STUDY

Interferon Alfa-2a in the Treatment of Behçet Disease

A Randomized Placebo-Controlled and Double-blind Study

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Objective: To determine the therapeutic efficacy of interferon alfa-2a in the treatment of Behçet disease.

Design: A randomized placebo-controlled and double-blind study.

Setting: University referral center.

Patients: Fifty patients with Behçet disease were involved in the study.

Intervention: The patients were given interferon alfa-2a, 6×10^6 IU, subcutaneously 3 times per week or placebo for 3 months, and examined clinically at weekly intervals.

Main Outcome Measures: For each mucocutaneous lesion and articular symptom, the mean frequency and duration were evaluated during the 3-month pretreatment, treatment, and follow-up periods. Pain for oral and genital ulcers was scored on a scale of 0 to 3. The ocular inflammatory score, the frequency of attacks, and changes in visual acuities for patients with ocular involvement were assessed before the study, at the end of treatment, and during the follow-up periods. In addition, overall responses at the end of the treatment period were graded as follows: complete remission, disappearance of all clinical signs and symptoms during treatment; partial remission, greater than a 50% decrease in the frequency, duration, and severity of pain for oral and genital ulcers and/or a decrease in the severity and frequency of ocular attacks; stable disease, less than a 50% change in the clinical signs and symptoms; and no effect or deterioration, ineffectiveness or worsening of clinical signs and symptoms.

Results: Twenty-three interferon alfa-2a– and 21 placebo-treated patients, ranging in age from 16 to 55 years (mean±SD age, 32.38±7.94 years), were evaluable for efficacy. Interferon alfa-2a treatment significantly decreased the duration ($P=.02$) and pain ($P=.01$) of oral ulcers and the frequency of genital ulcers ($P=.03$) and papulopustular lesions ($P=.01$). The mean frequency and duration of erythema nodosum–like lesions ($P=.77$ and .27, respectively) , thrombophlebitis ($P=.29$ and .61, respectively), and articular symptoms ($P=.92$ and .74, respectively) also decreased. But there were no statistically significant differences. An improvement in the severity and the frequency of ocular attacks occurred in 5 of 6 patients in the interferon alfa-2a–treated group and in 1 of 3 patients in the placebo-treated group. Of the 23 patients in the interferon alfa-2a–treated group, 15 responded to treatment (2 complete and 13 partial responses); and of the 21 patients in the placebo group, 3 responded to treatment (3 partial responses) ($P<.005$).

Conclusion: Interferon alfa-2a is an effective alternative treatment for Behçet disease, particularly for the management of the mucocutaneous lesions of the disease.

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BEHÇET DISEASE (BD) is a chronic, relapsing, multisystemic inflammatory process with the clinical features of mucocutaneous lesions and ocular, vascular, articular, gastrointestinal, urogenital, pulmonary, and neurologic involvement. The etiopathogenesis of the disease still remains unknown. Although several immunologic abnormalities have been demonstrated in patients with BD, the exact mechanism of the inflammatory changes occurring remains to be elucidated. The most likely hypothesis seems to be that of an autoimmune reaction set off by infectious agents, such as human herpesvirus 1 or *Streptococcus* species, in genetically predisposed individuals, and its basic pathologic process is vasculitis.[1-3]

No standard therapy has been established for the disease. However, a wide spectrum of therapeutic agents, including colchicine, levamisole hydrochloride,[4] corticosteroids, acyclovir, chloram-

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PATIENTS AND METHODS

Fifty patients with BD (19 females and 31 males; mean ± SD age, 32.92 ± 8.62 years; age range, 16-55 years), diagnosed as having BD according to the criteria of the International Study Group for Behçet's Disease,[16] were involved in the study between June 3, 1996, and March 31, 2000. Exclusion criteria consisted of patients who had hepatic, renal, cardiovascular, infectious, or other autoimmune disease; those with a coagulopathy; and those who had received recent systemic therapy for at least 12 weeks and topical therapy for at least 4 weeks before enrolling in the study. Pregnant or lactating women were not included in the study. We excluded patients who at the initiation of the treatment period had active cerebral or retinal vasculitis. Patients with irreversible bilateral eye disease and those who had cataract or posterior synechia that interfered with visual acuity or the fundus examination were also excluded.

