Infliximab for uveitis of Behçet's syndrome: a trend for earlier initiation

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ABSTRACT

Objective. *The prognosis of uveitis in Behçet's syndrome (BS) has improved over decades. Whether this is related to the use of more aggressive management strategies is not known.*

Methods. *This is a retrospective study of BS patients who received infliximab (IFX) for refractory eye disease between 2003–2015. The patients were divided into two groups according to the date of onset of IFX treatment as before and after 2013. We compared the two groups in terms of disease characteristics at the onset of IFX treatment and response to treatment.*

Results. *There were 43 patients in the old and 14 patients in the new group. The duration of uveitis and previous immunosuppressive treatment before the initiation of IFX were significantly shorter in the new group compared to the old group (p=0.043 and p=0.028, respectively). The baseline visual acuity (VA) at the initiation of IFX was better in the new group, but this was only significant for the left eye. Treatment with IFX was effective in both groups in preserving VA and this was more pronounced in the new group. Attack frequency under IFX was significantly lower in the new group (p<0.001).*

Conclusion. *IFX seems to be initiated earlier and also in less severe cases during the course of BS uveitis than before. Despite the few numbers of patients and relatively short duration of follow-up, our results give a hint that this change has improved the outcome.*

Introduction

Ocular involvement, occurring roughly in 50% of patients, is one of the most feared complications of Behçet's syndrome (BS). It is a combination of relapsing and remitting attacks of uveitis and retinal vasculitis affecting both eyes in the majority of involved patients and carrying a sight-threatening potential (1). Immunosuppressive agents constitute the mainstay of treatment for ocular involvement of BS. According to the updated EULAR recommendations for the Management of BS "any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as azathioprine, cyclosporine-A, interferon-alpha or monoclonal tumour necrosis factor (TNF)-alpha antagonists" (2).

Infliximab (IFX) and adalimumab (ADA) are increasingly used in the treatment of BS patients with uveitis when they are refractory to conventional immunosuppressives (3-6). With the exception of two phase 3 placebo controlled trials of ADA enrolling patients with active or inactive non-infectious uveitis with diverse aetiologies including BS, data on these agents are based on observational studies (7).

Recent studies suggest an improved outcome for BS patients with uveitis in terms of a better visual outcome and less ocular complications than before (8, 9). This might be well related to a decrease in the severity of BS over the last decades as has been reported by different groups (10, 11). However, the introduction of new and more potent therapeutic agents like biologics as well as the more effective use of immunosuppressives can be operative in this improvement. It has been reported that changes in the attitudes of physicians towards earlier initiation of biologic agents have improved the outcome of rheumatic diseases (12). The results of a small study on 13 Japanese BS patients reporting better visual outcome to IFX when initiated early support this view (13).

Since 2003 IFX is increasingly used in our clinic for several complications of BS including refractory uveitis. In this study our aim was to assess whether

our prescription patterns for initiating IFX in the treatment of uveitis have changed over time and if yes whether these changes have positively affected the outcome of our patients.

Methods

We retrospectively reviewed the charts of all BS patients who have been registered in our multidisciplinary outpatient centre and have received IFX because of uveitis. To be included in the study all patients had to fulfill the International Study Group Criteria for Behçet's Disease along with a sight-threatening posterior uveitis (14).

Data on the demographic characteristics of the patients, the course of uveitis before and under IFX and previous treatments were collected from the charts. Treatment response to IFX was assessed according to the recommendations of the Standardization of Uveitis Nomenclature (SUN) Working Group (15). The primary ocular outcome was the proportion of BS patients with improved, stable or worse visual acuity (VA) at the end of IFX therapy. We used the best corrected VA obtained at the beginning of IFX treatment and at the last visit under IFX treatment for visual outcome. We also determined the proportion of patients without uveitis relapse under IFX treatment and compared this with that occurring before initiation of IFX for a similar length of time which equaled the duration of IFX treatment in each patient. IFX was given at a dose of 5 mg/kg at weeks 0, 2 and 6 and then every 6-8 weeks. The combination of IFX with azathioprine and/or steroids was at the discretion of the ophthalmologist. All patients underwent screening for latent tuberculosis (Tb) prior to start of IFX and received INH prophylaxis for latent Tb when necessary.

