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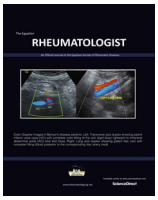

Original Article

Efficacy of infliximab in refractory posterior uveitis in Behcet's disease patients

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ABSTRACT

Aim of the work: Ocular manifestations are the main cause of morbidity in Behcet's disease (BD). Infliximab (IFX), a chimeric monoclonal antibody directed against tumor necrosis factor-alpha, may be efficient in refractory uveitis due to BD. The aim of this study was to assess the efficacy and safety of IFX in the treatment of patients with BD-associated refractory posterior uveitis (PU).

Patient and Methods: Twenty patients with refractory Behcet's PU received IFX therapy as intravenous infusions at the dose of 5 mg/kg at weeks 0,2, 6 (induction) and every 8 weeks for a maximum of 6 infusions.

Results: The mean age of the patients was 31.8 ± 9.1 years, disease duration was 8 ± 6 years and 17 (85%) were males. After the third IFX infusion (week 8) a complete remission of PU was recorded in 8/20 (40%) patients and partial remission in 12/20 (60%) patients. At the end of week 32 a complete remission of PU was recorded in a total of 14 (70%) patients. The visual acuity of the 36 affected eyes (16 bilateral and 4 unilateral) showed a significant improvement at the week 8, and at week 32, while there was no additional improvement at week 56. Relapse occurred in 6 patients (30%) between week 9 and week 18 with a mean of 13.5 weeks.

Conclusion: IFX infusion should be considered for the control of acute PU, whereas repeated long-term IFX infusions were effective in reducing the number of episodes in refractory PU with fast regression and complete remission of complications.

1. Introduction

Behcet's disease (BD) is a chronic, relapsing, systemic form of primary vasculitic disorder of unknown cause, mainly characterized by recurrent aphthous oral ulcers, genital ulcers and ocular inflammation [1]. The prevalence of BD is the highest in the Middle East, Mediterranean region and Asia. The usual age of onset is around 30 [2]. Ocular manifestations are the main cause of morbidity in BD [3]. The risk is highest in young men and lowest in women with late onset disease [4]. The disease can affect the anterior and/or posterior segment of the eye. The main manifestations include iridocyclitis, hypopyon, mild to moderate vitreitis, retinal vasculitis and occlusion of retinal vessels, optic disc hyperemia, and macular edema [5], and if not treated may cause blindness. The risk of blindness increases progressively reaching 25% at 10 years and remains constant thereafter [6]. Patients were observed to become blind in an average of 3.36 years after the onset of eye symptoms [7]. Visual acuity (VA) was reported to be affected in 50%–90% of cases to reach 6/60 or worse within four years after the onset [8]. Visual acuity affection differs significantly between patients from different geographical areas [9].

On treating posterior uveitis (PU) in Egyptian BD patients, intravitreal methotrexate (MTX) and retrobulbar steroids had a comparable efficacy with a high frequency of relapse [10]. Patients with poor vision were more frequently in India, Iran and Japan [11]. Although there are no controlled trials, the existing evidence suggests efficacy of infliximab (IFX) in treating BD patients with refractory uveoretinitis, entero-Behçet, neuro-Behçet, vascular BD and arthritis [12]. The aim of this study was to assess the efficacy

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and safety of IFX in the treatment of refractory PU in BD patients and to investigate its efficacy to reduce disease flare-up.

2. Patients and methods

Twenty BD patients who met the criteria of The International Criteria for Behçet's Disease (ICBD) [13], with refractory PU, attending the rheumatology clinic in Agouza Rheumatology & Rehabilitation Military Centre were involved in the current study. The study was approved by the local ethics committee and conforms to the declaration of Helsinki. All subjects gave informed consent and patient anonymity has been preserved.

At baseline all patients underwent the following investigations: history taking, physical examination, purified protein derivative (PPD) test, laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood cell count with differential count, renal and liver function and antinuclear antibody (ANA) titer were evaluated. Moreover, a careful screening for tuberculosis was made by detailed medical history, chest X-rays and PPD test.

Ophthalmologic evaluation consisted of a complete ocular examination including best-corrected Visual Acuity (Snellen chart of 0.1–1.0), slit-lamp biomicroscopy, tonometry and ophthalmoscope, optical coherence tomography (OCT), and fundus fluorescein angiography (FFA).

Inclusion criteria: Patients included were BD with chronic PU, with or without retinal vasculitis, resistant to a dose of prednisone $\geq$10 mg/day, and at least one immunosuppressive drug e.g. MTX, azathioprine (AZA), cyclosporine (CsA), or cyclophosphamide (CYC), after at least 12 months of treatment. *Exclusion criteria*: Patients with permanent blindness, a history of recent infections, malignancies or tuberculosis, positive PPD test and radiographic signs that would be considered contraindications to therapy with Tumor necrosis factor antagonists were excluded from the study. Pregnancy and breast feeding were additional exclusion criteria; contraception was recommended to females of childbearing potential.

