REVIEW ARTICLE

Evaluation of disease activity in uveoretinitis associated with Behçet’s disease

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ABSTRACT

Behçet’s disease is a multi-organ inflammatory disorder with systemic vasculitis of unknown etiology. Ocular lesions occur in about 70% of patients with Behçet’s disease, and it is more frequent and severe in men. The frequency of ocular inflammatory attacks has been used as a main outcome measure to assess the efficacy of therapy on uveoretinitis in patients with Behçet’s disease. The ocular Behçet’s disease research group of Japan have recently proposed a new scoring system, Behçet’s disease ocular attack score 24 (BOS24), to assess the disease activity of ocular Behçet’s disease. This review highlights the efficacy and application of the BOS24 scoring system in clinical practice for patients with ocular Behçet’s disease. In addition, a new semi-quantitative scoring system to evaluate the degree of retinal vascular leakage on fluorescein angiography reported by our group is described.

1. Introduction

Behçet’s disease is a multi-organ inflammatory disease with systemic vasculitis of unknown etiology [1]. Behçet’s disease is characterized by recurrent oral and genital mucous ulcers, dermic lesions and ocular inflammation [1,2]. Behçet’s disease can affect other systems involving the gastrointestinal tract, major blood vessels, and the central nervous system [1,2]. Behçet’s disease usually develops between the second and fourth decade of life and is rarely seen before puberty [3]. It is more common in men than in women and has a worse clinical course in young adult males [3]. Ocular lesions occur in more than 50% of patients with Behçet’s disease, and it is more frequent and severe in men [4]. Manifestation of ocular disease is mostly a bilateral, non-granulomatous panuveitis with a chronic, relapsing remitting course [4]. Although it has been reported that about 25% of patients with ocular lesions become blind despite treatment [5], visual prognosis has been improved with recent therapeutic approaches [2]. These include immunosuppressive drugs and biologics, such as TNF inhibitors [2,6,7].

Although the frequency of ocular attacks were used as a marker for disease activity to predict the clinical outcome of patients with ocular Behçet’s disease in previous studies [8–10], there are few reports to evaluate the severity of each ocular attack based on objective ocular findings. This review highlights the new disease score for uveoretinitis associated with Behçet’s disease, Behçet’s disease ocular attack score 24 (BOS24) [11] and retinal vascular leakage score on fluorescein angiography [12]. The importance of these disease activity score of ocular lesion in patients with Behçet’s disease is also discussed.

2. Characteristics of ocular findings in Behçet’s disease

Ocular manifestations of uveoretinitis associated with Behçet’s disease consist of anterior and posterior ocular findings [4,7]. Common anterior ocular findings are recurrent iridocyclitis, hypopyon, posterior synechia, and peripheral anterior synechia. Manifestation of ocular disease is mostly a bilateral, non-granulomatous panuveitis with a chronic, relapsing remitting course [4]. Although it has been reported that about 25% of patients with ocular lesions become blind despite treatment [5], visual prognosis has been improved with recent therapeutic approaches [2]. These include immunosuppressive drugs and biologics, such as TNF inhibitors [2,6,7].

Although the frequency of ocular attacks were used as a marker for disease activity to predict the clinical outcome of patients with ocular Behçet’s disease in previous studies [8–10], there are few reports to evaluate the severity of each ocular attack based on objective ocular findings. This review highlights the new disease score for uveoretinitis associated with Behçet’s disease, Behçet’s disease ocular attack score 24 (BOS24) [11] and retinal vascular leakage score on fluorescein angiography [12]. The importance of these disease activity score of ocular lesion in patients with Behçet’s disease is also discussed.

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vascular occlusion may lead to retinal non-perfusion area and retinal neovascularization.

Fundus fluorescein angiography is used to detect retinal vasculitic lesions in Behçet’s disease [4,7]. Common findings of fundus fluorescein angiography are hyper fluorescein of optic disc, vascular dye leakage from retinal capillaries (Figure 3), and staining of retinal vessels due to retinal perivasculitis. These findings may be observed even in eyes before ophthalmoscopic signs of clinically detectable retinal perivasculitis [7]. Retinal non-perfusion area due to the retinal vasculitic occlusion and dye leakage from new vessels from optic disc/ischemic retinal lesions are also observed as fluorescein angiographic findings of patients with ocular Behçet’s disease.

