Ocular Involvement in Behçet’s Disease

Yonca Aydın Akova and Sirel Gür Güngör
Başkent University Faculty of Medicine
Department of Ophthalmology
Turkey

1. Introduction
Behçet’s disease (BD) is a chronic, relapsing inflammatory disorder of unknown etiology and characterized by obstructive vasculitis. It can involve both the arteries and veins of almost any organ and characterized by recurrent oral and genital aphthous ulcers, ocular inflammation, and skin lesions. Behçet’s disease frequently involves the joints, the central nervous system, and the gastrointestinal tract as well. Behçet’s disease may be the best example of a disorder characterized mainly by its retinal vascular involvement, often with devastating results on the patient’s eyesight. First description of BD has been attributed to Hippocrates in the 5th century BC, in the “Third book of endemic diseases” (Nussenblatt, 2010). In 1937, Hulusi Behçet (1889-1948), a Turkish dermatologist (Behçet, 1937), reported three patients with a triad of symptoms: recurrent intraocular inflammatory episodes with oral and genital ulcerations.

2. Epidemiology

2.1 Geographic and ethnic distribution
Behçet’s disease is most common in the countries of the Eastern Mediterranean and in the Eastern rim of Asia, and is very frequently noted between 30° and 45° north latitude in Asian and European populations, which corresponds to the old Silk Route used by traders from the East to Europe (Ohno, 1986). The exact incidence, prevalence, and family occurrence of the disease are not well known. The highest prevalence being 80-420 cases per 100000 populations in Turkey has been reported (Azizlerli et al., 2003; Yazici, 1994; Yurdakul et al, 1988).

2.2 Sex
Many reports, mainly from Mediterranean basin and the Far East, have shown a preponderance of males to females in BD. Data have shown that men predominate in Japan (2:1), Lebanon (11:1), Greece (7.9:1), Egypt (5:1), Isreal (3:1), Turkey (3:1) and Iran (1.2:1), whereas women predominate in Germany (1:0.9), Brazil (1:0.7), and the United States (1:0.2) (Atmaca, 1989; Chajec & Fainaru, 1975; Hamdi & Abdalla, 1974; Mamo & Baghdassarian, 1964; Ozdal et al., 2002; Shimuzu, 1971).
2.3 Age
Although BD effects primarily young adults more frequently between the second and fourth decade of life and is rarely seen in children, the onset can occur at any age from infants to the elderly (Ghate et al., 1999; Kone-Paut et al., 1998; Önder & Gürer, 2000; Tugal-Tutkun et al., 2004).

2.4 Heredity
Familial occurrence is seen in 8-18% of Turkish patients with the disease (Onal et al., 2001), 15% of Koreans, 13% of Jews, and 2.6% of Chinese (Fietta, 2005). Additionally, several familial cases (Dundar et al, 1985; Vaiopoulus et al., 1996; Villanueva et al., 1993) and a pair of monozygotic brothers (Hamuryudan et al., 1991) concordant for the disease have been reported, but no consistent inheritance pattern has been confirmed.

3. Clinical features
The diagnosis of BD is based firmly on the presence of a set of clinical findings. The diagnostic criteria were first described in 1969 by Mason & Barnes (Mason & Barnes, 1969). Numerous sets of clinical criteria have been proposed for the diagnosis of BD (O’ Duffy, 1974; Zhang, 1980).

The most popular diagnostic system has been suggested by the Behçet’s Research Committee of Japan in 1974 (Behçet’s Disease Research Committee of Japan, 1974) (Table 1). The committee has revised the diagnostic criteria in 2003 (Kurokawa & Suzuki, 2004). The presence of ocular inflammation is given greater weight in the diagnosis in this system.

| Main symptoms: 1-Recurrent aphthous ulcers on oral mucosa; 2-Skin lesions (erythema nodosum, subcutaneous thrombophlebitis, follicular papules, acneiform papules, skin hypersensitivity); 3-Ocular lesions (anterior and/or posterior uveitis); 4-Genital ulcers
| Additional symptoms: 1-Arthritis without deformity or sclerosis; 2-Epididymitis; 3-Gastrointestinal lesion (ileocecal ulceration); 4-Vascular lesions; 5-Central nervous system lesions
| Criteria for diagnosis of disease types:
| Complete type: Four main symptoms
| Incomplete type: Three of the main symptoms, or two main symptoms and two additional symptoms; typical ocular lesion and another main symptom, or two additional symptoms
| BD suspected: Some main symptoms appear, but the case does not meet the criteria for the incomplete type; typical additional symptom is recurrent or becomes more severe
| Special lesions: Gastrointestinal lesions (abdominal pain and occult blood)
| Vascular lesions (vasculitis of aorta, artery, large or small veins)
| Neuronal lesions (headache, paresis, lesions of brain and spinal cord, mental symptoms)
| Laboratory data: 1-Negative or positive pathergy test; 2-Negative or positive prick test for vaccine for streptococci; 3-Inflammatory responses (increase of erythrocyte sedimentation rate, C-reactive protein positive, neutrophilia, increase in complement activity) |

Table 1. Revised Diagnostic Criteria proposed by the Behçet’s Disease Research Committee of Japan in 2003 (Kurokawa & Suzuki, 2004).
The diagnostic system that has been suggested by the International Study Group by Behçet’s Disease (International Study Group for Behçet’s Disease, 1990) requires the presence of oral ulceration in all patients plus any 2 of the following findings: genital ulceration, typically defined eye lesions, typically defined skin lesions, or a positive pathery test (Table 2).