To assess the changes in our prescribing patterns of IFX over time, we compared the patient characteristics and the delay time in initiating IFX for uveitis by dividing our patients into 2 groups according to the date of initiation of IFX. The old group consisted of patients starting IFX between January 2003 and December 2012 which were also the subjects of a previous study evaluating the efficacy of IFX in refractory uveitis of BS (16). The new group consisted of patients starting IFX between January 2013 and March 2015. Follow-up of the patients was censored at April 2016.

Table I. The demographic and treatment related characteristics of the old and new group patients.

	Old group (n=43)	New Group (n=14)	*p*-value
Mean ± SD age (years)	35 ± 8.6	37 ± 7.1	0.45
Male sex, n (%)	33 (77)	12 (86)	0.4
Median (IQR) duration of uveitis (months)	72 (45-131.5)	36.5 (11.5-86)	***0.043***
Median (IQR) duration of previous IS treatment (months)	60 (25-84)	26.5 (9-50.5)	***0.028***
Mean ± SD age at initiation of IFX treatment (years)	31 ± 8.4	33.8 ± 7.5	0.12
Median (IQR) duration of IFX treatment (months)	40 (18-50)	11.5 (8-20)	***<0.001***
Patients with combined IS under IFX, n (%)	37 (86)	12 (85.7)	0.9
Previous IS treatment, n (%)			
Azathioprine	43 (100)	12 (86)	0.06
Cyclosporine-A	42 (98)	12 (86)	0.08
Interferon alpha	38 (88)	11 (79)	0.3
Cyclophosphamide*	0	1 (7)	0.07
Median (IQR) logMAR of baseline VA for R eye	0.3 (0-2)	0.7 (0.1-1.7)	0.55
Median (IQR) logMAR of baseline VA for L eye	0.22 (0.07-1)	1.2 (0.4-2)	***0.006***

IFX: infliximab; IS: immunosuppressive.
*The patient had also superficial femoral artery occlusion.

Results

Table I shows the demographic as well as therapy related characteristics of the patients. The chart review revealed 57 BS patients (43 from the old group and 14 from the new group) who were treated with IFX because of sight-threatening uveitis. The 2 groups were similar in terms of male predominance, the use of previous immunosuppressive treatments and the mean age at the initiation of IFX treatment. However, the duration of uveitis as well as the duration of previous ımmunosuppressive treatment prior to the start of IFX treatment were significantly shorter in the new group. The median duration of IFX treatment was significantly longer in the old group but there was no difference regarding the percentage of patients using immunosuppressives in combination with IFX.

The baseline VA of the left eye of the new group was significantly better than that of the old group but the baseline VA of the right eye was similar between the groups (Table II). Six patients (43%) from the new group had no useful vision (LogMAR>1) in at least one eye at the time of initiation of IFX compared to 29 patients (67%) in the old group but the difference was not statistically significant (p=0.12). During treatment with IFX the mean VA was preserved in both groups for either eye. There was a trend in the new group with less worsening of VA in the right eye which did not reach statistical significance (for right eye p=0.08).

The percentage of patients having at least one attack in the right, left or both eyes before IFX was similar in both groups, but was significantly lower in the new group (7%) compared to that in the old group (53%) during treatment with IFX (p<0.001).

In the old group 20 of 43 patients were under IFX treatment. It was terminated in the remaining 23 patients (unrelated reasons=12, stable disease=4, adverse events=4 (2 allergic reactions, 1 pulmonary tuberculosis, 1 lung nodule), terminal disease=1, inefficacy=1, pregnancy=1). In the new group, 6 patients were still under IFX treatment, whereas therapy had been stopped in 8 patients. The reasons for discontinuation of IFX treatment were adverse events in 4 patients, unrelated reasons in 2 and stable disease in 2. Among the 4 adverse events, 3 were allergic reactions and 1 was pulmonary tuberculosis. The patient who was diagnosed as tuberculosis at the 6th month of IFX treatment despite INH prophylaxis was also receiving azathioprine, cyclosporine A and steroids.

Table II. Visual outcome variables of the new and old group patients.