Common ocular complications are secondary cataract and glaucoma, vitreous hemorrhages, chorioretinal and optic disc atrophy (Figure 4), retinal detachment, macular edema, and ocular hypotony (phthisis bulbi) [4]. Macular edema is observed even in the absence of ocular attacks.

3. Changes of frequency of ocular attacks before and after initiating TNF inhibitor

At present, the frequency of ocular inflammatory attacks has been used as a main outcome measure to assess the efficacy of therapy on uveoretinitis in patients with Behçet’s disease [8–10]. Ocular inflammatory attacks have been defined as the sudden onset of cells and/or flare in the anterior chamber or vitreous, or cellular infiltrates and/or hemorrhage in the retina, as observed by slit-lamp examination and/or indirect funduscopy. Repeated ocular attacks associated with occlusive retinal vasculitis develop ocular tissue (optic disc and retina) damage leading to decreased visual function [13]. Indeed, it has been reported that there is a significant association between higher frequency of ocular attacks and
poorer visual outcome during long-term follow-up [10]. Furthermore, severe inflammatory attacks in the posterior area often lead to permanent retinal damage, resulting in irreversible visual loss in patients with Behçet’s disease [13]. These findings indicate that control of ocular attacks is critical for maintaining quality of vision.

The European League Against Rheumatism (EULAR) have proposed recommendation for comprehensive treatment guideline for the management of Behçet’s disease [14]. EULAR have recommended that any patient with ocular Behçet’s disease affecting posterior segment should be on a treatment regime including azathioprine, cyclosporine, interferon-α (IFN-α) or monoclonal anti-tumor necrosis factor-α (TNF-α) antibodies and systemic corticosteroids should be used in combination with azathioprine or other immunosuppressive drugs [14].

IFN-α is known as naturally occurring cytokine with immunomodulatory properties. IFN-α shows to decrease NK cells, CD8+/CD3+ γδ T cells, and to reduce the expression of HLA-class I on CD14+ monocytes [15]. IFN-α has been effective in experimental autoimmune uveoretinitis (EAU) in rats [16]. IFN-α had been used successfully by rheumatologist and dermatologist to treat joint and skin lesions in Behçet’s disease [17]. The efficacy of IFN-α has been shown in patients with ocular Behçet’s disease [18,19]. The dosage of IFN-α have ranged from 3 million IU three times a week to 18 million IU three times a week, however the optimal dose and duration still need to be determined [3,4].

TNF-α is a fundamental cytokine involved in the inflammatory process. TNF-α has been considered to play a key role in the pathogenesis of Behçet’s disease [4]. TNF-α enhances the development of EAU in mice, and inhibition of TNF-α activity delays the onset of EAU or ameliorates the severity of EAU [20–22]. It has been reported that production of TNF-α from peripheral blood monocytes has been enhanced in Behçet’s disease patients in active uveoretinitis compared to both healthy subjects and patients with inactive uveoretinitis, suggesting that TNF-α plays an important role in the immunopathogenesis of uveoretinitis in Behçet’s disease [23].

There is a growing body of evidence that TNF-α inhibitors, such as infliximab (IFX: a recombinant chimeric monoclonal antibody) and adalimumab (ADA: a humanized monoclonal antibody), have been effective in reducing the frequency of ocular inflammatory attacks (Figure 5) and in improving visual outcome in refractory cases of Behçet’s disease associated uveoretinitis [11,24–38] Therefore, it is recommended that TNF inhibitors, including IFX and ADA, should be employed in intolerant patients or when the disease activity is not well controlled by immunosuppressive agents, including azathioprine or cyclosporine [39].

