[a], arthritis[a]	Allergy
Colchicine	[13–15]	p.o.	1–2 mg/day	Oral ulcers (?), genital ulcers, erythema nodosum, arthritis	Diarrhea, hepatotoxicity, cytopenia, myopathy
AZA	[16, 17]	p.o.	2 mg/kg/day	Oral ulcers, genital ulcers, arthritis, uveitis, gastrointestinal, uveitis	Nausea / vomiting, skin rash, cytopenia, drug interaction with allopurinol
Cyclosporine-A	[18–21]	p.o.	5 mg/kg/day	Uveitis	Occuring NBS [22, 23], hypertension, kidney failure, cosmetic side effects
Sulfasalazine	[24]	p.o.	2–4 g/day	Gastrointestinal	Headache, nausea, vomiting, abdominal pain, rash, itching, azoospermia
IFN-α	[25–30]	s.c.	6 million units, 3/week (3–9 million units)	Oral ulcers, genital ulcers, erythema nodosum, Papulopustular, uveitis, NBS[a], vascular[a], gastrointestinal[a]	Elevated transaminases, cytopenia, thyroid dysfunction, flu-like symptoms,
Infliximab (TNFi)	[21, 31–39]	i.v.	5 mg/kg 0–2–6 weeks Continue with every 6–8 weeks	Arthritis, uveitis, NBS, vascular, gastrointestinal	Injection side effects (for s.c.), infections, Viral hepatitis and TBC reactivation Precautions for cancer
Adalimumab (TNFi)	[35, 36, 40–42]	s.c.	40 mg / 2 weeks	Uveitis, NBS[a], vascular[a], gastrointestinal[a]	
Etanercept (TNFi)	[43]	s.c.	50 mg/week	Oral ulcers (?), genital ulcers, erythema nodosum, papulopustular	
Tocilizumab (IL-6i)	[44–51]	i.v.	8 mg/kg/4 weeks	Uveitis, NBS[a], amyloidosis[a]	Infections, viral hepatitis and TBC reactivation Elevated lipid parameters and transaminases
Secukinumab (IL-17i)	[52]	s.c.	150–300 mg/4 weeks	Oral ulcers[a], arthritis[a]	Injection side effects (for s.c.), infections, Precautions for inflammatory bowel disease (for secukinumab)
Ustekinumab (IL12/23i)	[53–55]	s.c.	45–90 mg 0–4–12 weeks Continue with every 12 weeks	Oral ulcers[a]	
Anakinra (IL-1i)	[56–59]	s.c.	100 mg /daily	Oral ulcers[a], genital ulcers[a], uveitis[a]	Injection side effects (for s.c.), infections
Canakinumab (IL-1i)	[59]	s.c.	150 mg / 6 weeks	Oral ulcers[a], genital ulcers[a], uveitis[a]	

[a]These drugs need to be experienced more and have more clinical studies for recommendation in these indications. They may be considered for selected refractory cases depending on clinicians' experiences. B.I.D: bis in die (two times each day); NBS: Neuro-Behcet's syndrome; Q.I.D: quater in die (four times each day); Ref.: References; T.I.D: ter in die (three times each day); TBC: tuberculosis.

recommended after collaboration with ophthalmologists. Also, treatment options should be tailored according to presence of poor prognostic factors, uveitis type (anterior, posterior or panuveitis) and severity.

High-dose systemic glucocorticoids may be preferred for patients with acute posterior uveitis attack due to rapidly starting effects, though they are not recommended to use solely without other drugs. They can be used as a bridging therapy up to the beginning of the other drug's effect.

Patients with isolated anterior uveitis can be treated with topical agents. Systemic immunosupressive drugs like AZA are recommended in case of the presence of some poor prognostic factors such as hypopyon, young age, early-onset disease and male gender [1].

