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Long-Term Efficacy of Infliximab for Treatment of Severe Behçet's Uveitis

Emanuela Interlandi[1]*, Pietro Leccese[2,3], Ignazio Olivieri[2,3] and Loredana Latanza[1]

[1]*Department of Ophthalmology, "A. Cardarelli" Hospital, Italy*

[2]*Department of Rheumatology, "San Carlo" Hospital, Italy*

[3]*Department of Rheumatology "Madonna delle Grazie" Hospital, Italy*

***Corresponding author:** *Emanuela Interlandi, Department of Ophthalmology, "A. Cardarelli" Hospital, Via Antonio Cardarelli 9, 80131, Naples, Italy, Tel: 0039-328 8847314, E-mail: dott.emanuelainterlandi@gmail.com*

Abstract

Introduction: Behçet's uveitis is a serious sight-threatening condition that may lead to blindness if not appropriately managed. The aim of the present study is to evaluate long-term effectiveness of infliximab in resistant Behçet's uveitis.

Methods: Medical records of 32 patients (56 eyes) were retrospectively analysed. Primary outcomes included ocular inflammatory activity, frequency of uveitis attacks and steroid-sparing effect.

Results: Mean follow-up was 33,2 months while mean age of patients at disease onset was 33,3 years. Ocular inflammation was bilateral in 75% of cases and consisted in panuveitis in 46,4 % of affected eyes. All patients received intravenous infusions of infliximab (5mg/kg) at weeks 0, 2, 4, 6 and every 6-8 weeks thereafter. Clinical remission was observed in 26 out 32 patients (81,2%). Mean number of uveitis attacks decreased from 2,56 to 0,65 during infliximab therapy (p<0.001) while systemic corticosteroids were tapered in 17 patients and suspended in 10 (31,2%).

Conclusions: Our study suggested that infliximab is long-term effective in resistant Behçet uveitis, improving visual prognosis and stabilising clinical course of disease in a large cohort of patients with various pattern of BD including neuro-behçet forms.

Keywords

Behçet's uveitis, Anti-TNFα, Infliximab

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder of unknown aetiology and relapsing course characterised by recurrent oral and genital ulcers, skin and eye lesions [1,2]. Ocular involvement mainly consists in non-granulomatous uveitis that may interest anterior segment, posterior segment or both (panuveitis). Severe forms of Behcet's uveitis may produce serious visual impairment with potential blindness of affected patients. Main goals of Behçet's uveitis management are prompt resolution of intraocular inflammation, prevention of recurrent attacks and preservation of vision. Tumor Necrosis Factor-α (TNFα) is a cytokine involved in establishment and maintenance of inflammatory response and, even specific aetiopathogenesis of BD is still unclear, experimental data suggest that TNFα may play a key-role in development of BD [3,4]. Infliximab is a chimeric monoclonal antibody binding with high affinity both soluble and membrane-bound TNFα molecules so to inhibit an extensive range of its biologic activities. Its use has greatly increased over last year's representing an effective therapeutic approach in BD [5-8] and previous studies have reported surprising results in severe forms of Behcet's uveitis [9-14].

We carried on a retrospective clinical study to evaluate the long-term efficacy of infliximab in large cohort of patients with severe and various forms Behçet's uveitis.

Materials and Methods

The study was conducted as a retrospective clinical data analysis of 32 patients with severe Behçet's uveitis treated with infliximab. All patients were recruited at our tertiary referral centre of Uveitis and Ocular Immunopathology where diagnosis of BD is based on ISG criteria [15] and treatment performed according to EULAR recommendations [16].

Primary outcomes included ocular inflammatory activity, frequency of uveitis attacks and steroid-sparing effect of infliximab; secondly we analysed changes of best corrected visual acuity (BCVA), impact of infliximab on traditional immunosuppressive therapy with disease modifying anti-rheumatic drugs (DMARDs) and occurrence of infliximab-related side effects. In all cases final records, resulting at the beginning of the present study, were compared with clinical data at baseline. Ocular inflammatory activity and relapses of anterior segment and vitreous were evaluated according to Standardization Uveitis Nomenclature (SUN) workshop criteria [17]. Posterior uveitis was evaluated by fundus ophthalmoscopy and fluorescein angiography (FA) while macular involvement was moreover assessed by Optical Coherence Tomography (OCT). Follow-up visits were performed every one-three months or less depending on clinical course of single

