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REVIEW

Experimental Therapeutic Solutions for Behcet's Disease

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Abstract: Behcet's disease (BD) is a chronic systemic vasculitis with inflammation attacks that involve multiple organs. In addition to numerous mucocutaneous symptoms, notably recurrent oral and genital ulcers, ocular, articular, vascular, gastrointestinal, cardiac, and neurological system involvement can be observed. Mucocutaneous lesions are the primary symptom of the disease in most patients, and they usually occur before major organ involvement and other symptoms of the disease. Recognizing the disease's mucocutaneous lesions is very important to diagnose at an early stage, control with appropriate treatment and close follow-up, and prevent major organ involvement. Genome-wide association studies (GWAS) in recent years have confirmed that HLA-B*51 is the most significant genetic predisposing factor. The majority of gene polymorphisms have been detected in molecules that respond to microorganisms and genes encoding cytokines and adhesion molecules. The infectious agent *S. sanguinis* -commonly found in the oral mucosa of patients with BD- or the differences in the salivary or intestinal microbiome composition can trigger innate immune-mediated inflammation sustained by acquired or adaptive immune responses. In antigen-presenting cells (APCs), epistatic interactions between HLA-B*51 and endoplasmic reticulum aminopeptidase 1 (ERAP1) variants lead to the disruption of T-cell homeostasis, especially the activation of Type1 T-helper and Th17 pathway and suppression of regulatory T-cells. Recent developments to clarify the disease's etiopathogenesis provided us with a better understanding of the mechanism of action of the relatively old drugs while opening a way for many new treatment methods. Apremilast has become an important option in the treatment of mucocutaneous symptoms with its high efficacy and safety. The disease increases the mortality rate, especially in young male patients. New treatments, especially anti-TNF-α agents, have provided significant progress and decreased the mortality rates with their rapid effect and high efficacy in patients with severe organ involvement and resistance to traditional immunosuppressive and immunomodulatory therapies. The use of IL-1, IL-6, IL-17, IL-12/IL-23 antagonists in different organ involvement has gradually increased, and the quality of life has significantly improved in many patients.

Keywords: Behcet's syndrome, algorithms, etiology, therapeutics, morbidity, mortality

Introduction

Behcet's disease (BD) is a systemic vasculitis distinguished by oral ulcers (OU), genital ulcers (GU), other mucocutaneous lesions (erythema nodosum [EN]-like lesions, papulopustular lesions [PPL], superficial thrombophlebitis, etc.), ocular, vascular, articular, gastrointestinal, neurological, and cardiac involvement. The disease of unknown etiology follows a chronic course with inflammatory attacks. BD usually occurs in the third or fourth decade.[1] The disease, which is observed worldwide, is more frequent in the ancient

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"Silk Road," extending from Japan to the Middle East and Mediterranean countries. The disease's prevalence in countries located on the ancient "Silk Road" has been reported as 14–20/100,000. Until now, the highest prevalence was reported from Turkey (420/100,000).[2] Population-based studies with large series conducted in the last 30 years show that the disease occurs at a similar rate in both genders.[1,3,4]

The disease's course is severe when it occurs at a young age, in male patients and those without regular treatment and follow-up.[4,5] BD adversely affects patients' quality of life and can lead to workday loss. In a multi-center study, Mumcu et al reported that male gender, early onset of illness, smoking, using immunosuppressive agents, ocular and vascular involvement are the most important factors increasing workday loss.[6] On the other hand, the disease increases the mortality rate, especially in young male patients. Large vessel involvement, neurological involvement, gastrointestinal system involvement, and cardiac involvement are the most important causes of mortality.[7] However, in most patients, BD starts with relatively mild symptoms (mucocutaneous involvement). Severe organ involvement occurs in the advanced stage of the disease.[8] Therefore, by providing early diagnosis, appropriate treatment, and regular follow-up, severe organ involvement can be prevented in a significant number of patients.

There is no definitive diagnostic laboratory test for the disease, and diagnosis is based on clinical findings. The common feature of the various diagnostic criteria used so far in the disease is that the diagnoses are based on mucocutaneous lesions, especially OU, GU, cutaneous lesions, and pathergy test positivity. The International Study Group's criteria for Behçet's Disease (ISBD) is the most widely used in diagnosis.[9]

The treatment's main goal should be to suppress new inflammatory attacks to prevent irreversible organ damage, especially in the early and active phases of the disease. It should be kept in mind that the management of patients with BD requires a multidisciplinary approach. Due to the increasing knowledge about BD etiopathogenesis, many new treatment options have become a part of the standard treatment in recent years. In this review, in the light of recent developments, the clinical spectrum and etiopathogenesis of the disease will be summarized, and we will focus primarily on the treatment. In addition to long-term and generally accepted treatment modalities in BD, new treatment approaches will be examined in detail.

Etiopathogenesis

The etiopathogenesis of the disease is not fully understood yet. There is a consensus that infectious agents can trigger BD.[10,11] The heat shock proteins (HSP) of Herpes simplex virus-1 and some streptococci strains, especially *S. sanguinis*, show significant similarity to human HSP; antibodies against HSPs of these microorganisms in individuals with a genetic predisposition are thought to initiate an immune response in humans by cross-reaction.[10,12,13] The fact that BD begins at the oral mucosa,[14] dental procedures, and surgical operations for chronic tonsillitis exacerbates the disease,[15,16] oral antimicrobial treatments are used successfully in BD, and oral hygiene is worse in BD patients compared to healthy people[17–19] suggest that oral microbial flora may play a role in disease pathogenesis. Recent studies suggest that differences in salivary or gut microbiome composition may also play a role in pathogenesis.[20,21] The salivary microbiota has been reported to have less diversity in BD patients than in healthy subjects.[20] The Major Histocompatibility Complex (MHC) profile seen in BD has been speculated to lead to the formation of a different intestinal bacterial profile and activation of the natural mucosal immune system.[22]

Shimizu et al[23] found that the *Lactobacillus* family and the genus *Bifidobacterium* increased gut microbiota in patients with BD compared to the control group. In another study of the same authors,[24] *Megamonas hypermegale* and *Butyrivibrio* species were found to be decreased and, consequently, the production of butyrate and propionate short-chain fatty acids in the intestine was reduced when compared to normal individuals. It has been emphasized that this situation may lead to a decrease in regulatory T cell response and activation of immunopathological effector T cell responses. An increase in short-chain fatty acid production by the gut microbiota or oral delivery of short-chain fatty acids may be one of the treatment targets to ameliorate skewed T cell differentiation in BD patients.[24] Even so, microbial factors and/or microbiome changes are not considered solely responsible for the pathogenesis. However, it should not be ignored that these may play a role in the disease's progression by causing immune system dysfunction in the presence of the appropriate genetic background.[25]

The most remarkable studies conducted for BD etiopathogenesis are elucidating the genetic aspects of the disease. BD's strongest genetic susceptibility factor is found in the MHC class I region, including HLA-B*51.

