Original Article

Treatment of Behçet Uveitis in Türkiye

Pınar Çakar Özdal[1], Fatime Nilüfer Yalçındağ[2], Yasemin Özdamar Erol[3], Merih Soylu[4], İlknur Tuğal-Tutkun[5]

[1]University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
[3]University of Health Sciences Türkiye, Etlik City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[4]Private Eye Clinic, Adana, Türkiye
[5]İstanbul Bayrampaşa Eye Hospital, İstanbul, Türkiye

Abstract

Objectives: Behçet uveitis (BU) is a potentially blinding disorder. The main determinant of visual prognosis is early and appropriate treatment that provides rapid suppression of inflammatory attacks, control of subclinical inflammation, and prevention of new attacks. Our study aimed to determine the Turkish uveitis specialists' approach regarding the treatment choices and management of special situations such as pregnancy, vaccination, and surgical planning in BU patients, and to increase information sharing and raise awareness of issues where knowledge is lacking.

Materials and Methods: A web-based survey including 16 questions about the treatment approach in ocular involvement of Behçet's disease was sent via e-mail to uveitis specialists in Türkiye. Based on the answers of 49 ophthalmologists who responded to the survey, we evaluated the approaches of uveitis specialists in our country to initiating treatment, selecting therapeutic agents, monitoring, switching and stopping treatment, and special situations such as surgical planning, vaccination, and pregnancy in BU patients.

Results: Uveitis specialists in our country mostly act in accordance with the guidelines in the decision to start treatment, selection of therapeutic agents, and monitoring the safety of treatment in BU. However, there is a lack of information about the therapeutic approach in pregnancy and vaccination practices. It was also observed that there is no consensus on the precautions to be taken before cataract surgery.

Conclusion: Our study has shown that there is a need for more detailed and widespread information sharing on treatment in preparation for ocular surgery, safety monitoring, drug use during pregnancy, and vaccination in BU patients.

Keywords: Behçet syndrome, uveitis, therapeutics, vaccination, pregnancy

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Address for Correspondence: Pınar Çakar Özdal, University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
E-mail: pinarozdal@hotmail.com **ORCID-ID:** orcid.org/0000-0002-5714-7172
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Introduction

Behçet's disease (BD) is a systemic vasculitis of unknown etiology characterized by chronic and recurrent oral aphthous ulcers, genital ulcers, skin lesions, and ocular, gastrointestinal, and central nervous system involvement. Ocular involvement is the most common organ involvement of the disease.[1,2,3,4] Epidemiologically, a multicenter national database study conducted in our country revealed that Behçet uveitis (BU) is the most common non-infectious cause of uveitis, with a rate of 25%.[5] Ocular involvement is characterized by non-granulomatous panuveitis attacks and retinal vasculitis. Attack frequency and severity vary among individuals and are the main determinant of visual prognosis.[1,2,3,4,6,7]

Fluorescein angiography (FA) is the gold standard for the early detection and evaluation of BU-related posterior segment involvement. The presence of optic disc (OD) leakage, macular edema, vasculitis-related leakage and occlusion, ischemia, and neovascularization are decisive in the choice of treatment. Appropriate treatment is critical to prevent future complications related to ocular involvement of BD. The aim of treatment in BU is to rapidly suppress intraocular inflammation, prevent relapses, and achieve clinical and angiographic remission. In treatment, systemic corticosteroids (CS) should be used short-term in the acute period to rapidly control inflammation. The use of CS long-term or as monotherapy has no place in current BU treatment. The efficacy of conventional immunosuppressive (CIS) drugs and biologic agents has been demonstrated by clinical trials. The use of these agents varies according to disease course and attack

severity, and is the most important determining factor for visual prognosis.[1,2,3,4,6,8]

We conducted a web-based survey study to evaluate treatment approaches to BU patients among ophthalmologists following uveitis patients in our country.

