

# Treatment of Systemic Involvement of Behçet's Disease

**Ragıp Ertaş\* and Atıl Avcı**

Clinic of Dermatology, Education and Research Hospital, Sağlık Bilimleri University, Turkey

**\*Corresponding author:** Ragıp Ertaş, Clinic of Dermatology, Education and Research Hospital, Sağlık Bilimleri University, Kayseri, Turkey; Email: ragipertas@yahoo.com

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Behçet's disease (**BD**) is a multi genetic, chronic systemic vasculitis with an unknown origin characterized by recurrent oral ulcers, mucocutaneous disorders and ocular findings, as well as articular, vascular, neurological, pulmonary, gastrointestinal, renal and genitourinary manifestations [1]. BD has a broad range of disease severity, some of minor manifestations such as arthritis and mucocutaneous disease, can reduce patients' quality of life but do not threaten vital organ functions. Some major manifestations of BD may be life-threatening, affecting the central nervous system, large vessels, renal, pulmonary and the gastrointestinal tract [2].

It is hard to introduce a single management strategy for patients with BD [3]. The aim of the treatment of BD is to provide and maintain remission and achieve a higher QOL score. The treatment strategy of BD should be based on the organ involved and the assessment of the severity of the disease [4]. There are some crucial factors that need to be considered when planning treatment for BS, for example male sex and disease onset at younger age (<25) are associated with more severe disease course. Additionally, duration of disease, symptom severity and frequent recurrences must be considered for the treatment of patients with BD [1].

In this chapter, we are going to discuss the treatment of following systemic manifestations of BD; arthritis, ocular disease, neurologic disease, gastrointestinal disease, renal disease, large artery involvement, venous thrombotic events.

# TREATMENT OF ARTHRITIS

Non-erosive and self-limited arthritis characteristic of patients with BD is rarely decisive in the level of therapy.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** The residual joint complaints can improve with NSAIDs and usually NSAIDs are sufficient in reducing arthralgia [4,5]. A previous study with azapropazone, had shown disappointing results [6]. Azapropazone (900mg/day) was only found superior compared with placebo for pain at day seven in that study [6]. In another recent study with indomethacin, eighty percent of patients with joint involvement responded to indomethacin (25mg four times daily for 3 months) therapy [7].
- **Colchicine:** The arthritis of BD can be treated with colchicine with divided doses ranged from 1 to 2 mg/day. Colchicine also has a protective effect against attacks of arthritis [4,8].
- **Azathioprine (AZT):** AZT is used at 2-3mg/kg/day dose in resistant arthritis and recurrent arthritis attacks of BD [9]. AZT is known as an effective glucocorticoid-sparing agent. Additionally beneficial response before three months should not be expected [9].
- **Glucocorticoids:** If the arthritis of patients with BD is not controlled by colchicine or NSAIDs, they may need low-dose prednisone starting with 10 mg/day as an initial dose and tapering to 5 mg/day. If the arthritis of BD arises with swollen joints with large effusions, intra-articular steroid injections can be applied [9]. Both tapering prednisone and intra-articular steroid injections are also useful for protecting the patient from long-term side effects of glucocorticoids.
- **Tumor necrosis factor- $\alpha$  inhibitors (Anti-TNF) and interferon- $\alpha$  (IFN- $\alpha$ ):** There is an increasing amount of studies that have been published regarding the use of immunosuppressive agents such as infliximab, etanercept, adalimumab and interferon- $\alpha$  in joint involvement of patients with BD [4]. A recent study which determines efficacy and safety of anti-TNF in patients with severe and/or refractory manifestations of BD, overall response rate was found 90.4%. Clinical response was observed in 70% of patients with joint involvement [10]. Even though, eye involvement is the most often indication for the usage of IFN- $\alpha$ , mucocutaneous and articular manifestations may also benefit from IFN- $\alpha$ 2a treatment. However, information about dosage and duration of IFN treatment has been lacking [11,12].
- **Promising agents:** The anti-IL-1 agents such as anakinra (IL-1 receptor antagonist) with 100 mg daily dose, canakinumab (anti-IL-1 $\beta$  monoclonal antibody) with 150mg/6-8 weeks dose and gevokizumab (recombinant humanized anti-IL-1 $\beta$ ) have been used in BS. Joint involvement is one of the main indications for anti-IL-1 treatment in patients with BD [11,12]. In addition, articular manifestations of BD may benefit from IFN- $\alpha$ 2a treatment [11].