The patients were observed for 3 months before the study. All attacks were recorded during this period. The research protocol was approved by the ethics committees, and all patients or their guardians gave signed informed consent. Administration of either placebo or interferon alfa-2a was commenced depending on the sequence randomly allocated to the subject. The dissolvent of interferon alfa-2a was used as placebo, which was identical in appearance to the interferon alfa-2a injection. Patients were given interferon alfa-2a, 6×10^6 IU, or placebo subcutaneously 3 times a week. Patients were informed about the study design and the possible adverse effects of the interferon alfa-2a therapy before study enrollment. Because the influenzalike symptoms that occur after injections are a well-known adverse effect of the interferon alfa-2a treatment and could hamper the performance of such a controlled study, subjects were given oral acetaminophen, 1000 mg before injections and 500 mg after 6 hours, during the first month of the therapy.

All signs and symptoms were recorded during the 3-month treatment period. The patients were examined clinically at weekly intervals and were followed up for another 3 months after the treatment. During all of these procedures, the subject was observed and assessed by an investigator (E.A.) who was blinded to the test medication being used. The results were based on a combination of the data obtained by the physician at clinic visits and the data reported by the patients on the occurrence of lesions between the visits. For each mucocutaneous lesion and articular symptom, the mean frequency and duration were evaluated during the pretreatment, treatment, and follow-up periods. The mean frequency and duration of lesions were calculated per patient. Pain for oral ulcers (OUs) and genital ulcers (GUs) was scored on a scale of 0 to 3 (0 indicates absent; 1, mild; 2, moderate; and 3, severe). The following pain scores, which were based on a system developed by Alpsoy et al[17] for patients with BD, were used. For OUs, 0 indicates no symptoms; 1, mild pain with eating/drinking and/or speaking; 2, moderate pain and partial difficulty in eating/drinking and/or speaking; and 3, severe pain and marked difficulty in eating/drinking and/or speaking. For GUs, 0 indicates no symptoms; 1, mild pain with physical activity; 2, moderate pain and partial difficulty in physical activity; and 3, severe pain and marked difficulty in physical activity. In addition, overall responses at the end of the treatment period were graded as follows: complete remission (CR), the disappearance of all clinical signs and symptoms during the treatment; partial remission (PR), greater than a 50% decrease in the frequency, duration, and severity of pain for OUs and GUs and/or a decrease in the severity and frequency of attacks for ocular involvement; stable disease, less than a 50% change in the clinical signs and symptoms; and no effect or deterioration, ineffectiveness or worsening of clinical signs and symptoms.

Patients with active eye disease were examined by an ophthalmologist (Y.O.) at weekly intervals (or daily when necessary); and patients without eye symptoms, at monthly intervals. The ophthalmologic examination included a Snellen visual acuity measurement, a slitlamp examination of the anterior segment, and direct and indirect ophthalmoscopy of the vitreous and fundus. Intraocular pressures were measured by applanation tonometry. Cells and flare in the anterior chamber and vitreous were graded from 0 to 4+. Ocular inflammatory scores,[18] frequency of attacks, and changes in visual acuities (a change of 2 lines in Snellen acuity is regarded as significant) for each patient were assessed before the study, at the end of treatment, and during the follow-up periods.

Adverse events were also documented during the treatment period. No patients were given any concurrent disease-specific or immunosuppressive systemic drugs during the 9-month study period. Topical corticosteroid drops and mydriatic agents remained available for patients with ocular involvement whenever necessary. A full blood cell count, including hemoglobin level, leukocyte count and differential, platelet count, and erythrocyte sedimentation rate, and routine biochemical tests were performed before treatment and repeated monthly. Abnormal test results and adverse reactions became new exclusion criteria.

The mean frequency and duration of each mucocutaneous lesion and articular symptom, and the pain of OUs and GUs in the pretreatment period, were compared with those of the treatment and posttreatment periods in the group of patients treated with interferon alfa-2a and placebo, and a repeated-measure analysis of variance was used to test the changes in groups. Differences in improvement ratings (overall responses) between groups were tested using the χ^2 test. $P \leq .05$ was accepted as significant.

bucil, cyclophosphamide,[5] cyclosporine,[6] azathioprine,[7] and thalidomide,[8] have been used in the treatment of the disease, with varying success; none of them result in cure of the disease, and some are associated with significant adverse effects.