### Diagnostic criteria of International Study Group for Behçet’s disease

<table>
<thead>
<tr>
<th>Recurrent Oral Ulceration</th>
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<tr>
<td>Minor or major aphthous lesions or herpetiform-like lesions observed by the physician or patient at least three times within a 12-month period.</td>
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<tr>
<th>Presence of Two Other Criteria</th>
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<tr>
<td>Recurrent genital ulceration: Observation by the physician or patient of the aphthous ulceration or scar is required.</td>
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<tr>
<td>Eye lesions: The ocular disease can include anterior and/or posterior uveitis, cells in the vitreous, or the presence of a retinal vasculitis.</td>
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<tr>
<td>Skin lesions: These changes, noted by the physician or patient, include erythema nodosum, pseudofolliculitis, and papulopustular lesions. In addition, lesions would include an acneiform nodule in postadolescent patients not receiving corticosteroid therapy.</td>
</tr>
<tr>
<td>Positive pathery test result: Read by physician at 24-48 hours.</td>
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#### 3.1 Oral aphthous ulcers

The common clinical finding in Behçet’s patients is the presence of recurrent mucocutaneous ulcers. Oral ulcerations are usually the initial symptom, occurring in 98% of the patients (Okada et al., 2004). They are painful, rounded, with surrounding erythema and pseudomembranous covering. The lesions are 3 to 15 mm in diameter and may occur in clusters. The lesions may be located anywhere in the oral cavity: the lips, gums, palate, tongue, uvula, and posterior pharynx. They usually heal in 7-10 days without scarring, but scarring occurs when a particularly large ulcer heals. The lesions may recur every 5 to 10 days, or every month, or even years apart without following any rule. The trauma to the oral mucosa can provoke them to appear strikingly reminiscent of the prick test (Wray et al., 1981) and the lesions can also occur in some individuals after eating certain type of foods.

#### 3.2 Genital ulcers

Genital ulcers occur in 75 to 87% of the BD patients (Smith & Shur, 2005). Genital ulcers can occur on the scrotum or penis in males. In females they can appear on the vulva and vaginal mucosa (Bonfioli & Orefice, 2005). Such ulcers can also be found on the perianal areas. Vulvar lesions frequently occur premenstrually (Nussenblatt, 2010). Genital lesions can be deep or may scar as they heal. Thus an examination of the genital region in a patient with suspected BD can be useful as a sign of old disease may be present. The genital lesions may be more painful in males.

#### 3.3 Skin lesions

Skin lesions occur in 75 to 87% of the patients (Smith & Shur, 2005). Erythema nodosum like painful and recurrent lesions are frequently noted on the anterior surface of the leg but can
be also seen on the face, neck, buttocks, and elsewhere. These lesions involute without ulceration and scarring, in several weeks, but they may indeed leave scars. Acne-like lesions or folliculitis are also common dermatologic lesions. They can appear on the back and face.

Forty percent of patients with BD exhibit a cutaneous phenomenon termed pathergy, in which sterile pustules develop at sites of spontaneous or induced trauma (venipuncture, injection of sterile saline). This phenomenon is not pathognomonic of BD, although it is an important criterion that can be used for the diagnosis (International Study Group for Behçet’s Disease, 1990). Dermatographia, another dermatologic phenomenon of cutaneous hypersensitivity, can also be found in one third to one half of the patients (Zafirakis & Foster, 2002).

3.4 Ocular involvement (Ocular Behçet’s disease)

The frequency of ocular involvement in patients with BD is approximately 70%–90% (Atmaca, 1989; Mochizuki et al., 1996; Verity et al., 1999). The characteristic ocular involvement is a relapsing remitting panuveitis. Table 3 summarizes the ocular findings. The ocular disease manifests approximately in 2-3 years after the initial symptoms noted (Tugal-Tutkun et al., 2004). Moreover, eye involvement may be the first presenting manifestation of BD in approximately 10% to 20% of the patients (Dilsen et al., 1986). The mean age at onset of uveitis is around 30 years. Males are more frequently involved, had an earlier disease onset, and had a more severe disease. Ocular involvement in BD occurs more commonly and severely among Japanese and Turkish patients (Özen, 1999; Tugal-Tutkun et al., 2004; Tursen et al., 2003).

The frequency of bilateral involvement ranges between 78% and 95% in most of the series (Atmaca, 1989; Barra et al., 1991; Mishima et al., 1979; Tugal-Tutkun et al., 2004). Bilateral but asymmetric ocular inflammation is a characteristic feature (Atmaca, 1989, Bhisitkul & Foster, 1996).

The ocular inflammatory episodes in BD are characteristically associated with a sudden severe onset of visual loss. Severity and number of repeated inflammatory attacks involving the posterior segment determine the extent of permanent structural changes and the resultant rate of irreversible visual loss. Because of that, Behçet panuveitis is a medical emergency, which must be treated immediately. Ocular involvement in patients with BD, especially posterior uveitis presence, is the primary indication of immunosuppressive treatment.

In 1970, Mamo reported that 90% of the untreated patients lost their vision over a mean period of 3.36 years (Mamo 1970). The severity of the visual loss is also correlated with the duration of the disease. Ben Ezra and Cohen (Ben Ezra & Cohen, 1986) reported that 74% of eyes lost useful visual acuity 6 to 10 years after the onset of uveitis despite intensive follow-up and treatment. In more recent studies, early and aggressive immunosuppressive treatment has been shown to reduce the rate of visual loss (Hamuryudan et al., 1997, Yazici & Ozyazgan, 1999, Kaklamani & Kaklamanis, 2001).

3.4.1 Anterior segment

Iridocyclitis may be isolated finding but is often generally is observed along with posterior- or panuveitis. The recurrent acute iridocyclitis attacks may persist for up to 2 to 3 months. However, the inflammation usually does not resolve completely between attacks. Mild to
moderate blurred vision, periorbital pain, photophobia, redness, reactive miosis, and lacrimation occur during acute attacks of anterior uveitis. Acute ciliary type of conjunctival vasodilatation and injection usually develops over a period of hours or days. In the slit lamp examination, there is an abundant number of floating cells and flare in the anterior chamber which indicates active inflammation. Small keratic precipitates may also be observed, typically in the lower corneal endothelium. The cells in the anterior chamber will move easily and slide over the corneal endothelium if the patient’s head is tilted. After the cells have disappeared, persistent flare may ensue in the long standing cases, indicating persistent vascular damage rather than active inflammation that may not merit treatment. In a study from Turkey, which the laser cell flare meter was used and a large number of patients with BD were examined, it was suggested that those eyes with flare measured at ≥6 photons/s had a higher possibility of recurrence (Tugal-Tutkun et al., 2008).