AZA and ciclosporin-A (CsA) are well-known options due to their most accumulated clinical experience and literature knowledge for preserving visual acuity and preventing relapses [16, 18–20]. AZA is effective in decreasing the number of patients with hypopyon uveitis and development of new eye disease, whereas CsA decreases the frequency and severity of ocular attacks [16, 19]. Adverse events of CsA such as renal dysfunction and hypertension should be kept in mind. Also, there is some evidence that renounces a possible association between CsA usage and occurrence of neurological disease (Neuro-Behcet's syndrome) [22, 23]. Methotrexate is also useful and an alternative option to AZA and CsA [71].

Biologic agents such as IFN-α and some TNFi such as infliximab are the other highly effective and proved options for posterior uveitis [21, 25–27, 31–33]. Adalimumab was evaluated in patients with non-infectious uveitis in a RCT [72]. This study included BS patients but their results were not reported separately. Additionally, adalimumab seems to improve visual acuity based on a few case series and reports [40, 41, 72].

Acute sight-threatening and severe uveitis is an emergency for patients with BS. Pulse methyl prednisolone 250–1000 mg for 1–3 days is recommended. Infliximab or IFN-α could be used as induction therapy for these patients [1, 60, 73]. There were no studies directly comparing TNFi and IFN-α. However, several open label uncontrolled studies and retrospective case series had studied the efficacy of both agents [73]. Remission rates were similar for infliximab and IFN-α, but the sustained remission rate was higher with IFN-α (71%) compared with infliximab (43%) although infliximab had rapid-onset of action [73].

Although another IL-1i gevokizumab study for BS uveitis failed to show efficacy, Canakinumab and anakinra seem to be useful alternatives in small groups with BS uveitis and they need more trials to show their efficacy [59, 74]. Also, there are a few case series and studies using golimumab and tocilizumab in BS uveitis [75–80].

Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbations as an adjunct to systemic treatment. However, complications were frequent (49%), with cataracts in 36%, increased intraocular pressure in 43% and glaucoma in 9% of the patients [73]. An algorithm for management of BS uveitis reflecting the approach of our Vasculitis Centre is shown in Figure 1.

Vascular-Behcet's syndrome

Venous type

Distribution of venous involvement could vary from a superficial vein thrombosis to a very severe superior/inferior vena cava thrombosis in BS. Vascular involvement has a more severe course especially among male patients with a younger age at disease onset. Extensive adherent thrombus formation is the typical finding of venous vessel involvement without an increase of thromboembolism [81]. Additionally, post-thrombotic syndrome is a major problem of patients with BS.

For the treatment of acute deep vein thrombosis in BS, glucocorticoids and immunosuppressives such as AZA and ciclosporin-A are recommended [1, 60]. Cyclophosphamide and TNFi should be preferred for cases with larger vein thrombosis or recurrent/refractory cases [34, 35].

