Behçet's Disease

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Contents

Core Messages

- This disease is mainly seen around the historical Silk Road area from East Asia to the Mediterranean region.
- Behçet's disease (BD) shows various recurrent systemic manifestations such as oral aphthous ulcers, skin lesions, genital ulcers, and intraocular inflammations.
- Biologicals seem to show favorable results with better prognosis than immunosuppressive drugs.

66.1 Definition

Behçet's disease (BD) is a relapsing multisystemic disorder with obliterative vasculitis affecting both arteries and veins including vasculopathy of capillaries. In 1937, Hulusi Behçet described oral aphthous ulcers, genital ulcers, and hypopyon uveitis as a triad [3].

The definition has since been expanded and modified to include multisystemic clinical features, such as central nervous system (CNS) involvement. The Behçet's Disease Research Committee of Japan defined "major" and "minor" criteria for diagnosis, with "complete," "incomplete," and "suspect" types of the disease

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(Table 66.1) [4]. The International Study Group (ISG) criteria require the presence of two of the four features: genital ulceration, eye lesions, positive pathergy test, and either of the skin lesions (folliculitis, papulopustular lesions, acneiform nodules, and/or erythema nodosum) in addition to oral ulceration (Table 66.2) [10]. Moreover, the Dilsen criteria include thrombophlebitis (Table 66.3) [12]. The Dilsen criteria and the IUSG criteria fit better to the European BD patients. On the basis of ophthalmic manifestations, four subgroups have been described: ocular BD, internal BD, neurological BD, and combined BD [5].

Table 66.1 Diagnostic criteria of Behçet's disease by the Behçet's Disease Research Committee of Japan

1. *Major symptoms*
A. Recurrent aphthous ulceration of the oral mucous membrane
B. Skin lesions
(a) Erythema nodosum-like lesions
(b) Thrombophlebitis
(c) Folliculitis or acne-like lesions
(d) Cutaneous hypersensitivity
C. Ocular symptoms
(a) Iridocyclitis
(b) Retinochoroiditis
(c) Sequelae of a and b
D. Genital ulcers
2. *Minor symptoms*
A. Arthritis
B. Intestinal lesions (intestinal Behçet's disease)
C. Epididymitis
D. Vascular lesions (angio-Behçet's disease)
E. Neuropsychiatric lesions (neuro-Behçet's disease)
3. *Examination*
Skin prick test
4. *Diagnosis*
A. Complete type: patients with all 4 major symptoms
B. Incomplete type
1. Patients with 3 major symptoms
2. Patients with 2 major symptoms and 2 minor symptoms
3. Patients with ocular symptoms and 1 another major symptom
4. Patients with ocular symptoms and 2 minor symptoms

Table 66.2 The International Study Group (ISG) criteria

These criteria require the presence of two of the four features below:	
1.	Genital ulcers
2.	Eye lesions
3.	Pathergy test
4.	Skin lesions (folliculitis, papulopustular lesions, acneiform nodules, and/or erythema nodosum)

Table 66.3 The Dilsen criteria of BD

These criteria require the presence of three of the five features below:	
1.	Recurrent oral ulcerations
2.	Recurrent genital ulcerations
3.	Skin lesions
4.	Eye lesions
5.	Thrombophlebitis
+)	Skin pathergy test
Other causative factors should be excluded	

66.2 Clinical Manifestations

66.2.1 General Disease

The common manifestations of BD are oral and genital ulcers (Table 66.4) [11]. They are long lasting, tend to relapse, and are very painful. The skin lesions occur in 41–94 %. Papulopustules, acneiform pseudofolliculitis, and erythema nodosa are common, but pyoderma, ulcerations, necrotizing lesions, Sweet syndrome (febrile neutrophilic dermatosis), and superficial thrombophlebitis may also occur. The pathergy phenomenon is positive in 19–53 %. Arthritis is seen in 47–69 % of patients. Although a rare manifestation, myositis may be either localized or generalized and has also been described in juvenile BD. Gastrointestinal manifestations occur in 3–30 % of patients; main symptoms are abdominal pain due to diarrhea and gastrointestinal bleeding. Diffuse ulcerations are more common than localized aphthous ulcers. Neurological manifestations are present in 8–31 % of BD patients. The site most commonly affected is the brainstem. Vascular manifestations such as thrombosis and arterial aneurysms occur in 28 %. Most commonly occlusions of superior or inferior