The hypopyon may be a presentation of iridocyclitis which has been described as a characteristic sign. Mamo and Baghdassarian (Mamo & Baghdassarian, 1964) reported that hypopyon has become an uncommon finding, this apparent decline to the advent of steroid management in controlling inflammatory response. It was reported that hypopyon present only in about one-tenth (Tugal-Tutkun et al., 2004) to one-third of BD patients (Ohno et al., 1986; Mishima et al., 1979). However, the development of hypopyon may be provoked by local trauma such as cataract surgery (Kim et al., 2002, Matsuo et al., 2001) or sudden interruption of the treatment in patient with Behçet uveitis. The hypopyon may occur in other types of anterior uveitis but the hypopyon in patients with BD is typical that shifts with gravity as the patient changes his head position. The microhypopyon may not be visible to the naked eye but seen only with the slit lamp or in the angle when gonioscopic examination is performed, called as angle hypopyon.

When the disease is particularly severe and long-standing, cyclitic membranes can form, (Inomata et al., 2003). Peripheral anterior synechia, posterior synechia and iris atrophy may develop during the course of repeated ocular inflammatory attacks. The presence of peripheral anterior synechia or iris bombe from pupillary seclusion may lead to secondary glaucoma. Neovascularization of the iris and secondary glaucoma may occur as a result of posterior segment ischemia and neovascularization. It is also an ominous sign, a prognosticator of poor outcome.

Cellular infiltration also occurs in the anterior vitreous cavity behind the lens. Vitreal cells tend to have more restricted circulation when compared the anterior chamber as a result of viscosity of vitreous gel.

Cataract formation is not unusual, due to either the inflammation or the corticosteroid therapy in these patients. Other less frequent anterior segment findings are episcleritis, scleritis, conjunctivitis, subconjunctival hemorrhage, conjunctival ulcers, filamentary keratitis, and corneal immune ring opacity (Colvard et al., 1977; Dursun et al., 2004; Matsuo et al., 2002; Zamir et al., 2003).

3.4.2 Posterior segment

Posterior segment involvement is a poor prognostic sign of ocular BD and is seen in up to 93% of patients with ocular disease (Atmaca & Batıoglu, 1994). The ocular inflammatory episodes in BD are characteristically associated with a sudden severe onset of visual loss.
that may gradually improve with remission. Recurrent attacks of posterior segment may lead to severe retinal damage and irreversible visual loss (Atmaca & Batıoglu, 1994).

The most common and universal posterior segment finding are vitritis and retinal perivasculitis involving both the arteries (periarteritis) and veins (periphelebitis). Active periphlebitis is characterized by a fluffy white haziness surrounding the vessel with patchy involvement and irregular outside extensions. Fluorescein angiography has been reported to reveal leakage from retinal vessels even in eyes without clinically detectable vasculitis (Atmaca, 1989). Vitritis is characterized by cellular infiltration and its products of the vitreous along with posterior segment involvement. Vitreous haze is usually severe and accompanied by serious posterior segment inflammation. The view of the fundus may be markedly obscured because of the vitreal haze.

Occlusive vasculitic attacks of the retina are the most commonly dreaded complication of posterior segment involvement. Examination of the retina will show areas of hemorrhage and infarction in the retina. If the occlusive vasculitic attack involves the macular region, the visual acuity will reduce.

The retinitis characterized by scattered superficial yellow-white solitary or multifocal infiltrates of the inner retina with indistinct margin, giving the retina a cloudy appearance with obstruction of the retinal vessels. The lesions are usually transient and heal without scarring. Massive deep retinal exudates involve the outer retinal layers and are associated with vascular obliteration. During the resolution of the posterior segment inflammation, that follows severe vitritis and vitreal haze, inflammatory cells accumulate in the inferior preretinal area, resemble a pearl necklace.

During the active phase, generalized vascular leakage with diffuse retinal or optic disc edema, optic disc hyperemia, venous engorgement, and intraretinal hemorrhages may also be observed.

The most common complication of ocular BD is cystoid macular edema (CME), which observed in approximately in half of the patients with uveitis. It may resolve with appropriate treatment or if untreated progress to persistent chronic macular damage and sequel of CME, with structural changes after recurrences resulting in permanent visual loss. In some cases, it may lead to form a partial or full-thickness macular hole formation (Sheu & Yang, 2004). Macular ischemia due to occlusive vasculitis, scarring, degeneration with pigment epithelial changes, and epiretinal membrane formation may also occur (Yılmaz et al, 2000).

In incomplete treated patients, gliotic inflammatory vessel sheathing, retinal ischemia, retinal atrophy, and retinal tear may occur (Akova et al., 1999). Disc swelling, papillitis, optic atrophy and papilledema due to increased intracranial pressure and dural sinus occlusion are the optic disc findings. In some cases, neovascularization of the iris, retina, or optic disc may develop. Tugal Tutkun et al. reported that intraocular inflammation is more frequent cause of neovascularization of optic disc than retinal vascular occlusion (Tugal-Tutkun et al., 2006). Neovascularization may cause to vitreoretinal hemorrhage and tractional retinal detachment (Elgin et al., 2004; Ghate & Jorizzo, 1999; Lee, 2001; Nussenblatt, 1997).

At the end stage of the ocular disease, the repeated episodes of posterior segment inflammation and complications cause total optic atrophy, vascular attenuation, and sheathing with occluded and sclerozed vessels, diffuse retinal atrophy with variable chorioretinal pigmentation and scarring.
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Table 3. The ocular findings.

