Research Article

Potential role of infliximab therapy in twelve Libyan patients with Behçet's disease

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Abstract

Background: The blocking of tumour necrosis factor-α (TNF-α) with the so-called anti TNF-α agents has turned into the most important tool in the management of a variety of autoimmune disorders.
Objective: To evaluate the therapeutic effect of infliximab on ocular and extraocular manifestations in patients with Behçet's disease (BD).
Methods: Twelve patients with active BD who were treated with infliximab at Tripoli Medical Center for more than 6 months were included in this study. Infliximab was initiated with 5mg/kg of body weight. Infusion given at (week 0, 2, 6 and every 8 week thereafter) as either first-line therapy in eight patients or given after failure of conventional immunosuppresants in the remaining four patients. All patients were assessed by clinical examination and inflammatory markers. The patients with ocular involvement were assessed clinically by an ophthalmologist every 2 months and those with neuro- Behçet's disease had in addition MRI assessment for the brain.
Results: The follow-up period after initial introduction of infliximab ranged from 6 to 36 months (mean±SD,15.5±7.4 months). Eight (67%) patients achieved remission without any relapse while two (17%) patients had only one relapse in the same organ during the period of follow up. One (8%) patient had relapse in another system and infliximab was stopped. One (8%) other patient had no response. Immunosuppresants were stopped in all patients except one and all were kept on low dose glucocorticoids. No drug side effects were reported. In eight patients who started on infliximab as first line therapy, the remission occurred in six patients (75%) while in the other four patients who were taking infliximab after failure of conventional immunosuppresants, the remission occurred in two patients (50%).
Conclusion: Infliximab is effective in inducing remission of BD. The good effect together with excellent tolerability suggests that infliximab can be used as first line drug in BD.

Keywords: Anti TNF-α, Infliximab, Behçet's disease

Introduction

Behçet's disease is an immune-mediated multisystem occlusive vasculitis of small blood vessels, especially venules, of unknown aetiology[1]. Formerly representing a disease of typically Mediterranean origin, Behcet's disease is now recognized in patients of various ethnicities all over the world, making it necessary to think about 'typical' disease manifestations in 'atypical' patients[2]. The manifestations of Behçet's disease may occur at many sites throughout the body. However, the disease seems to target certain organs and tissues. Ocular involvement can develop early in the disease course and lead to permanent vision loss in 20% of cases[3]. Ocular involvement can be in the form of posterior uveitis, anterior uveitis, or retinal vasculitis. Anterior uveitis presents with painful eyes, conjunctival redness, hypopyon, and decreased visual acuity, while posterior uveitis presents with painless decreased visual acuity and visual field floaters. A rare form of ocular involvement is retinal vasculitis which presents with painless decrease of vision with the possibility of floaters or visual field defects[3].

Neurological involvement most often occurs as a chronic meningoencephalitis. Lesions tend to occur in the brainstem, the basal ganglia and deep hemispheric white matter and may resemble those of multiple sclerosis. Brainstem atrophy is seen in chronic cases[4]. Neurological involvements range from aseptic meningitis to vascular thrombosis such as dural sinus thrombosis and organic brain syndrome manifesting with confusion, seizures, and memory loss[4]. Tumor necrosis factor – alpha (TNF-α) is a pleiotropic cytokine which plays a major role in the development, homeostasis, and adaptive responses of the immune system. In fact, it is central to the initiation and maintenance of inflammation in multiple autoimmune and nonautoimmune disorders. Infliximab is an IgG1 chimeric monoclonal antibody with a central human region and variable murine one. This agent binds both the soluble and the cell-bound TNF α but not TNF-β [5-7].

The blocking of TNF-α with the so-called anti TNF agents has turned into the most important tool in the management of a variety of disorders, such as rheumatoid arthritis RA, spondylo-arthropathies, inflammatory bowel disease and psoriasis[8]. Infliximab is now widely used throughout the world for the treatment of RA and a growing list of other inflammatory arthropathies[9]. Treatment with infliximab in RA produced a rapid and significant reduction in the number of tender and swollen joints and concentrations of serum C reactive protein (CRP)[10]. In ankylosing spondylitis, infliximab treatment was associated with significant improvement in all disease activity measures Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) compared with placebo[11]. In psoriatic arthritis, treatment with infliximab was associated with improvement in both the joint and skin manifestations[12]. The study aimed to assess the off-label use of infliximab in Behçet's disease.

Materials and Methods

Twelve patients fulfilled the international study group for BD[13] who were treated with infliximab at Tripoli Medical Center for more than 6 months were included in this study. Infliximab was initiated with 5mg/kg of body weight. Infusion given at (week 0, 2, 6 and every 8th week thereafter) as either first-line therapy in eight patients or given after failure of conventional immunosuppresants in the remaining four patients. All patients were assessed by clinical examination and inflammatory markers. The patients with ocular involvement were assessed clinically by an ophthalmologist every 2 months and those with neuro- Behçet's disease had in addition MRI assessment for the brain. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting infliximab were requested to monitor it's side effect during follow up. All these investigations were normal before starting infliximab and tuberculin test was negative.