- **Other:** Methotrexate and benzathine penicillin have not been well-studied in BD. If arthritis did not respond to NSAIDs or colchicine, methotrexate can be an alternative in the dose used in rheumatoid arthritis [5]. Benzathine penicillin with colchicine therapy suggests a beneficial effect for arthritis [9].

## TREATMENT OF OCULAR DISEASE

Ocular disease is one of the most dreaded involvement of BS [13,14]. Ocular disease occurs often in BS typically in the form of a relapsing and remitting pan-uveitis and causes eye symptoms, ranging from spontaneous remission to visual impairment or blindness, if left untreated [14]. The aim of the therapy in patients with eye involvement of BD must be the strict control of ocular inflammation to prevent the patient from the relapses [15]. In the short-term, topical and systemic corticosteroids typically are used for the treatment of ocular disease of BD, followed by non-corticosteroid, conventional systemic therapies such as methotrexate, azathioprine, chlorambucil, cyclosporine A, or cyclophosphamide often involving either an anti-TNF and IFN- $\alpha$  in the long-term therapy of BD [13,15]. The conventional systemic therapies have to be combined with prednisolone (0.5mg/kg/day). If the combination therapy is not effective, another conventional systemic therapy must be initiated [5]. Duration of therapy should be continued for at least 24 months depending upon the response status and severity of disease [1].

### Topical Treatment

Topical treatment can only be sufficient in the isolated anterior uveitis which is a rare variant of ocular involvement of BD [17]. Isolated anterior uveitis usually requires high-dose topical corticosteroids (prednisolone acetate, dexamethasone phosphate) and cycloplegic agents (mydriatic) such as scopolamine (0.25%) or cyclopentolate (1%), tropicamide (1%) and phenylephrine (2.5 and 10%), 2-3 times a day. Cycloplegic agents decrease pain by preventing spasm of papillary muscles and helps preventing formation of synechiae and scar tissue between the iris and the lens [17,18]. Similar to systemic corticosteroids, topical corticosteroids should be tapered progressively based on clinical findings for protecting the patient from long-term side effects of glucocorticoids such as secondary glaucoma and cataract [14]. Topical corticosteroids can be used nearly 6-8 weeks according to clinical response [17]. Topical NSAIDs such as indomethacin, diclofenac, and flurbiprofen can be used to potentiate the topical corticosteroids [17]. Subtenon or sub conjunctival injections of depot corticosteroids such as triamcinolone acetonide or methylprednisolone acetate, can be used every 2-4 weeks for 4-5 times in patients with resistant-severe anterior uveitis. Subconjunctival corticosteroid injection has a good therapeutic effect on hypopyon and fibrin clotting [17]. The physician must be careful about the complications such as conjunctival hemorrhage, scarring, encapsulated cyst, ptosis, and accidental eye perforation caused by the injections [17].

## Intravitreal Injection

In patients with intense and intractable posterior uveitis with instantaneous macular threat or those with recalcitrant macular edema can be treated with intravitreal injections of triamcinolone (IVTA) for two to six months [17,19,20]. The advantages of IVTA injection are rapid resolution of intraocular inflammation and vision restoration without systemic side effects [18]. However, there are some disadvantages of IVTA injection which require good monitoring such as cataract progression, endophthalmitis, secondary glaucoma, CMV retinitis and short duration of action [15,18-20]. IVTA injection is a good adjuvant treatment option in addition to systemic treatments in patients with ocular involvement of BD. However, IVTA has been less preferred by physicians due to its disadvantages [15]. Other alternatives of IVTA are intravitreal implants, slow-release dexamethasone and fluocinoloneacetonide agents that can be used in persistent macular edema [14].