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<tr>
<th><strong>ANTERIOR SEGMENT:</strong></th>
<th>1-Iridocyclitis ± hypopyon; 2-Secondary glaucoma; 3-Secondary cataract</th>
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**Less frequent findings:** 1-Episcleritis; 2-Scleritis; 3-Conjunctivitis; 4-Subconjunctival hemorrhage; 5-Conjunctival ulcers; 6-Filamentary keratitis; 7-Corneal immune ring opacity

<table>
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<tr>
<th><strong>POSTERIOR SEGMENT:</strong></th>
<th>1-Vitritis; 2-Retinal perivasculitis; 3-Retinal hemorrhage and infarction due to occlusive vasculitic attacks; 4-Retinitis; 5-Diffuse retinal or optic disc edema; 6-Optic disc hyperemia; 7-Venous engorgement; 8-Cystoid macular edema; 9-Macular ischemia; 10-Macular scarring; 11-Pigment epithelial changes; 12-Epiretinal membrane formation</th>
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**In incomplete treated patients:** 1-Vessel sheathing; 2-Retinal ischemia; 3-Retinal atrophy; 4-Retinal tear; 5-Disc swelling; 6-Papillitis; 7-Optic atrophy; 8-Papilledema; 9-Neovascularization of the iris, retina, or optic disc; 10-Vitreoretinal hemorrhage; 11-Tractional retinal detachment

**End stage ocular disease:** 1-Optic atrophy; 2-Vascular attenuation and sheathing; 3-Diffuse retinal atrophy

4. Behçet's disease in children

According to a French nationwide survey in 1993, the estimated prevalence of Behçet’s disease in children younger than 15 years of age is one in 600,000 (Kone-Paut et al., 1998). In a more recent study reviewing 761 patients in Turkey, almost 57% of patients with an identifiable diagnosis had BD, with being 10.4% juvenile onset disease (Kazokoglu et al., 2008). In pediatric uveitis series, the incidence of Behçet’s disease has been reported to be 0.5% to 2.2% in countries where the disease is uncommon (Kanski & Shun-Shin, 1984; Pivetti-Pezzi, 1996; Tugal-Tutkun et al., 1996). By comparison, in a study from Turkey, Soylu et al. reported that 11% of children with uveitis had juvenile onset of BD (Soylu et al., 1997). The study by Tugal-Tutkun from Turkey involving 36 pediatric cases with BD reported that the male patients outnumbered female patients by a ratio of 2.3 to 1. Onset of uveitis was in late childhood. Bilateral panuveitis with retinal vasculitis and retinal infiltrates was the typical presentation. Uveitis was the initial manifestation of the disease in only 8.3% of the patients (Tugal-Tutkun & Urgancioğlu, 2003).

5. Pathogenesis

The cause of BD is uncommon. It is believed to be due to an autoimmune process triggered by an infectious or environmental agent in a genetically predisposed individual (Pay, 2007; Kulaber, 2007).

5.1 Genetics and human leukocyte antigen (HLA) typing

The sibling ratio has been reported as 11.4-52.5% by Gül et al. Although environmental factors shared by families can influence familiar clustering they cannot account for this risk ratio, which supports a strong genetic background in BD (Gül et al, 2000).
HLA-B51 allele located in the MHC (major histocompatibility complex) locus, on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route, with a stronger association in Turkish and Japanese patients in comparison to Caucasians (Verity et al, 1999).

On the other hand, HLA-DR1 and HLA-DQw1 have been shown to be significantly decreased in patients with BD. This may indicate that an individual who carries these antigens is resistant to develop the disease. These results suggest that not only disease susceptibility but also resistant genes play an important role in the immunogenetic mechanism of BD (Numaga et al., 1988).

5.2 Environment (Infectious agents, heat shock proteins) and self-antigens

Individuals from endemic areas who have immigrated to areas with low prevalence of the disease have an intermediate risk for developing the disease, which suggest that environment, has some role in development of BD (Sakane et al., 1999, Zouboulis et al., 1997). Several microorganisms have been implicated in the pathology of BD, especially herpes simplex virus-1 and Streptococcus sangius (Direskeneli, 2001; Lehner, 1997; Verity et al, 1999).

5.3 Immunohistopathology

Immunohistopathologic studies of specimens taken from active inflammatory sites of BD patient support the findings of those found in the peripheral blood and indicate immune-complex mediated disease. Necrotizing, neutrophilic (leukocytoclastic) obliterative perivasculitis (phlebitis) and venous thrombosis with lymphocytic and monocytic cellular infiltration of veins, capillaries and the arteries of all sizes, with and without fibrin deposition in the vessel wall, is the hallmark of BD (George et al., 1997).

6. Diagnosis

There is no pathognomonic or sensitive test and histopathologic finding in BD. Therefore, it is mainly diagnosed on the clinical grounds alone and currently relies on the recognition and grouping together of sufficient clinical features in a patient. The criteria defined either by the International Study Group of Behçet’s Disease or the Japanese Research Committee of Behçet’s Disease is the most commonly used criteria. Although the clinical diagnosis, some tests may be helpful for evaluation and diagnosis of BD.

6.1 Fundus fluorescein angiography and indocyanine green angiography

Fluorescein angiography and indocyanin green angiography (ICG) can provide diagnostic clues and may be used in the follow-up of cases with Behçet uveitis (Matsuo et al., 1999). Vasculitic ocular changes in BD have been investigated in depth using FA. This technique can reveal dye leakage from retinal arteries, veins, and capillaries and also provides useful information about retinal vasculature. Fluorescein angiography is demonstrative of the retinal vasculitic lesions and reveals perivascular staining of the retina with vascular dye leakage of the dilated retinal capillaries during the acute stage, inflammation, and occlusion of the retinal vessels, even before ophthalmologic signs of detectable retinal perivasculitis clinically appear. The most characteristic fluorescein angiographic signs of Behçet’s uveitis are extensive leakage from small and large retinal and optic nerve vessels during early phases and staining in the late phases of the FA.
Early and profuse leakage from the optic nerve head during the early phase may be observed and in advanced cases, neovascularization on the optic disc and elsewhere may also be present. In some cases, the neovascularization on the optic disc and elsewhere may be overlooked during the fundus examination and it can be exposed in FA. Macular alterations including macular ischemia, cystoid macular edema, macular hole and epiretinal membrane can be seen by FA. Cystoid macular edema may be distinguished as typical late phase-pooling within the cystic spaces with a foveal patellaroid pattern. Atmaca reported that FA disclosed vasculitic changes in 6.3% of BD patients who had no abnormal finding on fundus examination (Atmaca, 1989). Fluorescein angiography is very important in the study and longitudinal care of patients with ocular BD. Fluorescein angiography does not provide adequate information about choroidal circulation. Indocyanine green angiography may be superior to FA by showing hyper- and hypo-fluorescent lesions, choroidal vessel leakage, irregular filling of the choriocapillaris and choroidal filling defects (Gedik et al., 2005). The ICG angiography findings described in the literature include optic disc hyperfluorescence, segmental staining of the retinal and choroidal vessels, choroidal fuzziness and hyperfluorescence, delayed perfusion of choriocapillaries, hypofluorescent plaques, and hyperfluorescent spots (Bozzoni-Pantaleoni et al., 2001; Klaeger et al., 2000).