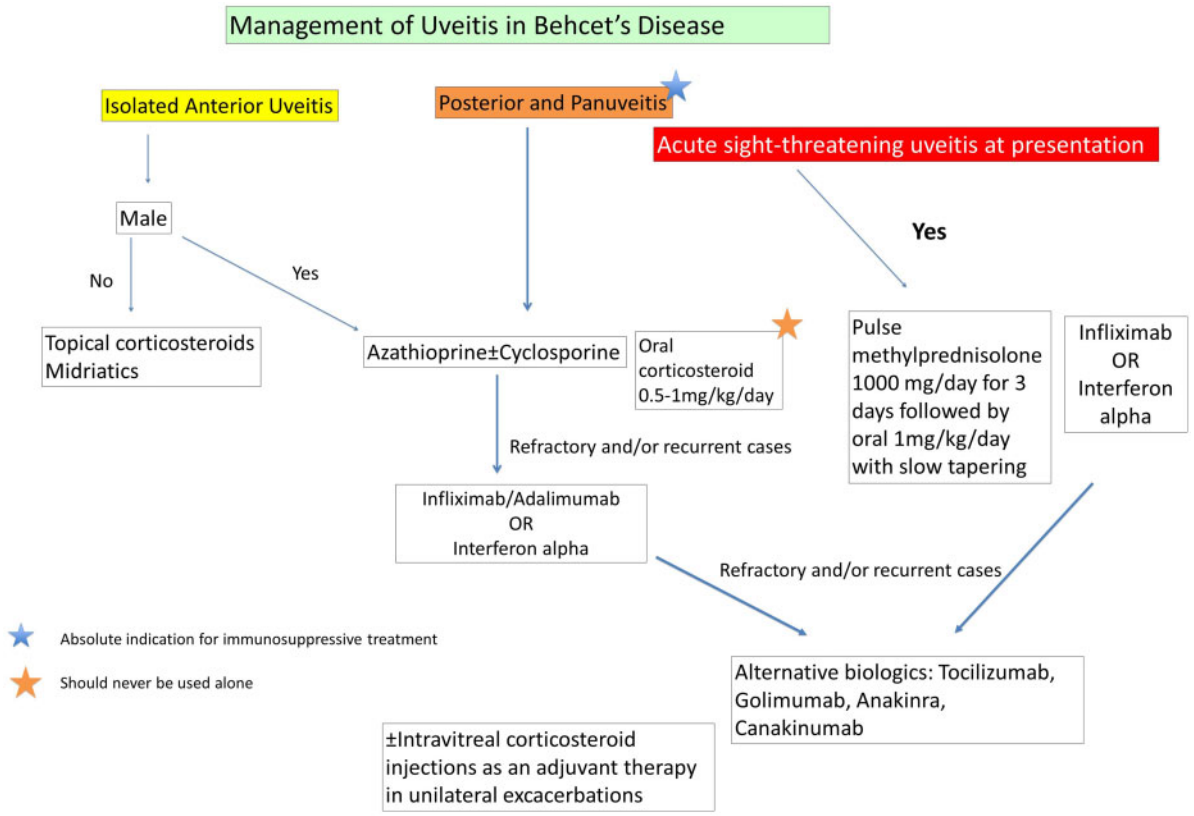
BS is an important cause of Budd-Chiari syndrome (BCS), especially in endemic areas for BS[8] [82]. It is essential to diagnose BS in a patient with BCS because mortality is extremely high if treated with only anticoagulation without immunosuppressive treatment.

There are a few cases with vascular involvement of BS in the literature treated with tocilizumab [45]. RCTs and more observational studies are needed for evaluating the efficacy of IFN-α and other biologics on vascular Behcet's syndrome.

Whether to use anticoagulation or not in managing venous thrombosis due to Behçet's syndrome (BS) has been debated for decades and the effects of adding anti-coagulants to immunosuppressives on relapse are controversial [83–86]. On the other hand, additional anticoagulation was associated with less post-thrombotic syndrome in a Doppler study comparing BS patients to non-BS cases in a small study [87]. A properly conducted RCT is required to clarify the role of anticoagulation in venous disease of BS. Nonetheless, anticoagulants may be considered for refractory cases and larger vein thrombosis (i.e. superior or inferior vena cava thrombosis and Budd-Chiari syndrome) [1]. However, provided the risk of fatal bleeding in general is low, ruling out the coexistent pulmonary artery aneurysms is preferred [84]. Anticoagulation data for BS is about classical agents such as warfarin and new oral anti-coagulants need RCTs and observational studies to illustrate their effects in BS [88].

Venous stasis and obliterative vasculitis are the major causes of leg ulcers in BS. A multidisciplinary approach consisting of rheumatology, dermatology and a vascular surgeon is important for an optimal treatment strategy [1, 2].