As described above, both infliximab and adalimumab have shown to be an effective treatment for ocular Behçet’s disease, the loss of efficacy and development of infusion reaction are observed in some patients over long-term use of infliximab and adalimumab [36,40]. Secondary failure and adverse events such as infusion reaction can be related to the development of anti-drug antibodies (ADA) during the course of treatment [41]. In deed, it has been reported that the development of anti-infliximab antibody is associated with low circulating drug level [42]. It is unclear whether the use of concomitant immunosuppressive drugs is capable of suppressing the production of ADA in the treatment of Behçet’s disease. In the majority of our patients, low-dose cyclosporine has been continued as
concomitant immunosuppressive therapy with the hope of reducing the immunogenicity of infliximab [43]. Our previous study has shown that infliximab therapy with low-dose cyclosporine is effective in a long-term sustained manner over 4 years of treatment in ocular Behçet’s disease [43]. Recently, Katsuyama and colleagues have revealed that infliximab plus cyclosporine combination therapy is well-tolerated and can reduce the frequency of ocular attacks over a long period of time without loss of response to infliximab plus cyclosporine combination therapy [44]. On the other hand, Fabiani and colleagues have demonstrated that concomitant immunosuppressive treatment does not affect the infliximab or adalimumab retention rate in ocular Behçet’s disease [38,40]. Large-scale prospective study is warranted to determine whether the use of concomitant immunosuppressive drugs is important to reduce the loss of efficacy and the incidence of infusion reaction in the treatment of infliximab/adalimumab for ocular Behçet’s disease.

4. Behçet’s disease ocular attack score 24 (BOS24)

As described above, the frequency of observed ocular inflammatory attacks has been used to evaluate the disease activity of uveoretinitis associated with Behçet’s disease. In addition, there are other measurements to assess the disease activity of ocular inflammation, such as location of inflammation site (anterior, posterior, or panuveitis) [30], the presence of severe ocular inflammatory signs (hypopyon, involvement of inflammation at posterior segment) [10,30], and the physician’s impression of the severity of each ocular attack (mild, moderate, severe) [30].

There are several scoring systems for assessing the disease activity in various autoimmune diseases, such as rheumatoid arthritis [45]. The disease activity score 28 (DAS28), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) have been widely accepted for assessing the activity of rheumatoid arthritis and used in daily clinical practice by rheumatologists [45,46]. These scoring systems allow for an unbiased, objective and quantitative assessment of disease activity of rheumatoid arthritis and help with the evaluation of efficacy of treatment and interpretation of clinical trials of new drugs. As described above, previous studies have focused on the frequency of ocular attacks and visual outcome to predict the clinical outcome of patients with Behçet’s disease [8–10]. However, there are few reports which assess the severity of each ocular attack based on objective ocular findings, such as cells in the anterior chambers or areas of retinal exudates/hemorrhages, and which do not include patient’s complaints or

Figure 6. BOS24 scoring system. The BOS24 consists of a maximum of 24 points summed from six parameters of ocular inflammation for each ocular attack, specifically anterior chamber cells (a maximum of 4 points), vitreous opacities (a maximum of 4 points), posterior pole lesions (a maximum of 4 points), subfoveal lesions (a maximum of 2 points), and optic disc lesions (a maximum of 2 points). For scoring retinal inflammatory signs, the retinal field is divided into the posterior pole and peripheral retina, with the latter divided into four areas for each quadrant. (With permission, From Kaburaki T, Namba K, Sonoda KH, Kezuka T, Keino H, Fukuhara T, Kamoi K, Nakai K, Mizuki N, Ohguro N; Ocular Behçet Disease Research Group of Japan. Behçet’s disease ocular attack score 24: evaluation of ocular disease activity before and after initiation of infliximab. Jpn J Ophthalmol 2014;58:120–30.)
subjective examinations, such as the best correction of visual acuity. Therefore, to develop a precise and practical scoring system for the evaluation of disease activity of uveoretinitis in patients with Behçet’s disease, the ocular Behçet’s disease research group of Japan, consisting of 10 major uveitis referral centers, established the BOS24 scoring system [11].

The BOS24 scoring system consists of a maximum of 24 points summed from 6 parameters of ocular inflammation for each ocular attack, specifically anterior chamber cells (a maximum of 4 points), vitreous opacities (a maximum of 4 points), peripheral fundus lesions (a maximum of 8 points), posterior pole lesions (a maximum of 4 points), subfoveal lesions (a maximum of 2 points), and optic disc lesions (a maximum of 2 points) (Figure 6). For scoring retinal inflammatory signs, the retinal field is divided into the posterior pole and peripheral retina, with the latter divided into four areas for each quadrant. In the BOS24 scoring system, cells in the anterior chamber (a maximum of 4 points) were graded using the scales presented by the SUN (Standardization of Uveitis Nomenclature) working group [47], and vitreous opacity (a maximum of 4 points) following the grading system for vitreal inflammatory activity reported by Nussenblatt et al. [48] BOS24 is determined by only objective ocular findings at each ocular attack, not

Figure 7. Scoring of BOS24 at ocular attack of a patient with Behçet’s disease. Since this patient had anterior chamber cells (1+)(1 point), two peripheral fundus lesions (4 points), posterior pole lesions (2 points), the total BOS24 score was 7 points.

