Long-term Efficacy and Safety of Low-Dose and Dose-Escalating Interferon Alfa-2a Therapy in Refractory Behçet Uveitis

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Objective: To investigate the long-term efficacy and safety of low-dose and dose-escalating therapy of interferon alfa-2a in the treatment of Behçet uveitis.

Methods: This study included 37 patients with refractory Behçet panuveitis unresponsive to conventional immunosuppressive therapy. Induction interferon alfa-2a therapy was given as a daily dose of 3.0 million IU (MIU) subcutaneously for 14 days. Maintenance dose was achieved with 3.0 MIU 3 times per week given subcutaneously. The dosage was increased sequentially to 4.5, 6.0, and 9.0 MIU 3 times per week if uveitis relapses occurred. Total therapy duration was 24 months. Primary outcome measure was control of uveitis with quiescence during maintenance therapy. Ocular relapses per patient-year before and after initiation of interferon alfa-2a therapy and a corticosteroid-sparing effect were secondary outcomes. We also estimated the rate of remission after discontinuing interferon alfa-2a therapy.

Results: During maintenance therapy, interferon alfa-2a controlled uveitis in 35 patients (95%). In 15 patients (41%), a maintenance dosage of 3.0 MIU 3 times per week controlled uveitis without any relapse. The rate of uveitis relapses decreased from 3.52 per patient-year before to 0.75 per patient-year after initiating interferon alfa-2a therapy. Seventeen patients were receiving systemic corticosteroids at the time of initiation of interferon therapy. During the maintenance stage, 9 patients were able to discontinue and 8 to taper systemic corticosteroid therapy. Survival analysis estimated that the rate of remission after discontinuation of interferon alfa-2a therapy was 76% by 3 months. The rate of remission remained stable thereafter.

Conclusion: A treatment protocol using a low-dose and dose-escalating therapy with interferon alfa-2a was able to control and achieve remission of uveitis in most patients with refractory ocular Behçet disease.


Behçet Disease (BD) is a multisystem vasculitis of unknown etiology, affecting arteries and veins of all sizes. Ocular involvement is characterized by a bilateral intraocular inflammation mostly affecting the posterior segment of the eye as panuveitis and retinal vasculitis. It has a relapsing-remitting course. Recurrent episodes of intraocular inflammation may eventually lead to blindness. Prognosis for eye disease in BD has improved substantially with the use of conventional immunosuppressive agents such as azathioprine sodium and/or cyclosporine. However, despite aggressive treatment with conventional immunosuppressive agents, some patients still experience relapses of uveitis. Refractory and sight-threatening uveitis in this particular group of patients with BD is challenging for the ophthalmologist.

In recent years, biologic agents have become popular in the management of inflammatory eye disease. Interferons are a group of cytokines that include interferon alfa-2a. To date, there are several reports on the use of interferon alfa-2a in the treatment of patients with Behçet uveitis refractory to conventional immunosuppressive agents. Some authors also reported on the use of interferon alfa-2a in other refractory and sight-threatening uveitis entities. However, there is no consensus about the ideal dose and duration of treatment for Behçet uveitis. In addition, adverse effects, including development of autoantibodies, thyroid hormone disturbances, severe depression, and leukopenia, have been reported as frequent and some as dose dependent. The occurrence of adverse effects with a higher-dose regimen may limit the use of the agent. Therefore, use of a low-dose regimen would also be expected to have fewer adverse effects. We report herein the long-term efficacy of interferon alfa-2a in the treatment of Behçet uveitis when using the...
minimally effective dose of interferon alfa-2a through a low-dose and dose-escalating regimen in patients otherwise unresponsive to conventional immunosuppressive therapy.

