Case Report

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Interferon-α2a treatment for refractory Behçet's disease

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Abstract:

We report a young male patient with Behçet's disease who suffered from sight-threatening recurrences under treatment with azathioprine, cyclosporine, and prednisolone. His uveitis responded well to antitumor necrosis factor (TNF)-alpha (adalimumab) for 5 months subsequently. Severe uveitis recurred soon after discontinuation of anti-TNF alpha therapy and could not be controlled well with reinstitution of the anti-TNF alpha therapy. Interferon-α2a (IFN-α2a) was then given along with low-dose oral prednisone (10 mg/day), and the uveitis responded well to this therapy. We continued a maintenance dose with of IFN-α2a three times/week for 2 years. Sight-threatening uveitis did not recur under IFN-α2a therapy, and the visual acuity improved from "counting fingers" to 20/100 in the right eye, while remaining stable with 20/20 vision in the left eye. The patient had flu-like symptoms, fever, and severe depression during IFN therapy, but an attempt to discontinue INF led to relapse within 1 month. This case report suggests that IFN-α2a could be an option for treatment in Behçet's uveitis. Further study is needed to clarify the efficacy and appropriate strategy for IFN-α2a therapy for Behçet's uveitis in Taiwan.

Keywords:

Behcet's Disease, interferon-α2a, uveitis

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystemic inflammatory disorder with common manifestations that include oral ulcers, genital ulcers, skin rashes, and uveitis. It can affect both the anterior and posterior segments of the eye and is characterized by obliterative vasculitis involving both arteries and veins.[1] BD is most common in the Far East, Middle East, and Mediterranean area, corresponding to the old Silk Route.[2] The prevalence varies greatly, with epidemiological studies showing about 1 in 10,000 in Japan,[3] but higher rates in Iran (42 in 10,000).[4] In Taiwan, one retrospective study in a tertiary referral center reported that BD accounted for 3.8% of cases of patients with uveitis.[5]

The definitive pathogenesis of BD disease is still uncertain, but it is clearly related to T-cell regulation. Numerous cytokines are associated with the disease, including interleukin-2 (IL-2), IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, interferon (IFN)-γ, and tumor necrosis factor-α (TNF-α).[6] Several medications are designed to suppress or modulate these cytokines to treat BD.

The goal of BD treatment is to control inflammation to achieve complete remission or at minimum to reduce the morbidity. This applies, especially to ocular BD, in which chronic relapsing ocular inflammation or vasculitis could cause visual disturbance, or even blindness; thus ocular BD should be treated more aggressively. Topical and systemic corticosteroids are commonly used for the initial treatment of Behçet's uveitis attacks, to achieve rapid inflammation suppression.[7] Azathioprine (AZA) is recommended as one of the initial immunosuppressive agents by the European League Against Rheumatism (EULAR),[8] and it has been proven to reduce the risk of relapses with long-term use.[9,10]

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Cyclosporine (CSA), a calcineurin inhibitor, is another widely used immunosuppressive agent for ocular BD, and it can decrease the frequency and severity of Behçet's uveitis. Moreover, one study showed that a combination of AZA and CSA is more effective than monotherapy.[11]

The development of biologic agents is another promising therapeutic strategy for ocular BD. TNF-α antagonists, including infliximab and adalimumab, have been approved as effective for the treatment of refractory Behçet's uveoretinitis,[12,13] but there is still a lack of head-to-head trials comparing these two therapies. Besides, for patient with severe or refractory eye involvement, infliximab was suggested to be added with AZA according to EULAR.[8]

IFN-α was the earliest biologic described as beneficial for Behçet's uveitis treatment, and its use can be traced back to as early as the 1980s.[14] Wechsler *et al*.[15] reported, in a case-series study between May 1995 and January 1999, that IFN-α therapy was efficient in all 8 cases with BD. Furthermore, corticosteroids were tapered from a mean dosage of 47 mg/day to 8.5 mg/day, and even so, visual acuity improved in all cases.

There are not many medications available for refractory Behcet's uveitis in Taiwan. This case report describes our experiences applying INF-α in the patient with refractory sight-threatening BD.