Interferons, a large family of glycoproteins, were first described in 1957 by Isaacs and Lindenmann,[9] and are known to produce a cellular response to the foreign constituents of microbes, tumors, and antigens. They have been used in the treatment of a wide group of diseases because of their antiviral, antimicrobial, antitumor, and immunomodulatory actions. Tsambaos et al[10] first introduced the systemic application of interferon alfa-2a in 3 patients with BD; these patients showed complete or almost complete remission of the mucocutaneous lesions and marked improvement of their systemic manifestations after treatment with 9 to 12×10^6 IU per day for 11 to 16 days. Since then, several uncontrolled studies[11-14]

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Demographic Data of the Patients With Behçet Disease*

Characteristic	Interferon Alfa-2a–Treated Group (n = 23)	Placebo Group (n = 21)	Total (N = 44)
Age, mean ± SD, y	32.82 ± 8.17	31.89 ± 7.85	32.38 ± 7.94
Male-female ratio	16:7	11:10	**27:17**
Duration of the disease, mean ± SD, y	6.54 ± 5.70	6.33 ± 5.83	6.44 ± 5.70
Oral ulcer	23	21	**44**
Genital ulcer	22	20	**42**
Papulopustular lesions	20	21	**41**
Erythema nodosum–like lesions	12	12	**24**
Thrombophlebitis	5	4	**9**
Articular symptoms	12	14	**26**
Ocular manifestations	6	3	**9**

*Data are given as number of patients unless otherwise indicated.

have been published, using interferon alfa-2a or interferon alfa-2b and giving the agent either daily or 3 times weekly. Promising results have been reported, especially with interferon alfa-2a. In a review of this literature, Zouboulis and Orfanos[15] concluded that most patients showed a worthwhile improvement in mucocutaneous lesions, arthritis, and ocular manifestations. A 2-month treatment, at least, is likely to be necessary to increase the effectiveness, and the disease generally relapses on discontinuation.

In addition to their immunomodulatory effects, ability to augment the decreased activity of a patient's natural killer cells, and capacity to inhibit neovascular proliferation, the antiviral activities of interferons, together with the putative association between BD and viral infection, particularly human herpesvirus 1, provide a rationale for testing their therapeutic potential. Therefore, the present randomized double-blind and placebo-controlled study was undertaken to investigate whether interferon alfa-2a is effective in the treatment of BD.

RESULTS

Of the 50 patients involved in the study, 23 in the interferon alfa-2a–treated group and 21 in the placebo group were evaluable for efficacy. The duration of the disease ranged from 6 months to 22 years. Treatment groups were not significantly different with respect to age ($P=.71$), duration ($P=.90$) , and male-female ratio ($\chi^2=1.36$; $P=.24$) at the beginning of the study (**Table**).

Six patients (2 in the interferon alfa-2a–treated group and 4 in the placebo group) failed to complete the study. The reasons for their withdrawal were severe eye disease in 3 patients (1 in the interferon alfa-2a–treated group and 2 in the placebo group), progressive mucocutaneous symptoms in 1 (in the interferon alfa-2a–treated group), new eye disease and mucocutaneous symptoms in 1 (in the placebo group), and progressive mucocutaneous and articular symptoms in 1 (in the placebo group). In all patients, medication was well tolerated, and no patients were withdrawn from the study because of adverse events.

MUCOCUTANEOUS LESIONS

Interferon alfa-2a treatment significantly decreased the duration (interaction of group by treatment effect: $F_{1.6,67.7}=4.24$, $P=.02$) and pain ($F_{1.8,76.8}=4.94$, $P=.01$) of OUs and the frequency of GUs ($F_{1.8,77.9}=3.93$, $P=.03$) and papulopustular lesions ($F_{1.5,64.8}=5.18$, $P=.01$). In most patients receiving interferon alfa-2a, OUs improved rapidly after the initiation of treatment. Some patients had mild, short-term (3-5 days), multiple, minor ulceration attacks. The mean frequency and duration of erythema nodosum–like lesions ($P=.77$ and .27, respectively) and of thrombophlebitis ($P=.29$ and .61, respectively) also decreased. But there were no statistically significant differences. Generally, all symptoms tended to return to pretreatment levels in the posttreatment follow-up period. In the placebo group, no significant difference was found in measured mucocutaneous lesion variables.