**METHODS**

A total of 37 patients with severe, refractory, sight-threatening uveitis due to BD were recruited into this prospective study from December 1, 2005, to April 30, 2010. Refractory and sight-threatening uveitis due to BD was defined as the presence of intraocular inflammation involving the posterior segment in the form of posterior uveitis or panuveitis and failing to respond to 1 or more conventional immunosuppressive agents. Patients with posterior or panuveitis due to BD who did not tolerate conventional immunosuppressive agents or in whom their use was contraindicated also started interferon alfa-2a therapy (Roferon-A; Roche Pharmaceuticals, Whitehouse Station, New Jersey). Patients with documentation of past immunosuppressive therapy and no control of intraocular inflammation before presentation were also accepted as having uveitis refractory to treatment.

A new treatment protocol that aimed to use a minimal dose of interferon alfa-2a was adjusted before the initiation of the study. Schematic illustration of the treatment protocol is shown in **Figure 1**. Other treatments with immunosuppressive agents, except for corticosteroids, were discontinued the day before the initiation of interferon alfa-2a therapy. The treatment protocol also included premedication with acetaminophen (paracetamol), 500 mg 4 times per day, and antihistamines during the induction of interferon alfa-2a therapy. For the induction of interferon alfa-2a therapy, the drug was given subcutaneously at a dosage of 3.0 million IU (MIU) per day for 14 days. A maintenance dose of interferon alfa-2a was achieved with subcutaneous administration of 3.0 MIU 3 times per week. During maintenance therapy, oral corticosteroid therapy was tapered to no more than 10 mg/d prednisone equivalent or, ideally, discontinued whenever control of intraocular inflammation was achieved. Any relapse of uveitis required an increase in the dose of interferon alfa-2a. After control of intraocular inflammation was achieved, the dosage of systemic corticosteroids was again rapidly tapered to a maximum of 10 mg/d prednisone equivalent or discontinued.

Patients with BD who fulfilled the criteria established by the International Study Group for Behcet’s Disease12 and met the inclusion criteria were included in the study. A complete medical history, including onset of ocular and systemic symptoms, was obtained at the start. All patients underwent complete ophthalmological examinations, along with complete blood cell count, liver function test, and evaluation of blood urea nitrogen and serum creatinine levels at the initiation of the treatment. These variables were reviewed at 6-week intervals in patients who showed control of intraocular inflammation with quiescence. Otherwise, these variables were evaluated as dic-

![Figure 1. Flowchart for induction and maintenance therapy with interferon alfa-2a. MIU indicates million international units.](https://example.com/figure1.png)
A total of 37 patients were included in the study. Median age at presentation was 29 (range, 18-52) years. Eleven patients (30%) were female and 26 (70%) were male. All patients were of white Turkish ethnicity. The characteristics of patients, extraocular manifestations, associated medical conditions, previous immunosuppressive therapies, number of previous methylprednisolone infusions, and total follow-up are given in Table 1.

Table 2 and Table 3 provide the ocular clinical features of the patients and outcomes of interferon alfa-2a therapy. Ocular involvement was bilateral in 31 patients (84%) and unilateral in 6 (16%), with a total of 68 eyes undergoing treatment. All patients had panuveitis that was characterized by retinal vasculitis in 29 patients (78%), retinitis in 30 (81%), vitritis in 37 (100%), papillitis in 8 (22%), and cystoid macular edema in 23 (62%). Of the 46 eyes with retinal vasculitis, 12 (26%) had vasoocclusive features revealed by fluorescein angiography as the presence of areas of capillary nonperfusion.

As seen in Table 3, the median duration of follow-up before recruitment was 6 (range, 1-69) months. The median exposure to interferon alfa-2a was 21 (range, 2-24) months, with a median duration of follow-up after interferon alfa-2a was 21 (range, 2-77) months. The primary outcome measure was control of intraocular inflammation with quiescence during interferon alfa-2a maintenance therapy using the described protocol. The rate of ocular relapses per patient-year before and after initiation of interferon alfa-2a therapy was reported as a secondary outcome. The ability to taper systemic corticosteroid therapy, with no more than a 10-mg/d prednisone equivalent dosage being considered as a successful taper, was also reported as a secondary outcome. Unexpected complaints and complications were recorded as adverse effects. The ability to maintain remission after discontinuation of therapy was determined by using survival analysis. The Kaplan-Meier method was used to estimate the survival curve.