Figure 8. Change in frequency of ocular attacks and BOS24-6M in a representative case with ocular Behçet’s disease before and after initiation of infliximab therapy. Although the frequency of ocular attack was six times and B024-6M was 33 points during the six months prior to initiation of infliximab therapy, the frequency of ocular attack and BO24-6M were reduced (ocular attacks: one time and BOS24-6M: 8 points) during the six months after initiation of infliximab therapy.
including the patient complaints or results of subjective examinations, such as visual acuity. The score is also only determined based on newly emerging inflammatory signs and is not influenced by chronic inflammation signs. The BOS24 over a 6-month period (BOS24-6M) is calculated by adding up the BOS24 for each attack during the target 6-month period (Figures 7 and 8).

Our group first determined the validity of the BOS24 scoring system. Five uveitis specialists examined the clinical records of 50 ocular attacks in 50 patients and assessed the severity of each ocular attack using the physician’s impression scores (1–10 points). We also evaluated the BOS24 scores independently based on the clinical records of the 50 ocular attacks. We then determined the differences between the physician’s impression scores and BOS24 among the five uveitis specialists. The average BOS24 was highly correlated with the average physician’s impression scores, whereas the coefficient of variance for BOS24 among the five specialists was much lower than that for the physician’s impression scores. The results suggest that

Figure 9. Relationship between physician’s impression score and BOS24. The average values for physician’s impression score and BOS24 among five doctors for judgment of the same ocular attack were directly plotted, and the correlation was examined using Spearman’s rank-correlation coefficient test. There was a significant relationship between the physician’s impression score and BOS24. (With permission, From Kaburaki T, Namba K, Sonoda KH, Kezuka T, Keino H, Fukushima T, Kamoi K, Nakai K, Mizuki N, Ohguro N; Ocular Behçet Disease Research Group of Japan. Behçet’s disease ocular attack score 24: evaluation of ocular disease activity before and after initiation of infliximab. Jpn J Ophthalmol 2014;58:120–30.)

Figure 10. Frequency of ocular attack and changes in BOS24-6M before and after initiation of infliximab therapy. (a) The numbers of ocular attacks in individual patients during each 6-month period before and after initiation of infliximab therapy were examined. (b) BOS24 in individual patients during the 6-month periods (BOS24-6M) before and after initiation of infliximab therapy were examined. (With permission, From Kaburaki T, Namba K, Sonoda KH, Kezuka T, Keino H, Fukushima T, Kamoi K, Nakai K, Mizuki N, Ohguro N; Ocular Behçet Disease Research Group of Japan. Behçet’s disease ocular attack score 24: evaluation of ocular disease activity before and after initiation of infliximab. Jpn J Ophthalmol 2014;58:120–30.)

Figure 11. Retinal and disc vascular leakage score in ocular Behçet’s disease. Fluorescein angiography is performed to assess the degree of background retinal and disc vascular leakage in patients with ocular Behçet’s disease. Extent of fluorescein leakage is graded on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) for the peripheral retina, the macula, and the optic disc.
Figure 12. Changes of fluorescein vascular leakage scores before and after initiation of infliximab therapy. (a) To assess the degree of vascular leakage, fluorescein angiography was performed at times of clinical quiescence prior to the initiation of infliximab therapy (baseline) and at the end of years 1, 2, 3, and 4 on infliximab. Degree of fluorescein leakage was graded on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) for the optic disc, the macula, and the peripheral retina of each study eye by masked graders, and averaged. The total vascular leakage score represents the sum of the scores for the disc, macula and peripheral retina in both eyes. The mean ± standard error for all patients is shown at each time point. *p ≤ .05 versus baseline. M = months. (b) Total vascular leakage scores are shown for individual patients at baseline and at the end of years 1, 2, 3, and 4 on infliximab. M = months. (From Keino H, Okada AA, Watanabe T, Taki W. Long-term efficacy of infliximab on background vascular leakage in patients with Behçet’s disease. Eye 2014;28:1100–1106).

