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Review Article

Ocular Involvement in Behcet's Disease: An Overview

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Abstract

Ocular involvement in Behçet's disease is frequent and may be associated with a poor functional prognosis. It can be inaugural in 20% of the cases or may develop 2 to 3 years after the beginning of the disease. Uveitis is the most common ocular manifestation and may be anterior, intermediate, posterior or panuveitis. The main goals in the management of ocular involvement are rapid suppression of intraocular inflammation, preservation of vision, and prevention of recurrences. The treatment is based on the use of systemic glucocorticosteroids and immunosuppressive agents. Recent developments like biological agents in the treatment of ocular Behçet's disease are promising with a rapid effect and high remission rates.

Keywords: *Behçet's Disease; Iridocyclitis; Retinal Vasculitis; Immunosuppressants; Biological Agents*

Introduction

Behçet's disease (BD) is a multi-system inflammatory disorder characterised by oral aphthous lesions and genital ulcerations, and may present with ocular manifestations, gastrointestinal involvement, skin lesions, neurologic disease, arthropathy, and vascular disease. The diagnosis relies mainly on clinical findings and can be challenging since there are no specific laboratory tests. The most commonly used diagnostic criterion is defined by the International Study Group for BD. Recurrent oral ulcer (that occurs at least three times a year), is mandatory for the diagnosis. In addition, two of the four major symptoms, including recurrent genital ulcers, eye lesion, skin lesions and a positive pathergy test, are sufficient for the diagnosis of BD [1]. Recent diagnostic criteria for Behcet's disease include ocular lesions, oral aphthous ulcerations, and genital aphthous ulcerations which are each assigned 2 points, while skin lesions, central nervous system involvement, and vascular manifestations are assigned 1 point each. The pathergy test, when used, was assigned 1 point. A patient scoring ≥ 4 points is classified as having Behcet's disease [2].

The etiology of BD remains unclear but currently some external environmental factors are believed to trigger BD in individuals with a particular genetic predisposition. It is also well established that HLA-B*51 is the most strongly associated genetic factor for this vasculitis [3].

Over two-thirds of patients with BD will develop ocular inflammation - most often bilateral panuveitis with retinal vasculitis. Corticosteroid therapy and cytostatic drugs were commonly used depending on the severity of the disease. Even with conventional therapy, nearly 25% of those patients experience reduced vision to 20/200 or less in their better seeing eye [4].

In this paper, we try to address a comprehensive review of important aspects of BD ocular involvement.

Ocular involvements of Behçet's disease

Ocular manifestations affects between 50% and 90% of BD patients depending on the geographic location of the population [5] (50 - 70% of affected men and 20 - 30% of affected women). They generally occur within the first 2- 4 years of the disease, and in nearly 80% of the patients, the manifestations are bilateral [6].

Non-infective uveitis is the most common ocular manifestation of BD and can involve the anterior, intermediate and posterior uveal tract or either in isolation, or in combination as panuveitis [7]. Uveitis typically presents with acute onset hypopyon and occlusive retinal vasculitis, with predominant inflammation of retinal veins [7].

Anterior segment involvement

Anterior uveitis, also known as iridocyclitis, is limited to the iris and the vitreous and it is of non-granulomatous nature. In ocular disease, uveitis with hypopyon (accumulation of cells and fibrin in the lower part of the anterior chamber of the eye) is the most characteristic ocular finding but a more common presentation is iridocyclitis without hypopyon, which is seen in two-thirds of the cases [8]. Examination reveals conjunctival injection, perilimbal flush, cells and flare in the anterior chamber, keratic precipitates and hypopyon.

Recurrent inflammatory attacks can result in structural changes of the anterior segment of the eye including iris atrophy and peripheral anterior synechiae.

The other anterior segment involvement include conjunctivitis, conjunctival ulcerations, and subconjunctival hemorrhages, episcleritis, scleritis, keratitis, and extraocular muscle paralysis.

These anterior ocular inflammation may recur repeatedly either unilaterally or bilaterally at any one time. In the majority of cases, hypopyon is resolved within several days, and anterior ocular inflammation becomes quiescent in 1- 2 weeks.

Posterior segment involvement

Vitreitis, retinitis, retinal exudates, hemorrhage, retinochoroiditis, optic disc hyperemia, panuveitis, occlusive panuveitic vasculitis, and cystoid macular edema (CME) are observed during the active inflammatory phase.