6.2 Ocular tests
Optical coherence tomography may be useful in detecting and monitoring the foveal thickness anatomically in BD patients with CME. The laser cell flare meter may be used in Behçet uveitis since eyes with flare measurements is related with a higher possibility of recurrence (Tugal-Tutkun et al., 2008).

6.3 Serologic studies
The erythrocyte sedimentation rate, C-reactive protein, and other acute-phase reactants, such as properdin factor b and α1-acid glycoprotein, may be shown elevated during the acute phase of BD (Özoran et al., 1996). An elevation in the level of β2-microglobulin (Aygündüz et al., 2002) and myeloperoxidase (Accardo-Palumbo et al., 2000), generated by activated neutrophils, have been reported. Serum levels of several cytokines, including TNF-α, IFN-γ, IL-1β, IL-6, IL-8 may be also elevated.

7. Treatment
The primary goals of management are symptom control, early suppression of inflammation and prevention of end-organ damage. Even though therapy of acute disease is essential, to prevent or at least to decrease the number of repetitive ocular and systemic inflammatory episodes is important. Drugs are frequently used in combination in order to maximize the efficacy while minimizing side effects. The choice of medication is based on the severity of the disease. In general, treatment should be more aggressive whenever the following are present: complete BD, involvement of CNS, vascular involvement, retinal and bilateral involvement, male sex, and a geographic origin as the Mediterranean basin or Far East (Mishima et al., 1979).

In general, the duration of treatment should be at least 6 months followed by a close monitoring of possible relapse afterwards; tough treatment courses may need to span a
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number of years. Many treatment modalities have been tried in ocular BD with varying claims of success. For the time being, the most commonly used agents are corticosteroids, cytotoxic drugs, colchicine, Cyc-A and tacrolimus (FK-506). Table 4 summarizes the treatment modalities.

7.1 Corticosteroids
Systemic or topical corticosteroids have a beneficial effect on the acute ocular inflammation of BD but their long term use is limited as a result of significant side effects, which requires the simultaneous use of other is drugs.

The application principal of corticosteroids, by whatever route, should initially be given at a large dose, and then tapered as quickly as possible over several weeks once the inflammation comes under control. Because of the inflammation may recur in reduction period, the corticosteroid treatment may be continued in a small dose for a long period.

7.1.1 Topical corticosteroids for ocular disease
Similar to other types of uveitis, in Behçet uveitis, strong steroids (prednisolone 1%, dexamethasone 0.1%, betamethasone) should be preferred to weaker ones. Since the solutions penetrates the cornea better than the suspensions or ointment, during the day the solutions should be preferred. The ointments may be used at bedtime.

Topical short-acting mydriatic and cycloplegic agents (e.g., tropicamide 1%, or cyclopentolate 1%) along with sympathomimetics such as phenylephrine 2.5-10% should simultaneously added to local corticosteroids to prevent photophobia and pain by relieving the spasm of the ciliary muscle and pupillary sphincter, thus promoting patient comfort. Additionally, these agents also prevent the development of new posterior synechia formation in cases with iridocyclitis.

7.1.2 Periocular corticosteroid injections
In severe anterior uveitis and hypopyon unresponsive to frequent topical ophthalmic drops, periocular route (subconjunctival, anterior parabulbar sub-Tenon capsule, or trans-septal orbital floor injections) can also be effective. Water soluble preparations (methylprednisolone sodium succinate), which diffuse from the depot more rapidly, are short-acting, even when steroids with a prolonged biological $t^{1/2}$ (dexamethasone sodium phosphate are used.

Acute attacks of vitritis, intermediate uveitis, CME, and mild posterior uveitis, especially if unilateral, can be treated with posterior parabulbar sub-Tenon capsule corticosteroid injections (under topical anesthesia) with or without systemic administration. Depot agents should be preferred such as triamcinolone acetonide or methylprednisolone acetate to achieve long-lasting effect.

7.1.3 Intravitreal corticosteroid injection
The intravitreal triamcinolone acetonide injection may be used as an adjunctive therapy for the treatment of panuveitis attacks and CME in patients with BD who are unresponsive or intolerant to systemic medications.

Sustained release intravitreal implants, including the fluocinolone acetonide implant and dexamethasone drug delivery system, offer an alternative therapy for chronic, recalcitrant posterior uveitis and CME. Studies in CME developed in retinal vein occlusion show
promising results that this treatment options may be effective in uveitis associated CME (Coscas et al., 2011; Haller JA et al., 2010).

### 7.1.4 Systemic corticosteroids for ocular Behçet’s disease

Acute and severe disease exacerbations of anterior uveitis, posterior, or panuveitis should be treated with higher dosages of systemic corticosteroid to offer a rapid response. Oral prednisolone 1-2 mg/kg/day given in a single morning dose after meals or intravenous pulse methylprednisolone 1 g/day for 3 consecutive days is preferred in concurrence with calcineurin inhibitors or other immunosuppressive drugs as steroid-sparing agents (Kaklamani & Kaklamanis, 2001, Toker et al., 2002). After remission of the disease has been obtained, it is gradually tapered to the maintenance dosage of 5-10 mg daily. Although oral corticosteroid monotherapy has palliative effect on ocular attacks, long-term treatment should be avoided since especially in patients with posterior segment involvement, it does not improve the visual prognosis and does not prevent the recurrent attacks of inflammation (Tugal-Tutkun et al, 2004).

### 7.2 Antimetabolites

#### 7.2.1 Azathioprine

In a large randomized, placebo-controlled trial, azathioprine 2.5 mg/kg/day in a dosage reduced the incidence, frequency, and severity of eye disease (Yazıcı et al., 1990). Early treatment with azathioprine is effective in controlling the attacks of posterior ocular inflammation and vasculitis, preventing recurrences, and improving the long-term visual prognosis of the disease (Greenwood et al., 1998; Nussenblatt, 1997).