Fig. 1 Algorithm for the management of Behcet's syndrome



Arterial type

The most lethal complication is pulmonary artery involvement that can manifest as aneurysms, thrombosis or both. High-dose glucocorticoids and cyclophosphamide are recommended for pulmonary artery aneurysms. Patients who achieve remission are switched to AZA for maintenance therapy. In refractory cases, cyclophosphamide may be replaced with infliximab [35–37]. In case of increased risk for major bleeding, intravascular interventional therapies and open surgery can be considered.

Aortic and/or peripheral artery aneurysms could be seen in the disease course of BS. The medical treatment of peripheral artery and aortic involvement is similar to that of pulmonary artery involvement [1]. However, surgery is usually required depending on the symptoms, type and size of the aneurysm and should be accompanied with immunosuppressive therapy. Immunosuppressive therapy decreases relapse risk and should be initiated in the perioperative setting if the surgical procedure does not perform for medical emergencies [89].

Intracardiac thrombosis

Intracardiac thrombosis is a rare complication of BS and there are not enough data for determining the condition, evidence-based treatment recommendations and prediction of prognosis. Many experts intend to treat it with immunosuppressives with or without anticoagulants like pulmonary arterial involvement major vessel involvement [90].

Nervous system involvement (Neuro-Behcet's syndrome)

Neuro-Behçet's syndrome (NBS) occurs in ∼5% of patients with BS; ∼75–80% of NBS cases present with central nervous system involvement, which is called 'parenchymal NBS (pNBS)' and affects the telencephalic–diencephalic junction, brainstem and spinal cord [91]. Although NBS is not common in the course of BS, it is related with significant mortality and morbidity. Relapses are seen in approximately half of the patients [28].

It should be kept in mind that there are no interventional studies and RCTs in NBS as in vascular involvement. Therefore, the data are usually obtained from observational studies.

Parenchymal involvement

Acute attacks of parenchymal involvement should be treated with high-dose glucocorticoids followed by slow tapering with or without pulse steroids, together with immunosuppressives such as AZA and TNFi (infliximab) advised by up-to-date EULAR recommendations [1]. TNFi could be considered in severe disease as first-line

or in refractory patients as a rescue treatment although there is no clear evidence to choose the appropriate patients to use AZA or TNFi treatments. It should be advised to avoid CsA because of neurological problems in BS [22, 23].

INF-α is another safe and tolerable choice in treatment of pNBS for refractory patients [29]. Cyclophosphamide may still be an alternative option for pNBS for selected patients [92]. Also, tocilizumab, which is effective in refractory pNBS in some reports, may be considered for selected cases after first choice treatments [46–49].

The chronic progressive form of NBS, which is another rare type, is more severe than acute-onset NBS and it may benefit from TNFi (infliximab) [84].

Non-parenchymal involvement

The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. [1]. There is a lack of data in the literature for adding immunosuppressive agents to corticosteroids [93–95]. Nevertheless, immunosuppressives may be considered for refractory or relapsing patients and also their potential harms and benefits should also be taken into account. Anticoagulants may be added for a short duration. If a decision has been made to start anticoagulants, it is crucial to exclude the presence of arterial aneurysms.

Gastrointestinal involvement (Entero-Behcet's syndrome)

Its prevalence shows a distinct geographic variation. Gastrointestinal involvement of BS should be confirmed by endoscopy and/or imaging. NSAID ulcers, inflammatory bowel disease and infections such as tuberculosis should be ruled out [1]. For severe and/or refractory patients such as perforation, major bleeding and obstruction, a multidisciplinary approach of rheumatologists along with gastroenterologists and surgeons is required [1, 2, 60].

Treatment recommendations are generally based on the data of BS and inflammatory bowel diseases and extrapolations. Glucocorticoids should be considered during acute exacerbations together with disease modifying agents such as sulfasalazine or AZA [17, 24, 38]. TNFi (infliximab) and/or thalidomide are recommended for refractory patients [7, 38, 42]. Data for usage of INF-α in Entero-Behcet's syndrome is limited to a case report [30].