Retinal vasculitis including the capillaries is one of the major characteristic fundal findings of BD.

Hyperemia and swelling of the optic disc are observed during inflammatory attacks and repeated recurrence of intraocular inflammations may cause neovascularization on the optic disc. The incidence of ischemic optic neuropathy is rare.

Recurrent attacks of uveitis especially with posterior segment involvement may result in permanent damage in the sensory retina, causing irreversible loss of vision.

Diagnosis of ocular Behçet's disease

Important ocular findings for diagnosis

As there is no sensitive or specific laboratory test or pathologic finding for the diagnosis of BD, the diagnosis of ocular BD is based on clinical findings obtained from slit-lamp biomicroscopy and ophthalmoscopy. In addition, fluorescein angiography (FA) and indocyanine green angiography (ICGA) examinations are seen to be helpful in the diagnosis.

Tugal-Tutkun., *et al.* in a systematic review the use of multimodal imaging in ocular BD, have emphasized the importance of routine color fundus photography and FA to document and monitor the location, extent, and progression of posterior segment involvement [9].

FA is indispensable for detecting leakage, non-perfusion, and neovascularization in the mid- to far-periphery and remains the method of choice for revealing retinal vascular and optic disc leakage. Optical coherence tomography (OCT), which provides highly relevant infor-

mation regarding macular anatomy, is used most frequently for the identification and management of cystoid macular edema (CME), for documentation of non-glaucomatous retinal nerve fiber layer (RNFL) defects associated with inner retinal atrophy following focal infarcts, and, through automated comparison to reference standards, for screening of glaucomatous or non-glaucomatous optic atrophy [10].

Among the ocular findings, those with high sensitivity and specificity are listed below [8]:

- Ocular findings (Recurrent iridocyclitis, Hypopyon, Diffuse vitreous opacity, Inflammatory retinal infiltrates with or without retinal hemorrhage).
- Fluorescein angiographic findings Fern-like fluorescein leakage from retinal vessels (retinal capillaritis) Hyperfluorescence in the macula (macular edema) Hyperfluorescence of the optic disc).

The possibility of BD has to be suspected ophthalmologically in a case that satisfies at least two following conditions: viz. 1 item from ''Ocular findings'', and at least 2 items (1 item is adequate in the case of ''Fern-like fluorescein leakage...'') from ''Fluorescein angiographic findings''.

Human leukocyte antigen (HLA)

Horie., *et al.* performed a meta-analysis of 18 articles to examine the strength of the association between HLA-B51 expression and uveitis in BD [11]. The authors found a strong association between HLA-B51 expression and ocular involvement in reports from the Middle (OR 1.87, p = 0.0045; Palestine, Turkey) and Far East (OR 2.40, p = 0.00030, Taiwan, Korea, Japan), but no association in reports from North Africa (OR 1.15, p = 0.77, Morocco, Tunisia) or Europe (OR1.29, p = 0.67; Ireland, Britain, Italy, Greece). HLA analysis should be performed for differential diagnosis in some cases [12].

Management of ocular involvement of Behçet's disease

Behçet's uveitis is one of the most difficult forms of uveitis to treat as it has a remitting and relapsing course, and recurrent inflammatory attacks may result in irreversible damage and significant visual loss. The aims of treatment is (1) to prompt attenuation of the severity of ocular inflammations at the exacerbation phase (acute-phase treatment); and (2) continuing to promote the remission phase to prevent subsequent ocular inflammatory attacks. Management of the disease is variable, with therapeutic options ranging from symptomatic relief through to systemic immunosuppression [7]. The mainstream treatment approach consists on the use of colchicine, cyclosporine, or other immunosuppressants as a preventive therapy; however, the current approach has been to gradually adopt the use of novel biologic agents such as infliximab.

Corticosteroid therapy

Treatment of uveitis in BD typically relies on the use of corticosteroids for acute exacerbations, with other immunosuppressive agents introduced to achieve long-term control [7].

For anterior uveitis, topical corticosteroids combined with a cycloplegic agent are frequently used as a first line therapy.

Unfortunately, disease activity often recurs on cessation of therapy; adjunctive immunosuppressive therapy is therefore used alongside corticosteroids to enable reduction of corticosteroid dosage, minimize side effects, and reduce relapse rates [13].