Case Report

A 23-year-old Asian male was diagnosed with BD, with initial presentation of panuveitis in both eyes, oral ulcers, genital ulcers, and erythema nodosum of the bilateral lower limbs dating back 5 years, fulfilling the International Study Group criteria for BD.[16] He was treated at first with corticosteroids, CSA, and colchicine, and his visual acuity recovered from 20/250 to 20/25 in the right eye, and from 20/25 to 20/20 in the left eye 2 months later. Afterward, an additional immunosuppressive agent, AZA, was added because of a recurrent flare-up [Figure 1]. In the first period of treatment, he also received adalimumab therapy, with an initial loading dose followed by a 40 mg subcutaneous injection every 2 weeks, but this was discontinued 5 months later because he was unable to afford the cost.

However, bilateral panuveitis recurred 2 months after discontinuation of adalimumab, and controlled by steroid pulse therapy and three combinations of immunosuppressants: CSA, AZA, and colchicine. Subsequently, there were still several sight-threatening recurrences and panuveitis nevertheless flared up even after treatment with adalimumab resumed. After pulse therapy, there was no recovery of vision in the right

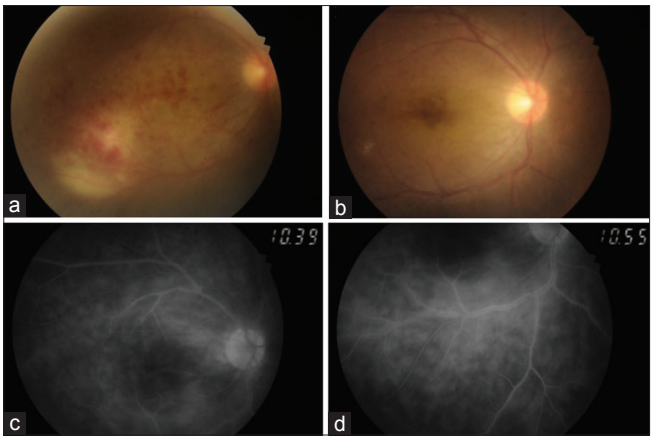

Figure 1: Sight-threatening flare-up in the right eye 6 months after confirmed diagnosis of Behcet's Disease. (a) Right eye: Macular hemorrhage and obliterative vasculitis with exudation. Visual acuity: "Counting fingers" at 15 cm. (b-d) Right eye: Two weeks later after combination treatment with azathioprine, corticosteroid, and cyclosporine. Exudation was reduced although there was still diffuse vascular leakage in fluorescein angiography

eye (the acuity was counting fingers at 20 cm), even though there was no active retinal lesion in the posterior pole of the right eye. In addition, there were multiple active retinal lesions approaching the posterior pole of the left eye [Figure 2]. We recommended either an alkylating agent or IFN-α2a therapy to rescue his vision, and after discussion, he decided to receive IFN-α2a therapy.

In October 2015, the therapy began with INF-α2a 6×10^6 IU subcutaneous injection/day for 2 weeks, as indicated in Kötter's treatment flow chart,[17] followed by 3×10^6 IU/day for 1 week because of improvement [Figure 3]. His condition continued to improve, so the frequency was decreased to IFN-α2a at 3×10^6 IU three times weekly. The prednisolone and AZA were tapered to 10 mg/day and 1 mg/kg/day, respectively, while CSA and colchicine were discontinued. Flu-like symptoms such as headache, fever, sore throat, and oral ulcers recurred at the 4th week but resolved after the resumption of colchicine. Therapy with IFN-α2a 3×10^6 IU 3 times weekly continued for a total of 5 months, and his vision improved (20/100 in the right eye and 20/20 in the left eye) without any major recurrence. All immunosuppressive agents were then discontinued, and the daily prednisolone dose was reduced to 5 mg.