More recently, intravitreal anti-VEGF (Vascular Endothelial Growth Factor), intravitreal infliximab and intravitreal adalimumab may be indicated in patients with severe eye involvement of BD [15,21,22]. Similar to IVTA, all of these intravitreal injections must still be used with caution and in appropriate indications [15].

## Conventional Systemic Treatments

- **Systemic glucocorticoids:** Low dose prednisone (1-2mg/kg/day) is usually given in a single morning dose for one month and tapered as quickly as possible to a maintenance dose of 5-7.5mg/day as tolerated or less after complete resolution of active inflammation for mild flares [15-17]. In addition, for severe posterior uveitis or panuveitis attacks of BS, pulse-dose steroids such as intravenous (iv) pulse methylprednisolone (1g/day) are sometimes empirically used for 3 days to obtain a rapid anti-inflammation for sight-threatening disease [17]. A recent study has shown that adding iv steroid pulse therapy (1gr, consecutively for 3 days) to conventional combination therapies such as cyclophosphamide, azathioprine and prednisolone for posterior uveitis and/or retinal vasculitis of BD may cause better improvement on visual acuity and fewer attacks during the first six months of therapy [23]. Long-term treatment with systemic corticosteroid should not be preferred because of the side-effects of corticosteroids such as glaucoma, cataract, gastrointestinal ulcers, osteoporosis, Cushing syndrome, diabetes mellitus, and exacerbations of infections [17]. Use of glucocorticoids is not recommended as a monotherapy to avoid the recurrence of the disease and the ineffectiveness in controlling retinal vessel involvement of BD [15,24].
- **Azathioprine (AZT):** AZT (orally, 2.5 mg/kg/day or 50-150mg/day) is administered to decrease attacks of hypopyon uveitis and development of new ocular disease in patients without eye involvement [14,17]. Uveitis of BD, especially with posterior segment involvement or panuveitis, should be treated with AZA and systemic corticosteroids. Azathioprine can

be used alone or in combination with corticosteroids and other immunosuppressive agents [14,17].

- **Cyclosporine:** As a quick acting agent, cyclosporine can be efficacious to reduce frequency and severity of uveitis attacks at a dose of 3-5mg/kg/day (in divided doses) in BD with severe ocular involvement, especially with retinal vasculitis [14,17]. The combination of cyclosporine with glucocorticoids is the most usual usage type. Also cyclosporine is frequently combined with AZT for severe eye involvement and in cases resistant to AZT; however controlled data that support the use of this combination is still lacking [15]. After the cessation of systemic glucocorticoids, cyclosporine is suggested to tapered down 10% of dose every month to avoid the relapse [17]. The major side effects such as high blood pressure which occurs in about 75% of cases, nephrotoxicity (25%) should be considered. Increased risk of parenchymal neuro-BM was demonstrated to be associated in patients treated with cyclosporine and it is contraindicated in patients with neurological involvement [17,24,25]. The long-term use of cyclosporine can be also limited by other minor side effects such as hirsutism, gingival hyperplasia, gastrointestinal disturbances, breast tenderness, hyperglycemia arrhythmia, headache, myelo suppression [13,15,17].
- **Cyclophosphamide:** Even though, the experience with cyclophosphamide was mostly on ocular disease of BM, new guidelines do not recommend the use of cyclophosphamide for the eye involvement of BD because of the lack of controlled trials and evidence of benefit on ocular disease of BD [4,9,24]. However, it may have a good therapeutic effect with a combination therapy on severe and resistant ocular involvement of BD. The efficacy of combination with cyclophosphamide (pulse,1gr/month for six months and every 2-3 months as needed), prednisolone (initiated;0.5mg/kg/day), and azathioprine (2-3mg/kg/day) was demonstrated in 295 patients followed for up to 10 years in a recent study [26]. Patients showed significant improvements in ocular involvement of BD. The suggested dose regimes are similar to those typically used for systemic vasculitis (500mg/m<sup>2</sup>/month-1gram/m<sup>2</sup>/month for six months with concomitant use of mesna or 2-3mg/kg/day orally).
- Methotrexate (**MTX**) has a limited effect on severe systemic involvements of BD. It can be used for less severe eye involvement of BD at a low dosage of 7.5-25mg/week with folic acid [17,27]. Also in a recent study on 682 patients, successful treatment of posterior uveitis with methotrexate (7.5-15mg/week) and prednisolone (0.5mg/kg/day) was demonstrated [27].
- Mycophenolate is another efficacious, good tolerated and less costly treatment alternative among the immunosuppressants. Mycophenolate can be used as a corticosteroid-sparing agent in uveitis of BD, if the other treatments are not possible [24].

