Treatment of Ocular Manifistations of Behcet's Disease with Interferon 2α

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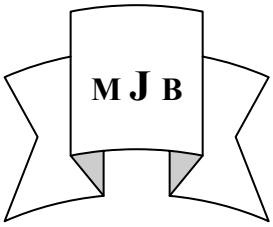

Abstract

Behcet's disease is a vasculitis of unknown etiology, it is most prevalent in Mediterranean area, the most serious problem is ocular involvement, and with the use of the immunosuppressive agents, ocular prognosis had significantly improved.

The interferon 2α is a biological agent used for the treatment of viral hepatitis and renal cell carcinoma. It is used now for the treatment of Behcet's disease, the mode of action of INF in Behcet's disease is still unknown, it has many immuno -modulatory effects, such as enhancement of HLA class (I) antigen expression on the lymphoid cells, T and NK cell cyto-toxicity, and it diverts the T cell response.

Forty patients had been studied through (2006 - 2008) in Merjan Teaching Hospital to compare the use of interferon 2α versus other immunosuppressive agents to show the difference especially in refractory eye problems and vascular involvement.

Six to nine million units of interferon per week were given subcutaneously to (20) patients whom either newly diagnosed or already had Behcet's disease and did not respond to other immunosuppressive agents , those patients are compared with other (20) patients whom already treated by other drugs like cyclosporine, azothioprine and other immunosuppressive agents .

The duration of the treatment with interferon was (3-6) months and ophthalmologist and rheumatologist did follow up for one year.

The mean age of the patients was (14-55) year, the group one included (14) males and (6) females while group two included (13) males and (7) females.

The group one showed dramatic response to interferon, especially among the newly diagnosed patients while those patients treated with other drugs got better response with the use of interferon alone.

Only three patients not responded to interferon, one was newly diagnosed and the other two were already diagnosed.

Thirteen patients showed complete remission or became stable during follow up period.

While in group two, (8) patients showed relapse after stopping therapy, (2) patients showed deterioration of the visual acuity and eye problems even with therapy and (10) patients showed complete remission in the follow up period

From this study, we found that interferon 2α is the newly emerged therapy of Behcet's disease and its complications that are not responding to ordinary therapy.

Interferon2α is useful in the treatment of Behcet's disease in Iraq and should be used to prevent serious problems of the disease like blindness and vascular obstruction.

الخلاصة

مرض بهجت من أمراض الأوعية الدموية المجهولة السبب ، ويكثر حدوث هذا المرض في دول حوض البحر الأبيض المتوسط ، ومن أكثر مشاكل المرض الخطيرة هو إصابة العين ، ولكن مع استخدام الأدوية المثبطة للمناعة تكون النتائج جيدة .

إن دواء الانترفيرون يستخدم لعلاج مرض التهاب الكبد الفايروسي ، ويستخدم الآن لعلاج مرض بهجت .

إن هذه الدراسة أجريت على (٤٠) مريض للفترة من ٢٠٠٦ ولغاية ٢٠٠٨ في مستشفى مرجان التعليمي ، للمقارنة بين استخدام هذا الدواء والأدوية الأخرى المثبطة للمناعة المستخدمة في علاج مرض بهجت . لقد تم حقن عشرون مريضاً بجرعة مقدارها ستة ملايين إلى تسعة ملايين وحدة علاجية من دواء الانترفيرون تحت الجلد أسبوعياً . وقد اجريت المقارنة مع عشرين مريضاً آخرين تناولوا أدوية أخرى مثل دواء السايكلوسبورين ، والازوثايوبرين ، والكورتيزون .

إن فترة العلاج بالانترفيرون تراوحت بين ثلاثة إلى ستة أشهر ، وقد تمت متابعة المرضى خلال هذه الفترة من قبل اختصاص العيون واختصاص المفاصل .

إن معدل أعمار المرضى كان (١٤ – ٥٥) سنة ، لقد أظهرت المجموعة الأولى التي عولجت بدواء الانترفيرون تحسناً ملحوظاً مع عدم حدوث انتكاسة ، بينما أظهرت المجموعة الثانية تحسناً عند عشرة مرضى ، وحدوث انتكاسة عند ستة آخرين عند توقف العلاج .

أظهرت هذه الدراسة ، أن علاج الانترفيرون هو العلاج الأمثل لمعالجة مرض بهجت ومضاعفاته التي لا تستجيب للعلاج الاعتيادي ، كما أن هذا العلاج يجب أن يستخدم لمنع حدوث مضاعفات المرض ، كالإصابة بالعمى وانسداد الأوعية الدموية .