For posterior ocular attacks, sub-Tenon's injection with dexamethasone is performed for posterior/panuveitis-type inflammation. Injection is continuously performed to reduce severe tissue damage and retinal edemas. High dose systemic corticosteroids are used for the treatment of severe posterior uveitis. Intravenous pulse methylprednisolone (1 g/day) is usually administered for 3 consecutive days to obtain a rapid anti-inflammatory effect. Then oral prednisone (1 mg/kg/day) is given and slowly tapered to a maintenance dose of 10 mg/day or less after complete resolution of active inflammation.

The important side effects of systemic corticosteroid treatment are elevation of intraocular pressure (IOP), cataract, cushingoid state, osteoporosis, diabetes mellitus, and exacerbations of infections.

Immunomodulatory therapy

Numerous immunosuppressive therapy have been used to treat BD, each with varying cellular and biochemical targets.

Cyclosporine A

Cyclosporine is an immunosuppressant that selectively inhibits T cells by suppressing intracellular calcineurin. It induces rapid suppression of intraocular inflammation and has been shown to reduce frequency and severity of uveitis attacks and is administered at the dose of 3 - 5 mg/kg/day in two divided doses. Despite its high efficacy, attention should be paid to cerebral nervous central symptoms and the frequently observed renal dysfunction [14].

Azathioprine

Azathioprine, an antimetabolite drug that interferes with purine incorporation into DNA and affects rapidly proliferating cells such as activated lymphocytes, is frequently employed for ocular BD treatment. It is orally administered at 2.5 mg/kg/day. The patients who received azathioprine treatment especially within 2 years after disease onset have a better visual prognosis. Saadoun., *et al.* have reported that in 157 BD patients treated with azathioprine for uveitis, 51.6% were complete responders, 41.4% were partial responders and 7% were non-responders [15].

Other immunosuppressive agents

Methotrexate, an antimetabolite drug that prevents the activation of folic acid, is suggested at the dose of 7.5 - 20 mg/week.

Cyclophosphamide, a fast-acting alkylating agent, showed favorable results in controlling uveitis, preventing ocular attacks, and maintaining a good VA for a long time in patients with BD. It can be administrated orally or intravenously.

Larkin and Lightman reported successfully treated Behçet patients by adding mycophenolate mofetil, an antimetabolite drug that blocks DNA synthesis by the inhibition of enzyme inosine monophosphate dehydrogenase, to their combination of steroid and cyclosporine [16].

Biological agents

Recently, biologic therapies have been used as an alternative treatment after corticosteroid and immunosuppressive therapies have failed. Outcomes of larger multicenter trials have recently been reported, providing an increasing quantity of convincing evidence for the benefit of biologic over traditional therapies. There are numerous benefits to the use of biologics, particularly with regard to quality of life and duration of treatment effect [7].

Numerous targets have been identified in the signaling pathway for potential therapeutic modulation [7].

Tumour necrosis factor - Alpha (TNF-α) inhibitors

Inflammation in BD is considered to be mediated predominantly by T helper type 1 (Th1) lymphocytes, releasing cytokines such as Tumour Necrosis Factor (TNF) and high levels of TNF have been detected in the aqueous humor of patients with Behçet's uveitis [17,18]. Infliximab and adalimumab were suggested as first line for patients with refractory BD-associated uveitis, and etanercept as second line [19].

Infliximab, a chimeric monoclonal antibody directed against TNF, has been shown to be effective in the treatment of Behçet-associated panuveitis in many studies [20,21].

Markomichelakis., *et al.* reported the outcome of a comparative study assessing the efficacy of a single intravenous infusion of infliximab versus intravitreal triamcinolone. They have demonstrated that infliximab was not only better at reducing ocular inflammation, but was also faster acting than corticosteroid therapy [22].

Recently, Hamza., *et al.* demonstrated the safety and efficacy of a single injection of intravitreal infliximab in a series of 20 BD patients with refractory uveitis. After 18 weeks follow-up, the authors reported a statistically significant improvement in mean visual acuity, reduction in mean central macular thickness, and reduction in mean vitreous haze scores [21].