## Biologic and Monoclonal Treatments

Recently, a large amount of studies have been done for demonstrating the efficacy and

tolerability of anti-TNF with infliximab (mouse-human chimeric monoclonal IgG1-antibody), etanercept (recombinant fusion protein of human IgG1), and adalimumab (humanized monoclonal IgG1-antibody) in BD [4,15,17]. Beneficial effects have been noted due to positive role of anti-TNF in the pathogenesis of BD uveitis [17]. It is known that the main indication for anti-TNF treatment in BD is refractory ocular involvement. Additionally, the beneficial effects of anti-TNF agents have been seen in extra ocular manifestations of BD [25]. Excessive cost and side effects, such as an increased risk of tuberculosis and opportunistic infections, lupus-like reactions, multiple sclerosis, dyspnea, congestive heart failure and hypotension and increased risk of malignancy are the main concerns of the anti-TNF agents [17].

- **Infliximab:** It is initiated with a dose of 5mg/kg at weeks at 0, 4, 8, 16, and 24 weeks or 0, 2, and 6 weeks and then, repeated infusions every 6-8 weeks are needed to maintain the remission [4,17,28]. The infliximab is known as a fast-acting drug in the treatment of BD. It can be an effective choice with a mild adverse event profile for severe and refractory sight-threatening cases of ocular BS [4]. The permanent lesions due to irreversible retinal damage is not expected to heal during the therapy of infliximab [4]. The combination therapies of infliximab with conventional systemic therapies such as corticosteroids, azathioprine, cyclosporine or methotrexate are superior to infliximab monotherapy [29].
- **Adalimumab:** An increasing number of publications suggest that adalimumab can be highly effective and safe for ocular involvement of BD, also adalimumab can be considered as a corticosteroid sparing drug [22,30,31]. Adalimumab is suggested to be used subcutaneously, at a dose of 40 mg every other week in ocular involvement of BD [24]. In case of switching from infliximab to adalimumab, improvement of eye lesion has been seen in patients with severe uveitis of BD [32].

In a panel of American Uveitis Society, it was suggested that infliximab and adalimumab can be administered as a first line treatment in ocular involvement of BD and also they mentioned that, infliximab and adalimumab may be more effective than etanercept in uveitis of BD [33]. However, due to high cost and possible side effects of TNF- $\alpha$ , biologics should be used in BD if there is a resistance to azathioprine or other conventional systemic therapies.

- **Golimumab:** As a new anti TNF- $\alpha$  with reduced immunogenicity and longer half-life, golimumab (humanized TNF- $\alpha$  monoclonal antibody) may be effective in ocular involvement of BD. Few data with low patient groups are available observing the efficacy and safety of golimumab in BD uveitis [28].
- **Etanercept:** Etanercept is found to be less effective in eye disease of BS due to lack of convincing data [33].
- **Interferon- $\alpha$  (IFN- $\alpha$ ):** It is another promising option with encouraging results in the treatment of BD uveitis. IFN- $\alpha$ -2a seems more effective than IFN- $\alpha$ -2b [15]. It is administered