Table 66.4 General manifestations of BD

1. Oral aphthous ulcerations	76.6–100 % [19, 31, 43, 47, 54]
2. Genital ulcerations	40–94 % [19, 34, 43, 54]
3. Skin lesions	29–94 % [20, 43]
4. Pathergy phenomenon	19–70 % [13, 34, 52]
5. Arthritis	8–69 % [20, 43]
6. Gastrointestinal manifestations	3–26 % [43]
7. Neurological manifestations	2–44 % [20, 43]
8. Vascular manifestations	6–37 % [43]
9. Cardiac manifestations	1–6 %
10. Epididymitis	5–22 % [14, 43, 53]

vena cava, femoral veins, cerebral veins, veins of the upper extremities, and portal veins occur. Rare findings include cardiac manifestations (1–6 %), epididymitis (4–31 %), and renal manifestations (less than 1 %) [11].

66.2.2 Ocular Disease

The primary manifestation of BD may start unilateral most often as an anterior uveitis, but later on, bilateral posterior uveitis occurs in 78 % of the cases, and 60 % of the patients develop panuveitis with a chronic relapsing course [49]. The disease is more severe in men than in women. Recurrences are common.

Hypopyon, typical for BD [29] (Fig. 66.1), is smooth with niveau and different from the more

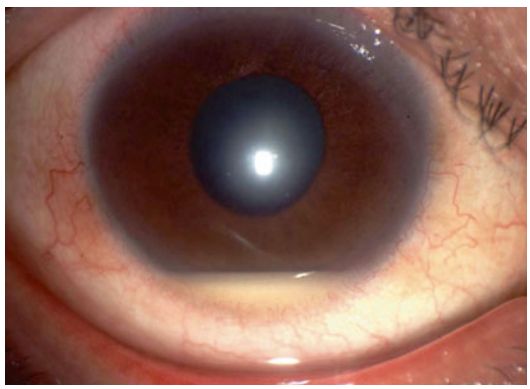

Fig. 66.1 Hypopyon in recurrent iridocyclitis is typical for BD. The hypopyon easily moves and curls up with patient's head tilt

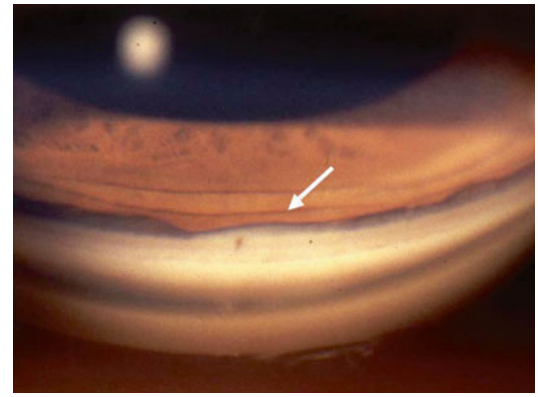

Fig. 66.2 Angle hypopyon (*arrow*) in recurrent acute iridocyclitis in BD

sticky hypopyon of HLA-B27-associated uveitis. The cells easily move and curl up with patient's head tilt. In eyes with severe iridocyclitis, in which hypopyon is not seen by direct slit-lamp examination, a small layering of leukocytes can be observed in the angle by gonioscopy, called "angle hypopyon" (Fig. 66.2). Nowadays, iridocyclitis with hypopyon occurs in only 12 % of BD patients with ocular involvement, probably due to earlier and more aggressive treatment, which has resulted in dampening inflammatory responses.

The inflammatory response in the anterior chamber in BD is nongranulomatous in nature. Patients often complain of redness, periorbital pain, photophobia, and blurred vision.

In the posterior segment, retinal vasculitis (of veins and arteries) is present in both peripheral and central vessels with retinal hemorrhages and soft exudates. These soft exudates include both chorioretinal infiltrates and retinal ischemic changes caused by occlusive vasculitis. Sometimes only soft exudates appear in the widespread retina with any degree of diffuse vitreous opacity (Fig. 66.3). These soft exudates resolve spontaneously in a few weeks, but a diffuse vitreous opacity may remain until a few months later. Optic disk is sometimes swollen and optic neuritis may be present. The macula is commonly affected (Fig. 66.4). After several posterior segment inflammations, consequently obliterated white retinal arteries with retinal and optic disk atrophy may appear.