Introduction

Behcet's disease is a vasculitis of unknown etiology usually multi systemic, it is most prevalent in Mediterranean countries, Asia and the Middle East, along (silk route). [1] Its main features are oral, genital, aphthous ulcers and other manifestations that include skin lesions, vasculitis or arthritis, usually oligoarthritis, and the involvement of blood vessels that include thrombophlebitis, thrombosis and aneurysms, and the central nervous system involvement. The disease is associated with (HLA B5).

The most serious problem is ocular involvement, which may lead to blindness. These manifestations include bilateral panuveitis running in chronic course, this may affect (60-80) % of patients. [2]

In most previous studies, blindness occurred in (20-50)% of patients within 5 years, [3] with increasing the use of the immunosuppressive therapy, the ocular prognosis had been improved. One of these agents was azthioprine, which is shown to maintain the visual acuity and prevent the development of eye lesions, (4) but this agent especially in severe panuveitis and retinal vasculitis may not act rapidly to prevent eye damage; and it acts slowly in the treatment of vascular involvement or central nervous system involvement. [4]

The cyclosporine A is another drug that act more rapidly on eye and other problems of Behcet's disease but because of its effect on kidney at a dose higher than 5 mg/Kg/day and the relapse that may occur with the stop of the treatment some time this limit its use. [5]

Cytotoxic therapy such as cyclophosphamide and chlorambucil are also used but to limited extent because of their toxicity. Colchicine only effective in skin, mucous and posterior uveitis, and the steroids is useful in short course only and not suitable for long term therapy. [6]

Interferon had been used in small selected cohorts with Behcet's disease, it shows efficacy in few open studies with up to (20) patients without ocular involvement.[7]

Recently they started to use this drug in the treatment of refractory eye diseases successfully treated with steroids, immune-suppressants, and INF in various combinations. [8]

The INF is used in the treatment of different types of malignancy and hepatitis due to viral origin and it is available in Iraq in few centers that deal only with oncology and gastroenterology.

The mode of action of INF in Behcet's disease is still unknown, it has many immunomodulatory effects, such as enhancement of HLA class (I) antigen expression on the lymphoid cells, T cells and NK cells cytotoxicity and it diverts the T cells response. [9]

INF also has immunosuppressive effects, which could directly suppress vasculitis, as it does, for example, it inhibits the adhesion of T cells to the endothelial cells. [10]

Patients and Methods

This study was done in Merjan Teaching Hospital during (2006 – 2008).

Forty patients with Behcet's disease with uveitis or vascular complications are the main target of the study had divided into two groups.

Group one was treated with interferon 2α while the other group was treated with traditional therapy that includes cyclosporine with steroids ± azthioprine.

All patients in both groups had examined for uveitis or other eye problems by experienced ophthalmologist in private clinic or referred from hospitals. The ophthalmic examination included visual acuity measurement by a snellens chart , slit lamp examination of the anterior segment, measuring of intraocular pressures by Goldmann applination tonometer, fundus examination by using indirect ophthalmoscope and (+90) volk lens with the aid of slit lamp.

The frequency of attacks and the changes in visual acuity for each patient at the start, the end of the study, and during follow-up period were reported. We consider improved visual acuity if the improvement of the visual acuity was at least (2) lines on Snellen's chart, and the same visual acuity if there is improvement in one line or no change in the vision and decrease visual acuity if there is worsening in one line or more.

Twenty patients were included in each group. The age of patients was range from (16 - 55) years. All patients of two groups have examined in rheumatology clinic in Merjan Teaching Hospital, sent for CBP, Doppler study for vascular problem patients. All diagnosed as Behcet's disease according to international guide line criteria or ACR criteria, patients with hepatic, renal, heart failure, infections and other autoimmune diseases were excluded from this study.

The follow-up period included monthly checking of visual acuity with ocular examination associated with assessment of response to the therapy and side effect of drug; all attacks were recorded during follow-up period.

The first group: (20) patients included (14) male and (6) female. Thirteen patients were already diagnosed as Behcet's disease, (12) of them had refractory eye disease and one has refractory vascular problem. The other (7) patients were newly diagnosed Behcet's disease.

All patients in this group received dose of (6 - 9) million units per week with small dose of steroids (prednisolone tab) less than (10) mg/day.

The second group: included (20) patients. They were (11) males and (9) females, with age range from (16 - 63) years. Two patients have newly diagnosed as Behcet's disease. All patients had ocular involvement and at first they started on cyclosporine with steroids, (2) patients received Azathioprine in addition to their treatment.

Results

All patients in group one who were treated with interferon Alfa showed dramatic response. Four patients of them were newly diagnosed Behcet's disease with uveitis were treated for (6) months showed complete remission

The ocular manifestations: twenty-four patients (60%) with uveitis involving both eyes and (16) patients (40%) with uveitis involving one eye.

Twenty-nine patients of both groups presented with anterior and posterior uveitis, (7) patients of both groups presented with posterior uveitis, and (4) patients of both groups presented with anterior uveitis.