In a retrospective study about 11 patients with Behçet's uveoretinitis refractory to conventional treatment, Infliximab/Cyclosporin combination therapy showed a promising treatment option as it appears to have an acceptable safety profile and can reduce the frequency and severity of ocular inflammatory attacks over a long period of time [23].

In the 2008 European League Against Rheumatism (EULAR) recommendations for the management of BD, any patient with BD-associated eye disease should initially be managed on a treatment regime that includes both azathioprine and systemic steroids, with the addition of either infliximab or cyclosporine A for patients with severe eye disease [24].

Adalimumab, a human-derived monoclonal antibody directed against TNF-α, has been demonstrated to be highly effective [25,26]. A 40 mg injection once every two weeks has been shown to be well tolerated. Adalimumab has predominantly been used when infliximab has been unsuccessful, or when patients opt for subcutaneous infusions rather than intravenous injections.

Etanercept, a fusion protein of two p75 TNF receptors and an Fc molecule, is not routinely used as a first-line agent in the management of BD-related uveitis and several studies using Etanercept have been reported [7]. The largest of these studies reported outcomes for 10 patients with severe uveitis in whom combination therapy with corticosteroid, azathioprine and cyclosporine-A had been ineffective [27]. Furthermore, Etanercept-induced ocular inflammation has also been reported in non-BD cohorts [7].

Golimumab, a monoclonal antibody to TNF-α that is administered subcutaneously once-monthly, may be effective in managing BD associated uveitis that is refractory to standard therapies and other biologic agents.

Rituximab

There is limited published evidence in the use of Rituximab, a monoclonal antibody to CD20 which acts through depletion of B-cells, for uveitis in BD [28,29].

A randomized, single blind pilot study involving 20 BD patients with refractory retinal vasculitis was performed by Davatchi., *et al* [30]. Patients were randomized to receive either two courses of rituximab at a dose of 1000 mg at 15-day intervals in combination with oral prednisolone and methotrexate (15 mg/week), or combination therapy comprising intravenous cyclophosphamide (1 g/month), azathioprine and prednisolone. No statistically significant difference was reported in improvement of retinal vasculitis between treatment groups. The two groups demonstrated a similar significant improvement in macular oedema [30].

Other biologic drugs

The use of Tocilizumab, a monoclonal antibody against the IL-6 receptor, is limited but encouraging in uveitis associated with BD [31].

Anakinra (IL-1 receptor antagonist), canakinumab (a human monoclonal antibody against IL-1β), Gevokizumab (a monoclonal antibody against IL-1β), were demonstrated to be promising for management of BD-related uveitis [32,33].

Hasanreisoglu., *et al.* reported their results in the use of interferon alpha-2a (IFNα2a) in 16 Turkish patients with refractory uveitis to combination therapy with azathioprine and cyclosporine. Clinical response and relapse rates in this cohort before and after switching to

IFNα2a were compared to a group of 23 patients with uveitis who were treated with a combination of azathioprine and cyclosporine. The authors noted that changing from combination therapy to IFNα2a in patients with frequent recurrences decreased the annual relapse rate from 2.4 ± 1.8 to 1.3 ± 2.0, a rate similar to the 0.8+/1.6 rate observed in the combination therapy group [34].

2018 EULAR recommendations for the management of eye involvement in BD [35]

Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine (IB), cyclosporine-A (IB), interferon alpha (IIA) or monoclonal anti-TNF antibodies (IIA). Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives (IIA). Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.

Ocular complications

Twenty-five percent to fifty percent of the patients may have poor final visual acuity despite the use of steroids and immunomodulatory agents [36]. In fact, inflammation and treatment modalities that are used may cause complications.

The major ocular complications include cystoid macular edema, secondary cataract (posterior subcapsular opacity) and secondary glaucoma, vitreous hemorrhage, retinal detachment, and ocular hypotony (phthisis bulbi). The progresses to a state of diffuse retinochoroidal atrophy with disseminated pigment proliferation at the terminal stage. Furthermore, optic atrophy may occur and cause irreversible visual dysfunction [8].

Conclusion

Ocular involvements in BD are frequent and the location of the inflammation is important both therapeutically and prognostically. Recent advances in ophthalmic imaging methods, early identification of high-risk group of patients and the use of biologic agents will improve the prognosis in this potentially blinding disease.

Disclosure Statement

The authors have no conflicts of interest to declare.

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