The study was approved by the ethics committee of the School of Medicine, Marmara University, and conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

### RESULTS

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months. With the protocol, interferon alfa-2a therapy controlled intraocular inflammation with achievement of quiescence in 35 of 37 patients (95%) (Figure 2). In 15 patients (41%), a maintenance interferon alfa-2a dosage of 3.0 MIU 3 times per week controlled inflammation without any relapse. Relapse of inflammation occurred in 22 patients (59%) requiring an increase in the dose of interferon alfa-2a during maintenance therapy. As described, the dose of interferon alfa-2a was increased for each uveitis relapse that occurred during maintenance therapy. The final maintenance dosage to achieve quiescence was 9.0 MIU 3 times per week in 3 patients (8%), 6.0 MIU 3 times per week in 8 (22%), and 4.5 MIU 3 times per week in 9 (24%). The 2 patients who experienced uveitis relapses despite a maintenance interferon alfa-2a dosage of 9.0 MIU 3 times per week switched to infliximab therapy.

Of the remaining 35 patients, 13 completed the predetermined total of 24 months of therapy. Discontinuation of interferon alfa-2a therapy resulted in remission in 10 patients (77%). The median duration of remission of Behçet uveitis after the termination of interferon alfa-2a therapy was 12 (range, 3–35) months. Three patients had a relapse of uveitis after discontinuation of therapy and restarted interferon alfa-2a therapy. Reinstitution of interferon alfa-2a therapy at a dosage of 3.0 MIU 3 times per week controlled intraocular inflammation with quiescence in all patients. Kaplan-Meier survival analysis estimated the rate of remission after discontinuation of interferon alfa-2a therapy as 84% by 1.5 months and as 76% by 3 months. The rate of remission remained stable thereafter.

Eighteen patients continue to receive interferon alfa-2a therapy with control of their uveitis. Two patients discontinued interferon alfa-2a therapy themselves after a total duration of therapy of 9 and 14 months. One had no flare-up of uveitis at the fourth month of discontinuation of therapy and was lost to follow-up thereafter. The other patient discontinued therapy owing to pregnancy. This patient had a relapse of uveitis right after she gave birth, and restarting interferon alfa-2a therapy was recommended; however, the patient was also lost to follow-up. Two patients were lost to follow-up after 21 and 16 months of therapy with interferon alfa-2a. These patients were free of intraocular inflammation while receiving 4.5 MIU of interferon alfa-2a 3 times per week for 19 and 14 months.

The rate of uveitis relapses decreased from 3.52 per patient-year before to 0.75 per patient-year after initiating interferon alfa-2a therapy. Seventeen patients were receiving systemic corticosteroids at the time of initiation of interferon alfa-2a therapy. While they were receiving conventional immunosuppressive agents, the mean dosage of concomitant systemic corticosteroids was 27.0 (range, 10–60) mg/d prednisone equivalent. Twelve were taking more than 10 (range, 20–60) mg/d, and 5 were taking 10 mg/d. During interferon alfa-2a maintenance therapy, 9 patients (33%) were able to discontinue systemic corticosteroid therapy completely, and the remaining 8 patients (47%) were able to taper systemic corticosteroid therapy to no more than 10 (range, 5–10) mg/d prednisone equivalent. Improvement of visual acuity as assessed by doubling of the visual angle occurred in 28 of 68 eyes (41%).

The adverse effects observed during therapy are summarized in the following tabulation.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>No. (%) of Patients (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flulike illness</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Elevation of serum liver enzymes</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Leukopenia*</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9 (24)</td>
</tr>
</tbody>
</table>

*Leukocyte count less than 4000/µL (to convert to number of cells x10⁹ per liter, multiply by 0.001).