All patients consented to participate in the study. The study was done after receiving consent from the Tripoli Medical Center ethical and research committee.

Data was analyzed using SPSS computer software package. Mean and standard deviation of the age and the period of follow up were calculated. P value to measure if there is significant difference between the mean of visual acuity before starting infliximab and at the last follow up were calculated using t- test. The p value to measure if there is significant difference between using infliximab as first or second line treatment was calculated using the Z approximation test to compare two proportions.

Results

Twelve patients included in the study, the mean age was 27 years (±SD 7.8 years), ten were males and two were females. The mean duration of taking infliximab was 15.6 months (± SD 7.2 months) (Table 1). The clinical characteristics for the twelve patients are shown in Table 2.

Table 1: Demographic and clinical characteristics of the twelve patients

Mean age at diagnosis	27 years ± (SD= 7.8 years)
Sex	
Male	10
Female	2
The mean duration of taking infliximab	15.6 months ± (SD=7.2 months)

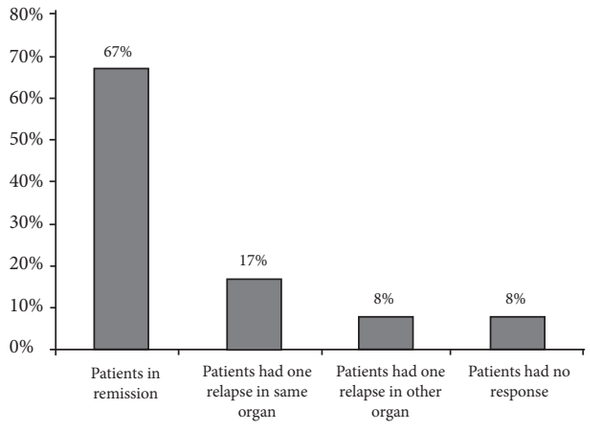
Table 2: Clinical characteristics of the twelve patients

Clinical features of BD	No. (%)
Oral ulcers	12 (100)
Genital ulcers	8 (67)
Skin lesions	4 (33)
Eye lesions	8 (67)
Vascular involvement	2 (17)
Neurological features	3 (25)
Pathergy test	2 (17)

Infliximab was started in these twelve patients for the following manifestations: In six patients the infliximab was started for ocular manifestations, two patients with neuro-Behcet's disease, one had mucocutaneous lesions, one had vascular involvement, one with ocular and neuro-Behçet's disease and one had ocular and vascular involvement.

Eight (67%) patients achieved remission without any relapse during the period of follow up. Two (17%) patients had only one relapse in the same organ. One had ocular attack 14 months after starting infliximab. The other patient had recurrence of oral ulcers and acne six months after starting infliximab. In one (8%) patient, infliximab was started to treat neuro-Behçet's manifestations. She had relapse in another organ (bilateral pulmonary embolism) and infliximab was stopped. One (8%) patient had no response; he had no change in visual acuity (only light perception in both eyes) (Figure 1).

Figure 1: The response of the twelve patients to infliximab



All patients started on oral prednisolone 60mg/day which tapered gradually to 5 mg/day.

Ten patients were on colchicin and three were on warfarin. One patient with ocular involvement was on cyclosporine and azathioprine consecutively and another one was on azathioprine only. One patient with

neuro-Behcet's disease was on cyclophosphamide and then on azathioprine. One patient had mucocutaneous features and treated by azathioprine, methotrexate and dapsone consecutively. After starting infliximab, immunosuppresants were stopped in all patients except one and all were kept on low dose glucocorticoids (5mg/day). Eight patients with ocular involvement had bilateral ocular involvement. Changes in affected eyes included panuveitis (50%), posterior uveitis (37%), anterior uveitis (12%), vitritis (38%), retinal vasculitis (31%), vitrous degeneration (6%), cytoid macular oedema (13%) and central retinal artery occlusion (6%). None of the patients had visual acuity worsening. At the final follow-up, mean right and left eye visual acuity respectively increased from (0.23± 0.33) at the baseline to (0.67±0.36) ($p<0.05$) and from (0.13±0.34)to (0.24±0.40) ($p<0.05$).

Six (75%) patients had no ocular attacks during their period of follow up; their last ophthalmologic assessment reported no active uveitis. one (12.5%) patient at the 10th dose of infliximab had one ocular attack (bilateral active uveitis) treated by increasing the dose of prednisolone (1mg/Kg/day) and then tapered gradually, thereafter there were no more ocular attacks. One (12.5%) patient had no response. Three patients who were assessed clinically and by MRI scan had Neuro-Behçet's Disease (NBD). MRI was done before taking infliximab and at the last visit (one year after taking infliximab). The first patient went in remission, with complete improvement of short term memory loss, left 6th cranial nerve palsy, hemiparesis and no more attacks of convulsions and complete disappearance of high signal intensity lesions in parietal area and brain stem. (Figure 2 a and b).

