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# Therapeutic Outcomes of Interferon-Alpha-2a Treatment in Behçet Uveitis

## Behçet Üveitinde İnterferon-Alfa-2a Tedavisi Sonuçları

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**ABSTRACT Objective:** To evaluate the efficacy and safety of interferon-alpha-2a (IFNα-2a) therapy in patients with Behçet uveitis. **Material and Methods:** The patients who were treated with IFNα-2a therapy due to Behçet uveitis refractory to conventional immunosuppressive therapies were evaluated retrospectively. The visual acuities, activity of ocular inflammation were recorded at each visit during the follow-up and ocular and systemic side effects were also monitored. The paired sample t-test was used in comparison of pre- and post-IFNα-2a visual acuity values. **Results:** Twenty-five patients (23 males and 2 females) with refractory Behçet uveitis were included in this study. The average patient age at the time of diagnosis was 28.96±7.56 years. The mean follow-up period after the initiation of IFNα-2a therapy was 18.16±12.12 months. The mean best corrected visual acuity (BCVA) at the last visit before IFNα-2a therapy was 0.48±0.32 in the right eye and 0.44±0.38 in the left eye. At the end of follow-up, the mean BCVA was 0,61 ± 0.36 in the right and 0.60 ± 0.38 in the left, which improved with IFNα-2a therapy in both eyes (p=0.010, p=0.003; respectively). The mean number of uveitis attacks per year was 2.74±0.96 before the IFNα-2a therapy. During the IFNα-2a therapy period, mean 1.17 uveitis attacks per year were observed in 6 patients. The complete or partial remission was achieved in 22 (88%) patients with IFNα-2a treatment. The IFNα-2a therapy was discontinued due to complete remission in 5 (20%) patients during follow-up. In 3 patients (treatment failure in 2 and progressive weight loss in 1), switch to anti-tumor necrosis factor was recommended. **Conclusion:** Interferon alpha-2a treatment is an effective and safe treatment option in Turkish population with Behçet uveitis refractory to conventional immunosuppressive therapies.

**Keywords:** Behçet disease; Behçet uveitis; interferon-alfa 2a; refractory uveitis

**ÖZET Amaç:** Behçet üveiti olgularında interferon-alfa-2a (IFNα-2a) tedavisinin etkinliği ve güvenirliliğini değerlendirmek. **Gereç ve Yöntemler:** Konvansiyonel immünsüpresif tedavilere dirençli Behçet üveiti nedeniyle IFNα-2a tedavisi alan olgular retrospektif olarak değerlendirildi. Görme keskinlikleri, oküler inflamasyon aktivitesi takip süresi boyunca her vizitte kaydedildi ve aynı zamanda oküler ve sistemik yan etkiler de takip edildi. İnterferon-alfa-2a öncesi ve sonrası görme keskinliği değerlerinin karşılaştırılmasında eşleştirilmiş örnek t-testi kullanıldı. **Bulgular:** Refrakter Behçet üveiti olan 25 olgu (23 erkek- 2 kadın) çalışmaya dahil edildi. Olguların ortalama tanı yaşı 28,96±7,56 yıl idi. Olguların IFNα-2a tedavisi başlangıcı sonrası ortalama takip süreleri 18,16±12,12 ay idi. İnterferon-alfa-2a tedavisi öncesi son vizitteki ortalama en iyi düzeltilmiş görme keskinliği (EİDGK) sağ gözde 0,48±0,32 ve sol gözde 0.44±0.38 idi. Takip süresi sonunda olguların EİDGK değerleri, IFNα-2a tedavisi ile her iki gözde de artış göstererek, sağ gözde 0,61±0,36, sol gözde 0,60±0,38'e ulaştı (sırasıyla; p=0,010, p=0,003). İnterferon-alfa-2a tedavisi öncesi olgularda ortalama 2,74±0,96 /yıl üveit atağı izlendi. İnterferon-alfa-2a tedavisi boyunca, 6 hastada ortalama 1,17/yıl üveit atağı izlendi. İnterferon-alfa-2a tedavisi ile 22 olguda (%88) tam veya kısmi remisyon sağlandı. Beş olguda (%20) IFNα-2a tedavisi tam remisyona ulaşıldığı için kesilerek takiplere devam edildi. Üç olguya (2 olgu tedavi yetersizliği, 1 olgu ilerleyici kilo kaybı nedeniyle) anti-tümör nekrozis faktör tedavisine geçiş önerildi. **Sonuç:** Konvansiyonel immünsüpresif tedavilere dirençli Behçet üveiti olan Türk popülasyonunda, IFNα-2a tedavisi etkili ve güvenilir bir tedavi seçeneğidir.