From the results of table (1), we found that (14) patients (70%) get improvement in the visual acuity after treatment and follow up period while (12) patients (60%) of group (2) get improvement in the visual acuity.

Five patients (25%) of group (1) had no changes or only one line

improvement in the visual acuity, while (6) patients (30%) of group (2) had no changes or one line improvement in the visual acuity.

Only one patient of group (1) and two patients of group (2) had deterioration of vision, which was irreversible because of retinal ischemia or macular scars as consequence of long-standing refractory retinal vasculitis. However, there are major differences between the two groups; that group (1) include patients refractory to other treatment that was used in group (2).

In the group one, (14) patients (70%) got rapid remission of mouth and skin lesions while in the group two, only (10) patients (50%) got remission with longer period.

Four patients with vascular lesions in group (1), those got more than (50%) improvement in Doppler study within one month of the treatment with interferon alpha.

The articular manifestations: the study showed no difference between both groups which were treated with steroids and different types of non-steroidal anti-inflammatory drugs.

Group 1

No	Sex	Age	BiL/Uni L	Therapy Duration	Other Therapy	History of Illness	1st threat or Refract	Aspirin	Recurrence	Stop Therapy	Other lesion	Side effect	visual Acute	ocular manifestations
1	♀	22	Bilateral	6 Months	10 Presolone	4 years	Refract	*	nil	_	CNS , Mouth	Fatigue only	↑	anter+post
2	♂	25	Bilateral	6 Months	10 Presolone	2 years	Refract	_	nil	_	Skin	nil	↑	anterior
3	♀	33	Unilateral	4 months	10 Presolone	2 years	Refract	_	nil	_	Mouth , Skin	Fatigue only	→	anter+post
4	♂	30	Bilateral	6 Months	10 Presolone	20 years	Refract	*	nil	_	skin, vascular	nil	↑	anterior
5	♂	45	Bilateral	6 Months	Presolone + Immur	3 years	Refract	_	nil	_	Mouth	Fatigue only	↑	anter+post
6	♀	35	Bilateral	6 Months	Presolone	1.5years	1st+ Refract	*	nil	_	Mouth	nil	↑	anter+post
7	♂	36	Unilateral	3 Months	10 Presolone	2.5years	Refract	_	nil	_	skin, vascular	Fatigue only	↑	anterior
8	♀	28	Bilateral	3 Months	10 Presolone	1 year	Refract	*	*	_	skin, vascular,mouth	*	→	anter+post
9	♂	40	Bilateral	4 months	10 Presolone	4 years	1st+ Refract	_	*	*	CNS , skin	nil	→	anter+post
10	♂	49	Bilateral	6 Months	10 Presolone	15 years	Refract	*	nil	_	skin, mouth	*	→	anter+post
11	♂	55	Bilateral	6 Months	cyclophoso	10 years	Refract	_	*	_	skin, mouth	nil	↓	poster
12	♂	24	Bilateral	6 Months	10 Presolone	1 years	Refract	_	nil	_	skin, mouth	*	↑	anter+post
13	♂	29	Unilateral	3 Months	10 Presolone	2.5 years	1st+ Refract	_	*	_	Mouth,skin,vascular	nil	↑	poster
14	♂	37	Unilateral	6 Months	10 Presolone	1 year	Refract	*	nil	_	CNS, skin	*	↑	posterior
15	♂	41	Bilateral	6 Months	10 Presolone	5 years	Refract	_	nil	_	CNS, mouth	nil	→	anter+post
16	♀	25	Unilateral	6 Months	10 Presolone	2 years	1st+ Refract	*	nil	_	mouth, skin	*	↑	anter+post
17	♂	26	Bilateral	6 Months	10 Presolone	1 year	Refract	_	nil	_	Skin	*	↑	anter+post
18	♀	14	Unilateral	3 Months	Mil	2 years	1st+ Refract	_	nil	_	Mouth , Skin	nil	↑	anter+post
19	♂	25	Bilateral	6 Months	10 Presolone	6months	Refract	_	nil	_	mouth, skin	*	↑	anter+post
20	♀	23	Bilateral	6 Months	10 Presolone	2 years	Refract	_	nil	_	mouth, skin	nil	↑	anter+post