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case and included BCVA evaluation, full slit-lamp examination, tonometry and FAG and/or OCT. Any uveitis reactivation requiring therapy adjustment, independently from ocular specific localization and visual function, was considered as uveitis attack. Ocular clinical remission was defined by the absence of active uveitis assessed by full ophthalmic evaluation, FAG and OCT analysis, independently from visual outcome and therapy in course. QuantiFERON-TB test (Cellestis Inc Carneige, Victoria, and Australia) was performed in all patients before infliximab administration and every three months during infliximab therapy to evaluate exposure to tuberculosis. In addition, full serological assessment testing both renal and hepatic function was performed at baseline and then every three months during infliximab administration. Effects of infliximab therapy on steroidal daily dose and BCVA were statistically analysed as ratio of the last record to baseline value and tested with T-tests of the ratios. Mean number of attacks observed during infliximab therapy was compared with mean number of attacks during pre-infliximab period calculated as a span of time, before infliximab administration, correspondent to follow-up time duration for each analysed case. BCVA is expressed as the logarithm of mean angle of resolution (log MAR). All values are reported as mean value with related standard deviation (SD). T-student test was adopted to calculate p-values in this study where p-value less than 0.05 were considered statistically significant. The analysis was done with the R-Development Core Team (2011).

Table 1: Main characteristics of patients at baseline

Sex	**No. of patients, (%)**
Male	21, (65.6)
Female	11, (34.4)
Age (years)	**Mean value (± SD), range**
At study beginning	40,8 (± 14.6), 13-71
At disease onset	33, 3 (± 13.7), 13-60
Systemic symptoms	**No. of patients, (%)**
Oral Aphtae	32, (100)
Skin lesions	23, (71.8)
Genital ulcers	13, (40.6)
Arthritis	12, (37.5)
Neuro-Behçet	10, (31.2)
HLA- B51	**No. of patients, (%)**
Positive	21, (65.6)
Uveitis duration (yrs)	**No. of patients, (%)**
1-3	10, (31.2)
4-6	6, (18.7)
> 6	16, (50)
Ocular involvement	**No. of patients, (%)**
Bilateral	24, (75)
Monolateral	8, (25)
Uveitis type	**No. of eyes, (%)**
Panuveitis	26, (46.4)
Posterior	24, (42.8)
Anterior, non- granulomatous	6, (10.7)

Results

Main characteristics of patients are reported in table 1. Study population consisted in 32 patients (56 eyes) 21 male and 11 female (M: F ratio of 2:1). Mean age of patients at the onset of disease was 33.3 years (± 13.7 SD); an association to HLA-B51 resulted in 21 patients (65.6%). Mean follow-up was 33,2 months (± 21.3 SD; range 6-72). Recurrent oral aphtae were observed in all patients, skin lesions resulted the second most common sign recurring in 71,8 % of cases, while 10 patients (31.2 %) presented neuro-Behçet pattern of disease.

Ocular inflammation occurred in 56 eyes with bilateral involvement in 75 % of cases and mainly consisted in panuveitis (46.4 % of affected eyes), while posterior uveitis and anterior uveitis occurred respectively in 42.8 and 10.7% of affected eyes (Table 1). All patients received infliximab in addition to DMARDs after