Figure 13. Color fundus photographs and fluorescein angiographic images of a patient at the baseline and on infliximab therapy. Color fundus photographs and fluorescein angiography images are shown for the right eye of a patient. (a) Fluorescein leakage from vessels at the optic disc, macula (left middle image), and peripheral retina (left lower image) was observed prior to initiating infliximab therapy. (b) This fluorescein leakage improved after three years on infliximab therapy (right middle and lower images). (From Keino H, Okada AA, Watanabe T, Taki W. Long-term efficacy of infliximab on background vascular leakage in patients with Behçet’s disease. Eye 2014;28:1100–1106).
BOS24 is highly correlated with scores based on the physician’s impression, and with a much lower variance among physicians (Figure 9).

5. Evaluation of the efficacy of infliximab on the frequency of ocular attacks in ocular Behçet’s disease using BOS24

Next, we examined the changes in the frequency of ocular attacks and ocular disease activity using BOS24 before and after initiation of infliximab therapy in patients with uveoretinitis associated with Behçet’s disease. A total of 150 patients treated at 10 regional university hospitals in Japan for ocular Behçet’s disease treated with infliximab were enrolled in this study [11]. As Figure 10(a) shows, the frequency of ocular attack was significantly decreased after initiation of infliximab at each interval during follow-up periods. The BOS24-6M value was also significantly reduced compared to that at the baseline over follow-up. Furthermore, the average BOS24 for each individual ocular attack was significantly reduced compared to that at the baseline during the first six months after starting infliximab therapy and continued to decrease gradually in each 6-month period thereafter (Figure 10(b)). These findings suggest that infliximab therapy is capable of reducing not only the total scores for disease activity during specific 6-month periods (BOS24-6M) but also the severity of individual ocular attacks. We believe that the BOS24 scoring system is an objective and quantitative method to measure the ocular disease activity in patients with Behçet’s disease.

6. Retinal vascular leakage score

Fundus fluorescein angiography has been widely used in ocular inflammatory disorders and is useful for the diagnosis of uveitis, in assessing the activity of inflammation in the posterior segment, and in monitoring the response to treatment [49]. Major fluorescein angiographic findings observed in uveitis are as follows: optic disc leakage, cystoid macular edema, retinal vascular staining/leakage, retinal/subretinal neovascularization, retinal staining/subretinal pooling, and retinal non-perfusion. However, the interpretation of fluorescein and indocyanine green angiographic findings has remained subjective and qualitative in most cases. Therefore, for grading posterior segment inflammation in uveitis eyes, the Angiographic Scoring for Uveitis Working Group (ASUWOG) have proposed a dual fluorescein and indocyanine green angiographic scoring system [50]. The fluorescein angiographic scoring system in the proposed system consists of nine angiographic signs, including optic disc hyperfluorescence, macular edema, retinal vascular staining/leakage, capillary leakage, retinal capillary non-perfusion, neovascularization of the optic disc (NVD), neovascularization elsewhere (NVE), pinpoint leaks, and retinal staining/pooling (a maximum score of 40 points) [50]. It has been reported that this scoring system has a moderate to substantial interobserver agreement in comparative fluorescein and indocyanine green angiographic total scores.

As described above, fluorescein leakage due to retinal vasculitis, including the choriocapillaris, is one of the major characteristics of ocular Behçet’s disease.
disease [4,7]. Continuous background retinal and disc vascular leakage is well documented even during periods of clinical quiescence [7], and such 'background inflammation' may also contribute to the slow destruction of ocular tissues and a decline in vision. Our group investigated whether infliximab therapy would affect the degree of background retinal and optic disc vascular leakage as assessed by fluorescein angiography at times of clinical quiescence [12,43]. For evaluating retinal and optic disc vascular leakage shown in fundus fluorescein angiography, the extent of fluorescein leakage was graded on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) for the peripheral