Materials and Methods

A survey consisting of 16 multiple-choice questions was prepared by the executive board of the Uvea-Behçet Division of the Turkish Ophthalmological Association (TOA). Via the TOA, this survey was sent by email in March 2023 to ophthalmologists actively following uveitis patients and they were asked to respond online. The 16 questions in the survey included 6 questions evaluating treatment preferences in different clinical presentations of BU, 4 questions about and tests to be ordered and precautions to be taken before initiating anti-tumor necrosis factor-alpha (TNF-α) agents and CIS treatment, 1 question about vaccination while using anti-TNF-α agents, 3 questions about drug selection before and during pregnancy, 1 question evaluating the steps of treatment discontinuation in BU patients, and 1 question evaluating pre-cataract surgery planning in BU patients. The survey questions and the participants' responses can be found in the Appendix 1.

We evaluated the distribution of the participants' responses to each question to determine the approaches of uveitis specialists in our country to the treatment of BU.

Results

A total of 62 ophthalmologists were invited to participate in the survey, and responses were received from 49 (79%). Based on the distribution of their responses to the survey questions (see appendix), we determined the following:

For patients presenting with a first ocular attack without vitreous haze but with OD staining with or without peripheral retinal capillary leakage on FA, azathioprine (AZA) was the most preferred therapeutic agent, and in cases with peripheral leakage, adding oral CS to treatment was preferred. However, in cases of diffuse FA leakage, intravenous (iv) pulse CS was most commonly preferred (39%), and the combination of adalimumab (ADA) + AZA was the most preferred additional treatment to iv pulse steroid (25%).

In a patient with OD staining and peripheral retinal capillary leakage detected on routine follow-up FA while under AZA therapy, the most preferred treatment options were adding ADA (53%) or cyclosporine-A (CSA) (31%).

In a patient with a panuveitis attack and diffuse capillary leakage on FA while under combined AZA + CSA therapy, the most frequently preferred approach was to start iv pulse CS and anti-TNF-α therapy with ADA or infliximab (IFX) (71%). In addition, 24% of the specialists preferred adding an anti-TNF-α agent without CS, so the total rate of anti-TNF-α preference for such cases was 95%.

The leading approach to a patient who developed a posterior uveitis attack while under ADA therapy at the standard dose (40 mg injection at 2-week intervals) was to switch to weekly ADA administration (69%). Only 12% of the specialists preferred to switch the anti-TNF-α agent.

In terms of routine laboratory examinations before the initiation of immunosuppressive therapy, the examinations selected by the participants were complete blood count (100%), liver and kidney function tests (100%), hepatitis markers and human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA) (88%), QuantiFERON test (QFT) (73%), syphilis serology (67%), and brain magnetic resonance imaging (MRI) (4%). For patients to be started on anti-TNF-α, QFT was selected by all participants (100%) and brain MRI was selected by 31% of the participants. While the majority of the participants (69%) responded that anti-TNF-α safety monitoring should be performed at 3-month intervals, 31% selected the option to be perform it at 6-month intervals.

For patients with an indication for anti-TNF-α therapy but positive QFT and exclusion of active tuberculosis, 96% of the participants preferred to start anti-TNF-α with isoniazid prophylaxis.

The majority of the participants stated that tetanus, coronavirus disease 2019, hepatitis, and pneumococcal vaccines could be administered while under biologic therapy. The live vaccine options were also selected by 10-14% of the participants.

Regarding the treatment approach during pregnancy, the most preferred options for patients with a unilateral posterior uveitis attack were intravitreal dexamethasone implantation and ADA therapy. A quarter of the participants selected certolizumab pegol for patients who had an attack after week 20 of pregnancy. For a patient planning to become pregnant, more than 70% of the participants preferred to discontinue AZA and CSA therapy 3 months in advance, but would continue ADA therapy.

The most important factor in the decision to reduce systemic therapy was the absence of OD staining and retinal vascular/capillary leakage on FA, which was selected by 86% of the participants.