OCULAR MANIFESTATIONS

There was a general improvement in ocular manifestations of patients receiving interferon alfa-2a therapy compared with their own pretreatment periods. Of 6 patients, 5 experienced a decrease in the severity and the frequency of attacks (3 CRs and 2 PRs). The therapy resulted in ineffectiveness in 1 patient. In the placebo group, only 1 patient experienced a decrease in the severity and the frequency of attacks, while 2 showed no effect or a deterioration of the ocular symptoms. In the interferon alfa-2a–treated group, 9 of 11 eyes maintained or improved their visual acuity. Five eyes had an improved acuity at the end of the treatment, and only 3 improved at the end of the follow-up period. In the placebo group, 2 of 6 eyes had an improved acuity, and 2 of 6 eyes maintained the same acuity. At the end of these 2 patients' follow-up period, 3 of the 4 eyes maintained their acuity and 1 still had an improved acuity. In the interferon alfa-2a–treated group, the inflammatory score decreased in 7 eyes. In 4 eyes, the score was unchanged. In the placebo group, the inflammatory score decreased in 3 eyes and remained unchanged at the end of the treatment in 3 eyes.

ARTICULAR SYMPTOMS

The mean frequency and duration of articular symptoms decreased during the 3-month treatment period in the interferon alfa-2a–treated group, but the difference was not statistically different. Articular symptoms also tended to return to pretreatment levels in the posttreatment follow-up period.

ADVERSE EFFECTS

The primary adverse effects of interferon alfa-2a therapy were mild flulike symptoms (fever, chills, headache, fatigue, and myalgia) that started a few hours after the injection and continued less than a day, especially within the first 2 weeks of treatment. Of 23 patients treated with interferon alfa-2a, 18 had flulike symptoms. Three patients in the placebo group also complained from similar symptoms after the injections without respect to the

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time of the treatment. Other adverse effects, including reversible alopecia (n=1), leukopenia (n=1), and diarrhea (n=1), were observed only in patients with BD treated with interferon alfa-2a.

OVERALL RESPONSE

Of the 23 patients in the interferon alfa-2a–treated group, 15 responded to treatment (2 CRs and 13 PRs); and of the 21 patients in the placebo group, 3 responded to treatment (3 PRs) ($\chi^2_3=14.7$, $P<.005$). Four patients in the interferon alfa-2a–treated group and 3 in the placebo group showed less than a 50% change, while 4 in the interferon alfa-2a–treated group and 15 in the placebo group experienced ineffectiveness or worsening of clinical signs and symptoms.

COMMENT

Oral ulcers and GUs, the most common of mucocutaneous lesions in patients with BD, are characterized by recurrent and painful ulcerations of the oral and genital mucosa, respectively. They are identical to aphthae (or aphthous stomatitis) in appearance, but they tend to be more frequent and multiple. Patients may have single or multiple ulcers that often present during a 1- to 4-week period. Oral ulcers and GUs are a required feature for the diagnosis of BD and often are the initial presenting sign. In our study, interferon alfa-2a treatment significantly decreased the duration and pain of OUs and the frequency of GUs. In most patients, OUs improved rapidly after the initiation of interferon alfa-2a treatment. Some patients had mild, short-term (3-5 days), multiple, minor ulceration attacks that have been reported previously.[11,19,20] Genital ulcers also improved rapidly, although some patients had mild short-term attacks within the 3-month treatment period. These results show that interferon alfa-2a treatment is effective on OUs and GUs, and this effect decreases gradually after the cessation of treatment. Other researchers[13-15,21] have noted similar results.