Individuals carrying the HLA-B*51/B5 allele had 5.78 times increased risk for developing BD than those without this allele.[26] Although the importance of the HLA-B*51 is already known, it is found to be positive in about 60% of patients. The frequency of HLA-B*51 also varies among populations. The role of HLA-B*51 in the genetic predisposition to the disease has been estimated around 12–19%.[27] To develop new hypotheses about the pathogenesis of complex immune system diseases in which genetic factors and environmental factors both play a role, Genome-Wide Association Studies (GWAS), which examine the representation status of thousands of genes, have been applied. GWAS studies have confirmed that HLA-B*51 is the strongest genetic susceptibility factor in BD.

On the other hand, new and non-HLA genes, including endoplasmic reticulum aminopeptidase 1 (ERAP1), IL-23 receptor (IL-23R), IL-23R/IL-12RB2, IL-10, and signal transducer and activator of transcription proteins (STATs) have also been identified.[28–32] Generally, gene polymorphisms related to BD have been detected in molecules that respond to microorganisms and genes encoding cytokines and adhesion molecules. Polymorphisms in these genes can affect the functions of the gene and also cause disease susceptibility. Identifying these new genes may play an essential role in determining the disease's genetic burden and perhaps defining new treatment targets in the future.

In recent years, the diseases in which innate immunity and subsequently acquired immunity are activated due to impaired barrier functions in tissues in contact with environmental factors (skin, oral mucosa, and gastrointestinal system) are called MHC-1 related diseases (MHC-1-opathy). BD overlaps with MHC-1-opathy group diseases in many aspects.[33] MHC-Class I alleles present exogenous peptides to CD8 + T cells either through endogenous peptides or through the mechanism called cross-presentation on the surface of APCs. The antigens presented by these molecules and their mechanisms are not fully understood. In recent years, the relationship detected between HLA-B*51 and ERAP1 has given some clues to understand this possible pathological mechanism. ERAP1 polymorphism is a significant genetic susceptibility factor frequently found among patients with BD in GWAS studies.[34,35] ERAP1 encodes an enzyme, amino-peptidase, which is essential in the processing of MHC-class I related peptides. This enzyme trims the N-terminal of the peptides and ensures them to reach an ideal length. ERAP1 polymorphisms have been identified as risk factors in patients with BD who are HLA-B*51 positive. It is inherited recessively in patients with BD who are only HLA-B*51 positive. The ERAP1 rs17482078 (p. Arg725Gln) polymorphism affects this enzyme's peptide specificity by altering the enzyme activity. Thus, the peptide loading onto the antigen-binding groove of HLA-B*51 is affected.[36–38] In a recent study, Giza et al showed that the presentation of these modified peptides with HLA-B*51 has a vital role in disease pathogenesis.[39]

BD starts with the triggering of innate immunity and continues with the activation of acquired immunity.[25] The "danger model" proposed by Matzinger is characterized by an excessive immune response against external stimuli. In this model, innate immunity is primarily activated, and the production of Th-1 and Th-17 related acquired immune response cytokines from innate immune cells such as macrophages and dendritic cells is triggered.[40,41] BD is also considered a neutrophilic vasculitis, and the pathogenic roles of neutrophils, a member of innate immunity, are well-known.[42] The fact that neutrophils probably being hyperactive through HLA-B*51 and form perivascular infiltration may contribute to the tissue damage seen in BD.[43,44] Also, activation of neutrophils can lead to oxidative stress and the release of Th-1 related cytokines.[44] Testosterone may also contribute to the activation of neutrophils and Th-1 cells.[45] This situation may explain why BD is more severe in male patients. Natural killer (NK) cells may also play a role by increasing CD4+ Th-1 cell responses, especially in the active phase of the disease.[46,47]

Immune system dysregulation, altered T cell balance, and particularly the suppression of T regulatory cells' activity by activation of the Th1/Th17 pathway are thought to play an essential role in the pathogenesis of BD.[42] The number of Th-17 cells has increased in the cutaneous lesions of BD.[48] Patients with BD in the active stages of uveitis, OU, GU, and articular symptoms had significantly higher IL-17 levels than patients in the inactive phases of the same symptoms.[49,50] Under Th-17 stimulating conditions, IFN-γ release from T cells increases along with IL-17, and this situation further triggers neutrophil activation and the delayed immune response.[40] In the acute attack phase of BD, while Th-17 and IL-17 pathways were active, decreased Treg and IL-10 levels were reported.[46,51] Th-1 pathway and Th-1 pathway-related cytokines (IL-2, IL-12, IL-18 and IFN-γ) are increased during the active stages of the disease.[52] TNF-α, a pro-inflammatory cytokine, plays a central role in the autoimmune response, induction and maintenance of

inflammation.[52] It contributes to the systemic inflammatory response seen in BD by being released from both innate immune cells, and acquired immune cells, such as Th-1 and Th-17 and it becomes a critical target molecule in the treatment of the disease.[53]

Consequently, environmental factors (*S. sanguinis*, etc.) or differences in salivary or gut microbiome composition can trigger innate immune system-mediated inflammation sustained by acquired or adaptive immune responses. Epistatic interactions between HLA-B*51 and ERAP1 variants disrupt T cell homeostasis. In particular, activation of the Th 1 and Th17 pathways and suppression of Treg cells are observed. This leads to the activation of neutrophils and intense neutrophil infiltration in the affected organs in the early inflammation stage.

Clinical Picture

OU, GU, and the other cutaneous lesions and ocular lesions, and arthropathy are the most frequently reported clinical symptoms of BD in all countries. Mucocutaneous lesions are the most common causes for a patient to consult a doctor, and they occur before major organ involvement in most of the patients. For this reason, good knowledge of the mucocutaneous lesions can enable physicians dealing with BD to diagnose the disease early and change the prognosis of the disease positively.[3,8,54] OU and GU are characterized by recurrent, painful ulcerations of the oral mucosa, and genital skin/mucosa. Recurrent and bipolar OU and GU strongly indicate BD when any other reason does not explain them. OU seen in BD is similar to recurrent aphthous stomatitis (RAS) in terms of clinical appearance and course; however, it recurs more frequently, the number of lesions is higher in its attacks, and is located more frequently in different anatomical areas of the mouth (Figure 1). Also, major ulcers (> 1 cm) are more frequent in BD than in RAS patients.[55] Although the appearance and course of GU are similar to OU, they are deeper and recur less frequently. Deeply located ulcers mostly heal with scarring (Figure 2). Therefore, patients with suspected BD should be investigated for scars from previous lesions, even if there is no active GU at the time of admission.[56] PPL is found in at least 3/4 of the cases. It is distinguished by folliculitis or acne-like sterile papulopustular lesions on an erythematous background. EN-like lesions are seen in up to 40% of patients, and it is more frequent in female patients. They are characterized by painful, tender, oval-rounded, erythematous nodules on the anterior and lateral surfaces of the tibia. Superficial thrombophlebitis is observed in roughly one-quarter of the cases. It is more common in male patients and is distinguished by an often erythematous induration that can be palpated throughout the course of a vein, especially in the legs.[57,58]

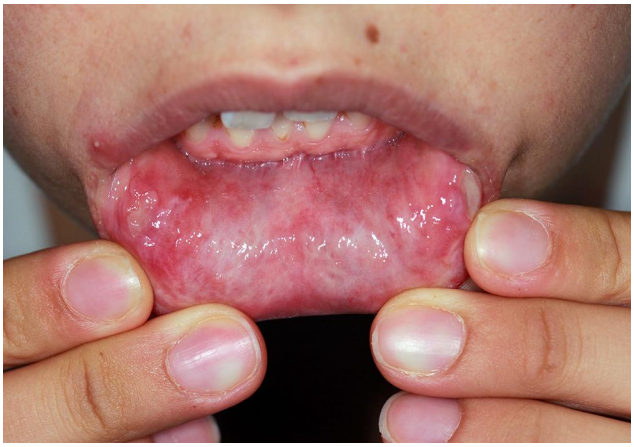

Figure 1 Oral ulcers on the lower lip mucosa.