Figure 2-a: MRI brain showed area of high signal intensity before infliximab (Arrow)

(a)

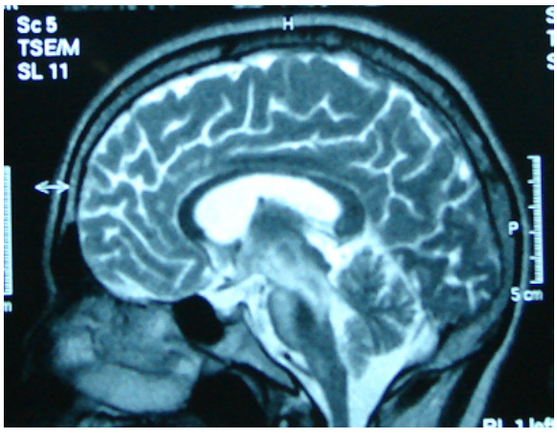
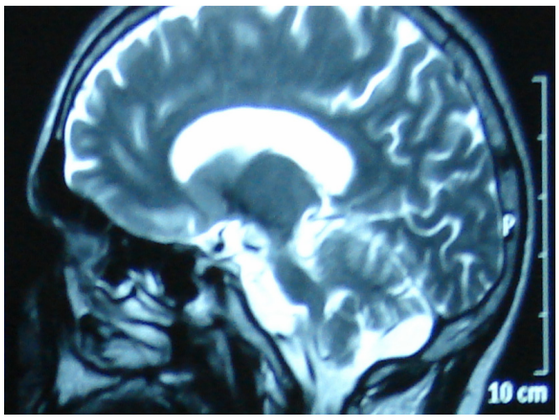


Figure 2-b: MRI brain showed disappearance of high signal intensity area after infliximab (Arrow)

(b)



The second patient had significant clinical improvement with complete improvement of right side hemiparesis. But he still had emotional lability and very mild dysarthria. MRI scan showed high signal intensity lesions in frontoparietal area before starting infliximab and the presence of some residual lesions one year after. The third patient had no significant clinical improvement. She still had dysarthria and paraparesis but urine incontinence was improved, her MRI scan showed periventricular and spinal cord high signal intensity lesions before starting infliximab and no improvement occurred in the last MRI. This patient had bilateral pulmonary embolism one year after starting infliximab and it was stopped. There were two patients with vascular involvement. One patient had recurrent left femoral vein thrombosis. At two months follow up, the ESR was decreased from 52 mm/hr to 12 mm/hr. Doppler ultrasound of left lower limb showed patent deep venous system. The other patient had also left femoral vein thrombosis. During follow up the ESR decreased from 30 mm/hr to 5 mm/hr. Doppler ultrasound showed normal left femoral vein. In one patient the infliximab was started because he had refractory mucocutaneous features which manifested by recurrent erythema nodosum on legs and forearms, recurrent oral ulcers and recurrent pustules over the chest. This patient was on methotrexate, azathioprine, colchicine and dapsone which were used consecutively and didn't show any improvement. The patient from the 2nd dose to the 6 dose was in remission. Then he developed a relapse in term of pustules on chest and oral ulcers, for that we planned to increase the frequency of

infliximab every 6th week instead of 8 weeks and he went in remission thereafter. No drug side effect occurred in these twelve patients.

Discussion

In eight patients who started on infliximab as first line therapy, the remission occurred in 6 (75%) patients while in the other four who were taking infliximab after failure of conventional immunosuppresants, the remission occurred in two (50%). The p-value was 0.20 which is not statistically significant. There was no statistically significant difference between using infliximab as first or second line treatment in our patients and this was because of small number of patients in our study. For comparison we recommend to do large randomised controlled studies to decide either to use it as first or second line treatment.

In a multicenter study of infliximab for refractory uveoretinitis in Behcet's' disease done in Japan by Okada *et al*[14], the efficacy of infliximab was analyzed in 50 patients. The mean best-corrected visual acuity improved from 0.736 at the first infliximab infusion to 0.616 at the end of one year (p=0.01). They concluded that, at the end of one year, uveoretinitis had improved or improved some what in 92% of patients, accompanied by improvement in the mean visual acuity. Another study by Adler *et al*[2] which included seven cases with vascular involvement concluded that, there is a striking effect of infliximab in severe vascular BD. They confirmed the fact that surgery of inflamed blood vessels should be avoided, that no foreign material such as stents should be used during active inflammation, and that disease remission should be achieved before surgery is performed. Still there are no large studies on infliximab treatment in Neuro-Behçet's Disease NBD. Zeydan *et al*[15] reported 11 patients with NBD treated with infliximab in their inpatient clinic. Four patients showed clinically significant improvement and seven patients were in remission. In our study, we had three patients, one was in remission, one showed significant clinical improvement and one had no response. The finding of our small cohort should be confirmed using a standard controlled trial.

Conclusion

Infliximab is effective in inducing remission of BD. The good effect together with excellent tolerability suggests that infliximab can be used as first line drug in BD.

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