at the doses ranging from 3 to 9million IU/daily subcutaneously, most often three times weekly [17]. Mono therapy of interferon- $\alpha$ -2a may be an effective choice in the treatment of retinal vasculitis or ocular disease refractory to the conventional systemic treatments [17]. Low tolerability of interferon- $\alpha$  is seen in cases requiring immediate and high dose treatment such as vision-threatening eye disease of BD [15]. Therefore, it is easier to initiate anti-TNF agents in rescue therapy, however it can be replaced with IFN in long-term treatment [15]. Furthermore, randomized studies are needed to reveal this issue. Flu-like symptoms and other toxicities, including depression, are not uncommon and limit the use of this medication. The cessation of all immunosuppressive drugs is required in the use of IFN- $\alpha$  in patients with BD. Because of the antagonistic effect of systemic corticosteroids, they should be tapered to a dose of 10 mg/day prednisolone as soon as possible [17]. The most seen adverse effect of IFN- $\alpha$  is flu-like reaction (90%). IFN- $\alpha$  can induce toxicities and autoimmune disorders such as fever, mild leucopenia (30%), alopecia (10%). Depression (8%), transient paresthesia, elevated liver enzymes, epilepsy, thyroiditis, systemic lupus erythematosus, inflammatory arthritis, vasculitis, myositis, and diabetes may also be seen during the long-term therapy [11,17]. IFN- $\alpha$  has been recommended in the guidelines with an equal value to anti-TNF- $\alpha$  [34].

➤ **Promising agents:** Recently, three anti-IL-1 agents have been evaluated in BD:

1. Anakinra (IL-1 receptor antagonist),
2. Canakinumab (anti IL-1 $\beta$  monoclonal antibody),
3. Gevokizumab (recombinant humanized anti-IL-1 $\beta$ ) [11,35].

Anakinra (100mg/day) has been mentioned as an effective therapeutic option for BS with no serious adverse effects except for local site reactions caused by anakinra [11,36]. Canakinumab has recently shown as a possible useful drug in the management of ocular involvement of BD. Canakinumab was initiated at a dosage of 150 mg every 4-8 weeks [11,37]. The efficacy of gevokizumab was observed in seven BD patients with ocular involvement resistant to other immunosuppressives. Gevokizumab at a dose of 0.3 mg/kg, was administered and rapidly sustained reduction in intraocular inflammation was achieved despite the cessation of immunosuppressives [38]. Anti-IL-1 therapy accepted as a safer option in tuberculosis endemic countries than anti-TNF- $\alpha$  because of the low risk of tuberculosis [39]. Due to lack of controlled study, these agents should be initiated with caution [17].

➤ There is increasing number of evidence for the role of new biologic treatments including tocilizumab (humanized IL-6 receptor antibody) for neurologic involvement, amyloidosis and eye disease, alemtuzumab (humanized monoclonal antibody against CD52) for neurologic and eye disease, and ustekinumab (human monoclonal antibody against IL-12 and IL-23) in the management of BD [11,40]. A monoclonal vascular endothelial growth factor antagonist, bevacizumab, was shown to be effective in BS-related macular edema.

Rituximab (a chimeric monoclonal antibody against B-cell antigen CD20) has also shown good efficacy in patients with severe ocular involvement of BD which are resistant to other conventional treatments of uveitis [24,41]. Also, opposing results were obtained in some studies [11].

Secukinumab (IL-17 monoclonal antibody) and daclizumab (IL-2 receptor antibody) were found to be ineffective in BD with uveitis [40].

## Laser Photocoagulation and Surgical Treatments

Argon laser photocoagulation can be used in the management of retinal vein occlusions with severe retinal ischemia in order to avoid neo vascularization of retina [15]. Surgical procedures such as peripheral Iridectomy, cataract surgery and vitrectomy may be indicated in the treatment of complications during the management of ocular involvement of BD [15,17].