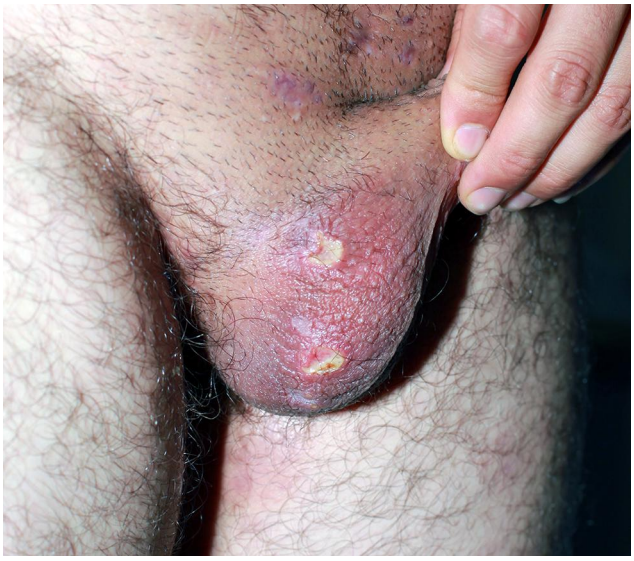

Figure 2 Genital ulcers and their scars on the scrotum.

Pathergy test, one of the disease's diagnostic criteria, refers to the hypersensitivity reaction that develops in the area where a needle was inserted. Similar to the spontaneously occurring PPL of BD, it is associated with a papule or pustule on an erythematous base at the needle-prick site 48 hours after applying a sterile needle penetrated to the corium of an avascular site on the forearm. While the average test positivity is 50% in Japan and Mediterranean countries, this rate is lower in western countries, which decreases the diagnostic value of the test.[57,58]

Ocular involvement, seen in about half of the patients, is one of disease's most serious complications. It is more common and more severe in male patients and can cause visual impairment in approximately %15 patients with recurrent inflammatory attacks.[59,60] Ocular involvement can occur as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis, affecting both eyes. Posterior uveitis or panuveitis occurs in most patients. Articular involvement is seen in approximately half of the patients. Frequently, it occurs with a monoarticular or oligoarticular pattern. The attacks last a few weeks but usually do not cause deformity. The most frequently affected joint is the knee, followed by the ankle, wrist, and elbow, respectively.[61] Being a systemic vasculitis, BD can affect all vessels regardless of diameter. The venous system is the main area of involvement, and superficial thrombophlebitis is the most common type of venous involvement. Inferior and superior vena cava thrombosis, dural venous sinus thrombosis, and Budd-Chiari syndrome can be seen, and these symptoms are associated with poor prognosis. The pulmonary artery aneurysm is rare, but it is the most important cause of mortality.[5,62] Neurological involvement is relatively rare, but it is one of the most serious complications of the disease due to its severe prognosis. Neurological involvement is seen more frequently in male patients. Most patients have brainstem involvement, hemispheric symptoms, and parenchymal involvement, including spinal cord lesions and meningoencephalitis.[63] Gastrointestinal involvement is characterized by volcano-shaped or punched-out mucosal ulcers localized mainly in the ileocecal region, although they can be seen throughout the gastrointestinal tract.[64] In the course of BD, there may be endocarditis, myocarditis, pericarditis, intracardiac thrombus, endomyocardial fibrosis, coronary arthritis, myocardial infarction, and valve diseases.[65–67] Arterial and venous involvement has been reported more frequently in patients with cardiac involvement than in patients without cardiac involvement.[68]

Treatment

The treatment is determined by many variables such as the organ involved, the severity of the involvement, the frequency of the attacks, and the patient's age and gender. The success of treatment increases with early diagnosis and early treatment of the disease. Irreversible organ damage can be prevented with effective treatment, especially in the disease's early and active stages. Controlled studies on BD are mostly limited to mucocutaneous, articular, and ocular involvement. There are no controlled studies in treating severe organ involvement because of the rarity of these conditions and ethical concerns. In this review, treatment suggestions have been developed based on the symptom/s that bring the patient to the physician. Although the recommendations are mainly based on controlled studies, it also includes important studies, guidelines, reviews of experts in this field and finally, our personal experience in clinical practice. From a holistic point of view, a symptom-based algorithmic approach has been proposed to manage BD. The "Oxford System" has been used in determining the level of evidence and the strength of the recommendation.[69] Table 1 summarizes the spectrum of action of topical and systemic treatments used in BD.

Mucocutaneous Involvement

Topical Treatment

The number of controlled studies on the use of topical treatments in BD is limited. As we mentioned above, OU seen in BD are clinically identical to RAS, and there are more controlled studies with a large series of RAS in the literature. Therefore, in clinical practice, RAS-related treatment approaches can be used in the OU treatment of BD.[1]

Triamcinolone acetonide,[70] sucralfate,[71] and pentoxifylline[72] are effective in OU of BD in randomized controlled studies. Triamcinolone acetonide 0.1% ointment (3 times a day) was more effective on OU than phenytoin syrup (2 teaspoons of syrup in half a glass of warm water as a mouthwash for 4–5 minutes, 3 times a day) at the end of one week.[70] Sucralfate, which protects the mucous membranes by covering like a barrier, accelerates wound healing and reduces mucosal ulcers' frequency and pain more than placebo when used 4 times a day for 3 months.[71] When it is applied in 4 divided doses and used together with colchicine, pentoxifylline 1000 mg/day, which increases erythrocyte elasticity, decreases blood viscosity and improves microcirculatory flow and tissue perfusion, provided a significant reduction in the duration and pain of OU when compared to the use of colchicine alone, at the end of 2 weeks.[72]

Antimicrobial agents[73] such as Listerine^{R} (Johnson & Johnson, New Brunswick, NJ, USA), chlorhexidine gel,[74] penicillin G potassium troches,[75] minocycline,[76] tetracycline suspension,[77] triclosan mouth rinse,[78] amlexanox,[79] 5-aminosalicylate,[80] camel thorn distillate,[81] diclofenac,[82] lasers,[83] and silver nitrate[84] are other treatments shown to be effective in RAS patients and can also be used in BD patients.