Table 2: Main outcomes

Case n./age/ sex	Uveitis type	Uveitis duration (yrs)	Follow-up (mo)	Attacks 1 (no.)	Attacks 2 (no.)	CS 1 (mg/day)	CS 2 (mg/day)	Uveitis remission
1/30/M	OU: PU	15	60	6	3	25	25	Yes
2/39/M	OU: PU	6	72	1	1	50	0	Yes
3/28/M	OU: Post	2	24	1	1	25	0	Yes
4/46/F	OU: Post	3	36	2	1	50	5	Yes
5/23/M	OU: Post	1	12	1	0	5	5	Yes
6/30/M	RE: PU LE: Post	4	24	2	0	10	10	No
7/31/M	OU: Post	10	36	1	0	50	0	Yes
8/28/F	LE: PU	3	12	2	0	50	0	Yes
9/48/F	OU: PU	10	72	9	0	50	0	Yes
10/64/F	LE: PU	4	36	3	1	25	0	Yes
11/49/F	OU: AU	9	12	2	1	50	5	Yes
12/49/M	OU: PU	9	36	2	0	50	10	Yes
13/43/M	OU: PU	13	36	4	0	25	25	No
14/61/F	OU: PU	8	12	1	0	25	15	Yes
15/42/M	LE: Post	7	15	2	0	25	5	Yes
16/48/F	LE: PU	6	6	1	1	50	50	No
17/32/M	OU: Post	1	58	4	1	50	25	No
18/71/F	OU: AU	15	19	1	0	30	25	Yes
19/65/F	RE: AU LE: PU	9	10	2	0	25	5	Yes
20/20/M	OU: Post	1	12	3	0	50	15	Yes
21/26/M	OU: Post	10	39	3	0	20	5	Yes
22/47/F	OU: PU	12	12	3	0	10	5	Yes
23/32/M	LE: Post	4	48	1	1	50	0	Yes
24/28/M	LE: PU	3	15	4	0	15	10	Yes
25/62/F	OU: PU	13	48	6	1	25	5	Yes
26/34/M	RE: Post	5	48	1	0	5	0	Yes
27/37/M	RE: PU LE:AU	28	72	2	0	10	5	Yes
28/56/M	OU: Post	2	18	1	2	25	5	Yes
29/57/M	OU: Post	11	36	2	5	10	10	No
30/32/M	OU: Post	1	60	1	0	50	0	Yes
31/13/M	LE: PU	1	6	3	0	10	5	No
32/34/M	OU: PU	11	62	5	2	50	0	Yes

Attacks 1: Attacks of uveitis during pre-infliximab period, attacks 2: Attacks of uveitis during infliximab therapy, CS1: Corticosteroids dose at baseline, CS2: corticosteroids dose at last record before beginning of the study, OU: both eyes, RE: Right Eye, LE: Left Eye, PU: Panuveitis, POST: Posterior Uveitis, AU: Anterior Uveitis.

deterioration of general and/or ocular conditions, despite maximal tolerated immunosuppressive dose, or following systemic toxicity in response to them. CS consisted in oral prednisone at starting dose of 1 mg/kg/day gradually tapered during follow-up or intravenous metilprednisolone (1 g/day for three days) then followed by oral prednisone. Azathioprine (AZA) and cyclosporine-A (CSA) dosage was respectively 100-150 mg/day and 3-5 mg/kg/day. Colchicine (Colch) and methotrexate (MTX) dose, when given, was respectively 0.5-1.5 mg/day and 7.5-20 mg/kg/week. The intravenous infusions of infliximab (5 mg/kg) were administered at weeks 0,2,4,6, and every 6-8 weeks thereafter, depending on uveitis severity, until the beginning of the study. In no case adjustment or increasing of infliximab dose was adopted over full follow-up time. Table 2 resumes main outcomes of the study. Clinical remission was observed in 26 out 32 patients (81.25%). Mean number of uveitis attacks decreased from 2.56 during pre-infliximab period to 0.65 during infliximab therapy ($p<0.001$). During infliximab therapy uveitis attacks decreased in 81.2% of patients and almost 60% of them had no uveitis relapses while 12.5% had no variation between pre-infliximab and infliximab period. Systemic CS were gradually tapered in 17 patients (53%) and even suspended in 10 (31.2%) of them while mean daily dose decreased from 31.25 to 8.91 mg ($p<0.001$). Secondary endpoints of the study are listed in Table 3. Mean BCVA of worse eye improved from 0.52 log MAR at baseline to 0.47 log MAR ($p=0.2$) during infliximab therapy. This parameter resulted stable in 48.2% of affected eyes (27 eyes) while improved and worsened respectively in 26.8% and 25% of the eyes. Therapy with DMARDs was discontinued in nine patients (28%) and tapered from two to one medication in three patients (9.4%). Six patients (case n. 1,6,13,16,29 and 31) were switched to adalimumab following loss of efficacy of infliximab while patient n. 17 was switched to interferon-α (3.000.000 UI per 3/week) due to lack of effect after 6 months of infliximab therapy with consequent deterioration of ocular conditions. Patient n.10 discontinued infliximab, along with any other systemic therapy, as a consequence of sustained clinical remission.

