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Original Article

Interferon Alfa-2b Therapy in Mucocutaneous Manifestations of Behçet's Disease

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Abstract

Background: Viral infections such as Epstein-Barr virus and Herpes simplex virus may play a role in the pathogenesis of Behçet's disease (BD). Interferons (INF) are natural defense mechanisms against viruses and inhibit their activities by enhancing major histocompatibility complex class I and cytokine expression. This study evaluated the efficacy of INF-α-2b on mucocutaneous lesions of BD.

Methods: In this open label clinical trial, 12 patients were chosen sequentially from cases referred to the Rheumatology Unit of the Ghaem Hospital of Mashhad University of Medical Sciences, Mashhad, Iran, with inclusion criteria of active BD without central nervous system or ophthalmic involvement. They received subcutaneous injections of 3 million units of IFN-α-2b three times a week for six months. The numbers and the sizes of lesions were evaluated monthly with the objective and subjective assessments of disease activity.

Results: The average dose of interferon prescribed was 2.71 million units during six months. The numbers and sizes of oral, genital and cutaneous lesions decreased significantly with less pain and longer duration of remission. The most common side effects were flu-like symptoms and bone pain reported by 8 patients with temporary impotence in two males and local reactions as erythema and edema of the upper extremities in two patients.

Conclusion: INF-α-2b seems to be an effective therapy for mucocutaneous lesions of Behçet's disease.
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Keywords ● Behçet's disease ● mucocutaneous lesions ● INF-α-2b

Introduction

Behçet's disease (BD) is a type of vasculitis syndrome that involves mucocutaneous, ophthalmic, and central nervous system (CNS) parts of the body.[1,2] The etiology of this syndrome is still unknown, although genetic susceptibility (HLA-B51), environmental factors, and more importantly oral *Saprophytic streptococci*, especially *sanguis* subtype, viral infections such as Epstain-Barr virus (EBV), Herpes simplex virus (HSV) and *Mycobacterium tuberculosis* may all play a role in the pathogenesis of BD.[3-5] The presence of a part of HSV-1 genome in leukocytes of some patients exposed to HSV-1 and reduced cellular responses in patients may implicate

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the suspicious role of this or a similar virus in the pathogenesis of BD.

The dominance of lymphocytes and modified cell-mediated immunity may lead to hyperactivity of lymphocytes in vascular and mucocutaneous lesions. This supports the hypothesis that immunomodulators, such as interferons with their antitumor, antiviral, and antiproliferative effects may lead to regression of lesions and suppression of immune response.[6-10] The objective of the present study, therefore, was to determine the clinical effect of IFN-α-2b on active mucocutaneous manifestations of BD.

Patients and Methods

Conduction of the present study was approved by the Ethical Committee of Mashhad University of Medical Sciences, Mashhad, Iran. Twelve patients (six women and six men) were enrolled in the study during years 1999 to 2002 received interferon (INF) therapy. They were chosen sequentially from cases referred to the Rheumatology Unit of the Ghaem Hospital of Mashhad University of Medical Sciences, according to the international diagnostic criteria for BD.[11,12] The diagnosis of BD syndrome based on the presence of at least one aphtous or genital lesion at the beginning of the evaluation, evidence of disease activity, the presence of dermatologic manifestations as well as stabilization of the dose of corticosteroid at least one month prior to the start of evaluation in patients receiving such a treatment. The exclusion criteria consisted of active retinal disease, episodes of recent active infection, leukopenia (WBC < 3,000/mm^3), thrombocytopenia (platelet counts < 100,000/mm^3), liver function test abnormalities, pregnancy and lactation. Other exclusion criteria were, recent medical problems involving liver, lung or heart, any history of chemotherapy such as colchicine, dapson, and levamisol. Cases with intraocular or intraarticular steroid injection or other experimental medication during the previous 3 months as well as newly-prescribed steroid drugs over the same period were also excluded from the study.

Initially, patients were informed about the perspective of the trial, side effects and considerations of INF therapy and if agreed a written consent was obtained. Thereafter, subcutaneous injections of 3 million units INF-α-2b (Heberon-R, Cuba) started three times per week for a period of six months on alternate days. Anticipated flu-like syndromes including fever after IFN injection were pretreated with 1000 mg acetaminophen/day in the first week and thereafter electively for its recurrences. Laboratory assessments consisting of CBC, liver function tests and HBsAg were made initially and repeated every two months. Ophthalmologic evaluation was also performed at the beginning and the end of the trial. An internist evaluated the disease activity index monthly by a scoring system. This involved the number of aphtae, or genital lesions, the size of the largest aphtae or lesion (diameter in mm), inflamed and tender joints, or the number of typical skin lesions such as pseudofolliculitis and erythema nodosa. Subjective evaluation of the pain associated with patient's aphtous lesion scored from zero (no pain) to 10 (severe disabling pain) by visual analog scales (VAS) with objective assessment of the disease activity from zero (remission) to 10 (severe).