Table 1 Effectiveness of Therapeutic Agents Used in the Treatment of Behçet's Disease

Topical Therapeutic Agent	Efficacy Spectrum of Therapeutic Options
Corticosteroids[70,197,198] (for triamcinolone acetonide*)	Reduce the pain severity and accelerate the healing duration of OU and GU
Tetracycline[77]	Decreases the pain severity and the healing duration of OU
Sucralfate*[71]	Decreases the frequency, healing time and pain of OU, and the healing time and pain of GU
Amlexanox[79,199,200]	Decreases the pain severity and healing duration of OU
Antimicrobial agents, Anti-inflammatory agents, Anaesthetics, Silver nitrate[73–75,78,84]	Decrease the pain severity of OU
Wet dressing[1]	Decreases the pain severity and the healing duration of EN and STP
Camel thorn distillate[81]	Reduces the ulcer size and the pain severity
5-aminosalicylic acid[80]	Decreases the OU healing duration
CO2 laser[83]	Reduces the OU pain
Nd:YAG laser[201]	Causes immediate relief of pain and faster healing
Minocycline[76,202]	Decreases the pain severity
Pimecrolimus*[85,86]	Decrease the pain severity of GU and accelerates the healing process of GU
Pentoxifylline*[72]	Decreases the duration and pain of OU
Systemic Therapeutic Agent	**Efficacy Spectrum of Therapeutic options**
Corticosteroids[54,68,93,121] [93] *(for depot corticosteroid)	Mucocutaneous lesions (OU, GU, STP, ExU), acute uveitis, neurologic disease, vascular involvement, severe gastrointestinal involvement, cardiac involvement
Colchicine[90,91] *	Mucocutaneous lesions (GU, EN, PPL) and arthralgia/arthritis
Dapsone[104] *	Mucocutaneous lesions (OU, GU, EN, PPL), arthritis and epididymitis
Apremilast[94,95] *	Mucocutaneous lesions (OU, GU)
Azathioprine[68,98,121] *	Mucocutaneous lesions (OU, GU), arthritis, uveitis, neurologic disease, vascular involvement, severe gastrointestinal involvement
Thalidomide[99,188–190] *	Mucocutaneous lesions (OU, GU, PPL), gastrointestinal involvement
Interferon alfa[103,122,123,203] *	Mucocutaneous lesions (OU, GU, PPL), arthritis, uveitis
CyclosporinA[130,131] *	Mucocutaneous lesions (OU, GU, PPL, STP, EN), ocular, articular and vascular involvement
Anti-TNF alfa agents[101,102] [101] *(for etanercept)	Mucocutaneous lesions (OU, GU, PPL, EN), arthritis, vascular, gastrointestinal and ocular disease
Rebamipide[106] *	Mucocutaneous lesions (OU)
Zinc sulphate[105] *	Mucocutaneous lesions (OU)
Levamisole[108] *	Mucocutaneous lesions (OU, GU), arthritis and uveitis
Anakinra and Canakinumab[110–116,204]	Mucocutaneous lesions, articular involvement, uveitis and neurological involvement
Ustekinumab[118]	Mucocutaneous lesions (OU), articular involvement,
Secukinumab[126]	Mucocutaneous lesions, articular involvement
Tocilizumab[140,141]	Vascular involvement and uveitis
Isotretinoin[107] *	Mucocutaneous lesions (OU)
Mycophenolate mofetil[109,167]	Mucocutaneous lesions, neurological involvement
Cyclophosphamide[68,149,162]	Severe vascular involvement, neurological involvement, cardiac involvement

Note: Randomized controlled studies are indicated by an asterisk (*).
Abbreviations: OU, oral ulcers; GU, genital ulcers; EN, erythema nodosum-like lesions; PPL, papulopustular lesions; STP, superficial thrombophlebitis; ExU, extragenital ulcerations.

Pimecrolimus cream, twice a day, accelerated the healing time of GU significantly in patients with BD compared to placebo.[85] The combination of topical pimecrolimus and colchicine 1–2 mg/day, used twice a day, provided a significant reduction in the pain severity of GU compared to colchicine alone.[86] Another option commonly used in clinical practice in GU treatment is corticosteroids. Although there are no controlled studies, potent corticosteroid ointments have been successfully used in GU treatment in the early stages of lesions, alone or in combination with antiseptics.[87]

EN-like lesions and superficial thrombophlebitis may benefit from wet dressing with 3–5% aluminum subacetate (Burrow) solution.[1] Bed rest should be recommended in these patients. For PPL, however, local treatment expectancy is relatively rare; antiseptic containing corticosteroids or antibiotics may be used for this purpose.[54]

The effects of topical agents are probably limited to the application area. They are often used in the treatment of BD as an adjunct to systemic treatment. However, there may be a subgroup of patients in which a topical treatment approach alone can be used, such as patients without major organ involvement and no new attacks for a long time, female or elderly patients without severe organ involvement.

Systemic Treatment

In the absence of severe organ involvement, systemic therapy is usually based on the severity and clinical spectrum of mucocutaneous symptoms. Colchicine, 0.5 mg, 2–4 times a day, is usually preferred as the first-line treatment in managing OU, GU, EN-like lesions, and PPL.[88] It suppresses the adhesion and recruitment of neutrophils by preventing microtubule polymerization. In the first placebo-controlled study of 35 patients,[89] colchicine was effective in reducing the number of EN-like lesions. In the second placebo-controlled study involving 116 patients, colchicine reduced the frequency of GU and EN-like lesions in female patients.[90] In the most recent, randomized, double-blind, crossover study involving 169 patients, significant improvement was found in the disease activity index and OU, GU, EN-like lesions, and PPL.[91] The main difference between the last study and the previous ones is the difference in the medication's effectiveness on OU and PPL. Open studies and our clinical observations confirm that colchicine is also effective on OU and PPL besides GU, EN-like lesions, especially in those with mild severity of the disease. Once a month, 1.2 million U benzathine penicillin can be added to colchicine treatment for patients for whom colchicine is not adequate alone. Combination therapy decreases OU and EN-like lesions' duration and the frequency of GU compared to those receiving colchicine alone.[92]

Systemic corticosteroids can be used to control acute, severe mucocutaneous attacks rapidly. Prednisolone is usually used in major OU attacks, large and deep GU, and extensive and severe EN-like lesions and/or superficial thrombophlebitis. Prednisolone is usually started at a dose of 40–60 mg/day and tapered off within 4 to 6 weeks. Long-term use of corticosteroids should be avoided because of their side effects and their inability to prevent new attacks. In patients, who will be using corticosteroids, it is recommended to start treatment with an agent such as colchicine. In patients with active mucocutaneous lesions without ocular or major organ involvement, low-dose depot corticosteroid (40 mg methylprednisolone acetate every 3 weeks) is useful in the control of EN-like lesions, especially in female patients.[93] However, this result does not mean that this compound will not affect other disease symptoms when used daily and at higher doses.