Group 2

No	Sex	Age	BiL / Uni L	old Re	New Re	Duration	Recurrence	Visual acuity	Ocular manifestation	Dose of cyclo
1	♂	40	. BiL	Steroid	cyclosorine	1year	nil	↑	anter+ post	5mg
2	♂	35	BiL	Steroid	Cyclosporin	4 year	nil	↑	anter+ post	5mg
3	♂	30	Uni L	Steroid	cyclosorine	5 year	*	→	posterior	5mg
4	♀	25	Uni L	Steroid	Cyclosporin	3 months	nil	↑	anter+ post	5mg
5	♂	18	Uni L	Steroid	Cyclosporin	2 year	*	→	anter+ post	5mg
6	♀	16	BiL	Steroid	cyclosporine	3 years	nil	↑	posterior	5mg
7	♂	60	BiL	Steroid	cyclosporine	5 years	*	→	anter+ post	5mg
8	♂	40	BiL	nil	cyclosporine	3 months	nil	→	posterior	5mg
9	♀	35	Uni L	nil	cyclosporine	1 year	nil	↑	anter+ post	5mg
10	♂	40	Uni L	Steroid	cyclosporine	2 year	*	→	anter+ post	5mg
11	♀	30	BiL	steroid	cyclosporine	11 months	nil	↑	anter+ post	5mg
12	♀	14	Uni L	Steroid	cyclosporine	6 months	nil	↓	anter+ post	5mg
13	♀	12	Uni L	Steroid	cyclosporine	2 years	*	→	anter+ post	5mg
14	♂	15	BiL	Steroid	Cyclosporin	15 years	nil	↑	posterior	5mg
15	♂	20	BiL	Stero	Cyclosporin, Immun	2 years	*	↑	anter+ post	5mg
16	♂	45	Uni L	Steroid	Cyclosporin	1 year	nil	↓	anter+ post	5mg
17	♀	35	BiL	Steroid	Cyclosporin	6 months	*	↑	anter+ post	5mg
18	♂	63	BiL	nil	Cyclosporin	6 months	nil	↑	anter+ post	5mg
19	♂	50	Uni L	steroid	Cyclosporin	3 year	*	↑	anter+ post	5mg
20	♂	35	Uni L	NiL	Cyclosporin	6 months	nil	↑	anterior	5mg

Discussion

Interferon 2α was effective (95%) and rapidly acting (time of response (2 - 4) weeks) for treatment of Behcet's disease with severe ocular involvement, no new ocular involvement during the fellow up period and the incidence of relapse is low.

For cyclosporine the effectiveness was between (80-91) %, [11, 12] the side effects were frequent and the number of relapses during dose-reduction was high.

As comparison of data reported, it seems that interferon 2α had approximately the same response rate as cyclosporine, but it would lead to more stable response with less ocular relapses, and it is used for patients who were not responding to other drugs.

Conclusion

Interferon 2α may be superior to the standard therapy especially for severe attacks of pan-uveitis and retinal vasculitis due to its rapid action, restoration of the visual acuity and its potential for complete remission after tapering of medication without relapses.

References

1. Yazici H. Behcet's disease. In: Klippel JH, Dieppe PA, eds. Rheumatology. St Louis: Mosby 1998:7.26.1-2.
2. BenEzra D, Cohen E. Treatment and Visual Prognosis in Behcet's Disease. Br. J. Ophthalmal. 1986; 70: 589-92.
3. Kotter I, Eckstein AK, Stubiger N, et al. Treatment of Ocular Symptoms of Behcet's with Interferon α2-a Pilot Study. Br. J. Ophthalmol. 1998; 82: 488-94.
4. 4-Yazici H, Pazarli H, Barnes CG, et al. A Controlled Trial of Azothioprine in Behcet's Syndrome. Engl. J. Med.1990; 322:281-5.
5. Ben Ezra D, Cohen E , Chajek T, et al. Evaluation of Conventional Therapy Versus Cyclosporine A in Behcet's Syndrome. Transplant Proc. 1988; 20: 136-43.
6. Bang of Behcet's Disease. Yonsei Med. J. 1997; 38: 401-10.
7. Tsambaos D, Eichelberg D, Goos M. Behcet's Syndrome: Treatment with Recombinant Leukocyte Alpha-interferon. Arch. Dermatol. Res. 1986; 278: 335-6.
8. Feron EJ, Rothova A, van Hagen PM, et al. Interferon α-2b for Refractory Ocular Behcet's Disease. Lancet 1994; 343: 1428.
9. Belardelli F, Gresser I. The Neglected Role of Type One Interferon in the T-cell Response: Implication for its Clinical Use. Immunol. Today. 1996; 22: 1183-4.
10. Eguchi K, Kawakami A, Nakashima M, et al. Interferon-alpha and Dexamethasone Inhibit Adhesion of T Cells and Synovial Cells. Clin. Exp. Immuno. 1992; 88: 448-54.
11. Boyvat A. Sisman-Solak C, Gurler A. Long Term Effects of Interferon α2-a Treatment in Behcet's Disease. Dermatology. 2000; 201: 40-43
12. Alosoy E, Er H, Durusoy C, Yilmaz E. The Use of Sucralfate Suspension in the Treatment of Oral and Genital Ulcerations of Behcet's Disease: a Randomized, Placebo-controlled and Double Blind Study. Arch. Dermatol. 1999; 135: 529-532.