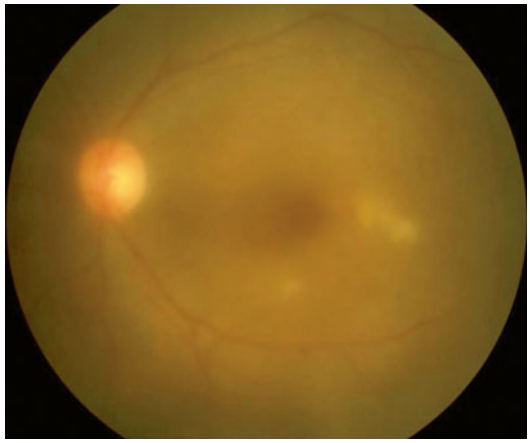

Fig. 66.3 Mild ocular attack near the macula, with soft exudates and mild vitreous opacity

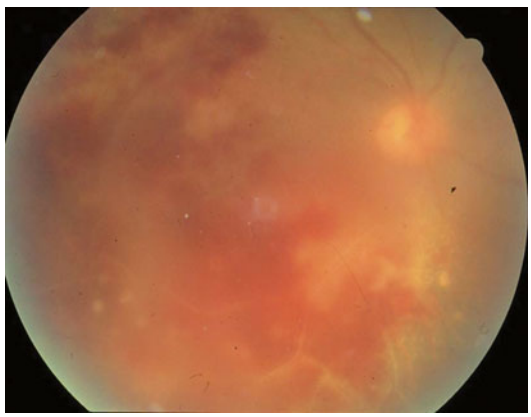

Fig. 66.4 Severe ocular attack in the posterior segment, leading to retinitis and retinal vasculitis (veins and arteries), with retinal hemorrhages and soft exudates

Due to necrotizing obliterative vasculitis, which may be found either in the anterior or posterior segment or, more commonly, in both, neovascularization at the optic disk or at the periphery can lead to retinal detachment with or without vitreous hemorrhage and neovascular glaucoma. This complication used to lead to enucleation before.

Repeated intraocular inflammation causes complicated cataract and secondary glaucoma. Both open-angle and angle-closure glaucoma or even pupillary block (iris bombé) may result. Ciliary body involvement may lead to low intraocular pressure and eventually phthisis bulbi. This is the main cause of permanent visual loss in this disease (Fig. 66.5). IOL implantation seems to be no risk factor for induction of recurrences with adequate pre- and postoperative strategy (see Chap. 34).

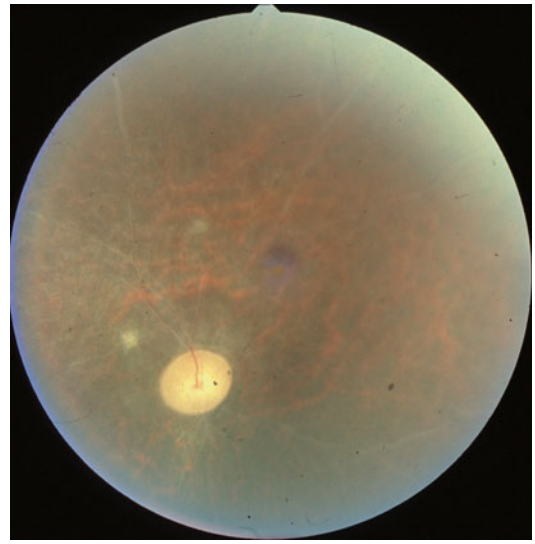

Fig. 66.5 Ocular fundus in the end stage with diffuse chorioretinal atrophy

66.3 Etiology and Pathogenesis

The exact etiology and pathogenesis of BD still remain unclear. A high prevalence of BD is found among the Asian and Eurasian populations along the historical Silk Road from East Asia to the Mediterranean region. There is a strong association between HLA-B51 and BD patients in many different ethnic groups around the historical Silk Route: 50–80 % of the patients possess HLA-B51 [41]. In spite of the genetic background, there are not so many family cases as found in other genetic diseases. It is interesting to note that there are no BD patients in the Japanese immigrant population in Hawaii [26] and very few patients only in Brazil (Fig. 66.6). These facts suggest that besides genetic factors there may also be some environmental factors playing an important role in the pathogenesis of BD. There are some reports on the association between BD and external factors, such as *Streptococcus sanguinis*, organophosphates,