However, the patient complained about a depressed mood and reported suicidal ideation during therapy. He even attempted suicide once, by charcoal fume inhalation but was stopped by his uncle. He was referred to a psychiatrist and prescribed antidepressant drugs. He usually developed a high fever, reaching about 40° C, after INF injection, and this bothered him so much that in the 15th month, he requested a halt to INF injections. In the month after discontinuation, however,

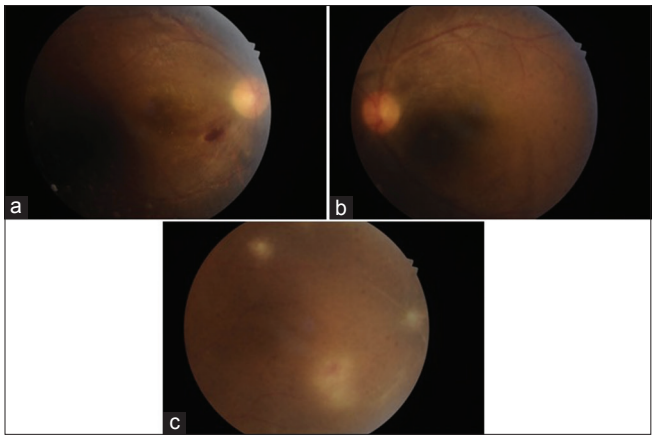

Figure 2: Images of eyes after pulse therapy for recurrence of symptoms, which happened even after 2 months of adalimumab treatment. (a) Right eye: Vitritis is absent, no other active lesions in the posterior pole but poor vision persists; (b) Left eye: Central view. (c) Left eye: Temporal view showing multiple whitish retinal lesions approaching the posterior pole

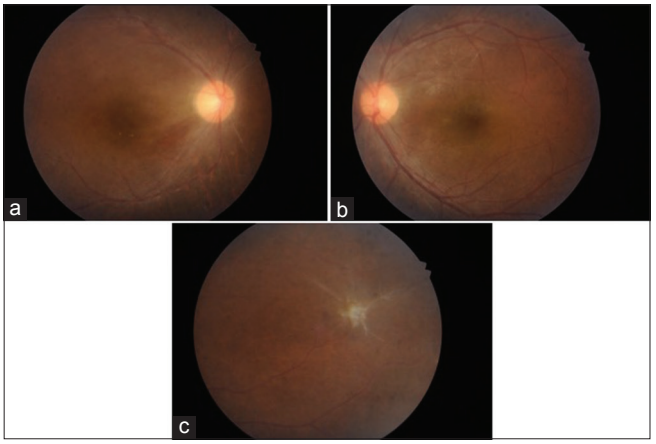

Figure 3: Images of eyes 2 weeks later, after therapy with interferon-α2a (a) Right eye: no active retinitis or vasculitis are apparent, and no obvious macula lesion; (b) Left eye: central view; (c) Left eye: temporal view showing that the previously seen whitish patches with active inflammation had disappeared, and there was one asterisk-like scar surrounded by sheathing vessels

his vision in the right eye worsened because of another recurrence. Thus, a maintenance dose of IFN-α2a was resumed at 3×10^6 IU three times weekly, and 2 weeks later, his vision had recovered to 20/100. We tried to taper the frequency to twice per week, but this was not effective, so we have continued the same maintenance dose up to the present. The patient received IFN-α2a therapy without other immunosuppressive agents, but combined with a low-dose corticosteroid, which relieved the fever when taken before INF injection. There was no major recurrence such as panuveitis or macular lesion, and his visual acuity has been stable. As for his depression, he claims that the negative or hopeless thinking is now absent and that he no longer feels a need for antidepressant drugs. There has been no other complication of long-term IFN therapy so far.

Discussion

Treatment of refractory Behcet's uveitis is so challenging that it can easily cause vision loss if not adequately controlled. In our case, the patient responded well at first to treatment with a corticosteroid, AZA, and CSA, but afterward, he continued to experience flare-ups that repeatedly worsened his vision. TNF-α has been approved as an important inflammation mediator in BD,[18] and several publications have shown that TNF-α antagonists can reduce the inflammation caused by BD and can decrease the frequency of ocular attacks.[12,13,19,20] A prospective, multicenter study in Japan recruited 63 patients with BD,[19] and analyzed the efficacy of infliximab in 50 patients after exclusion. The study showed a 92% response rate, and 44% of the patients were flare-up free during a 1-year period. Another TNF-α antagonist, adalimumab, has been approved as beneficial in patients with refractory uveitis,[13] and showed association with an improvement of symptoms and decline in inflammatory activity. Our patient received adalimumab during the 5-months period, but this treatment could not be maintained because of its high cost. A recurrence occurred 2 months after discontinuation of adalimumab and was not resolved even under renewed treatment with adalimumab, AZA, CSA, and prednisolone.