**Anahtar Kelimeler:** Behçet hastalığı; Behçet üveiti; interferon-alfa 2a; refrakter üveit.

Behçet disease (BD) was first described by Hulusi Behçet in 1937 and he described oral ulcer, genital ulcer, and uveitis as the classic triad.[1] Behçet disease is an idiopathic, chronic, multisystem inflammatory disease with a relapsing-remitting episode.[2-5] Behçet disease is most commonly found in the Far East, Middle East, and Mediterranean area, corresponding to the old Silk Route and is endemi-

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cally higher in Turkey.[2] Ocular involvement frequency of BD is reported between 25-96% and; it can be the first sign of the disease in 10-20% of cases.[3] Bilateral non-granulomatous panuveitis and retinal vasculitis are the main ocular manifestations of BD.[4,5]

In posterior involvement of ocular BD, azathioprine (AZA), cyclosporin-A (CsA), interferon alpha-2a (IFNα-2a) or monoclonal anti-tumor necrosis factor antibodies (anti-TNFα) should be preferred as treatment options according to 2018 European League Against Rheumatism (EULAR) recommendations.[6] Conventional immunosuppressive therapies are the first choice for ocular involvement of BD. Combined AZA and CsA therapy is more effective than monotherapy, but patients who do not respond to combined therapy are also frequently seen.[5]

Interferon alpha-2a and other biological agents including anti-TNFα therapy are good options in the treatment of BD uveitis refractory to conventional therapies.[7] Recently, patients with an initial or recurrent visual-threatening uveitis attacks are recommended to be treated with high-dose glucocorticoids, anti-TNFα or IFNα-2a.[6] The experience with the use of these agents in BD has increased significantly in recent years. Although there are many studies on these agents, the long-term efficacy and tolerability of these agents is still a question to be answered.[8-10]

The purpose of this study is to report the efficacy and tolerability of IFNα-2a therapy in Turkish patients with refractory Behçet uveitis.

## MATERIAL AND METHODS

We reviewed the medical records of consecutive 25 patients with posterior uveitis due to BD who had been treated with IFNα-2a between January 2011 - June 2018 in Beyoglu Eye Research and Training Hospital. The ethical aspect of this study was approved by the Ethics Committee of Okmeydani Research and Training Hospital (1123/ 05.02.2019). The study protocol was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained for all patients.

The patients with less than 6 months follow-up period and the patients with irregular follow-up were excluded from the study.

The diagnosis of the patients was made according to 'International Study Group for Behçet Disease Criteria'.[11] Patients were systematically followed in uveitis department in our tertiary institution. All patients were initially treated with conventional immunosuppressive therapy combined with corticosteroids before IFNα-2a treatment. Systemic therapy was started with using corticosteroids (methylprednisolone, 1 mg/kg/day) in combination with AZA (2-3 mg/kg per day) and/or CsA (3–5 mg/kg per day). If the dual combination was not enough, as a third-line treatment, a triple combination of corticosteroid, AZA and CsA was initiated. When these therapies were not efficacious to control inflammation or any serious side effect was observed, medications were replaced to IFNα-2a (Roferon-A®; Roche Pharmaceuticals, Whitehouse Station, New Jersey, US) treatment. All other systemic immunomodulatory agents were discontinued and the dose of corticosteroids reduced under 10 mg/day, one day before the initiation of IFNα-2a treatment. IFNα-2a treatment was initiated subcutaneously with a dose of 6 MIU/day for 7-10 days according to disease resolution. All patients were warned and also were given paracetamol for flu-like symptoms. After remission induction period, dose of IFNα-2a was tapered down to 3 MIU per day and it was further tapered to every other day and then once in three days according to individual manifestations and laboratory. All patients were examined 10 days after IFNα-2a initiation, at the 4th week, and then every 4-6 weeks. A routine ophthalmologic examination (best corrected visual acuity (BCVA) via Snellen chart, biomicroscopy, tonometry, fundus examination) and optical coherence tomography (OCT) performed at every visit. Fundus fluorescein angiography (FFA) and digital color fundus photographs were performed at least once and when reducing or discontinuing IFNα-2a, and also whenever necessary in all patients. The complete blood count and the routine biochemical profile were performed at each visit. Systemic side effects and ocular relapses were recorded. When IFNα-2a was ineffective or intolerable adverse events were observed, therapy was switched to anti-TNFα (after loading dose; every other week, subcutaneous 40 mg Adalimumab).