For a patient under combined anti-TNF-α and CIS therapy, 43% of the participants preferred to add oral CS before elective cataract surgery, 31% considered it sufficient to start topical CS, and 23% would make no change to treatment.

Discussion

This study reveals the approaches taken in the treatment of BU by Turkish ophthalmologists actively following uveitis patients. We observed that the respondents initiated immunomodulatory therapy in patients with posterior segment involvement. AZA was the first-choice immunosuppressive agent for mild involvement, while ADA was preferred as the anti-TNF-α agent in cases of more severe involvement or non-response to CIS therapy, and increasing the frequency of ADA administration was preferred in case of non-response to the standard ADA regimen. It was understood that most of the specialists adhered to national guidelines regarding preparation for and safety monitoring of biologic therapy.

Due to the high incidence of BD-related uveitis in Türkiye and the potential risk of blindness, it is important that the treatment approaches of ophthalmologists who actively follow uveitis patients in our country are standard and adhere to current guidelines and the official Health Practices Communique. In 2018, the European League Against Rheumatism (EULAR) published updated evidence-based recommendations for the management and treatment of BD.[9] According to these recommendations, AZA, CSA, interferon alpha, or monoclonal anti-TNF-α antibody therapy should be initiated in all Behçet's patients with involvement of the posterior segment of the eye. Systemic CS should only be used in combination with AZA or other immunosuppressive drugs. An acute, vision-threatening uveitis attack should be treated with high-dose CS, IFX, or interferon alpha, and in unilateral attacks, intravitreal bolus CS injection should only be administered in addition to systemic therapy.[9] According to an expert committee of the American Uveitis Society, monoclonal anti-TNF-α agents should be used as the first choice in the treatment of BU.[10] Interferon alpha was used in the treatment of BU in Türkiye in the 2000s, and publications reported successful results in the treatment of refractory BU.[11,12,13,14,15,16] However, it is no longer used since being withdrawn from the market in 2020. Therefore, interferon was not included as an option in the survey questions.

Monoclonal anti-TNF agents were introduced in the 2000s,[17] but until recently they were used as an off-label treatment regimen in patients who were unresponsive or intolerant to CIS and interferon therapy. In Türkiye, ADA has been licensed for use in the treatment of non-infectious uveitis involving the posterior segment, including BU, since December 2018. The licensed use of ADA may have played a role in its high selection rate in the survey responses.

Recognizing posterior segment involvement is of prognostic significance in BU. FA is considered the gold standard in the detection and monitoring of posterior segment inflammation in BU.[3,18] It is known that posterior segment involvement can be detected by FA in patients with no clinical signs of intraocular inflammation.[19] OD staining and fern-like retinal capillary leakage are the most common FA findings of BU.[1,2,3,4] In their FA study, Keorochana et al.[20] reported OD hyperfluorescence at a rate of 73% and diffuse vascular leakage in most eyes of patients with BU. In another study by Mamdouh et al.[21], subclinical uveitis activity was detected with FA in 52.1% of 23 eyes with inactive BU. Kabaalioglu Guner et al.[22] showed in their recent study including 162 eyes that 90 of them were clinically inactive but considered active according to FA findings. In a clinically quiet eye between attacks, OD staining and retinal capillary leakage observed on FA are the main signs of persistent subclinical inflammation. This suggests that systemic treatment is indicated or that the current systemic treatment is inadequate.[1,2,3,4,13,14,15] Therefore, these FA findings were specifically included in the survey questions.