![Image](image-url)
retina, the macula, and the optic disc in a masked fashion (Figure 11) [12]. The total vascular leakage score was shown as the sum of the scores for the disc, macula and peripheral retina in both eyes. As shown in Figures 12 and 13, the total vascular leakage score with infliximab treatment was significantly reduced compared to that at the baseline. In addition, reduction of the fluorescein angiography vascular leakage score was maintained over a 4-year period in the majority of patients [43]. Our recent study also compared the efficacy of infliximab therapy on refractory uveoretinitis between Behçet’s disease patients with a short duration (<18 months) versus those with a long duration (>18 months) of their ocular disease [51]. Although there was no significant difference between either group with regard to the frequency of ocular attack and the BOS24-6M score, vascular leakage scores of the retina and optic disc were significantly reduced in the short duration group compared to those in the long duration group during infliximab therapy (Figure 14). However, some degree of fluorescein leakage was still observed in patients with long duration of ocular Behçet’s disease after starting infliximab therapy (Figure 14 and 15). These findings are likely to be due to the permanent damage to retinal and optic disc vessels. Therefore, we believe that careful interpretation of vascular leakage score in patients with long duration of ocular Behçet’s disease is necessary. With regard to visual outcomes in both short duration and long duration group, the percentage of eyes with a best corrected visual acuity of 1.0 or better was 100% in the short duration group, compared to 21% in the long duration group over a two-year follow-up (Figure 16). This indicates that early remission induction with infliximab may be more effective in reducing background retinal and disc vascular leakage, and in achieving good visual outcome in Behçet’s disease patients with refractory uveoretinitis.

It has been documented that retinal and optic disc atrophy are major causes of morbidity in Behçet’s disease [4,52], and it is believed that damage to these intraocular structures occurs not only due to acute inflammatory attacks but also to chronic smoldering inflammation, as evidenced by background vascular leakage. Indeed, it has been reported that the location of vasculitis, retinal arterial narrowing, and macular leakage on initial fluorescein angiography are significantly associated with final visual acuity [53]. Thus, suppression of such chronic vascular leakage, whether via infliximab therapy or other treatments, would be expected to aid in the preservation of ocular tissue and visual function. These findings suggest that vascular leakage on fluorescein angiography may serve as an important surrogate marker for the degree of inflammatory control for Behçet’s disease patients on various drug regimens. Recently, Shirahama and colleagues have demonstrated that the fluorescein angiography leakage score assessed using our scoring system was significantly increased in the active phase compared with the convalescent phase in patients with Behçet’s disease [54]. Taken together, our semi-quantitative scoring system to evaluate vascular leakage on fluorescein angiography may be a useful method for assessing the degree of intraocular inflammation in patients with ocular Behçet’s disease.
7. Conclusions

This review has described the efficacy of the BOS24 scoring system and a new semi-quantitative scoring system to evaluate the degree of retinal vascular leakage on fluorescein angiography in clinical practice for patients with ocular Behc¸et’s disease. Since BOS24 scoring system is an objective and quantitative measurement to evaluate the disease activity in patients with ocular Behc¸et’s disease, not only the frequency of ocular attacks but the BOS24 scores may be useful as biomarker to determine the timing of initiation of TNF inhibitors for patients with refractory ocular inflammation and the timing of withdrawal of TNF inhibitors in patients with complete remission of ocular inflammation under treatment with TNF inhibitors. Further investigations and accumulation of evidence are warranted to improve these scoring systems.