A prospective large case-series study[13] showed that adalimumab improved intraocular inflammation in patients with refractory uveitis, but it also reported that nine patients had severe relapses during treatment, and one of them was diagnosed as BD. This was why we decided to switch medications earlier.

Alpsoy *et al.*[21] described a double-blind, placebo-controlled study that reported a significant reduction in disease duration, pain of oral ulcers, and frequency of genital ulcers in an IFN-treated group. Five of six patients with ocular manifestations had fewer ocular attacks with IFN therapy, with complete remission seen in three patients and partial remission in two patients. In Kötter's study,[17] a promising response rate to IFN therapy was reported for ocular BD (92%), and mean visual acuity rose significantly, from 0.56 to 0.84, at week 24. Seventeen of 50 patients had been off treatment, with a mean 29.5-month disease-free period. In our patient, his vision could be improved to 20/100 in the right eye, but an attempt to cease treatment failed because a sight-threatening recurrence occurred 1 month after discontinuing IFN. Kötter[17] also reported 27 patients (54%) who continue to need controlled maintenance doses of 3×10^6 IU three times weekly. There was no panuveitis or macular involvement in our patient with the IFN-α2a maintenance dose, and he could omit other immunosuppressants with the exception

of intermittent use of colchicine for oral ulcers, while prednisolone was tapered to one 5 mg dose/injection day.

The reported adverse effects of INF-α2a use for Behçet's uveitis include a flu-like syndrome (100%), redness at the injection site (100%), leukopenia (40%), alopecia (24%), and depression (8%).[17] Our patient complained about sore throats and oral ulcers in the early stage of IFN therapy, but these could be resolved by colchicine. We examined his hemogram monthly, and no leukopenia was apparent. He had severe depression in the 1 year, with suicidal ideation and even a suicide attempt, but felt better with antidepressants, then he could keep stable mood without antidepressants afterward. According to his statement, the febrile condition was the most annoying complication for his daily life, interfering with his work and study. Oral prednisolone could relieve the fever when taken before INF subcutaneous injection.