It is noteworthy that in the evaluation of the respondents' treatment preferences in three different case scenarios presenting without clinically significant posterior segment involvement but with subclinical involvement on FA, treatment was selected according to the FA findings. AZA is still used as the first choice in cases with relatively mild involvement because its efficacy in the treatment of BD was demonstrated in a randomized controlled trial, and patients who start AZA early are known to have a better visual prognosis in long-term follow-up.[23,24] On the other hand, combined immunosuppressive or anti-TNF-α treatment regimens are selected in patients presenting with diffuse capillary leakage on FA or in patients with peripheral leakage while receiving AZA therapy. In case of attacks involving the posterior segment and diffuse leakage while under combined immunosuppressive therapy, administering iv pulse CS and starting an anti-TNF-α agent are most preferred. Markomichelakis et al.[25] reported that in the treatment of BU attacks, a more rapid effect was obtained with a single IFX infusion compared to intravitreal triamcinolone acetonide or iv pulse CS administration. However, Turkish specialists still prefer iv pulse CS for the treatment of attacks in patients planned to start anti-TNF-α therapy. In clinical practice, the fact that tests must be performed before initiating anti-TNF-α and obtaining the results takes a few days may also play a role in this preference. The participants' answers suggest that they consider the need for rapid and strong suppression of the BU attack. Nearly all (95%) of the specialists who participated in this study preferred to start anti-TNF-α in a BU patient with severe involvement, especially if observed to be resistant to conventional treatment. This approach is consistent with literature data demonstrating the efficacy of both IFX and ADA therapy in patients resistant to conventional drugs.[17,26,27,28,29,30]

If an attack is observed while using an anti-TNF-α agent, the agent should be switched to another anti-TNF or its dose and frequency should be adjusted.[31,32,33,34,35] In our survey, the most preferred approach to a patient who has an attack during standard-dose ADA therapy was to increase the frequency of ADA administration. It has been reported that increasing the ADA dose via weekly injections may be sufficient to control inflammation in cases of non-infectious uveitis or scleritis after primary or secondary failure of biweekly ADA therapy.[35,36]

Before initiating treatment with CIS or biologic agents, all patients should be evaluated in terms of complete blood count, liver and kidney function tests, systemic comorbidities such as hepatitis and tuberculosis, history of malignancy, pregnancy/breastfeeding, and immunization history.[4,37] The adverse effects of CIS drugs include myelosuppression and hepatonephrotoxicity.[37] The majority of specialists in our study seem to perform examinations in accordance with standard norms.

Anti-TNF-α drugs also have potential adverse effects such as causing demyelinating disease, predisposing to infection (tuberculosis, hepatitis B-C, and HIV), inducing autoantibody production, and increasing the risk of malignancy.[6,31,34,37,38,39,40,41,42,43] In a study evaluating the results of IFX therapy in patients with BU, Ohno et al.[39] reported a 0.3% rate of tuberculosis and less than 1% prevalence of lupus-like syndrome, demyelinating disease, and malignancies during the 2-year study period. In our country, the use of anti-TNF-α

is reported to increase the risk of tuberculosis by 10-20 times.[43] In ophthalmology practice, the QFT screening test is frequently used in the evaluation of tuberculosis. All participants in our study marked the QFT for the systemic examination to be performed before anti-TNF-α therapy. The risk of demyelinating disease is evaluated by brain MRI. In our study, approximately one-third of the specialists selected the brain MRI option. This rate may be related to the lack of routine MRI for neuro-BD in asymptomatic Behçet patients. However, screening for demyelinating disease is imperative in patients with idiopathic intermediate uveitis before starting anti-TNF-α therapy. It is interesting that a small number of specialists selected HLA-B51 and pathergy tests among the systemic evaluation options in our study, because it is known that HLA-B51 positivity has no place in the uveitis diagnosis algorithm or treatment selection, and the pathergy test is not a determinant of treatment in the pre-treatment evaluation.[6,7]

The regulation on the safety of anti-TNF drugs provides a "Drug Safety Monitoring Form" and specifies that monitoring with this form is required at 3-month intervals. In response to the question in our survey regarding how often this follow-up form should be repeated, 69.4% of the participants answered 3 months and 30.6% answered 6 months.