Disclosure statement

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References

[1] Sakane T, Takeno M, Suzuki N, et al. Behc¸et’s disease. N Engl J Med. 1999;341(17):1284–1291.
[2] Greco A, De Virgilio A, Ralli M, et al. Behc¸et’s disease: new insights into pathophysiology, clinical features and treatment options. Autoimmun Rev. 2018;17(6):567–575.
[3] Mendes D, Correia M, Barbedo M, et al. Behc¸et’s disease-a contemporary review. J Autoimmun. 2009;32(3–4):178–188.
[4] Evereklioglu C. Current concepts in the etiology and treatment of Behc¸et disease. Surv Ophthalmol. 2005;50(4):297–305.
[5] Zeidan MJ, Saadoun D, Garrido M, et al. Behc¸et’s disease physiopathology: a contemporary review. Auto Immun Highlights. 2016;7:4.
[6] Okada AA. Behc¸et’s disease: general concepts and recent advances. Curr Opin Ophthalmol. 2006;17:551–556.
[7] Namba K, Goto H, Kaburaki T, et al. A major review: current aspects of ocular behc¸et’s disease in Japan. Ocul Immunol Inflamm. 2015;23(Suppl 1):S1–S23.
[8] Kotake S, Ichiishi A, Kosaka S, et al. Low dose cyclosporin treatment for ocular lesions of Behc¸et’s disease. Nippon Ganka Gakkai Zasshi. 1992;96:1290–1294.
[9] Yoshida A, Kawashima H, Motoyama Y, et al. Comparison of patients with Behc¸et’s disease in the 1980s and 1990s. Ophthalmology. 2004;111(4):810–815.
[10] Kaburaki T, Araki F, Takamoto M, et al. Best-corrected visual acuity and frequency of ocular attacks during the initial 10 years in patients with Behc¸et’s disease. Graefes Arch Clin Exp Ophthalmol. 2010; 248(5):709–714.
[11] Kaburaki T, Namba K, Sonoda KH, et al. Behc¸et’s disease ocular attack score 24: evaluation of ocular disease activity before and after initiation of infliximab. Jpn J Ophthalmol. 2014;58(2):120–130.
[12] Keino H, Okada AA, Watanabe T, et al. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behc¸et’s disease on infliximab therapy. Br J Ophthalmol. 2011;95(9):1245–1250.
[13] Takeuchi M, Hokama H, Tsukahara R, et al. Risk and prognostic factors of poor visual outcome in Behc¸et’s disease with ocular involvement. Graefes Arch Clin Exp Ophthalmol. 2005;243(11):1147–1152.
[14] Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behc¸et’s syndrome. Ann Rheum Dis. 2018;77(6):808–818.
[15] Treusch M, Vonthein R, Baur M, et al. Influence of human recombinant interferon-alpha2a (rhIFN-alpha2a) on altered lymphocyte subpopulations and monocytes in Behc¸et’s disease. Rheumatology (Oxford). 2004;43(10):1275–1282.
[16] Okada AA, Keino H, Fukai T, et al. Effect of type I interferon on experimental autoimmune uveoretinitis in rats. Ocul Immunol Inflamm. 1998;6(4):215–226.
[17] Hamuryudan V, Moral F, Yurdakul S, et al. Systemic interferon alpha 2b treatment in Behc¸et’s syndrome. J Rheumatol. 1994;21:1098–1100.
[18] Kötter I, Zierhubt M, Eckstein AK, et al. Human recombinant interferon alfa-2a for the treatment of Behc¸et’s disease with sight threatening posterior or panuveitis. Br J Ophthalmol. 2003;87:423–431.
[19] Deuter CM, Zierhubt M, Möhle A, et al. Long-term remission after cessation of interferon-2-b treatment in patients with severe uveitis due to Behc¸et’s disease. Arthritis Rheum. 2010;62(9):2796–2805.
[20] Nakamura S, Yamakawa T, Sugita M, et al. The role of tumor necrosis factor-alpha in the induction of experimental autoimmune uveoretinitis in mice. Invest Ophthalmol Vis Sci. 1994;35(11):3884–3889.
[21] Dick AD, McMenamin PG, Korner H, et al. Inhibition of tumor necrosis factor activity minimizes target organ damage in experimental autoimmune uveoretinitis despite quantitatively normal activated T cell traffic to the retina. Eur J Immunol. 1996;26(5):1018–1025.
[22] Sartani G, Silver PB, Rizzo LV, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest Ophthalmol Vis Sci. 1996;37(11):2211–2218.
[23] Nakamura S, Sugita M, Tanaka S, et al. Enhanced production of in vitro tumor necrosis factor-alpha from monocytes in Behc¸et’s disease. Nippon Ganka Gakkai Zasshi. 1992;96:1282–1285.
[24] Stfikakis PP, Theodossiadis PG, Katsiaris CG, et al. Effect of infliximab on sight-threatening panuveitis in Behc¸et’s disease. Lancet. 2001;358(9278):295–296.
[25] Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behc¸et’s disease with refractory uveoretinitis. J Rheumatol. 2004;31:1362–1368.