Apremilast, an oral phosphodiesterase-4 inhibitor, is one of the most exciting treatment choices for BD in recent years. In the Phase 2 study, apremilast (30 mg, twice a day) decreased the number of OU and GU and was effective in reducing pain due to OU.[94] In a randomized, placebo-controlled, double-blind Phase 3 study, in patients with BD with active OU, without major organ involvement, apremilast significantly reduced the OU count and OU pain when compared to placebo, and this effect was observed as early as 1 week. Normally, the response seen at 12 weeks was prolonged to 28 weeks. In double-blind studies, the side effect profile was similar between apremilast and placebo. Diarrhea, nausea, and headache caused by apremilast are generally mild to moderate.[95] Following this study, apremilast was approved by the FDA in patients with BD with active OU who had been previously treated with at least one nonbiological agent. Recently, real-life data on the use of apremilast in BD have also been published. Lopalco et al noted that apremilast decreased the number of OU and GU at the end of 3 months significantly compared to baseline and the number of active OU and OU attacks was still lower than the baseline at the end of 6 months.[96] At the end of the 3rd month of treatment, the pain score was found to be significantly lower than the baseline, and this effect continued in the 6th month. Also, the disease activity score was significantly lower than the baseline at the end of the 3rd and 6th months. In the study of De Luca et al, at the end of the 12th week, a significant decrease was found in the number of OU and GU, disease activity score, and pain score using apremilast in patients with BD who were resistant or intolerant to conventional treatment. This clinical improvement enabled corticosteroid dose reduction and corticosteroid discontinuation. There was a significant improvement in the quality of life of the patients compared to the baseline. In 4 of 12 patients, the treatment was discontinued mostly due to diarrhea.[97] In conclusion, apremilast is a candidate to be an important treatment option in patients with colchicine-resistant mucocutaneous symptoms, with a relatively lower side effect profile than immunosuppressive treatments. It can be evaluated as an important alternative in the first step in patients who do not respond to previous treatments (Table 2).

In the randomized, placebo-controlled, double-blind study of Yazici et al,[98] azathioprine was used at a dose of 2.5 mg/kg/day and decreased the frequency of OU and GU when compared to placebo. Anti-TNF-α agents may also be recommended as the second-line treatment in refractory cases. When used at a dose of 25 mg, 2 days a week in a placebo-controlled study, etanercept had a rapid effect, especially on GU and EN-like lesions, and significantly reduced the numbers of OU, EN-like lesions, and PPL.[99] In multiple and open studies with large series, infliximab and adalimumab were found to be effective at a rate of 88% in mucocutaneous lesions in severe cases and/or cases resistant to immunosuppressive agents, with no significant difference in effect.[100] Interferon-alpha 2a treatment (3 times a week, 6 million U) significantly decreased the healing time and pain of OU and the frequency of GU and PPL at the end of 3 months in a placebo-controlled study.[101] Cyclosporine-A used at a dose of 5 mg/kg/day was found to be more effective than conventional treatment (prednisolone, azathioprine) on OU, GU, superficial thrombophlebitis, and cutaneous lesions in a randomized controlled study.[102] In a randomized, placebo-controlled, double-blind study conducted by Hamuryudan et al,[103] thalidomide used at a dose of 100–300 mg/day provided long-term remission in OU, GU, and PPL. However, this agent should be used only in selected patients with care because of its potential side effects. It should also be kept in mind that nodular lesions may increase during thalidomide treatment.[103]

In a double-blind, placebo-controlled study, dapsone has been shown to reduce the number, healing time, and frequency of OU and the number of GU, EN-like lesions, and PPL when compared to placebo.[104] Dapsone, an antineutrophilic activity like colchicine, can be an alternative to colchicine in treating mucocutaneous manifestations of BD in regions without glucose-6-phosphate dehydrogenase deficiency. It has also been reported that the use of oral zinc sulfate (300 mg/day, 6 months) provided improvement in mucocutaneous symptoms without any significant side effects.[105] Rebamipide (300 mg/day, 6 months), a gastroprotective drug, significantly reduced the OU count and pain level compared to placebo.[106] In the study of Sharrquie et al,[107] isotretinoin, used for 12 weeks at a dose of 20 mg/day, provided a significant improvement in the clinical symptom index and OU and skin manifestation parameters compared to placebo. Levamisole (3x50 mg, 2 days/w) was found more effective on OU and GU than placebo.[108] Dapsone, zinc sulfate, rebamipide, isotretinoin, and levamisole might have been considered in the treatment's previous steps because of their controlled studies showing promising results. However, these treatments were not included in the previous steps because of the reason(s) summarized below. Relatively few patients were included in these publications; there have not been new publications about these treatments; new and more effective treatments have emerged in recent years; effectiveness is limited to OU (rebamipide). Enteric-coated mycophenolate mofetil (6 months, 720 mg twice a day) is another treatment that can be preferred in patients with mucocutaneous symptoms, resistant to at least one of the standard treatment methods as a second-line treatment.[109]

There is a growing body of research on the use of IL-1 antagonists in BD. The IL-1 receptor antagonist anakinra (ANA) and the full human anti-IL-1β antibody canakinumab (CAN) had good clinical results in patients with BD.[110–115] In a multicenter retrospective study,[116] 90% of patients received ANA (100 mg/day) and 10% CAN (150 mg every 6–8 weeks) as the initial treatment. Complete remission (CR) was achieved in all 13 patients on anti-IL-1 treatment for 12 months. In 6 of these patients they switched from ANA to CAN during the treatment. During the 12-month follow-up, 8 of 30 patients were switched to non-anti IL-1 antagonist treatment due to ineffectiveness or loss of effect. During the study process, no serious adverse effect was developed. A mild local cutaneous reaction developed in 15% of the group receiving ANA, and no adverse effects developed in the group receiving CAN. These data indicate that anti-IL-1β antagonists are effective and safe in BD.

There are two studies on the use of ustekinumab, a monoclonal antibody developed against IL-12 and IL-23 p40 subunit.[117,118] In the first study,[117] 14 BD patients with colchicine-resistant active OU were included in the study. 45 or 90 mg subcutaneous ustekinumab injection was administered on the first day, the first month, and every 3 months. At the end of the 12th week, 64% CR (defined as no OU), 21% partial response (PR) was obtained, while no response was obtained for 14%. Ustekinumab reduced the corticosteroid dose, decreased disease activity score, and treatment was discontinued in one patient due to headache. In another multicenter, prospective, open-label study,[118] 30 BD patients with colchicine-resistant active OU were included to study. CR (defined as no OU) was achieved in 60% of patients at the end of 12 weeks and 88.9% of patients at the end of 24