Cutaneous lesions of the disease are varied and include mainly papulopustular lesions, erythema nodosum–like lesions, and superficial thrombophlebitis. Papulopustular lesions, the most common type of skin lesions in patients with BD, are cutaneous sterile, follicular, or acnelike lesions on a erythematous base that appear as a papule and in 24 to 48 hours become a pustule.[22] Erythema nodosum–like lesions occur mainly on the lower extremities, but can also be seen on the face, neck, and buttocks. The lesions generally resolve within 2 to 3 weeks with residual pigmentation, but recurrences are common. Superficial thrombophlebitis is frequently confused with erythema nodosum. The subcutaneous venules of the extremities, especially in male patients, tend to develop thrombosis, leading to sclerosis. The small vein can be palpated as a stringlike hardening of the subcutaneous tissue with reddening of the overlying skin.[5] In our study, the mean frequency of papulopustular lesions statistically significantly decreased with interferon alfa-2a treatment. The mean frequency and duration of erythema nodosum–like lesions and thrombophlebitis also decreased. But there were no statistically significant differences because of, most likely, few patients with erythema nodosum–like lesions and thrombophlebitis. Previous studies[12,13,20,21,23] have also reported marked improvements in the respected cutaneous symptoms with treatment with interferon alfa-2a.

Ocular involvement is a serious complication of BD. It is characterized by repeated, explosive, ocular inflammatory attacks that may lead to blindness in up to 25% of the eyes.[24] Symptoms are bilateral in most of the patients. Young male patients are at an increased risk for the severe complications of ocular involvement, and they usually require aggressive treatment with immunosuppressive agents. Previous studies[23,25-31] have reported encouraging results from the use of interferon alfa-2a in patients with BD. The treatment of ocular symptoms of the disease with interferon alfa-2a alone or in combination with low-dose corticosteroids led to CR or PR in 21 of 23 patients with BD (18 CRs and 3 PRs). We have also observed an improvement in ocular manifestations of patients receiving interferon alfa-2a therapy. Five of 6 patients in the interferon alfa-2a–treated group and 1 of 3 in the placebo group experienced improvement. Although patients treated with interferon alfa-2a had better results regarding the severity and the frequency of attacks, visual acuity, and the inflammatory score, they all tended to return to pretreatment levels during the follow-up period. Because of the limitations at study enrollment, the number of the patients did not lead us to apply a statistical evaluation. In addition, the durations of the treatment and follow-up periods, compared with those of previous studies, were not sufficient to draw a final conclusion. But, it seems likely that interferon alfa-2a therapy may be a therapeutic alternative in the treatment of ocular symptoms. However, because some patients experienced recurrences under the treatment, we cannot recommend interferon alfa-2a treatment alone as a first-line treatment choice.

The beneficial effects of interferon alfa-2a therapy for articular symptoms have been previously reported.[10,11,21,25,28-30] We also observed a decrease in the mean frequency and duration of articular symptoms during the treatment period in the interferon alfa-2a–treated group, but the difference was not statistically different. In addition, the decrease in the mean frequency and duration of articular symptoms did not persist during the follow-up period.

The primary adverse effects of interferon alfa-2a therapy are flulike symptoms that start a few hours after the initiation of the therapy and continue less than a day. Nausea, vomiting, anorexia, diarrhea, weight loss, hematologic changes, and a transient increase of hepatic transaminase levels are seen less frequently.[15] In our study, almost every patient given interferon alfa-2a manifest a flulike syndrome, especially within the first 2 weeks of the treatment. Because the patients were given oral acetaminophen before and after the interferon alfa-2a injections during the first month of the therapy, flulike symptoms were mild and tolerable. Interestingly, 3 patients in the placebo group also complained from similar symptoms after the injections without respect to the time of the treatment. Other adverse effects, including reversible alopecia, leukopenia, and diarrhea, were observed

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only in patients with BD receiving interferon alfa-2a treatment.

In our study, interferon alfa-2a significantly decreased the duration and pain of OUs and the frequency of GUs and papulopustular lesions. The mean frequency and duration of erythema nodosum–like lesions, thrombophlebitis, and articular symptoms also decreased. We have also observed an improvement in ocular manifestations. However, all symptoms tended to return to pretreatment levels during the follow-up period. This suggests a possible need for maintenance therapy. Although several effective treatments for BD exist, none of them result in cure of the disease and some are associated with significant adverse effects compared with interferon alfa-2a treatment. Therefore, our results indicate that interferon alfa-2a treatment may be an effective alternative, particularly for the mucocutaneous lesions of BD.

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