The ocular signs and symptoms of patients and the findings obtained from FFA and OCT were evaluated, and their characteristics such as age, gender, age of the diagnosis of BD, features and activity of ocular inflammation, previous treatments and their duration, the initiation time of IFNα-2a therapy, the reason for transition to IFNα-2a therapy, the average number of uveitis attacks per year before and after IFNα-2a treatment were recorded. The BCVA values of patients at the time of diagnosis at the last visit before IFNα-2a treatment, the maximum BCVA values achieved by IFNα-2a therapy, and the final BCVA values after IFNα-2a were recorded.

The program of IBM SPSS Statistics v20 was used for statistical analysis. Descriptive statistics were given as mean±standard deviation (SD) and n (%). After evaluating the normality of the data with the Shapiro-Wilk test; the paired sample t-test was used to compare dependent numerical measurements such as pre- and post-IFNα-2a visual acuity values. If $p<0.05$, the difference between values was considered statistically significant.

## RESULTS

25 patients (23 males and 2 females) with Behçet uveitis treated with IFNα-2a were included in this study. The average age of patients at the time of diagnosis was 28.96 ± 7.56 years. The mean follow-up duration was 38.12 ± 23.02 months. IFNα-2a therapy was started at a mean 16.79 ± 13.19 months after the first line treatment, and the patients were followed for an average of 18.16 ± 12.12 months under the IFNα-2a therapy.

The initial BCVA was 0.34 ± 0.32 in the right eye and 0.44 ± 0.36 in the left eye. The mean BCVA before IFNα-2a therapy was 0.48 ± 0.32 in the right eye and 0.44 ± 0.38 in the left eye. The best BCVA was achieved after a median of 4.2 months of IFNα-2a therapy and was found to be 0.68 ± 0.32 in the right eye and 0.70 ± 0.34 in the left eye. The final BCVA was 0,61 ± 0.36 in the right eye and 0.60 ± 0.38 in the left eye. The BCVA improved at the final visit in both eyes compared to the period before IFNα-2a therapy (p= 0.010, p= 0.003; respectively) (Table 1). BCVA improved or remained unchanged in all patients except for 3 eyes of 3 patients during the follow-up period.

The mean number of uveitis attacks per year was 2.74 ± 0.96 before the IFNα-2a therapy. After IFNα-2a therapy, mean 1.17 uveitis attacks per year were observed in 6 patients.

All of the patients had bilateral eye involvement. Before the treatment of IFNα-2a, 6 patients (24%) had unilateral and 17 patients (68%) had bilateral anterior uveitis. There was no anterior segment involvement in 2 patients (8%). All patients had vitritis (bilateral in 23 patients, unilateral in 2 patient). Eleven patients (44%) had bilateral retinitis, and 10 patients (40%) had unilateral retinitis. Except one, vasculitis was observed by FFA in all patients (bilateral in 22 patients (88%), unilateral in 2 patients (8%)). Thirteen patients (52%) were evaluated as bilateral panuveitis and 7 patients (28%) were evaluated as unilateral panuveitis. Bilateral in 11 patients (44%) and unilateral in 7 patients (28%) cystoid macular edema accompanied other uveitis findings. Bilateral hyperfluorescence of the optic disc was observed in 15 patients (60%) by FFA. At the same time, neovascularization was detected in 3 eyes (12%).

The reasons for the transition to IFNα-2a treatment were the previous treatment-related complications in 7 (28%) patients and the non-response to previous treatments in 18 (72%) patients. During the follow-up period, patients received mean 903.18 MIU IFNα-2a.