Table 2 Evidence-Based Algorithmic Treatment for Mucocutaneous Behcet's Disease

Recommended Treatment Step	Treatments and Their Category of Evidence	Strength of Recommendation
1st Line	Systemic Colchicine (1B), Colchicine + Benzathine penicillin (1B), Corticosteroids (1B-3), Apremilast (1B) Topical OU: Sucralfate (1B), Corticosteroids (1B), Pentoxifylline (1B), Treatments with proven efficacy for RAS by RCT (1B) GU: Sucralfate (1B), Pimecrolimus (1B), Corticosteroid + Antiseptic (4), Creams/ointments that provide scatrisation such as Triticum vulgare aqueous extract (4), Centella asiatica extract (4), Dexpanthenol (4)	A-D
2nd Line	Systemic Azathioprine (1B), Cyclosporine A (1B), IFN-alpha (1B), Etanercept (1B), Adalimumab (3), Infliximab (3), Thalidomide (1B), Dapsone (1B), Zinc sulphate (1B), Rebamipide (1B), Levamisole (1B), Isotretinoin (1B), Mycophenolate mofetil (3C) Topical Physical agents for RAS with proven efficacy by RCT (Silver nitrate, CO2 laser, Nd YAG laser) (1B), Wet Dressing (4)**, Bed Rest (4)**	A-D
3rd Line	Systemic Ustekinumab (3), IL-1 antagonists (3), Secukinumab (3) Topical Intralesional corticosteroid injection (4)	C-D

Note: **For EN-like lesions and thrombophlebitis.
Abbreviation: RCT, randomised controlled trial.

weeks by injecting 90 mg subcutaneous ustekinumab on day 1, the first month, and every 3 months. Serious adverse effect has not been observed. Ustekinumab appears to be a promising and safe treatment for colchicine-resistant OU.

As an IL-17 antagonist, secukinumab has been used in psoriatic arthritis, and ankylosing spondylitis and its efficacy in BD are being investigated due to similarities of its pathogenesis and clinical characteristics to seronegative arthritis. On 5 BD patients with OU and articular symptoms resistant to colchicine, conventional disease-modifying anti-rheumatic drugs (DMARDs), and at least one anti-TNF-α agent, secukinumab 150 mg (4 patients) or 300 mg (1 patient) were used once a month. The patient receiving 300 mg reached CR (50% reduction in OU count) within 3 months. Half of the 4 patients who received 150 mg reached CR in the 6th month, but relapse was observed in one patient who also reached CR. CR was achieved using 300 mg in patients with relapse and in whom CR could not be reached.[119] On the other hand, two BD cases have been reported to be triggered by the use of secukinumab.[120] Table 2 shows evidence-based algorithmic treatment for mucocutaneous BD.

Articular Involvement

The effect of colchicine on arthritis and arthralgia has been shown with randomized placebo-controlled studies.[89,91] Therefore, colchicine is recommended as a first-line treatment in patients with arthritis.[121] Calguneri et al[92] showed that when benzathine penicillin (1.2 million U, every 3 weeks) was combined with colchicine treatment, the number of arthritis attacks was decreased, and the duration of the attack-free period was prolonged compared to the colchicine group alone. Azathioprine, used for 2 years at the dose of 2.5 mg/kg/day, significantly reduced arthritis incidence compared to placebo.[98] Azathioprine may be preferred in patients with recurrent arthritis and/or refractory disease. IFN-alpha 2a (3 days a week, 3–12 million U) can alleviate the symptoms of arthritis and arthralgia.[7] Studies have shown that IFN-alpha 2a (3 days a week, 6–9 million U) and IFN-alpha 2b (3 days a week, 5 million U) treatments reduce the number of arthritis attacks and shorten the duration of arthritis.[122–124] Infliximab and adalimumab were effective in 70% of patients with severe articular involvement resistant to immunosuppressive agents (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, cyclosporine-A) and IFN-

alpha.[100] Although systemic corticosteroids and nonsteroidal anti-inflammatory drugs are widely used to treat symptoms associated with arthritis, the results from controlled trials with azapropazone or intramuscular methylprednisolone acetate have been disappointing.[93,125] In patients with mono-arthritis, intra-articular corticosteroid injections may be considered besides systemic treatment.[121]

In a multicenter, prospective, open-label study, with ustekinumab treatment (90 mg at inclusion, at week 4, and then every 12 weeks), no arthritis was detected in any of the patients during the treatment process, and there was a decrease in articular involvement compared to baseline at the end of 12, 24, 36 and 48 weeks. At the end of the 4-year follow-up, arthralgia continued in only 15% of the patients.[118]

In a multicenter, retrospective study, with secukinumab treatment (150 mg/month, 300 mg/month in polyarticular involvement), 66.7% of the patients showed a significant improvement in articular symptoms within 3 months, and sustained remission was achieved in 84.6% of the patients.[126] In another multicenter, retrospective study, complete improvement in articular symptoms (CR) was achieved in all patients after 12 months of treatment with IL-1 antagonists (100 mg/day ANA and 150 mg CAN every 6–8 weeks).[116] Ustekinumab, secukinumab, and IL-1 antagonists can be used as an alternative treatment option in treatment-resistant cases. Table 3 summarizes the evidence-based algorithmic treatment for articular BD.

Ocular Involvement

To prevent irreversible losses in visual acuity, it is crucial to suppress inflammatory attacks quickly and prevent relapses.[127129] In acute attacks, when the anterior part of the eye is involved (anterior uveitis), topically applied corticosteroid eye drops combined with mydriatics or cycloplegic agents can control the disease. Subconjunctival or posterior sub-Tenon corticosteroid injections according to the severity of eye involvement, and intravitreal corticosteroid injections in acute attacks limited to one eye can be administered in suitable patients. However, these treatments are recommended to be combined with systemic treatments.[121]

Table 3 Evidence-Based Algorithmic Treatment for Articular Behcet's Disease

Recommended Treatment Step	Treatments and Their Category of Evidence	Strength of Recommendation
1st Line	Colchicine (1B), Colchicine + Benzathine penicillin (1B)	A
2nd Line	Azathioprine (1B), IFN-alpha (3), Infliximab (3), Adalimumab (3)	A-C
3rd Line	Ustekinumab (3), IL-1 antagonists (3), Secukinumab (3)	C

Systemic corticosteroids can be used in unresponsive and/or acute inflammatory ocular attacks of posterior uveitis, panuveitis, and retinal vasculitis.[121] Systemic corticosteroid therapy may not be sufficient when administered alone. It is generally recommended to be used in conjunction with systemic immunosuppressive treatment.[121] The first randomized controlled trial of an immunosuppressive agent in ocular involvement is related to azathioprine. Azathioprine treatment was effective in uveitis compared to placebo and significantly reduced patients' corticosteroid requirement and improved visual acuity. Also, the development of new ocular diseases was significantly reduced in azathioprine users.[98] Cyclosporine-A has been found superior to both colchicine[130] and conventional therapies (prednisolone, chlorambucil) in reducing the frequency and severity of ocular attacks.[130,131] Some experts suggest that although there is no controlled study of combining azathioprine or cyclosporin-A with anti-TNF-α agents, combined therapy will increase success.[121] Anti-TNF-α agents can also be used alone or in combination with these agents in severe and/or resistant cases to cyclosporine A, azathioprine, systemic corticosteroids. In a placebo-controlled phase 3 study, including patients with BD, adalimumab (a loading dose of 80 mg followed by a dose of 40 mg every 2 weeks) was associated with a lower risk of uveitis exacerbation or visual impairment in non-infectious active intermediate, posterior uveitis and panuveitis.[132] Recent, multicenter and large series studies have shown that adalimumab (40 mg/every 2 weeks subcutaneously) and infliximab (3–5 mg/kg iv at 0, 2, 6 days, and then every 4–8 weeks) are effective and relatively safe options for ocular involvement resistant to conventional treatments.[133,134] In a multicenter study involving 177 patients, these two agents were compared with each other. After 1 year of treatment, a significant improvement was observed in all ocular parameters in both groups. However, improvement in some parameters (improvement in anterior chamber inflammation, vitritis, and best-corrected visual acuity) was more pronounced in patients using adalimumab than in infliximab.[135] Switching