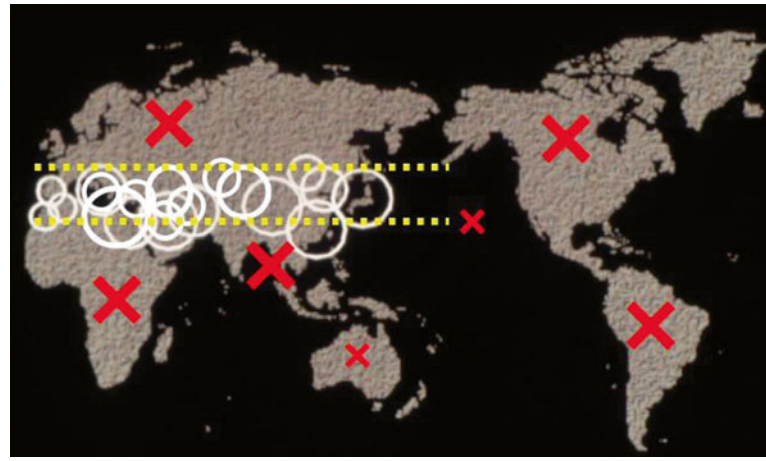

Fig. 66.6 Geographic distribution of BD in the world. High-prevalence area (*O*) of BD is found among the Asian and Eurasian populations along the historical Silk Route from East Asia to the Mediterranean region. On the other hand, BD is rarely seen in other areas (*x*)

mycobacterial 65-kDa heat shock protein peptides, and some heavy metals [17, 18, 30].

The most characteristic pathological feature is the occlusive necrotizing nongranulomatous vasculitis and perivasculitis. In these inflamed sites, neutrophil accumulation is found [28]. In addition, neutrophils obtained from patients with BD have a high ability of chemotaxis and hydroxyl radical production [37, 46]. There are also many reports of an abnormality of T cells and cytokines [6, 7, 9, 15, 42, 45]. Therefore, the etiology of BD probably depends on certain immunological abnormalities triggered by external environmental factors in individuals with particular genetic backgrounds.

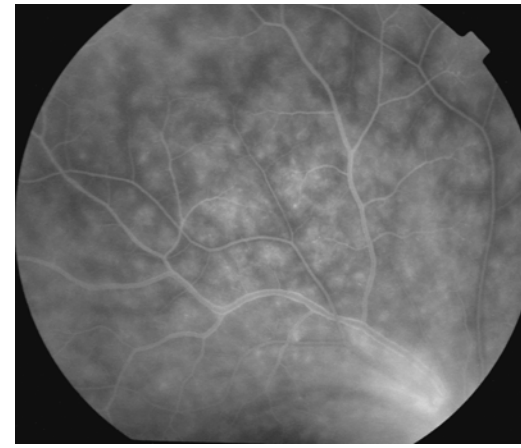

Fig. 66.7 "Fern-leaf"-shaped leakage from retinal capillary. Fluorescein angiography shows dye leakage from retinal capillary, and the shape is like a fern leaf. This finding is seen even in the convalescent stage

66.4 Diagnosis

The diagnosis of ocular BD is essentially a clinical one. In terms of eye disease, the presence of retinal infiltrates with uveitis and retinal vessel involvement is very characteristic. HLA typing may be helpful in some cases. Fluorescein is not diagnostic but is used to assess the extent of vascular involvement and retinal damage.

Fluorescein Angiography

Fluorescein angiography (FA) can show better the details of the retinal vessels in the acute stage than ophthalmoscopy. It can reveal areas of nonperfusion due to retinal artery occlusion, leakage from capillary vessels, vascular remodeling, and neovascularization. However, FA is more useful for early diagnosis [2], and it may reveal "fern-leaf"-shaped leakages from retinal capillary even in the convalescent stage (Fig. 66.7). This finding is one of the characteristic features of BD, but is not pathognomonic.