No relevant adverse reactions were recorded in the study population. Nevertheless patient's n. 15 and 16 developed a mild acute bronchitis during first year of therapy as possible even uncertain infliximab-related side effect; in these patients infliximab was promptly discontinued. Patient n. 15 was definitively switched to interferon-α while patient n.16 was then retreated with infliximab and finally switched to adalimumab for loss of efficacy.

Discussion

Ocular inflammation is one of the most serious clinical manifestations in course of BD. Despite an appropriate therapy many patients may suffer uveitis sight-threatening relapses with consequent irreversible visual loss. Experimental data suggest the possible role of TNFα in Behçet's uveitis pathogenesis demonstrating a higher concentration of this cytokine in aqueous humour and serum of affected patients or an increased number of cells producing TNFα during the active phases of disease [3-4]. The documented efficacy of infliximab for treatment of many systemic inflammatory and autoimmune diseases induced experimental use of this drug for treatment of BD and severe Behçet's uveitis [5-14].

The present study retrospectively analyses long-term clinical course of a large cohort of patients affected by severe Behçet's uveitis treated with infliximab in addition to conventional immunosuppressive therapy. S. Al Rashidi et al. have recently reported favourable results of infliximab in 19 patients with Behcet's uveitis retrospectively analysed [14]. In their study 47% of patients achieved complete remission associated to a BCVA ≥ 20/40 in 71% of

Table 3: Secondary outcomes

Case n./age/sex	BCVA 1 (RE/LE)	BCVA 2 (RE/LE)	DMARDs 1	DMARDs 2	Infliximab therapy	Adverse effects to infliximab
1/30/M	HM/1	HM/1.3	AZA/CSA	AZA/ADA	Suspended (loss of efficacy)	no
2/39/M	0/1	0/1	CSA	CSA	Continued	no
3/28/M	1/1	0/0	CSA	CSA	Continued	no
4/46/F	HM/HM	1.79/HM	CSA	-	Continued	no
5/23/M	0.15/0.69	0.15/0.69	AZA	AZA	Continued	no
6/30/M	1/0	0.22/0	CSA	Colch/ADA	Suspended (loss of efficacy)	no
7/31/M	HM/0.3	HM/0.045	CSA	-	Continued	no
8/28/F	0.15	0.22	AZA	AZA	Continued	no
9/48/F	0/2.09	0.096/2.09	AZA/CSA	-	Continued	no
10/64/F	1.48	HM	CSA	-	Continued	no
11/49/F	0.22/0.39	0.3/0.15	CSA/Colch	AZA/Colch	Continued	no
12/49/M	0/0.045	0/0.045	CSA	-	Continued	no
13/43/M	0.045/0.15	0.045/0.69	AZA/CSA	AZA/ADA	Suspended (loss of efficacy)	no
14/61/F	0.22/0.69	0.22/0.69	CSA	CSA	Continued	no
15/42/M	0	0	AZA/CSA	CSA/ INFα	Suspended (adverse effect)	acute bronchitis
16/48/F	0.69	1	CSA	CSA/ADA	Suspended (adverse effect/loss of efficacy)	acute bronchitis
17/32/M	0/0.39	0.22/1	CSA	CSA/INFα	Suspended (lack of effect)	no
18/71/F	1/0.3	1/0.3	CSA	MTX	Continued	no
19/65/F	0/0.3	0/0.096	AZA	AZA/	Continued	no
20/20/M	1.79/1.3	1/1	AZA/CSA	AZA	Continued	no
21/26/M	0.096/0.096	0/0	AZA	-	Continued	no
22/47/F	HM/1	HM/1	AZA/CSA	AZA	Continued	no
23/32/M	0.15	0.15	CSA	-	Continued	no
24/28/M	0.69	0.69	AZA	AZA	Continued	no
25/62/F	1.79/1.79	1.48/1.79	AZA/CSA	AZA	Continued	no
26/34/M	0.096	0.096	CSA	AZA	Continued	no
27/37/M	1.79/1.79	1.48/1.79	AZA	MTX	Continued	no
28/56/M	0.69/1.79	1.79/2.09	CSA	-	Continued	no
29/57/M	2.09/1	2.09/1.79	CSA	Colch/ADA	Suspended (loss of efficacy)	no
30/32/M	0/0.096	-0.04/0.045	AZA/CSA	-	Continued	no
31/13/M	0.39	0.39	CSA	CSA/ADA	Suspended (loss of efficacy)	no
32/34/M	1.79/0.15	HM/0.045	CSA	CSA	Continued	no