Miscellaneous features

Amyloidosis is an uncommon but highly morbid complication of BS and it causes end-stage renal failure [96]. Definite predictors for development of End stage renal disease are unknown in amyloidosis of BS. However, early recognition of these patients and awareness of clinicians about this rare complication is quite important. Amyloidosis-related symptoms and findings (e.g. proteinuria) may be treatable with tocilizumab or INF-α in some cases, according to data from our cohort and literature [50, 51, 97].

Follow-up

Male patients with an early age of disease-onset BS have a more severe disease course [98]. The heavy burden of the disease and organ damages occur in the first

Table 2 Parameters using for evaluation of clinical features in BS

Clinical features	Parameters
Mucocutaneous lesions(Oral ulcers, genital ulcers, papulopustular and nodular lesions)	• Count of lesions • Lesion diameter • Frequency • Severity • Painfulness
Arthritis	• Count of tender and swollen joints
Eye involvement	• Uveitis type • Involvement side (right or left) • Frequency • Visual acuity • Slit lamp and fundoscopic examination findings • Intraocular pressure
Vascular involvement	• Examination findings • Imaging findings
Neurological involvement	• Neurological examination findings • Neuro-imaging findings • Neurological damage scores (EDSS or modified Rankin Scale etc.)
Gastrointestinal involvement	• Stool features (blood etc.) • Abdominal symptoms • Diarrhea frequency • Endoscopic examination findings

EDSS: Expanded Disability Status Scale.

years of course (especially the first 5 years) and then it simmers down [28]. This phenomenon is known as 'disease burn-out' [99, 100]. It prompts more aggressive treatment and increased caution during follow-up in such patients. As the disease manifestations usually abate over time, treatment may be tapered and even stopped [13].

Patients are usually seen every 1–6 months depending on the involvement and severity of their features. Parameters related to clinical features of BS and any new manifestations are recorded in each visit. These parameters, which can be useful in follow-up, are summarized in Table 2.

Vascular involvement is screened in patients with elevated acute phase reactants and/or fever even if they do not have typical symptoms.

There is no consensus on when to stop the treatment in BS patients in remission. Moreover, remission has not been well defined in BS as it is difficult to conclude whether the stable disease is due to the treatment itself or due to the relapsing remitting nature of the disease. Additionally, it is difficult to define a standard protocol for all BS patients for stopping treatment, because men and younger patients have a higher risk of relapse. The decision to stop treatment for patients with only mucocutaneous involvement is somewhat easier and can be made together with the patient depending on how much these lesions impair the patient's quality of life. In patients with major organ involvement, immunosuppressives are tapered after 2–5 years of remission depending on the patient's age, gender, severity of involvement and the amount of damage.

Conclusion

The best way to organize the management of a patient with BS requires a multidisciplinary collaboration. Age, gender, type and severity of organ involvement, disease duration, patients' preferences, and organ-specific prognostic factors should be taken into account when considering treatment options.

The evidence on the management of BS mostly comes from RCTs for mucocutaneous lesions, arthritis and uveitis. On the other hand, treatment strategies of vascular, neurologic and gastrointestinal involvement are mostly based on uncontrolled studies. Therefore, future RCTs and multi-centre observational studies in these fields will contribute to improving evidence levels for treatment recommendations of these domains. Even though biologic agents such as IFN-α and TNFi have been increasingly used, there are still unmet needs in BS. A study of head-to-head comparison of IFN-α with TNFi is one of the required studies. To anticoagulate or not is the other important question for BS patients with venous involvement. Other agents in the biologic era such as tocilizumab, ustekinumab and rituximab are not under the scope of this review. Also, usage of new oral anti-coagulants in BS are another lacking data area in literature and should be investigated. Even so, other agents in the biologic era such as low-dose interleukin-2 inhibitors, tocilizumab, secukinumab, ustekinumab and rituximab need more studies to show their efficacy in BS.

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