Cutaneous Hypersensitivity

Skin prick test (pathergy test) with a sterilized needle or intradermal injection of saline

sometimes shows a positive reaction like a pustule or bleb, but this reaction is not specific to BD. This phenomenon is often shown after blood collection. Due to this hypersensitivity, tuberculin skin test often is strongly positive even without *Mycobacterium tuberculosis* infection of tuberculosis.

Blood Test

Blood examination shows increased erythrocyte sedimentation rate, elevated C-reactive protein, and increased white blood cell count, especially neutrophils.

HLA Typing

HLA-B51 (HLA-B*5101) is positive in 50–70 % of the patients but is not essential for the diagnosis.

66.5 Differential Diagnosis

Hypopyon is one of the characteristic findings in BD. HLA-B27-associated uveitis or metastatic endophthalmitis may also exhibit hypopyon, but they rarely form a niveau. Another characteristic finding is retinal vasculitis. However, clinical features of this disease are different from those in tuberculosis, sarcoidosis, multiple sclerosis, acute retinal necrosis syndrome, or TINU which also may lead to retinal vasculitis.

66.6 Treatment

There is no standard treatment regimen that is common in the world. Therefore, different protocols for the treatment are used in each region. In addition, the clinical effects of each treatment seem to differ from one patient to another. Broadly, the strategy of BD treatment is classified in two ways: (1) treatment of acute inflammatory attacks and (2) suppression of future recurrent inflammatory attacks.

Acute inflammatory attacks should be treated immediately to minimize the damage to ocular tissues especially at the posterior segment.

For anterior uveitis, subconjunctival injection of soluble corticosteroids, e.g., 2 mg of dexamethasone, is effective in addition to frequent administration of betamethasone or prednisolone acetate eyedrops (e.g., every hour) in addition to mydriatic agents.

Regarding local therapy, for posterior segment inflammation, posterior sub-Tenon's injection of soluble corticosteroids, e.g., 4 mg of dexamethasone, is effective. Repeated daily injection may be required for a week according to the severity of ocular attacks.

Regarding systemic therapy, there is general agreement that posterior segment inflammation needs systemic corticosteroid treatment (1–1.5 mg/kg body weight per day) or in severe cases additional immunosuppressive treatment.

Colchicine

Colchicine has the effect to inhibit the migration of granulocytes into the inflamed tissue. Since hypermobility and hyperreactivity of leukocytes in BD patients have been shown, Matsumura and Mizushima reported the effects of colchicine to suppress the frequency of acute inflammatory attacks in BD [28]. The adequate dose is 0.5–1.0 mg/day. Kotter et al. from Germany reported that colchicine was partially effective in 66 % of their BD patients [22]. However, in a double-blind study, Actulga et al. could not show significant efficacy of colchicine in BD, though the number of the patients was small [1].

Cytotoxic Agents

Cytotoxic agents such as cyclophosphamide and chlorambucil are cheap. Chlorambucil used to be the drug of choice for the treatment of BD but today is mostly used in developing countries mainly because it represents a cheaper alternative. Azathioprine has been shown to maintain

visual acuity and prevent development of eye disease [16, 51]; however, these drugs are not effective enough to completely suppress the recurrent inflammation in severe cases.

Azathioprine is, besides cyclosporine, the only drug which has been shown to be effective in BD by a RCT.

Cyclosporine

According to the results of a double-masked trial of cyclosporine versus colchicine, it was revealed that cyclosporine was more effective in reducing the frequency of ocular attacks than colchicine [27]. The initial dose of cyclosporine is usually 5 mg/kg/day, and the dosage is adjusted according to the trough level or the area under the blood-concentration-time curve during the first 4 h after cyclosporine administration (AUC_{0-4}). Colchicine should be stopped to avoid interacting side effects including myositis. Rarely, in severe cases, a combination of colchicine, cyclosporine, and azathioprine may be administered together. Due to its nephrotoxicity [38], some patients are required to reduce the dosage or stop the treatment. Central nervous system (CNS) symptoms are also considered as side effects of cyclosporine especially in BD patients. Kotake et al. reported that 25.5 % of Behçet's patients on cyclosporine developed CNS symptoms, whereas only 6.6 % of the patients did without cyclosporine [21].