between agents seems possible in patients with unresponsiveness to any of these drugs or patients with adverse events.[121] IFN-alpha 2a is another alternative in patients resistant to corticosteroids and traditional immunosuppressive agents, and its effectiveness has been shown in controlled[102] and open studies.[122,136] This compound is effective and safe in the long-term treatment of severe uveitis (3 million units thrice a week).[122,136] IFN-alpha decreases the need for corticosteroids and immunosuppressive agents and increases the quality of life.[137]

Randomized, placebo-controlled studies on gevokizumab, an IL-1β antagonist, and secukinumab, show that these two agents are far from achieving their goals.[138,139] Monoclonal antibodies targeting these two cytokines play an important role in etiopathogenesis. The eye has a highly protected microenvironment; this may be one reason why eye involvement is relatively resistant to these treatments. On the other hand, studies show that tocilizumab, an IL-6 blocker, can be an effective treatment option in uveitis resistant to immunosuppressive agents.[140,141] Table 4 shows evidence-based algorithmic treatment for ocular BD.

Vascular Involvement

The treatment of vascular BD symptoms varies according to the affected vascular area and the nature of this involvement. Inflammation of vascular structures in BD profoundly affects the treatment approach.

Table 4 Evidence-Based Algorithmic Treatment for Ocular Behcet's Disease

Recommended Treatment Step	Treatments and Their Category of Evidence	Strength of Recommendation
1st Line	Systemic Azathioprine (1B), Cyclosporine-A (1B), Corticosteroids (3) Topical* Corticosteroids + mydriatics and/or cycloplegic agents (3)	A-C
2nd Line	Adalimumab (1B), Infliximab (2B), IFN-alpha (2A)	A-B
3rd Line	Tocilizumab (3)	C

Note: *It should be considered as a part of systemic therapy.

Venous Involvement

Acute deep vein thrombosis (DVT) treatment is based on systemic corticosteroids and immunosuppressive agents such as azathioprine, cyclosporine-A, cyclophosphamide.[121,142,143] Immunosuppressive treatment is crucial to prevent relapse and reduce the risk of post-thrombotic syndrome.[142] There is no evidence that one immunosuppressive agent should be preferred over others.[121] However, cyclophosphamide may be preserved for patients with extensive thrombosis in larger vessels such as the vena cava due to its potential severe side effects.[121] The use of anticoagulants in DVT is still controversial.[142]

In a meta-analysis, the combined use of immunosuppressive agents and anticoagulants was found to be more effective in preventing the relapse risk of DVT than using anticoagulants alone. However, treatment with anticoagulants and immunosuppressive agents did not provide a significant benefit in preventing relapses compared to immunosuppressive agents alone.[121,144-146] On the other hand, a retrospective study shows that not using anticoagulants increases the risk of post-thrombotic syndrome.[147]

Anti-TNF-α agents may be considered in patients with resistant DVT.[121] Anti-TNF-α agents can also be used in combination with conventional DMARDs[148,149] or interferon-alpha.[150]

Arterial Involvement

Primary management of pulmonary artery aneurysms and thrombosis is carried out with high-dose corticosteroids and cyclophosphamide.[121,149,150] Anti-TNF-α agents, particularly infliximab, can be life-saving in treatment-resistant cases.[121,151] The mortality rate is high in patients undergoing surgical treatment, and surgery should not be preferred except for life-threatening situations.[150,152,153] Embolization may be necessary for patients with a high risk of bleeding.[149,153,154]

If peripheral arterial aneurysms are small and asymptomatic and have a low risk of rupture, medical treatment with high-dose corticosteroids and cyclophosphamide may be sufficient.[154–156] Surgery or stenting is required to treat all peripheral artery aneurysms in those who do not have these features.

In a retrospective study,[157] tocilizumab was used at a dose of 8 mg/kg every 4 weeks in 7 patients with resistant arterial involvement who were poorly controlled with corticosteroids and immunosuppressive agents. After a mean follow-up of 19 months, all clinical symptoms and blood markers of inflammation improved, and no new-onset, arterial or venous lesions were reported during follow-up.

Table 5 Evidence-Based Algorithmic Treatment for Vasculo-Behcet's Disease

Vascular Involvement	Recommended Treatment Step	Treatments and Their Category of Evidence	Strength of Recommendation
Venous	1st Line	Corticosteroids (3), Azathioprine (3), Cyclosporine A (3)	C
	2nd Line	Cyclophosphamide (3), Anti-TNF-α agents (3)	C
	3rd Line	IFN-alpha (3), Anticoagulants (3)*	C
Arterial	1st Line	Corticosteroids (3), Cyclophosphamide (3)	C
	2nd Line	Anti-TNF-α agents (Infliximab) (3)	C
	3rd Line	Tocilizumab (3), Surgery (3), Anticoagulants (3)*	C

Note: *Since thrombosis in BD is due to systemic inflammation and the clot formed is tightly adhered to the vessel wall and the risk of pulmonary embolism is relatively low, immunosuppressive therapy is preferred over anticoagulant therapy.

Therefore, tocilizumab with immunosuppressive agents and corticosteroids may be a good alternative in managing active refractory vasculo-BD. Table 5 summarizes the evidence-based algorithmic treatment for vasculo-BD.

Neurological Involvement

Acute parenchymal attacks should be treated with high doses of corticosteroids. Corticosteroid treatment usually begins with pulse intravenous methylprednisolone at a dose of 1 gr/day, which can be given for up to 7 days, and continues with oral prednisolone or prednisone given at a dose of 1 mg/kg/day for 1 month and this treatment is reduced by 5–10 mg in every 10–15 days. Azathioprine (2–2.5 mg/kg/day) is added to this treatment. In patients with progressive neurological involvement who persist or relapse despite corticosteroids and/or azathioprine, anti-TNF-α agents may be preferred as effective first-line therapy.[158–161] Anti-TNF-α agents, particularly infliximab, have been associated with a high response rate of 80%. Anti-TNF-α agents can prevent the risk of relapse and disability.[100,121,158–161] Cyclophosphamide may be an alternative, and it can be preferred in patients with parenchymal involvement having severe and poor prognostic factors. Cyclophosphamide can be administered orally (1–3 mg/kg/day) or pulse intravenously (500–1000 mg/m^2 every month for 6–9 months). In a retrospective study comparing three different therapeutic regimes (corticosteroids alone, azathioprine + corticosteroids, cyclophosphamide + corticosteroids), no significant difference in long-term outcomes was reported. However, a longer event-free survival was achieved in patients with a severe disability who were initially treated with high dose corticosteroids + intravenous cyclophosphamide.[162] Tocilizumab (8 mg/kg every 4 weeks for a mean period of 24 months) provided partial remission in two patients and near-complete remission in one patient of three patients with neuro-BD, who were resistant to immunosuppressive and anti-TNF-α agents, and these effects could be achieved in a relatively short time, such as months.[163] ANA[110,116] and CAN[110] have also been reported to be effective in neuro-BD resistant to other immunosuppressive therapies. Since limited data are available for IFN-alpha,[164,165] methotrexate,[166] and mycophenolate mofetil,[167] their use is recommended in selected cases.