## TREATMENT OF NEUROLOGIC DISEASE

Central nervous system is one of the most serious involvement of BD. The same protocol of eye (posterior uveitis) treatment of severe BD protocol should be used for nervous system lesions such as focal parenchymal lesions, encephalitis, and medium-vessel vasculitis [5]. Corticosteroids are the first-choice agents for parenchymal involvement and dural sinus thrombosis [34]. Pulse methylprednisolone (1000mg, consecutively for 5-10days, iv) can be used for the acute attacks of parenchymal lesions. Oral methylprednisolone, 1mg/kg/day should be continued for up to one month, or until recovery is seen [42]. Corticosteroids should be administered with a dose tapering strategy during the next 3-6 months. Combination of anticoagulation with corticosteroids can be used after systemic large vessel diseases including pulmonary and peripheral artery aneurysms are excluded [34]. Also, in the combination therapy, azathioprine can be used as a first-line agent with alternatives such as mycophenolate, methotrexate, and cyclophosphamide while tapering down the dose of corticosteroids [34]. Different from the eye treatment of BD, cyclophosphamide is the main treatment agent for the Neuro-Behçet (**NB**) with systemic arterial involvement [42]. Cyclosporine is not recommended in the management of neurological involvement of BD unless necessary for eye disease of BD [5,34]. As with ocular disease, resistant or aggressive NB can be treated with anti-TNF- $\alpha$  or interferon- $\alpha$  [42]. An anti-IL-6 receptor antibody, tocilizumab, and a humanized monoclonal antibody against CD52, alemtuzumab, IFN- $\alpha$  and IVIG are the promising agents in the treatment of NB [4,11,40,43].

## TREATMENT OF GASTROINTESTINAL DISEASE

Gastrointestinal involvement of BD is diagnosed with abdominal pain, diarrhea, bleeding or rarely perforations [44]. Perforation is seen due to deep penetrating ulcers in the terminal ileum, ileocolonic region or the colon [44]. Endoscopic appearance of lesions and also the treatment protocols including, 5-aminosalicylic acid, immunosuppressive agents, and biological agents, either used mono therapy or in combination are very similar to Crohn disease [42,44]. Avoiding from the recurrences, surgical procedures, and irreversible damage of gastrointestinal



involvement of BD are the main goals of the early treatment [44]. There are no controlled trials available [44].

- **5-Aminosalicylic Acid (5-ASA)/Sulfasalazine (SSZ):** In the non-randomized clinical studies and case series, it was reported that 5-ASA/SSZ is effective in treating esophageal and gastrointestinal disease of BD [45,46]. 5-ASA/SSZ at a dose of 2-4g/day, can be used as an empirical therapy in all cases of gastrointestinal BD [45,47]. It may be used in first-line therapy of mild gastrointestinal involvement of BD [48].
- **Corticosteroids:** It can be initiated as a first-line therapy at a dose of 0.5-1mg/kg/day which should be tapered to 10mg/day within two to three months in patients with severe gastrointestinal involvement of BD such as recurrent gastrointestinal bleeding, or when treatment with 5-ASA/SSZ is insufficient [45]. Physician also should be careful about gastrointestinal side effects of corticosteroids including bleeding or perforation [45].
- **Azathioprine (AZT)/6-mercaptopurine:** Azathioprine is initiated at a dose of 25-50mg/day with increase every 2-4week to 2.0-2.5mg/kg and 6-mercaptopurine is initiated at a dose of 0.5mg/kg, with increase every 2-4weeks to 1.0-1.5mg/kg [45]. Thiopurines are widely used to treat patients with moderate to severe or refractory intestinal BD such as corticosteroid-dependent or corticosteroid-resistant patients [48]. Thiopurines are recommended to decrease reoperation rates in patients with who already had undergone surgical interventions [45,48]. Very recently, Hatemi reported that, azathioprine can be used for first-line therapy in gastrointestinal involvement of BD, because remission was seen in 65% of their patients without any relapse during nearly six years [46]. Recently, with a study in intestinal BD patients who received 5-ASA or thiopurine therapy after surgery it was shown that, postoperative recurrence rate was lower in thiopurine group [49].
- **Thalidomide (THD):** THD is an anti-inflammatory and immuno modulatory drug which has shown to have a beneficial effect on gastrointestinal involvement of BD due to its inhibitory effect on TNF- $\alpha$  [48,50]. There is a pilot-study from Korea about the efficacy of THD in patients with intestinal BD who had previously failed immunosuppressant treatments, showed dramatic improvement in clinical symptoms with a dose of THD from 2mg/kg/day to 3mg/kg [51]. More recently Hatemi reported that, clinical and endoscopic remission was seen with TNF- $\alpha$  antagonists and/or thalidomide in about 75% of the patients with intestinal BD refractory to the conventional therapies [52]. Sayarlioglu reported a patient who was refractory to all treatments such as intense immuno suppressives and gone multiple surgeries. Patient was treated with thalidomide (100mg/day) after the third surgery without intestinal perforations during the observation time for four months [50].
- **Anti-TNF- $\alpha$ :** With an increasing number of literature, the anti-TNFs such as infliximab, adalimumab and etanercept for steroid dependent and refractory intestinal BD have been