According to the algorithms in the national guideline for tuberculosis diagnosis and treatment, for patients planned to start anti-TNF-α who have positive QFT results and no active tuberculosis infection, it is recommended to initiate prophylactic isoniazid therapy and continue for 9 months, while starting combined anti-tuberculosis therapy is not recommended.[43] Consistent with this, 96% of the participants stated that anti-TNF-α treatment could be initiated with isoniazid in a patient with positive QFT but no active tuberculosis.

In patients receiving anti-TNF-α, non-live vaccines can be administered without needing to discontinue treatment. In addition, if the clinical picture is suitable, performing vaccination after interrupting ongoing immunosuppressive therapy long enough for the pharmacokinetic elimination of the drug increases the efficacy of the vaccine. It is not recommended to administer live vaccines (BCG, measles/mumps/rubella, varicella, oral polio, yellow fever, rotavirus) during anti-TNF-α therapy. When a live vaccine is necessary for a patient receiving immunosuppressive therapy, the benefits should outweigh the possible risks and treatment should be interrupted taking into account the duration of the microbe and the half-life of the drug, with the live vaccine administered after an appropriate time interval.[44,45,46] The fact that up to 14% of the participants in our study marked live vaccine options when asked which vaccines they prefer to administer without interruption of biologic therapy suggests that there is a lack of knowledge on this subject.

The use and management of CIS or anti-TNF-α drugs before and during pregnancy differ. Data on this subject are limited. The EULAR recommendations on the use of anti-rheumatic drugs in pregnancy advise carefully weighing the risk of harm to the fetus with treatment against the harm to mother and fetus without treatment, as well as involving other relevant branches such as rheumatology and gynecology in the treatment decision and obtaining the mother's informed consent. AZA, CSA, and tacrolimus are among the few agents that can be used for maintenance or attack suppression during pregnancy.[47] The 2020 American College of Rheumatology (ACR) guideline states that AZA is the safest CIS drug that patients with rheumatism and musculoskeletal system can use during pregnancy, while CSA and tacrolimus are recommended conditionally.[48] In both the EULAR and ACR recommendations, methotrexate, mycophenolate mofetil, leflunomide, and cyclophosphamide are listed as CIS agents that should not be used.[47,48] Guidelines on the use of anti-TNF-α in pregnancy indicate that ADA, IFX, and golimumab can be used in the first trimester, and certolizumab pegol can be used throughout pregnancy.[47,48,49,50] Certolizumab pegol, a monoclonal fragment antigen-binding "Fab" region antibody fragment, is the safest anti-TNF-α agent to use during pregnancy as it cannot cross the placenta due to its lack of the Fc segment.[47,48,49,50] In addition, intravitreal CS injections can be used as an adjunct agent during pregnancy, in unilateral cases, and in the presence of refractory macular edema.[6,51,52,53] In our study, intravitreal dexamethasone implant (51%) and ADA (32.6%) were the most preferred treatment preferences for a Behçet's patient in the first 20 weeks of pregnancy with bilateral ocular involvement but presenting with a unilateral uveitis attack, while intravitreal dexamethasone implant (34.7%), ADA (34.7%), and certolizumab pegol (25%) were selected for such patients at 21 weeks of pregnancy or later. These results suggest that further information is needed on the safety of certolizumab pegol in pregnancy. The most accurate and reliable approach is to schedule drug use in advance for patients planning to conceive. Guidelines recommend becoming pregnant during a period of rheumatological disease inactivity. In patients using AZA and CSA, discontinuing treatment is recommended 3 months before pregnancy planning. Discontinuing ADA and IFX is not recommended according to the guidelines.[47,48,49,50] While most participants did not consider it necessary to discontinue ADA therapy, they stated that they would discontinue AZA and CSA treatment 3 months in advance.