Corticosteroids

Systemic corticosteroids are used in acute attacks for the suppression of tissue damage, as well as in chronic cases with no or minimal recurrence under the therapy. However, in very acute cases, the use of any immunosuppressive agent would not lead to a fast control of the disease. If the attacks are very severe, high-dose oral corticosteroids or biologicals are needed. Corticosteroids should not be given alone. Sometimes rapid tapering of corticosteroids leads to severe recurrence of ocular attacks. In refractory cases, another agent or combination of corticosteroids and immunosuppressive agents, depending on the disease severity, should be started immediately. This will lead to faster control and reduce the risk of a flare up during corticosteroid tapering.

TNF-α Blocking Agents

Production of tumor necrosis factor-alpha (TNF-α) has been shown to be significantly enhanced in patients with BD [35]. Therefore, TNF-α is closely associated with the immunopathogenesis of BD. There are data available in ocular BD for the two agents infliximab and adalimumab.

Infliximab

Infliximab is an anti-TNF-α chimeric monoclonal antibody composed of an antigen-binding variable region from mice with high affinity to human TNF-α and a constant region of human IgG1 (see Chap. 21). Infliximab shows an excellent efficacy to suppress BD. In Japan, an open-label trial was performed in Behçet's patients who were refractory to cyclosporine therapy [40]. Infliximab was administered 4 times at weeks 0, 2, 6, and 10 at doses of either 5 or 10 mg/kg by intravenous infusion. The frequency of ocular attacks per 14 weeks decreased from 3.96 to 0.98 times in the 5 mg/kg group and from 3.79 to 0.16 times in the 10 mg/kg group (Fig. 66.8). Based on these results, administration of 5 mg/kg of infliximab was approved in Japan from January 2007 for BD complicated with refractory posterior uveitis which does not respond to conventional therapy.

Some complications have been reported including infusion reaction and infections. Especially screening tests for tuberculosis have to be performed before starting infliximab. If there is some suspicion for inactive tuberculosis, the additional administration of antituberculous agents is recommended to prevent reactivation of the disease of the disease, but often infliximab should not be used.

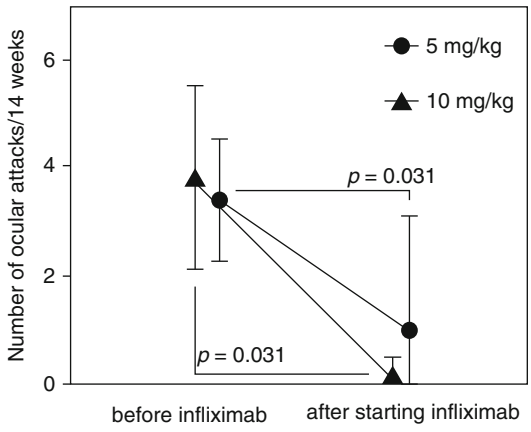

Fig. 66.8 Clinical effects of infliximab in BD. Open-labeled trial of infliximab in patients with BD with refractory posterior uveitis showed that the frequency of ocular attacks per 14 weeks decreased from 4.0 to 1.0 times in the 5 mg/kg group and from 3.8 to 0.2 times in the 10 mg/kg group

Adalimumab

Adalimumab is also an anti-TNF-α antibody, but it is fully humanized, whereas infliximab is human-murine chimeric (see Chap. 21). Mushtaq et al. reported 3 cases who were switched from infliximab to adalimumab [32]. All three patients had sight-threatening bilateral panuveitis with BD that was poorly responsive to conventional immunosuppression. The introduction of infliximab therapy stabilized their ocular disease. Due to the difficulty in attending the hospital or coping with the intravenous infusion, they switched to adalimumab can be self-administered as 40 mg subcutaneously. Switching to adalimumab has maintained their disease in remission and prevented relapse.

Interferon Alpha-2a (IFNα-2a)

Results of various open, prospective studies indicate that recombinant human interferon alfa-2a (rhIFNα-2a) is effective in ocular BD (see Chap. 27). Kötter et al. [24] reported a complete remission rate of 92 % in their 50 patients. Similar results are published from France [8], Turkey [48], and another group from Germany [25]. Reperfusion of acute-occluded retinal vessels and complete regression of retinal neovascularization have been observed [44, 50]. Besides this especially the massive reduction of associated macular edema is remarkable.