#### 7.2.2 Mycophenolate mofetil

Initial evidence for mycophenolate mofetil’s efficacy has been reported in animal models of ocular inflammation (Chanaud et al, 1995; Dick et al, 1998). Previous literature on mycophenolate mofetil in patients with ocular inflammation, including patients with BD, consists of prospective pilot studies in refractory uveitis (Kilmartin et al., 1998; Larkin G & Lightman 1999; Zierhut et al., 2001) and retrospective case series (Baltatzis et al., 2003; Choudhary et al., 2006; Doycheva et al., 2007; Greiner et al., 2002; Lau et al., 2003; Siepmann et al., 2006; Thorne et al., 2005). This relatively large series makes a significant contribution to the literature on mycophenolate mofetil therapy for uveitis and confirms that mycophenolate mofetil is both effective and well tolerated. Additionally, it was reported that mycophenolate mofetil is an effective agent also in the treatment for uveitis in children, with marked steroid-sparing potential and an acceptable side effect profile (Doycheva et al. 2007). There is not a prospective study on mycophenolate mofetil in patients with Behçet uveitis. Since mycophenolate mofetil is effective in the other type of uveitis, it may be suggested that this agent is cures Behçet uveitis.

### 7.3 Calcineurin inhibitors

#### 7.3.1 Cyclosporine-A

Cyclosporin-A (5 mg/kg/day in 2 divided doses) is effective in the treatment in most of BD features, especially in posterior segment disease. Cyclosporine-A, when used in combination with corticosteroids, has a corticosteroid-sparing effect, permitting the use of lower dosages
of corticosteroids. In ocular disease, it has been shown to decrease the frequency and severity of acute uveitis most rapidly (Binder et al, 1987; Kaklamani & Kaklamanis, 2001) and combined therapy with azathioprine is more effective than monotherapy with a better outcome in ocular disease (Sakane & Takeno, 2000; Yazici, 2002; Yazici & Özyazgan, 1999). If combined therapy is applied, lesser dosage of both agents is possible. Cyclosporine-A is a cytostatic agent, and therefore the inflammation may recur when the therapy is tapered or withdrawn (rebound phenomenon). Because of that, patients generally need to continue treatment for several years.

7.3.2 Tacrolimus
Tacrolimus (FK-506) has also been used to treat refractory posterior uveitis in BD with limited experience (PO 0.05-0.20 mg/kg/day b.i.d) (Kilmartin et al, 1998). In comparison with CycA, tacrolimus has different side effect profiles, which may be an important issue in the choice of this therapy (Tanabe, 2003). Tacrolimus is less frequently associated hyperlipidemia, hirsutism, gingival hypertrophy, but it may induce diabetes mellitus (Marshall, 2004).

7.4 Alkylating agents
7.4.1 Chlorambucil
Chlorambucil was the first immunosuppressive drug to be used in patients with ocular BD (Zafirakis & Foster, 2002). The use of this agent is not preferred in Behçet uveitis since its side effects and slow acting characteristic. Tabbara (Tabbara, 1983) reported long term results with chlorambucil that were disappointing, with 755 of eyes in patients treated with chlorambucil as monotherapy having visual acuity of 20/200 or less. These results could be explained by the fact that chlorambucil, a slow acting agent, suppresses the immune system slowly, which would be a disadvantage, as rapid immunosuppression is usually desirable for BD patients.

7.4.2 Cyclophosphamide
Cyclophosphamide is even more toxic than chlorambucil and it should be reserved for very refractory sight-threatening ocular BD patients. Cyclophosphamide has been utilized widely in Japan with favorable results in controlling uveitis, preventing ocular attacks, and maintain good visual acuity for long periods in BD patients (Hijikata & Masuda, 1978). It has been shown that cyclophosphamide is superior to steroids in suppressing ocular inflammation in BD patients in the acute phase (Gills & Buckley, 1970; Oniki et al., 1976). Foster et al (Foster et al., 1991) have shown that both cyclophosphamide and chlorambucil were superior to Cyc-A in the management of the posterior segment manifestations of BD. In contrary, Ozyazgan et al reported (Ozyazgan et al., 1992) that intravenous cyclophosphamide was less effective than oral CycA, especially during the first 6 months of the treatment.

7.5 Current concepts
7.5.1 Interferon-α
Clinical trials on IFN-α have shown encouraging results in the treatment of severe refractory uveitis in BD combined with corticosteroid and immunosuppressive therapy. Initial treatment modalities and doses are ranging from three to nine million IU daily versus
thrice-a-week regimen, as well as duration of IFN-α2a administration and corticosteroid therapy tapering; vary widely, among reported studies. Kötter et al demonstrated in their open-label prospective study that recombinant human IFN-α2a at a daily dosage of 6 million IU for at least 14 days is effective in ocular BD (Kötter et al., 2003), leading to significant improvement of visual acuity with complete remission of ocular retinal vasculitis in the majority of the patients. Sight-threatening ocular disease has responded to IFN-α2a in 92% of the cases.

Tugal-Tutkun et al. reported that IFN-α2a was effective for the treatment of Behçet’s patients with NVD, who were treated with intensive anti-inflammatory drugs, conventional immunosuppressive treatment and retinal laser photocoagulation without success (Tugal–Tutkun et al., 2006).

Recently a retrospective report of IFN-α2a use in 7 children with corticosteroid dependent Behçet uveitis with clinical improvement was published, allowing corticosteroid dose reduction in 5 patients (Guillaume-Czitrom et al., 2007).

7.5.2 Anti-TNF-α biological agents

TNF-α is a fundamental cytokine in the establishment and maintenance of the inflammatory response. At present, there are 3 TNF-α inhibitors available: infliximab, are recombinant chimeric monoclonal antibody; adalimumab, a humanized monoclonal antibody; and the fusion protein human p75 TNF-α receptor IgG1 etanercept (Ehrlich, 1997).

7.5.2.1 Infliximab

Infliximab is a human-murine chimeric anti TNF IgG1 monoclonal antibody. It binds to human TNF-α and neutralized its activity (Saravanan & Hamilton, 2002).