The response to therapy was calculated by a composite score (0–7) obtained by the sum of the grade of severity of inflammatory infiltrate and retinal vasculitis [14] and graded as follows: *Complete remission*: presence of <1 cellular reaction (scale 0–4), and remission of vasculitis (0–3 score) at fundus examination and FFA (0 absence of vasculitis, 1 vasculitis of peripheral retinal vessels, 2 posterior pole vasculitis and 3 vasculitis with evidence of areas of retinal necrosis). *Partial remission*: improvement of at least 50% of inflammation and retinal vasculitis scores. Absent: absence of any improvement or <50% of uveitis scores.

Treatment regimen: At baseline, all patients suspended the current immunosuppressive therapy, except the corticosteroids (CS). All patients were on CS 20-40 mg/day at enrollment in the study. AZA 100–150 mg/day was started. In addition, all subjects received IFX 2-h intravenous infusions at the dose of 5 mg/kg at weeks 0,2,6 (induction) and every 8 weeks for a maximum of 6 infusions after induction i.e. follow up period is 12 month after induction. IFX-dose escalation through infusion-interval shortening to 6 weeks was allowed in non responders or in those with partial remission according to the judgment of the physician. In responders, CS dose was tapered till withdrawal. Other immunosuppressant agents (other than AZA) and concomitant local CS injections were not allowed. Patients failing to achieve at least a partial remission after the third infusion of IFX withdrew from the study were planned to receive prednisone 1 mg/kg/day and an immunosuppressant different from that employed before the study entry.

All patients had a complete evaluation by an ophthalmologist, a rheumatologist and at baseline and over the follow-up visits that were scheduled after the first, third IFX infusion (week 8) and then every 8 weeks or before in case of relapse. FFA examination was scheduled at baseline, week 8, 32, and 56, and when needed.

Statistical analysis: The Statistical Package of Social Science Software program, version 15 (SPSS) was used for statistical analysis. Data was summarized using mean or median and standard deviation for quantitative variables and frequency and percentage for qualitative variables. Comparison between groups was done using independent sample t-test and repeated measures ANOVA (with Bonferroni multiple comparison adjustment) for quantitative variables, chi square test or Fisher's exact test for qualitative variables. P values $\leq$0.05 were considered statistically significant.

3. Results

Seventeen patients were males (85%), with female: male ratio 1:5.6. The mean age of the patients was 31.8 ± 9.1 years, with mean disease duration of 8 ± 6 years, while the mean age of onset of the uveitis in those patients was 23.7 ± 6 years. Uveitis was the presenting symptom preceding the other symptoms of BD in 2 (10%) patients, appeared with other manifestations of the disease in 12 (60%) patients, and followed the other manifestations in 6 (30%) patients. Disease manifestations of all patients are presented in Table 1. Central nervous system manifestations in the form of headache, seizures, dural sinus thrombosis, ataxia, aphasia, pseudo bulbar palsy, hemiplegia, were found in 6 (30%) patients; one of them had history of stroke. Skin lesions in the form of erythema nodosum, pseudofolliculitis and papulopustular lesions occurred in 11 (55%) patients. Uveitis in the 16 patients was bilateral (80%). Thirteen patients (65%) had PU only, while 7 patients (35%) had panuveitis.

History of immunosuppressive treatments that were given to the patients before inclusion into the study included MTX as weekly injection in 2 patients at a dose of 25 mg/week for 24 months, AZA orally at a dose of 100–150 mg/day in 3 patients for a mean duration of 24.3 ± 1.5 months, CsA orally in 9 patients at a dose of 100-300 mg/day for a mean duration of 21.8 ± 11.3 months and CYC in one patient as I.V. monthly (0.75 mg/cm^3) for 6 months and every 3 months for 6 times. CsA and AZA were used orally in 5 patients for a mean duration of 22.6 ± 2.9 months.

After the third IFX infusion (week 8) a complete remission of PU was recorded in 8/20 (40%) patients, partial remission in 12/20 (60%) patients. 2/8 patients with complete remission after induction went into relapse, after 12 and 16 weeks. They received extra two infusions (6 weeks apart) to get into a remission again. At the end of week 32 a complete remission of PU was recorded in other 6/12 patients, partial remission in 6/12. 4/6 patients that showed complete remission after week 32 went into a relapse, after 9, 12, 17, and 18 weeks, at weeks 41, 44, 49 and 50. They received

Table 1
Disease manifestations of the Behçet's disease patients.

Manifestation n (%)	BD patients (n = 20)
Oral ulcers	20 (100)
Genital ulcers	17 (85)
Fever	5 (25)
Fatigue	6 (30)
Arthritis	12 (60)
Arthralgia	11 (55)
Eye involvement	20 (100)
Skin involvement	11 (55)
CNS involvement	6 (30)
Arterial thrombosis	1 (5)
Venous thrombosis	4 (20)
Superficial thrombophlebitis	6 (30)

BD: Behçet's disease, CNS: central nervous system.

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