BCVA 1 (logMAR) and DMARDs 1 refer to data at baseline, BCVA 2 (logMAR) and DMARDs 2 refer to data at last record before beginning of the study, RE/LE: Right Eye/Left Eye, HM: Hand Movement, CS: Corticosteroids, CSA: Cyclosporin A, AZA: Azathioprine, Colch: Colchicine, MTX: Methotrexate, INFα: Interferon-α, ADA: Adalimumab

cases. A Japanese prospective multicenter study of 2012 has analysed efficacy of infliximab in 50 patients affected by Behçet's uveitis [13]. After 12-month follow-up the authors report improvement in ocular inflammation in 69% of cases associated to reduction of mean number of uveitis attacks from 2.66 at baseline to 0.79. Adverse reactions occurred in 56% of patients but none of them was evaluated as serious. Although steroid-sparing effect is not evaluated and despite a shorter follow-up time, their final outcomes are quite similar to ours. In 2008 K. F. Tabbara conduced an interesting retrospective study where efficacy of infliximab (Group 2 including 10 patients) is compared with conventional immunosuppressants (Group 1 including 33 patients) on overall 43 patients with Behçet's uveitis [12]. After two-year follow-up, mean overall attacks resulted 1.2 in Group 2 compared to 6.3 in Group 1 while BCVA resulted ≥ 20/50 in 50% of patients treated with infliximab respect to 6% of patients treated with conventional therapy. Also in this study safety of infliximab was good with mild infusion reactions observed in two patients.

Despite differences in study design, inclusion criteria and time of follow- up our results on infliximab efficacy are quite consistent with previously mentioned studies [12-14].

In our study infliximab therapy induced uveitis remission in 81.2% of treated patients associated to an improvement of BCVA, at least in one eye, in 14 patients (43.7%). A statistically significant decreasing of uveitis attacks ($p<0.001$) was moreover observed as well as a considerable steroid-sparing effect up to complete suspension of systemic CS in ten patients (31.2%). Improving of BCVA in the worse eye was moreover observed even though no statistically significant ($p=0.2$). This could be probably due to development, in many of our patient, of irreversible structural changes of retina like optic or macular atrophy as consequence of a long-lasting relapsing uveitis. BCVA improvement, indeed, appeared less evident in patients with longer uveitis duration. In our study uveitis duration, as well as panuveitis subtype, moreover influenced steroid-sparing effect of infliximab that was less significant in patients with longer uveitis duration and panuveitis. In six of our patients infliximab was suspended after loss of therapeutic effect. This phenomenon could be investigated in particular genetic configuration of patients so to influence duration of therapeutic response to infliximab. Moreover, even antibodies measurement was not performed in our patients, it could be hypothesized human anti-chimeric antibodies to be implicated in progressive decline of therapeutic effect of infliximab in these patients [18].

Infliximab demonstrated to be quite well tolerated in our patients unless long-term administration equal or more than 12 months in 87.5% of cases and up to 60 months or more in 43.75% of them and only two patients developed a mild acute bronchitis during infliximab administration. Unlike of what described in literature [19,20] we didn't observe cases of tuberculosis and/or severe infective pneumonia and this might probably correlate with relative young age of our cohort. Thus far severe uveitis associated to Behçet's disease represents a serious sight- threatening condition whose prognosis depends on a prompt diagnosis and adequate treatment. In our patients infliximab therapy permitted a good control of ocular inflammation and relapses, stabilizing clinical course and improving visual prognosis of treated patients.

This study represents one the best-detailed research examining efficacy of infliximab in patients affected by long lasting, severe and various forms of uveitis in course of BD including moreover 10 patients with neuro-Behçet. Ocular findings of patients are accurately described and effectiveness of infliximab is assessed through a meticulous statistical elaboration of many primary and secondary parameters.

Nevertheless randomized, controlled trials including a larger number of patients for a longer follow-up are strongly desirable to better delineate safety and efficacy of infliximab for treatment of severe Behçet's uveitis.

Ethical Statement

The study was designed and conducted according to the guidelines of the Helsinki declaration. Local ethics committee approval and patient's written informed consent were obtained before study procedures were undertaken.

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