A meta-analysis of observational studies with cyclosporine-A showed that the risk of nervous system involvement is increased in patients using this agent.[168–171] Therefore, cyclosporine-A should be avoided in BD patients with neurological involvement, even when the nervous system involvement is no longer active.[121]

In the acute attack treatment of cerebral venous thrombosis, corticosteroids are started at high doses, and the dose is reduced according to the response. Short-term anticoagulants can be used, especially in patients with prothrombotic tendency. It has not been demonstrated that adding immunosuppressive agents to these treatments has any benefits. In the first phase, the use of immunosuppressive agents may not be recommended as relapses are uncommon.[121] However, in resistant and relapsed cases, azathioprine, cyclophosphamide, and anti-TNF-α agents can be used.[172,173] Table 6 summarizes the evidence-based algorithmic treatment for neuro-BD.

Gastrointestinal Involvement

The treatment approach in gastrointestinal system involvement is generally determined according to the severity of the involvement. In mild cases, it would be wise to start treatment with five aminosalicylate derivatives and salazosulfapyridine.[174] Azathioprine can be considered in unresponsive or severe cases.[121] In unresponsive cases, oral or intravenous high-dose corticosteroids can be used.[175,176] Corticosteroids are thought to accelerate the healing of ulcers in acute exacerbations. However,

Table 6 Evidence-Based Algorithmic Treatment for Neuro-Behcet's Disease

Neurological Involvement	Recommended Treatment Step	Treatments and Their Category of Evidence	Strength of Recommendation
Parenchymal	1st Line	Corticosteroids (3), Azathiopürine (3), Anti-TNF-α agents (Infliximab) (2B)	B-C
	2nd Line	Cyclophosphamide (3)	C
	3rd Line	Tocilizumab (3), IL-1 antagonists (3), Mycophenolate mofetil (3), IFN-alpha (3), Methotrexate (3)	C
Non-parenchymal	1st Line	Corticosteroids (3), Anticoagulants (3)	C
	2nd Line	Azathiopürine (3), Anti-TNF-α agents (Infliximab) (3)	C
	3rd Line	Cyclophosphamide (3)	C

since high doses of corticosteroids have the potential to trigger perforation, they should be used with a well-calculated benefit-to-harm ratio.[57] The current evidence on the efficacy of corticosteroids in gastrointestinal involvement is insufficient to recommend their routine use in clinical practice.[176] Occasionally, colchicine is administered empirically, but there is insufficient evidence regarding its use.[174] Colchicine should not be used alone in mucosal inflammation and ulcers.[174]

The absolute indications of surgical treatments are intestinal perforation, severe stricture, large abscesses, and massive gastrointestinal bleeding.[174] Immunosuppressive agents reduce the risk of postoperative recurrence and complications in such patients.[121] Relative indications of surgery are; resistance to medical treatment and intestinal complications affecting the quality of life.[174] Enteral nutrition therapy with elemental diets may be useful in inducing remission and is indicated for patients resistant to drug therapy and those with severe intestinal disorders such as stenosis.[174]

In recent years, the most crucial development in this field is anti-TNF-α agents in many cases with high success rates. Therefore, it can be considered as a suitable alternative for those with severe symptoms resistant to azathioprine.[177,178] Infliximab is useful in the rapid induction and maintenance of remission in intestinal BD.[179–181] Adalimumab also shows a similar efficacy profile to infliximab in patients with resistant or severe intestinal BD.[182–184] Etanercept,[185] golimumab,[186] and certolizumab[187] are other anti-TNF-α agents found to be effective in intestinal BD.

Thalidomide can be administered successfully in cases with gastrointestinal involvement resistant to immunosuppressive agents such as corticosteroids and azathioprine.[188–190] It has been suggested that methotrexate may be useful in intestinal BD as combination therapy with infliximab.[178] IL-1 antagonists, ANA and CAN[110,114,116] and IL-6 antagonist tocilizumab[140] have also been studied in patients with BD, including, but not limited to, intestinal BD. These agents may be useful in intestinal BD. Ustekinumab has been approved for treating Crohn's disease, which shows some similarities with intestinal BD in terms of genetic background, clinical features, and treatment. This treatment has not yet been studied in intestinal BD.[191] Table 7 shows evidence-based algorithmic treatment for intestinal BD.

Cardiac Involvement

Cardiac complications are one of the leading causes of death in patients with BD. Therefore, early diagnosis and treatment of these complications are of great importance. Since cardiac involvement is rare, there are no large series and controlled studies in the literature. There is no standard protocol for remission and maintenance treatment.

Table 7 Evidence-Based Algorithmic Treatment for Gastrointestinal Behcet's Disease

Recommended Treatment Step	Treatments and Category of Evidence	Strength of Recommendation
1st Line	5-aminosalicylate (3), Salazosulfapyridine (3)	C
2nd Line	Azathioprine (3), Anti-TNF-α agents (3), Methotrexate (3), Thalidomide (3), Corticosteroids (4), Surgery* (3)	B-D
3rd Line	Tacrolimus (3), IL-1 antagonists (3), Tocilizumab (3)	C-D

Note: *Intestinal perforation, severe stricture, large abscess, and massive gastrointestinal bleedings, may constitute the absolute indications for surgery.

Pericarditis can be treated with aspirin, colchicine, and/or immunosuppressive agents.[68] The main therapeutic approach in acute myocardial infarction is based on revascularization (surgical or percutaneous).[68,192] Corticosteroids, immunosuppressive agents, surgery, or anticoagulant therapy, may be used in the intracardiac thrombus.[68,192] The surgical approach may be preferred in addition to immunosuppressive therapy in endomyocardial fibrosis and coronary aneurysm.[68,192–194] In cardiac failure, high dose corticosteroids and conventional heart failure therapy may improve cardiac performance.[192,195]

Kwon et al[196] reported that anticoagulants such as coumadin could cause aneurysm formation and enlargement in BD. Intracardiac thrombotic events are caused by blood pooling due to endothelial or myocardial damage secondary to inflammation. Therefore, some authors do not recommend anticoagulants, as they may cause bleeding in patients with thrombotic complications.

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