All patients experienced a flulike syndrome associated with myalgia and fever in the first week of initiation of therapy. However, it was well controlled with pre-medication using acetaminophen in all but 6 patients who required the addition of systemic nonsteroidal anti-inflammatory agents. The second most common complication observed was weight loss, which we believe is attributable to interferon alfa-2a and the low corticosteroid threshold after the initiation of therapy. Depression was not encountered. No adverse effect required manipulation of the dose or discontinuation of interferon alfa-2a therapy.

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Recent publications have reported a beneficial effect of the use of interferon alfa-2a in the treatment of refractory and sight-threatening uveitis associated with BD. However, there is no consensus about the ideal dose and duration of the treatment for Behçet uveitis. We proposed to use a minimal effective dose of interferon alfa-2a in the treatment of refractory uveitis associated with BD. For the purpose of the study, a new treatment protocol of low-dose interferon alfa-2a with dose escalation was adjusted. This treatment protocol uses 3.0 MIU of interferon alfa-2a for 14 days during the induction phase and 3.0 MIU of interferon alfa-2a 3 times per week during maintenance therapy. The dosage is sequentially increased to 4.5, 6.0, and 9.0 MIU 3 times per week for each individual uveitis relapse. The dose of systemic corticosteroids is rapidly tapered and ideally discontinued. The total duration of interferon alfa-2a therapy is 24 months.

In some previous studies, the induction therapy that is given for the initial 28 days usually involved a higher dose of interferon alfa-2a starting with 6.0 MIU, as first suggested by Kötter et al. The dose of interferon alfa-2a was then gradually tapered to 3.0 MIU if there was improvement. The main difference of our strategy is the approach of starting at a lower dose, with increases in cases that require it because of relapses of intraocular inflammation. In this way the patient avoids a higher dose, which would be expected to have more adverse effects. Indeed, we were able to control the inflammation with a 3.0-MIU maintenance dose in 41% of cases, all of which were refractory to previous treatment with conventional immunosuppressive agents. In their initial report, Kötter et al. observed an overall response of ocular manifestations of 92% with their previously described protocol. The rate of control intraocular inflammation with quiescence was determined as 95% in our series, which is similar to that described by the other authors. Ocular relapses occurred in 18% of patients, and the mean number of relapses in the responders was 0.4 (range, 0-15). In our study population, 59% of patients had relapses of uveitis that required an increase in the dose of interferon alfa-2a. We calculated the relapse rate in patient-years and concluded that the relapse rate declined from 3.52 per patient-year before to 0.75 per patient-year after initiating interferon alfa-2a therapy. In addition, by using lower doses of interferon alfa-2a, the adverse effects were fewer than those reported by Kötter et al., who
reported leukopenia in 40%, depression in 8%, thyroiditis in 4%, and occurrence of autoantibodies in 22% of their patients. Again similar to our findings, in their latest publication, Kotter et al reported a 94% partial or complete response of uveitis with the use of interferon alfa-2a therapy.

With regard to discontinuation of therapy and remission rate after discontinuation, Kotter et al were able to discontinue therapy in 40% of patients. The mean duration of observation after discontinuation of therapy was 29.5 months. In our series, 13 patients (37%) completed 24 months of therapy as determined by the study protocol. Discontinuation of interferon alfa-2a therapy resulted in remission in 10 of the 13 patients (77%). The median duration of remission of Behçet uveitis after the termination of interferon alfa-2a therapy was 12 months. Kaplan-Meier survival analysis estimated the rate of remission after discontinuation of interferon alfa-2a therapy as 76% by 3 months. The rate of remission remained stable thereafter.