In BU patients, a relationship between FA findings and visual prognosis and increased risk of recurrent uveitis attacks in the presence of persistent angiographic leakage have been demonstrated.[20,54] Clinical remission is not sufficient in the decision to terminate treatment. Remission is said to be complete if a "dry angiogram" is obtained; i.e., there is no staining of the OD or retinal vascular/capillary leakage on FA.[4,8,55] The high selection rate of the angiographic remission condition in the survey question about the decision to terminate treatment indicates that the specialists take the right approach in this regard.

Cataract development is one of the most common complications seen in BU, reported at rates of 31-77% in large series.[56,57,58,59] When planning cataract surgery in Behçet's patients, issues of concern are the possibility that visual acuity may not increase in eyes with permanent structural damage in the posterior segment, and the risk of developing severe

postoperative inflammation and triggering a uveitis attack. It has been reported that Behçet's patients have good cataract surgery outcomes, provided that preoperative inflammation is well controlled.[60,61,62,63,64,65] A meta-analysis study examining the results of uveitic cataract surgery indicated that visual results were worse in eyes with active inflammation during surgery and highlighted the importance of controlling inflammation for more than 2 months preoperatively.[66] Matsuo et al.[63] reported that a history of uveitis attack within 1 year preoperatively in Behçet's patients was associated with risk of postoperative attacks, so the disease should be inactive for at least 6 months preoperatively. The questions in our survey provided no specific information about preoperative attack history or duration of remission; only the preoperative prophylaxis approach was questioned for a patient who was in remission under combined biologic and immunosuppressive treatment regimen and not receiving CS. Although several studies have reported the use of perioperative iv, oral, topical, or intravitreal CS in uveitic cataract surgery, there is no standard prophylaxis protocol.[67,68] It is reported to be safe to perform cataract surgery within one week after the last IFX infusion in Behçet's patients who are in remission under the IFX treatment regimen, with no need for another prophylactic approach.[60,61] In our study, 22% of the participants did not consider any prophylaxis necessary in a patient receiving anti-TNF-α and immunosuppressive therapy, while 43% deemed it necessary to initiate oral steroids and 31% topical steroids. These results show that there is no standard approach.

Study Limitations

One of the most important limitations of our study is that the ophthalmologists participating in the survey were of different seniority, so their experiences with uveitis differed. Another limitation is that the clinical vignettes created for the survey do not include all possible scenarios. Furthermore, the survey questions were multiple-choice, and the respondents were not given the opportunity to give different answers. Therefore, the results obtained may not represent a general approach.

Conclusion

The management and treatment of BU pose serious challenges due to the different clinical aspects. Despite the rapid development of new imaging methods in recent years, FA remains the gold standard in the diagnosis, treatment selection, and follow-up of the disease. Treatment options should be determined according to the patient's general health status and the severity of their clinical findings. Although previously our goal in treatment was to suppress attacks and provide clinical remission, thanks to current biologic agents, our goal is now to prevent attacks by suppressing subclinical inflammation and to achieve a permanent remission in which vision is preserved. Whether clinical or subclinical, posterior segment involvement is an absolute indication for the initiation of immunosuppressive therapy in BU. The visual prognosis can be markedly improved by starting directly with biologic agents in severe cases, switching to biologics in cases unresponsive to CIS agents, changing biologic agents when necessary, and waiting for a period of uveitis inactivity for all surgical procedures except emergencies. Determining the treatment approaches of Turkish uveitis specialists will make it possible to increase their awareness about the early initiation of biologic agents in BU and to share the knowledge and experience that will enable better management of BU patients. This study showed that more detailed and widespread information sharing is needed on the topics of CIS and anti-TNF-α therapy preparation, safety monitoring, drug use during pregnancy, vaccination, and surgery in BU.

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Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Authorship Contributions

Concept: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Design: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Data Collection or Processing: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Analysis or Interpretation: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Literature Search: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y., Writing: P.Ç.Ö., Y.Ö.E., M.S., İ.T-T., F.N.Y.

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