Patients were examined by a neurologist and an ophthalmologist upon entry and discharge. According to the study protocol, a therapeutic response was defined as 50% or more improvement in different categories. Efficacy measurements consisted of the total numbers of oral, genital and cutaneous lesions, swollen and/or tender joints, and the patient's pain score on the VAS, the presence or absence of CNS or eye disease and the physician's evaluation of disease. Relapse was defined as 50% or more deterioration from the previous visit in any category of involvement.

Results

Mean age of the female and male patients under study were 26.1 (range 18-37) and 31.3 (range 20-53) yrs respectively. The mean duration of the disease was 6 yrs. All patients were HBsAg negative. Two female patients had past history of oral HSV-1. Ten of the 12 patients (patient # 1-3, 5-7, and 9-12) completed the six months course of the treatment. INF therapy discontinued in patient # 4 because there was no response to INF therapy even with 15 million units of INF-α-2b per week for two months. INF treatment suspended for two weeks in patient # 8, because of severe local reactions as diffuse erythema and edema of the injected limb after the second injection. Treatment continued by reducing the dose of INF-α-2b to six million units per week for two more months and then terminated.

The dose of INF-α-2b decreased to 6 million units per week after 5 months in two patients, because they showed complete remission with no relapse. Two patients were receiving prednisolone for three months before INF therapy. One of these patients, who were on 5 mg prednisolone per day, the dose was reduced to 2.5 mg/day after three months and then dis-

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continued without relapse. The second patient was receiving 10 mg/day prednisolone. This dose continued without any change for the whole period of INF therapy.

Changes in the number of aphtae and genital lesions of each patient are summarized in Tables 1 and 2. The size and the number of aphtae decreased significantly during INF therapy. In two patients some small painless aphtae relapsed from time to time with prolonged remission of about 20 days. At the start of INF therapy, aphtae were present in 11 patients, with the mean±SD number being 3.1±1.7 per patient (Table 1) and mean±SD size of 3.2±1.7 mm. At the end of the study, only two patients had aphtae with the mean±SD number 0.40±0.9, and the mean±SD size of 0.4±0.8 mm. At the onset of the study, genital ulcers (Table 2) were present in four patients with the mean±SD number of 1.1±1.8 per patient, and the mean±SD size of 2.2±3.6 mm. None of these patients, except patient # 4, had genital ulcers at the end of the study. Patient # 4 did not respond to INF therapy despite increasing the dose to 15 million units per week for a period four months. INF therapy was discontinued in this patient and substituted with 20 mg/day of prednisolone.

Table 1: Number of oral aphtae at the start, during 6 months INF-α-2b therapy and at the end of the treatment.

Patients#	start	1	2	3	4	5	6	end
1	1	2	0	2	1	0	0	0
2	5	1	0	1	0	0	0	0
3	0	0	0	0	0	0	0	0
4	3	3	4	2	2	-	-	-
5	3	3	0	2	0	0	0	0
6	3	0	0	0	0	0	0	0
7	2	2	0	0	2	0	0	0
8	3	3	0	-	-	-	-	-
9	5	3	2	0	1	2	0	1
10	4	2	1	0	2	0	0	0
11	5	5	2	1	2	1	3	3
12	3	2	0	0	0	0	0	0
Total	37	26	9	8	10	3	3	4
Range	0-5	0-5	0-4	0-2	0-2	0-2	0-3	0-3
Mean	3.1	2.2	0.8	0.7	0.9	0.3	0.3	0.4

Skin lesions consisted of erythema nodosa in one patient, pseudo-folliculitis in four, and typical skin lesions in one patient, with total number of 31 and mean number of 3.44 per patient ranging from 0 to 12. They responded well to INF therapy and did not show relapse after healing. In five patients, at the beginning of the treatment articular manifestations observed in five patients were arthralgia without detectable arthritis. One of these patients did not follow the course of treatment. Three showed fluctuations in their symptoms and one exhibited complete remission.

Subjective response evaluated by VAS from zero to 10 and monthly objective evaluation are summarized and in Table 3. The results showed a decline in subjective and objective scores in all categories of clinical findings. The mean number of lesions at the end of the study dropped from 6.7, at onset of the treatment to 0.40. During the course of the study none of these patients developed new ocular, CNS or vascular lesions. There was not laboratory evidence of any side effects such as leukopenia or liver function test abnormalities during INF therapy. At the end of the study the daily dose of INF-α-2b was reduced from its initial dose of three million to 2.71 million units.

Table 2: Number of genital lesions at the start, during 6 months INF-α-2b therapy and at the end of the treatment.