Wechsler et al previously used a similar dose of interferon alfa-2a for the treatment of severe and refractory uveitis associated with BD. In their retrospective and preliminary report, 8 patients were described. The dosage of interferon alfa-2a was 3 MIU given 3 times per week throughout the treatment. The treatment controlled intraocular inflammation with improvement of visual acuity. The authors were able to taper the dose of systemic corticosteroids, similar to our conclusions. In a recent retrospective study, Gueudry et al reported on the long-term efficacy of the same treatment protocol used by Wechsler et al. The authors were able to control intraocular inflammation in 88% of their patients, with significant improvement in visual acuity and decrease in the relapse rate of uveitis. Our treatment protocol differs from that one: we used a low-dose regimen and dose escalation. Because Behçet uveitis is characterized by relapsing-remitting courses of intraocular inflammation, the aim should be complete inactivity or quiescence rather than improvement. Therefore, we switched to a higher dose of interferon alfa-2a in cases of partial response and if quiescence could not be achieved. We have also previously reported the differences between the 2 regimens elsewhere. We assume that a higher rate of control of uveitis (95% vs 88%) may be related to dose escalation by increasing the dose of interferon alfa-2a when needed because of relapses of uveitis during the maintenance therapy.

The ability to taper systemic corticosteroid therapy, which was a secondary outcome measure in this study, is an important variable when judging the efficacy of an immunosuppressive therapy. We were able to completely discontinue (53% of patients) or to taper systemic corticosteroid therapy to no more than 10 mg/d prednisone equivalents (47% of patients) in all patients who formerly received long-term systemic corticosteroid therapy. The mean systemic corticosteroid dosage decreased from 27.0 mg/d before to 9.4 mg/d after initiation of interferon alfa-2a therapy.

In addition to allowing the patient to avoid potential adverse effects that occur with higher doses, a low-dose interferon alfa-2a regimen has a lower overall cost compared with regimens using higher doses. We calculated the overall cost of interferon alfa-2a therapy for 2 different maintenance regimens for Turkey. Although the approximate cost of maintenance therapy with interferon alfa-2a given as 3.0 MIU 3 times per week is US $3500 per year, it would be approximately US $9400 per year for a maintenance regimen using 9.0 MIU 3 times per week. Thus, using a minimal effective dose of interferon alfa-2a with dose escalation would affect the overall cost markedly.

There is obviously a need to conduct randomized controlled trials. However, the study population herein is of a particular type, with refractory and sight-threatening uveitis associated with BD. As a measure of disease severity, 38% of our patients who were receiving conventional immunosuppressive therapy needed at least 1 infusion of methylprednisolone because of severe uveitis flare-up. Another shortcoming may be the lack of evaluation of extraocular manifestations of the disease. It has previously been reported that the frequency of extraocular manifestations of the disease is lower in patients with ocular involvement than in those without. Furthermore, it has also been shown that the use of systemic interferon was effective in the treatment of arthritis and mucocutaneous lesions of BD.

We would like to point out the associated medical conditions of the patients reported herein. Two of our patients had aseptic bone necrosis necessitating discontinuation of systemic corticosteroid therapy. In 1 patient, conventional immunosuppressive agents had to be withheld owing to severe anemia associated with thalassemia. Extensive condyloma acuminatum encountered in another patient completely resolved after the initiation of interferon alfa-2a therapy. Two of our patients had active pulmonary tuberculosis and were treated with antituberculosis agents. Uveitis specialists may encounter patients with associated systemic medical conditions such as these or viral diseases such as chronic hepatitis B or C virus. We speculate that the use of interferon alfa-2a in the treatment of uveitis may also result in beneficial effects for the associated medical conditions, especially those caused by viral diseases, and may circumvent certain adverse effects of other immunosuppressive treatments.

We conclude that, at a lower dose, interferon alfa-2a is an effective and well-tolerated agent in controlling severe sight-threatening Behçet uveitis resistant to conventional immunosuppressive agents. This approach also has the advantage of a lower overall cost and avoids potential adverse effects of higher-dose regimens. A partial response or unresponsiveness can be managed by increasing the dose of interferons with a dose-escalation regimen.

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REFERENCES


Correction

Error in Figure Legend. In the Editorial titled “Arnall Patz, MD: The Spirit of Collaboration” by Ferris, published in the December 2010 issue of the Archives (2010;128[12]:1602-1603), the Figure legend should have appeared as follows: “Arnall Patz, MD. Portrait of Dr Patz by Howard Schatz, first fellow on Arnall Patz’s Retinal Vascular Service.” This article was corrected online.