After IFNα-2a treatment, 19 (76%) patients were in remission without any relapse. In 2 out of the other 6 patients, uveitis attack occurred due to irregularity in the patient's drug use. In 2 out of 6 patients, the dose of IFNα-2a was increased and the uveitis attack

**TABLE 1:** Visual acuity changes in patients with IFNα-2a treatment.

| Mean BCVA | Before IFNα-2a therapy | Final visit | p value |
|---|---|---|---|
| Right eye | 0.48 ± 0.32 | 0,61 ± 0.36 | 0.010* |
| Left eye | 0.44 ± 0.38 | 0.60 ± 0.38 | 0.003* |

BCVA: Best corrected visual acuity (via Snellen chart), IFNα-2a: Interferon alpha-2a.
*: Statistically significant difference (p<0.05), p values based on paired sample t-test.

was controlled. Two were considered to be unresponsive to treatment and the switch to anti-TNF was recommended. When the reason for initiation IFN treatment of these 6 patients who had attacks with IFN therapy was investigated; it was noted that 3 patients switched to IFN therapy due to unresponsiveness to conventional immunosuppressive therapy; the other 3 patients due to side effects caused by the previous therapy.

IFNα-2a treatment was discontinued due to complete remission in 5 (20%) patients during follow-up. In these patients, IFNα-2a treatment was stopped after an average of 17.56 ± 6.12 months. All of these patients had sustained remission after discontinuation of treatment, and the patients were followed up for an average of 14.2 ± 8.84 months (range 8-27 months) without medication.

The IFNα-2a dose of 17 patients who continued to use IFNα-2a ranged from 3 MIU once every 2 days to 3MIU two days per week.

When all patients were evaluated, IFNα-2a treatment was considered successful in 22 (88%) patients. The transition to anti-TNF treatment was recommended for the other 3 patients (2 treatment failure, 1 weight loss).

All patients experienced flu-like symptoms. Eight (32%) patients had other complications related to IFNα-2a treatment. Lymphopenia in 3 (12%) patients, weight loss in 2 (8%) patients, abnormally high liver function parameters in 2 (8%) patients and mild depression in 1 (4%) patient were observed. With the exception of a patient with weight loss, treatment did not have to be discontinued due to these complications.

During follow-up period, epiretinal membrane (ERM) in 3 (12%) patients, steroid-induced glaucoma in 2 (8%) patients, macular hole (MH) in 2 (8%) patients, branch retinal vein occlusion in 2 (8%) patients, cataract in 1 (4%) patient, and steroid induced glaucoma with ERM in 2 (8%) patients were observed. Surgical methods were used to treat these ocular complications in 5 (20%) patients. One patient underwent phacoemulsification surgery, one patient underwent trabeculectomy due to steroid induced glaucoma, 2 patients underwent pars plana vitrectomy (PPV) due to MH and ERM and 1 patient underwent both PPV and trabeculectomy surgeries due to steroid induced glaucoma with ERM.

## DISCUSSION

Behçet uveitis is a serious condition that can cause permanent vision loss and ocular damage in the young population. The etiopathogenesis of BD is still not well known, but it is clearly related to T-cell regulation.[12] Numerous cytokines including interleukin-2 (IL-2), IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, IFN-γ, and TNF-α are associated with the disease. Several therapeutic options are aimed to suppress or modulate these cytokines to treat BD.[13,14] Interferon-alpha-2a is the oldest biological agent used in the treatment of Behçet uveitis since the early 1980s and has shown beneficial effects on controlling the ocular inflammation.[14] Interferon-alpha-2a is a promising drug in patients with Behçet uveitis who cannot be controlled by conventional therapies or in patients experiencing side effects due to these treatments and, its positive effect in these cases has also been demonstrated by several studies.[8-10,14-16]

Kötter et al. reported a response rate of 92% to IFN-α-2a in Behçet uveitis.[17] Tugal-Tutkun et al. followed partial or complete response in 91% of the cases.[16] In the study of Kavandi et al., the response to treatment was reported as 83.3%.[15] Again, Krause et al. reported the rate of response to treatment as 78%, while Yalcindag et al. reported it as 83%.[18,19] In this study, this rate was determined as 92%.