Patients#	start	1	2	3	4	5	6	end
1	0	0	0	0	0	0	0	0
2	4	1	0	0	0	0	0	0
3	1	1	0	0	0	0	0	0
4	5	3	1	0	2	-	-	-
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	-	-	-	-	-
9	0	0	0	0	0	0	0	0
10	3	2	0	0	1	0	0	0
11	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0
Total	13	7	1	0	3	0	0	0
Range	0-5	0-3	0-1	0	0-2	0	0	0
Mean	1.1	0.6	0.1	0	0.3	0	0	0

Table 3: Details on clinical and medical changes at the start, during 6 months INF-α-2b therapy and at the end of the treatment.

	start	1	2	3	4	5	6	end
No. of Patients	12	12	12	11	11	10	10	10
Mucocutaneous lesions								
Total No.	81	40	16	10	16	3	3	4
Mean	6.75	3.33	1.33	0.90	1.4	0.3	0.3	0.40
Range	0-22	0-11	0-7	0-4	0-6	0-2	0-3	0-3
Subjective evaluation of pain*								
Total	92	86	38	32	32	8	6	6
Mean	7.66	7.16	3.16	2.90	2.9	0.71	0.60	0.60
Range	3-10	1-10	0-10	0-8	0-10	0-7	0-6	0-6
Objective evaluation of disease								
Total	84	66	29	25	26	4	5	5
Mean	7	5.50	2.41	2.20	2.30	0.40	0.50	0.50
Interferon dose (million units)								
Mean	3	2.88	2.88	3.25	3.25	3	2.71	2.71
Range	-	2-3	2-3	3-5	3-5	-	2-3	2-3

*Visual analog score of 0-10 cm.

The most common complication was a flu-like syndrome with fever and bone pain in eight patients, which was easily controlled by taking 500 to 1000 mg/day acetaminophen

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orally. In six patients, this symptom disappeared gradually, whereas in two patients it persisted during the course of INF therapy but alleviated by taking acetaminophen before each INF injection. Local adverse reactions such as edema and erythema of the injected limb were present in two patients that led to the suspension of medication for two weeks in one patient followed by its continuation with a reducing the dose to six million units per week. In two male patients transient impotency was reported which resolved by the end of 6 months.

Discussion

Patients with BD without active ophtalmic or CNS lesions were treated with INF-α-2b in an open label clinical trial. Because of flu-like symptoms after INF-α-2b injection, a double blind placebo control trial was virtually impossible to perform.[12,13] As demonstrated in Tables 1-3, a striking decrease in the total number of lesions were found during therapy. The efficacy of INF therapy was evidenced by the reduction in the diameter of aphtous lesions. All skin lesions that observed at the beginning of the study disappeared at the end of INF therapy. These reduced sign of inflammation were matched by reductions in subjective and objective evaluations of the scores that showed a decrease from 92 and 84 at the start of the treatment to six and five at the end of the study respectively. Because all lesions of BD were unpredictable in terms of exacerbation and remission patterns, it was difficult to show convincing treatment benefits, especially in an open label design. However, the notable reductions in signs of inflammation were unlikely to have occurred by chance. In favor of a real therapeutic response were the findings that 8 patients were still in remission with no lesions at the end of 6 months.

It is unlikely that INF-α-2b can induce permanent remission in BD. INF-α-2b has antiviral activity and this is why it was originally conceived as a treatment for BD. Results of this study showed the reduction of mucosal ulcerations, cutaneous lesions and arthritis during INF-α-2b therapy as reported by other investigators.[14-25] There was a tendency to relapse in the post-treatment phase, although no relapse or any main symptomatic lesions were reported in most cases up to four months after therapy like what was reported by Hamuryudan et al.[13] A partial response to IINF-α-2b therapy and relapse of aphtous lesions were found only in one patient after discontinuation of INF therapy.

The only symptom that was not totally parallel to mucocutaneous lesions was arthralgia that showed remission in one case. In addition, the fluctuation of symptoms in the absence of real remission was observed in three patients. However, because of the presence of arthralgia, but not arthritis, the objective response evaluation was difficult to achieve. In general, weight-bearing joints that were involved in the process of degenerative joint disease were also affected in these patients; therefore it was difficult to distinguish the symptoms of the two entities subjectively. Consistent with other studies we did not find ocular or CNS diseases.[12,13]

We did not find any serious side effects like seizure and psychosis that reported by O'Duffy et al.[12] The main limitation imposed on our patients was the high cost of therapy, compared with other medications such as oral or topical steroids, colchicine or even immunosuppressive agents. The present therapeutic schedule was not compared with other treatment procedures as case control study; therefore in post treatment observation phases the history of the patients could be suitable for the evaluation of relapses after discontinuation of INF therapy.

Conclusion

Interferon therapy seems to be effective in controlling mucocutaneous lesions of Behçet's disease. The use of INF-α-2b, as an induction therapy in acute ocular or CNS involvement is suggested for its rapid onset of action.

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