In an open label trial by Tugal-Tutkun et al., they investigated the efficacy of infliximab in 13 BD patients with uveitis resistant the combination therapy of azathioprine, Cyc-A, and corticosteroids. Following 4 infusions of infliximab (5mg/kg) administrated at weeks 0, 2, 4, and 14, combined with azathioprine and corticosteroids, 4 patients remained attacks-free for 22 weeks. The mean number of uveitis attacks and daily corticosteroid doses were significantly lower during the infusion period than the previous-treatment period (Tugal-Tutkun et al., 2005).

In a recent study (Tabbara et al., 2008) the outcome of retinal vasculitis in BD treated with conventional immunosuppressive therapy (prednisone, azathioprine, cyclosporine, or methotrexate) was compared to ones treated with infliximab. The authors reported that infliximab (5mg/kg per infusion) induced a mean remission period of 17 months in BD compared to a mean remission period of 5 months in patients treated with conventional immunosuppressive agents. These results suggest that TNF-α blocking agent should be considered for the prevention of vision-threatening retinal vasculitis caused by BD. In this study 60% of the patients developed optic atrophy in the conventional therapy group compared to 30% in the infliximab group. Prevention of the optic nerve vasculitis by infliximab may be desirable in order to prevent optic atrophy.

Retinal vasculitis in BD requires multiple infliximab infusion. Relapses have been reported to occur with complete cessation of infliximab infusion (Tognon et al., 2007; Toubi et al., 2005). The clinical results obtained from these studies suggest that infliximab is effective in suppressing the inflammatory episodes of retinal vasculitis and preserves visual function in BD patients. The exact dosage and frequency of infliximab therapy remain undetermined.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effects</th>
<th>Side effects</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Inhibition of cyclo-oxygenase and lipo-oxygenase pathways. By inhibition of phospholipase A2, corticosteroids reduce arachidonic acid formation, and inhibit prostaglandins, leukotriens, and thromboxane.</td>
<td>Decreases lymphocyte migration and chemotaxis, circulating monocytes, macrophage activity, the levels of complement and interleukins.</td>
<td>Hypertension, hyperglycemia, weight gain, fluid retention, electrolyte disturbance, peptic ulcers, Cushing syndrome, osteoporosis, mental status changes and growth retardation in the pediatric group. Local side effects; secondary cataract and intraocular pressure elevation. Acute ocular and systemic inflammation</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
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<tr>
<td>Azathioprine</td>
<td>Converted to -mercaptodihydro which is converted to 6-thiothioguanine nucleotides and inhibits purine ring synthesis and, consequently, DNA and RNA synthesis</td>
<td>Inhibits the proliferation of T and B lymphocytes</td>
<td>Gastrointestinal intolerance, bone marrow suppression, infection, and azoospermia. Posterior ocular inflammation, arthritis, oral and genital ulceration</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folate analog and interferes with its action</td>
<td>Hepatotoxicity, renal toxicity, gastrointestinal toxicity and bone marrow depression</td>
<td>Neuro-BD, severe mucocutaneous involvement, and anterior uveitis</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Converted to mycophenolic acid, which prevents replication of T and B lymphocytes by selectively inhibiting inosine-5-monophosphate</td>
<td>Does not inhibit the early production of IL-2 or the production cytokines of T-helper-cell clones belonging to the Th0 and Th2 subsets. Because mycophenolate mofetil works at a later stage in the T-</td>
<td>Posterior ocular inflammation</td>
</tr>
<tr>
<td>Treatment</td>
<td>Effects</td>
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<tr>
<td>dehydrogenase and consequently</td>
<td>cell cycle, it acts synergistically with other immunosuppressive agents</td>
<td></td>
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<tr>
<td>Calcineurin inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A</td>
<td>Interfere with the activation and recruitment of T lymphocytes</td>
<td>Selectively suppresses CD4+ T lymphocytes</td>
<td>Neurotoxicity, hepatotoxicity, nephrotoxicity, hypertension, hirsutism, paraesthesia, gastrointestinal manifestations, hyperlipidemia, and gingival hyperplasia Posterior ocular inflammation and most of the BD features</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Interfere with the activation and recruitment of T lymphocytes</td>
<td>Selectively suppresses CD4+ T lymphocytes</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Interferes with DNA replication by cross-link, and causes decreased B and T cell functions</td>
<td>Slow acting agent</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Similar with chlorambucil</td>
<td>Fast acting agent</td>
<td>Pulmonary fibrosis, renal toxicity, and hemorrhagic cystitis Refractory sight-threatening ocular BD patients</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Inhibits neutrophil migration by interfering with microtubule formation</td>
<td>Gastrointestinal intolerance, alopecia and bone marrow suppression</td>
<td>Mucocutaneous and articular involvement</td>
</tr>
<tr>
<td>Treatment</td>
<td>Effects</td>
<td>Side effects</td>
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<tr>
<td><strong>Dapsone</strong></td>
<td>Modifying neutrophil chemotaxis with antioxidant properties</td>
<td></td>
<td>Oragenital ulcers and cutaneous manifestations</td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td>Diminishes TNF production and activity and decreases neutrophil migration</td>
<td>Teratogenicity, peripheral neuropathy, sedation, dizziness, headache, nausea, and weight gain</td>
<td>Oragenital ulcers, skin lesions, neurological and gastrointestinal involvement</td>
</tr>
<tr>
<td><strong>Interferon-α</strong></td>
<td>Reduces the number of circulating γδ-T cells, to increase HLA1 expression on peripheral monocytes in BD patients and to inhibits T cell adhesion to endothelial cells</td>
<td>Flu-like illness, leukopenia, thrombocytopenia, agranulocytopenia, bone marrow fibrosis, alopecia, pruritus, and depression</td>
<td>Refractory posterior uveitis</td>
</tr>
<tr>
<td><strong>Anti-TNF-α biological agents</strong></td>
<td></td>
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<tr>
<td><strong>Infliximab</strong></td>
<td>Binds to human TNF-α and neutralized its activity</td>
<td>Infections, reactivation of tuberculosis, anaphylaxis, demyelination, lymphoma, and a development of auto-antibodies against double-stranded deoxyribonucleic acid</td>
<td>All manifestations of both systemic and ocular BD</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td>Binds to human TNF-α and neutralized its activity</td>
<td></td>
<td>Mucocutaneous manifestations</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>Binds to human TNF-α and neutralized its activity</td>
<td></td>
<td>Refractory sight-threatening ocular BD patients</td>
</tr>
</tbody>
</table>

Table 4. The treatment modalities.
7.5.2.2 Etanercept

Etanercept is a dimeric fusion protein of the p75 kD TNF-α receptor and Fc portion of human IgG1 (Maini & Taylor, 2000). It is produced by recombinant DNA technology, has a good tolerability, and is administered by subcutaneous injection (Thomas-Golbanov & Sridharan, 2001). A recent experimental study from Turkey has demonstrated that etanercept has a definite effect on the treatment of endotoxin-induced uveitis in rats (Avunduk et al., 2004). Clinically, beneficial effects have been observed with etanercept in maintaining visual acuity in BD patients with refractory uveitis, although the effect was not sustained in the post-treatment follow-up (Melikoglu et al., 2002).