used as induction therapy and also as the maintenance therapy [45,48,53,54]. Among anti-TNFs, IFX was the most frequently used in intestinal BD [44,48]. Combination therapy with IFX and methotrexate was also shown as an effective and safe option for the refractory intestinal BD [55].

- **Other:** Oral tacrolimus and intra-arterial steroid injections into the mesenteric arteries can be used in refractory intestinal BD [56,57].
- **Promising agents:** Tocilizumab (anti-IL-6 receptor antibody) and anti-IL-1 agents are the promising therapies in the treatment of intestinal involvement of BD [45].
- **Hematopoietic stem cell transplantation (HSCT):** As an alternative for BD patients with refractory and severe organ involvement, especially gastrointestinal involvement, HSCT may be done with a caution because of the complications such as infections, graft versus host disease, and hepatic, renal, and pulmonary damage that can be fatal [45,58].
- **Surgery:** Medical treatment resistance and serious complications such as perforation, persistent bleeding, fistulae, obstructions, and abdominal masses, are the indications of the surgical treatments [45].

## TREATMENT OF VASCULAR INVOLVEMENT

### Medical Treatment

Aggressive immunosuppressive medical treatment is necessary in pulmonary artery involvement (PAI), Budd-Chiari syndrome, and peripheral arterial aneurysms/occlusions of BD [59]. Cyclophosphamide (iv, 1gr/monthly, for 6-12 months; if remission is sustained, switch to AZT, 2.5mg/kg/day) and gluco corticoid pulses (methylprednisolone, 1gr/3days consecutively, followed by prednisolone 1mg/kg/day, tapered over 2-5 months) are used as aggressive medical treatment [59]. AZT with or without short-term glucocorticoids or interferon- $\alpha$  agents can be used in other types of venous thrombosis. The resistant cases can be treated with anti-TNF agents such as IFN and ADA [42]. The initiation of anticoagulation has no additional efficacy because of the rare occasion of the true pulmonary thromboembolism in BD and needs to be avoided [42,59].

### Vascular Interventions and Surgeries

Surgery of pulmonary artery aneurysms and venous thrombosis is not suggested due to its possible complications [42,59]. However, non-pulmonary peripheral arterial aneurysms can be treated successfully with surgical procedures such as aorta-bi-iliac bypass or synthetic graft insertion [42]. Endovascular embolization can be used successfully in PAI [42]. However, it is not useful in ruptured or giant aneurysms [59]. Surgical resection and lobectomies can be alternative procedures for the giant aneurysms in some cases [59].

**Table 1: Treatment of Systemic Involvement of Behçet's Disease: A practical scheme [42,60].**

Systemic involvement of BD	1	2	3	4	In all steps
Arthritis	NSAIDs	Colchicine	Azathioprine / low dose prednisone	Interferon- $\alpha$ / TNF- $\alpha$ inhibitors	Glucocorticoids
Ocular disease	Topical and systemic glucocorticoids	Azathioprine	Azathioprine if not sufficient add cyclosporine-A	Interferon- $\alpha$ / TNF- $\alpha$ inhibitors	
Neurologic disease	Systemic glucocorticoids	Azathioprine	Cyclophosphamide	Interferon- $\alpha$ / TNF- $\alpha$ inhibitors	
Gastrointestinal disease	5-ASA derivatives	Azathioprine	Thalidomide	Interferon- $\alpha$ / TNF- $\alpha$ inhibitors	
Vascular disease	Systemic glucocorticoids	Azathioprine	Cyclophosphamide induction for arterial aneurysms	Interferon- $\alpha$ / TNF- $\alpha$ inhibitors	

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