	Old group (n=43)	New Group (n=14)	*p*-value
Patients with attacks			
before IFX, n (%)	32 (74.4)	10 (71.4)	0.8
under IFX, n (%)	23 (53.4)	1 (7)	***0.002***
Outcome of VA after IFX therapy			
improved, n (%)			
R eye	14 (32)	3 (21)	0.4
L eye	14 (32)	5 (36)	0.8
stable, n (%)			
R eye	12 (28)	9 (64)	***0.01***
L eye	21 (49)	8 (57)	0.5
worse, n (%)			
R eye	17 (40)	2 (14)	0.08
L eye	7 (16)	1 (7)	0.39
Baseline VA (median logMAR) of R eye*	0.7	0.26	
Final VA (median logMAR) of R eye*	0.7	0.31	
Baseline VA (median logMAR) of L eye*	1.2	0.22	
Final VA (median logMAR) of L eye*	1.0	0.22	

*There is no significant difference between baseline VA and final VA in both eyes under IFX therapy.

Discussion

In this survey, we compared the visual outcome of BS patients with uveitis who initiated IFX therapy before and after 2013. Our previous impression on the earlier initiation of IFX therapy in the new group was evident in this study. Although the demographic characteristics of both groups were similar, the duration of uveitis and length of previous immunosuppressive treatment were shorter in the new group. In both groups IFX was successful in preserving VA but in the new group there were significantly more patients becoming free of ocular attacks under IFX. Also the proportion of patients with worsening VA was less in the new group but the difference did not reach statistical significance. These findings might be the result of earlier initiation of IFX in the new group but the possible effect of shorter follow-up of the new group patients cannot be excluded.

The EULAR recommendations for the management of BS advocates the use of immunosuppressives such as azathioprine, cyclosporine-A, interferon-alpha or monoclonal anti-TNFs for BS patients with posterior uveitis (2). However, there is no consensus on the best time to start anti-TNFs or whether these agents should be reserved for patients who are refractory to conventional immunosuppressives such as azathioprine and cyclosporine-A. Another problem is that "refractory" disease has not been defined for BS uveitis.

There is no data to guide us on the choice between monoclonal anti-TNFs. Although a vast amount data has accumulated with infliximab, none of the published studies are prospective controlled studies. The only anti-TNF that was studied for uveitis in randomised controlled trials (RCT) is adalimumab. The first RCT with this agent was conducted among patients with active non-infectious intermediate, posterior or panuveitis (7). The primary outcome, time to treatment failure was longer and the number of patients with treatment failure was lower in the adalimumab group compared to placebo. The second RCT that was conducted among inactive patients with non-infectious uveitis also showed similar results (17). However, in this study there were few patients with BS and their results were not analysed separately. Apart from this trial, case series showing beneficial results with adalimumab for Behçet's uveitis have been published (18-20). Finally, a recent report on golimumab showed beneficial results and enabled the tapering of corticosteroids in BS patients (21).

According to a recent study from Japan early remission induction with IFX in BS uveitis may be more effective in reducing background retinal and disc vascular leakage and in achieving good visual outcomes (13). In that small-sampled study, 7 patients with a uveitis duration of <18 months had more pronounced reductions in vascular leakage scores when compared the 6 patients with an uveitis duration of >18 months. We could not find such a clear difference between our old and new groups which may be explained by the fact that our new group started IFX therapy considerably later (median disease duration of 36 months) than that study. In addition, 50% of our patients in the new group had no useful vision at the beginning of the therapy. On the other hand, despite initial poor logMAR values only 3 eyes worsened under IFX (Table II).

In 2004, Tugal-Tutkun *et al*. reported that the risk of vision loss was lower in BS patients treated after 1990 than those treated before 1990 because of the more aggressive treatment approach (22). Cingu *et al*. also reported a similar result with the comparison of 1990–1994 and 2000–2004 (9).

In our new group only one patient with multiple immunosuppressive experiences developed tuberculosis despite being on INH therapy. Tuberculosis still remains a concern in anti-TNF treatment, especially in endemic countries. Moreover, BS patients are at higher risk for tuberculosis (23) and caution is required regarding the development of tuberculosis in such patients.

In addition to the retrospective nature of this study, our limitations were the low number of patients and the short duration of follow-up under IFX. However due to the close follow-up of these patients our data is robust in showing the efficacy of IFX, especially when started before permanent damage has occurred.

In conclusion; our study indicates a significant recent trend towards an earlier initiation of IFX in BS uveitis over time which might also effect the visual outcome positively.

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