To the best of our knowledge, this is the first case report of long-term control of Behçet's uveitis with IFN-α2a in Taiwan. Several studies of the long-term efficacy of IFN-α2a have been reported in the past decade.[22-24] The remission rates varied from 88% to 98.1%, and the rate of visual acuity improvement varied from 30% to 90%.[17,22-25] Therefore, IFN-α2a can be an option for the treatment of refractory Behçet's uveitis. Further study is needed to fully understand the efficacy and safety of IFN-α2a for Taiwanese patients with Behçet's uveitis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. Zierhut M, Pavesio C, Ohno S, Oréfice F, Rao NA, editors. Intraocular Inflammation. Germany: Springer; 2016.
2. Michelson JB, Chisari FV. Behçet's disease. Surv Ophthalmol 1982;26:190-203.
3. Mishima S, Masuda K, Izawa Y, Mochizuki M, Namba K. The eighth Frederick H. Verhoeff Lecture. Presented by Saiichi Mishima, MD Behçet's disease in Japan: Ophthalmologic aspects. Trans Am Ophthalmol Soc 1979;77:225-79.
4. Davatchi F, Jamshidi AR, Banihashemi AT, Gholami J, Forouzanfar MH, Akhlaghi M, *et al.* WHO-ILAR COPCORD study (Stage 1, urban study) in Iran. J Rheumatol 2008;35:1384.
5. Chen SC, Chuang CT, Chu MY, Sheu SJ. Patterns and etiologies of uveitis at a tertiary referral center in Taiwan. Ocul Immunol Inflamm 2017;25:S31-8.
6. Zhou ZY, Chen SL, Shen N, Lu Y. Cytokines and Behcet's disease. Autoimmun Rev 2012;11:699-704.
7. Ozguler Y, Hatemi G, Yazici H. Management of Behçet's syndrome. Curr Opin Rheumatol 2014;26:285-91.
8. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, *et al.* EULAR recommendations for the management of Behçet disease. Ann Rheum Dis 2008;67:1656-62.
9. Yazici H, Pazarli H, Barnes CG, Tüzün Y, Ozyazgan Y, Silman A, *et al.* A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990;322:281-5.
10. Saadoun D, Wechsler B, Terrada C, Hajage D, Le Thi Huong D, Resche-Rigon M, *et al.* Azathioprine in severe uveitis of Behçet's disease. Arthritis Care Res (Hoboken) 2010;62:1733-8.
11. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, *et al.* Management of Behçet disease: A systematic literature review for the European League Against Rheumatism evidence-based recommendations for the management of Behçet disease. Ann Rheum Dis 2009;68:1528-34.
12. Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, *et al.* Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 2004;31:1362-8.
13. Díaz-Llopis M, Salom D, Garcia-de-Vicuña C, Cordero-Coma M, Ortega G, Ortego N, *et al.* Treatment of refractory uveitis with adalimumab: A prospective multicenter study of 131 patients. Ophthalmology 2012;119:1575-81.
14. Zouboulis CC, Orfanos CE. Treatment of Adamantiades-Behçet disease with systemic interferon alfa. Arch Dermatol 1998;134:1010-6.
15. Wechsler B, Bodaghi B, Huong DL, Fardeau C, Amoura Z, Cassoux N, *et al.* Efficacy of interferon alfa-2a in severe and refractory uveitis associated with Behçet's disease. Ocul Immunol Inflamm 2000;8:293-301.
16. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990;335:1078-80.
17. Kötter I, Zierhut M, Eckstein AK, Vonthein R, Ness T, Günaydin I, *et al.* Human recombinant interferon Alfa-2a for the treatment of Behçet's disease with sight threatening posterior or panuveitis. Br J Ophthalmol 2003;87:423-31.
18. Düzgün N, Ayaşlioğlu E, Tutkak H, Aydintuğ OT. Cytokine inhibitors: Soluble tumor necrosis factor receptor 1 and interleukin-1 receptor antagonist in Behçet's disease. Rheumatol Int 2005;25:1-5.
19. Okada AA, Goto H, Ohno S, Mochizuki M, Ocular Behçet's Disease Research Group Of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. Arch Ophthalmol 2012;130:592-8.
20. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, *et al.* Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: An open-label trial. Arthritis Rheum 2005;52:2478-84.
21. Alpsoy E, Durusoy C, Yilmaz E, Ozgurel Y, Ermis O, Yazar S, *et al.* Interferon alfa-2a in the treatment of Behçet disease: A randomized placebo-controlled and double-blind study. Arch Dermatol 2002;138:467-71.
22. Onal S, Kazokoglu H, Koc A, Akman M, Bavbek T, Direskeneli H, *et al.* Long-term efficacy and safety of low-dose and dose-escalating interferon alfa-2a therapy in refractory Behçet uveitis. Arch Ophthalmol 2011;129:288-94.

23. Gueudry J, Wechsler B, Terrada C, Gendron G, Cassoux N, Fardeau C, *et al.* Long-term efficacy and safety of low-dose interferon alpha2a therapy in severe uveitis associated with Behçet disease. Am J Ophthalmol 2008;146:837-440.
24. Deuter CM, Zierhut M, Möhle A, Vonthein R, Stöbiger N, Kötter I, *et al.* Long-term remission after cessation of interferon-α treatment in patients with severe uveitis due to Behçet's disease. Arthritis Rheum 2010;62:2796-805.
25. Krause L, Altenburg A, Pleyer U, Köhler AK, Zouboulis CC, Foerster MH, *et al.* Longterm visual prognosis of patients with ocular Adamantiades-Behçet's disease treated with interferon-alpha-2a. J Rheumatol 2008;35:896-903.