7.5.2.3 Adalimumab

This agent has maintained disease remission in 3 patients with uveitis with no recurrences and stable visual acuity during the follow-up after whom being switched from infliximab to adalimumab (Mushtaq et al., 2007). Van Laar Jam et al reported that 6 patients with refractory disease (2 of them uveitis) were treated with adalimumab (with or without other therapies) and showed clinical improvement (Van Laar et al., 2007). A recent study involving 11 patients reported that adalimumab has been shown to improve visual acuity and also to have a corticosteroid and immunosuppressive sparing effect. It can induce and maintain sustained remission of the disease (Bawazeer et al., 2010).

7.6 Management of ocular complications

Cataract formation is especially common, both because of the recurrent inflammation and as a consequence of the steroid treatment. Cataract surgery should be delayed until uveitis has been quiescent for at least 3 months. Perioperative anti-inflammatory therapy, including topical, periocular, intracameral, intravitreal, or even systemic corticosteroid, should be aggressively employed with intensive pre-, intra and post-surgery. Immunosuppressive drugs should be continued during the pre- and postoperative period. During the surgery minimum trauma should be given to the eye and minimal corneal incision should be performed. Complete removal of cortical material is important and a posterior chamber intraocular lens should be placed into the capsular bag. Intense fibrinoid reaction may still develop postoperatively. Nd:YAG laser capsulotomy may be needed in many cases for secondary posterior capsule opacifications which are frequently seen in the eyes with uveitis. With appropriate preoperative and postoperative suppression of inflammation, phacoemulsification and intraocular lens implantation are safe procedures leading to visual improvement in patients with BD without preexisting fundus lesions (Berker et al., 2004; Ciftci & Ozdemir, 1996; Gungor et al., 2008). Secondary and neovascular glaucoma may be responsible for vision loss in BD patients. Initial therapy with topical and systemic antiglaucoma medications may not suffice. Secondary glaucomas in BD with or without pupillary block and angle-closure glaucoma, if present, may be treated with Nd:YAG-laser iridotomy or surgical peripheral iridectomy, diode-laser cyclodestruction, trabeculectomy with antimetabolites or aqueous drainage implants, as indicated (Elgin et al., 2004; Yalvaç et al., 2004). Cyclocryotherapy may be indicated for neovascular glaucoma and enucleation for cosmetic reasons or painful eyes. Pars plana vitrectomy may be indicated in case of epiretinal membrane, macular hole, or vitreous hemorrhage along with retinal photocoagulation in cases of retinal tears. Retinal
detachment is therefore common in the later stages of the disease. Phthisis bulbi with or without iris neovascularization usually follows retinal detachment. Development of retinal and optic disc neovascularization is a major complication of the repeated attacks on the retinal vasculature. This neovascularization is attributed to the BD vasculopathy leading to retinal hypoxia. Meticulous evaluation of retina is very important for the early diagnosis of neovascularization. Control of the inflammation is important; additionally laser photocoagulation of the ischemic area is helpful. Intravitreal anti-vascular endothelial growth factor agent might be applied.

8. Prognosis

BD has a variable course characterized by relapses and remissions. Prognosis depends on the clinical involvement. Loss of visual acuity and neurological disease are major causes of morbidity and mortality. Prognosis of BD improved in the last decade due to the use of modern therapy modalities, including IFN-α and anti TNF-α blockers, and a more aggressive treatment strategy. Despite modern treatment, the disease still carries a poor visual prognosis with one-quarter of the patients blind (Kump et al., 2008; Yoshida et al., 2004). Sakamoto et al (Sakamoto et al., 1995) did try to determine prognostic factors for visual outcome. They concluded that skin lesions, arthritis and posterior uveitis attacks were linked to loss of vision, whereas female sex, disease free interval, and anterior attacks were related to retention of vision. Demiroğlu et al (Demiroğlu et al., 1997) reported that age of 30 years or less, male sex, vascular thrombosis, and CNS involvement were risk factors for ocular disease. Recently, Kaçmaz et al. conducted a study to estimate the risk of structural ocular complications and loss of visual acuity in cases with BD. They reported that loss of visual acuity and ocular complications might occur in patients with ocular inflammation associated with BD, even with aggressive therapy. Ongoing inflammation during follow-up, presence or occurrence of posterior synechia, hypotony, and elevated IOP were associated with an increased risk of loss of visual acuity (Kaçmaz et al., 2008).

9. Conclusions

Behçet’s disease is a multi-system inflammatory disease, characterized by relapsing inflammation. Although intraocular inflammation may involve anterior or posterior segment, the hallmark of BD is the presence of panuveitis and vasculitis, and the sequela of the posterior segment inflammation appears to be sight-threatening. Corticosteroids are used to control acute inflammation, but have little effect in controlling recurrences. Conventional immunosuppression agents (most frequently azathioprine and Cyc-A) are the most frequently used agents in preventing recurrences in BD. However conventional immunosuppressive agents may take several weeks to show significant clinical effect and induce remission. In cases resistant to these agents, IFN-α2a and anti-TNF agents (esp. infliximab) give promising results in the treatment of Behçet uveitis. However, controlled randomized studies are necessary to determine the optimum doses and duration of therapy and specify the role of these immunomodulatory agents in the therapeutic regimen. In addition to this, new treatment agents are still needed.
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6338-9, Philadelphia, Pennsylvania.
This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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