At the induction of this treatment, 3 to 6 million international units (IU) of rhIFNα-2a are injected subcutaneously daily, which will be reduced according to the clinical effect, typically in between 3 weeks to 3 mio IU every second day, and continued to taper until 6–12 months. There are no uniform dosages, reaching from every day to three times a week, what seems to explain the different recurrence rates [23]. Because IFN has shown rapid effect, it has been suggested to stop all immunosuppressive drugs 1 day prior to the initiation of IFN and also lower the dosage of corticosteroids, since they block NFκB, what is needed for IFN to enter the cell. Recently the recurrence rate and the 5-year visual acuity rate for ocular BD, treated with rhIFNα-2a, have been investigated. Deuter et al. [11] found that during a mean follow-up of 85 months (60–132 months) after initiation of rhIFNα-2a 90.2 % of 41 eyes improved or remained stable. There was no loss of originally better visual acuity. No patient had developed a pale optic nerve. The relapse-free period in the same group was at least 2 years in 60.9 % and at least 6 years in 26.1 %, what shows that rhIFNα-2a can be stopped without resulting in recurrences. It does not need to be given prophylactically.

Intravitreal Injection of Triamcinolone Acetonide (IVTA)

Repeated IVTA in BD refractory to conventional therapy has been shown to prevent the recurrence of posterior uveitis [39]. However, recurrences developed once the TA particle disappeared from the vitreous cavity. IVTA may need to be performed repeatedly before TA particle disappear. Despite preventing systemic complications, the high incidence of complications after intravitreal injection (progression of cataract and increased intraocular pressure) reduces its value, and today,

this regimen should only be considered for BD failing to respond to other alternatives, especially when threatening vision.

Granulocytapheresis

An open prospective study showed efficacy of a selective granulocytapheresis in patients with refractory uveoretinitis of BD [36]. This granulocytapheresis was done with an Adacolumn filled with cellulose acetate beads which adsorb granulocytes and monocytes from the peripheral blood in the column. Each patient received 5 Adacolumn sessions at one session/week over 5 consecutive weeks. The frequency of ocular attacks was significantly reduced after the treatment in comparison with the one before the treatment in 6 months. This treatment has already been used for the treatment of ulcerative colitis, and no severe adverse events have been described [33].

66.7 Prognosis

Visual prognosis of BD depends on the site and the frequency of the acute inflammatory events. In patients with only anterior segment inflammation, visual prognosis is good. However, patients with frequent posterior segment inflammation usually have poor prognosis for the visual acuity. Only a single attack around the macular area may cause permanent loss of vision in severe cases. Table 66.5 shows the visual prognosis presented in some reports. With the conventional immunosuppressive therapies, including cyclosporine, chlorambucil, azathioprine, and steroids, 16–73 % of the BD patients showed poor visual acuity, less than 20/200. In the recent results with the biological interferon alpha the visual prognosis was much better; the visual acuity was less than 20/200 in 12.5–19 % of the BD patients. Infliximab also has favorable effects on the visual prognosis. Our data show that 77 % of the patients have marked effects with almost no uveoretinitis recurrence as long as treated (unpublished data). The average visual acuity is improved one or two lines compared with before treatment.

Table 66.5 Residual visual acuity during follow-up

Study	Follow-up period	Results
Conventional immunosuppression		
Mishima (1976)	5 years	50 % VA < 20/200
BenEzra (1986)	6–10 years	74 % VA ≤ 20/200
Cochereau-Massin (1992)	6 years	16 % VA < 20/200
Whitcup (1994)	4 years	24 % VA ↓
Zierhut (1995)	5 years	73 % VA < 20/200
Interferon alpha		
Krause (2008)	7 years	19 % VA < 20/200
Gueudry (2008)	7 years	72 % VA ↑/=
Deuter (2010)	6 years	12.5 % VA ≤ 20/200

VA visual acuity

Take-Home Pearls

- BD patients lose their visual function due to repeated ocular inflammatory attacks leading to occlusive vasculopathy of vessels in the retina and the optic nerve.
- Recently introduced biologicals, e.g., infliximab and IFNα-2a, lead to much better prognosis compared to treatment with other immunosuppressive and cytotoxic agents.

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