Tugal-Tutkun et al. followed the patients for 24 months after discontinuing treatment and reported complete remission in 20% of the patients.[16] The complete remission rate was reported as 58.3% in the study by Kavandi et al. and 60% in the study by Yalcindag et al.[15,19] In this study, we observed a complete remission rate of 20%. Although these patients were followed for an average of 14.2 months after discontinuing IFNα-2a, no recurrence was observed without medication.

The positive effect of the IFNα-2a treatment on the visual acuity has been shown in many studies. Stable or improved visual acuity was reported as 97% in a study by Tugal-Tutkun et al., as 92% in a study

by Krause et al., as 100% in a study by Yalcindag et al., as 97% in a study by Kötter et al. In this study, BCVA improved or was stable in 47 (94%) eyes of total 50 eyes after IFNα-2a therapy when compared with pre-IFNα-2a period.[16-19]

There was a statistically significant improvement in the BCVA values when compared with the last visit before the IFNα-2a therapy and the final visit after IFNα-2a therapy ($p<0.05$). This result was consistent with the study of Tugal-Tutkun et al.[16]

There is still no consensus about the initial dose, despite the efficacy of IFNα-2a therapy shown in previous studies. Kavandi et al., Tugal-Tutkun et al. and Kötter et al. started treatment with 6MIU dose as in our study.[15-17] Furthermore, Hasanreisoglu et al. and Yalcındag et al. preferred 4.5 MIU as the initial dose of the treatment.[19,20] In addition, Onal et al. and Lee et al. began treatment with lower doses such as 3MIU and found the efficacy to be similar with high dose.[21,22] Further study is required to determine the appropriate starting dose and treatment protocol for IFNα-2a.

The reported adverse effects of IFNα-2a use for Behçet uveitis include a flu-like syndrome (100%), redness at the injection site (100%), leukopenia (40%), alopecia (24%), and depression (8%).[17] In previous studies, flu-like symptoms have been reported as the most common side effect of IFNα-2a. Yalcındag et al., Tugal-Tutkun et al. and Hasanreisoglu et al. also observed this side effect in all cases similar to this study.[16,19,20] Leukopenia rates were reported to be 14-40% in different studies.[16,17,23] However, studies with lower doses of IFNα-2a reported lower rates of side effects.[21,22] In this study, flu-like symptoms was observed in all patients (100%) and leukopenia was the second most common complication in 12% of the patients. The other adverse effects were abnormally high liver function parameters (8%), weight loss (8%) and depression (4%). Leukopenia and high liver function parameters have been reversible with dose adjustment. The case of depression was consulted to the psychiatrist and was evaluated mild depression. The dosage of the treatment was reduced in this patient who has been in remission, after dose adjustment there was no need to discontinue therapy. In an adolescent patient, IFNα-2a treatment was discontinued due to excessive weight loss. Although only one of our patients had to discontinue treatment due to side effects, we recommend following the patients closely and adjusting the dose of treatment for side effects.

The limitations of this study were the retrospective nature of the study and the low number of patients.

## CONCLUSION

Interferon alpha-2a is an effective and safe option for treatment in Turkish patients with Behçet uveitis who are resistant to conventional treatment and who cannot use conventional treatment due to side effects. In addition, the positive effect on the visual acuity is the major advantages of this treatment. Further study is needed to fully understand the efficacy and safety of IFNα-2a therapy and to determine the appropriate treatment protocol for Turkish patients with Behçet uveitis.

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### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Burcu Kemer Atik, Çiğdem Altan;* ***Design:*** *Burcu Kemer Atik, Berna Başarır;* ***Control/Supervision:*** *Berna Başarır, Çiğdem Altan;* ***Data Collection and/or Processing:*** *Burcu Kemer Atik;* ***Analysis and/or Interpretation:*** *Burcu Kemer Atik;* ***Literature Review:*** *Burcu Kemer Atik;* ***Writing the Article:*** *Burcu Kemer Atik, Çiğdem Altan;* ***Critical Review:*** *Çiğdem Altan, Berna Başarır;* ***References and Fundings:*** *Çiğdem Altan;* ***Materials:*** *Berna Başarır.*

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