Induction of ocular Behçet's disease remission after short-term treatment with infliximab: a case series of 11 patients with a follow-up from 4 to 16 years

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ABSTRACT

Objective. *Initial recommendations on anti-TNF treatment for Behçet's disease (BD) included an intravenous infliximab infusion for acute posterior uveitis to achieve a fast-onset response. We aimed to examine the long-term outcome of our patients with acute sight-threatening BD who received successful short-term treatment with infliximab.*

Methods. *We performed a retrospective longitudinal outcome study including consecutive patients who responded to one infliximab infusion (5mg/kg) for BD-associated acute posterior uveitis or panuveitis, followed, or not, by one or two additional infusions.*

Results. *Twelve patients (aged 51±14 years, mean±SD, 67% men) with bilateral (n=9) or unilateral (n=3) ocular attack (relapsing in 9 patients) achieved resolution of ocular inflammation within 4 weeks after the first infusion of infliximab, given as add-on to azathioprine (n=9) or to azathioprine/cyclosporine combination. Ten of 12 patients received a second infusion at 4 weeks and 9 of them received a third infusion at 8 weeks from baseline. Except from a patient who relapsed after 6 months and responded to infliximab re-treatment, 11 patients remain ocular relapse-free during follow-up, ranging from 4 to 16 years (10±4). Five patients (45%) discontinued azathioprine being in full BD remission and remain any drug-free at end of follow-up.*

Conclusion. *Successful short-term infliximab treatment combined with conventional immunosuppressives for BD-associated sight-threatening uveitis may lead to remission for many years thereafter. This observation may suggest that infliximab as a first-line therapy should be promptly administered to every patient with ocular BD for rapid remission of ocular inflammation and preservation of visual acuity.*

Introduction

Behçet's disease (BD), also known as Adamantiades-Behçet's disease (1) is a chronic, relapsing inflammatory pleiomorphic disorder classified among the vasculitides and has increased prevalence in countries along the ancient Silk Road (1, 2). BD may have a mild course with recurrent oral ulcers being the main symptom. Other clinical manifestations include genital ulcers, pustular skin lesions, arthritis, ocular, neurological and gastrointestinal manifestationsand thrombotic complications, which may lead to severe morbidity and increased mortality (2-5).

Ocular inflammation is usually bilateral and may lead to significant visual impairment or visual loss if left untreated. Conventional synthetic immunosuppressive drugs often fail to induce and/or maintain remission, but anti-TNF monoclonal antibodies have been used in the past 15 years with remarkable success (6-9). According to the 2018 EULAR recommendations, patients presenting with an initial or recurrent episode of acute sight threatening uveitis should be treated with high dose glucocorticoids, infliximab or interferon-α (10). On the other hand, initial recommendations on anti-TNF treatment in BD, published in 2007, included a single intravenous infliximab infusion for acute posterior uveitis to achieve a fast-onset response (11). This approach has been shown to be more effective and faster in clearing ocular inflammation than intravenous methylprednisolone pulses (12) and infliximab seems to be initiated earlier and in less severe cases in the course of BD than few years ago, as it is associated with better visual oucome (5, 13).

Moreover, anti-TNF monoclonal antibodies given for ocular BD for one to two years may induce long-term ocular remission after their discontin-

uation (14, 15). Based on the above, we aimed to examine the long-term outcome of BD patients who received successful short-term infliximab therapy for acute sight-threatening uveitis in our centre.

Patients and methods

For this longitudinal outcome study a flow-chart review was retrospectively performed in the last trimester of 2018, including consecutive patients diagnosed according to the International Study group for BD criteria (16), who have been treated with infliximab for ocular involvement and followed up at least once yearly in our center in collaboration with a dedicated Ophthalmology Department, since 2001. Patients eligible for the study's analysis were those who achieved complete remission of ocular inflammation after administration of the first infliximab infusion and received, or not, up to 3 monthly infusions. Complete remission was defined as the absence of signs of active ocular inflammation, as described in detail elsewhere (12). Information on characteristics of ocular attack, other BD clinical manifestations, prior and concomitant drug use at baseline and during follow-up was recorded. The study was approved by Laikon Hospital Institutional Body Review and all subjects provided informed consent according to the Declaration of Helsinki.

Results

Overall we identified 12 patients, aged 51.5±14.3 (mean±SD) years, 67% men, with disease duration of 12.3±5.7 years, who received one infliximab infusion for acute sight-threatening inflammation, either at the first attack (n=3) or for relapsing attacks (n=9) and achieved a complete response, thus, being eligible for the study's analysis. Infliximab was well tolerated in all. Number of infliximab infusions, previous and concomitant treatment and BD-associated clinical manifestations are shown in Table I.

Characteristics of ocular inflammation, as well as visual acuity prior to infliximab treatment and at end of follow-up, are shown in Table II. Eleven of 12 patients (92%) remain in complete long-term ocular remission (mean 9.9±3.9, range 3.7–15.6 years) without ever experiencing an ocular relapse. The remaining patient relapsed 6 months after infliximab discontinuation, but subsequently responded to anti-TNF re-treatment, which is continued to date. Five patients were also able to discontinue concomitant treatment and are currently any drug free for a median of 14.5 (IQR 11.6–14.8) years. All but 2 patients had a significant amelioration of visual acuity (VA) at the end of follow-up compared to baseline; these 2 patients developed cataract with subsequent deterioration of the visual acuity in one eye respectively (Table II).

Table I. Demographics and BD characteristics of 12 patients treated successfully with short term infliximab therapy for ocular BD.

		BD patients
Age, years (mean±SD)		51.5 ± 14.3
Men (n)		8/12
Current disease duration, years (mean±SD)		12.3 ± 5.7
Disease duration at anti-TNF treatment initiation, years (median (IQR))		**1.5 (0.75-5)**
Clinical manifestations prior to/at infliximab administration, n		
	Ocular involvement	**9/12**
	Arthritis	**6/0**
	Severe mucocutaneous	**4/2**
	Deep vein thrombosis	**3/0**
	Orchitis/epididimytis	**2/0**
	Gastrointestinal involvement	**1/0**
Treatment prior to infliximab, n	Azathioprine	**7**
	Cyclosporine	**4**
	Methotrexate	**1**
	Colchicine	**5**
Number of infliximab infusions	1	2
	2	1
	3	9
Concomitant treatment	None	0
	Azathioprine	9
	Azathioprine+cyclosporine	3

Cases 1-3: first uveitis attack

Case 1. A 35-year-old woman with severe orogenital ulcers and bilateral panuveitis developed severe VA reduction (counting fingers) in the left and 0.6 in the right eye. She had grade 1 anterior chamber cells, retinal vasculitis, optic neuritis, and cystoid macular oedema (CME). She remains in remission for 7.3 years, after two infliximab infusions one month apart with concomitant azathioprine, which continues to date.

Case 2. A 40-year-old woman with severe oral ulcers and pseudofolliculitis developed unilateral panuveitis with severe VA reduction (counting fingers). She had grade 1 anterior chamber cells, retinal vasculitis, and CME. She remains in remission for 6.5 years, after 3 infliximab infusions one month apart with concomitant azathioprine and cyclosporine-A, both of which continue to date.

Case 3. A 54-year-old man with a 6-year BD history experienced bilateral panuveitis while receiving colchicine and low dose steroids, with severe VA reduction (CF in the left and 0.9 in the right eye) and grade 3 anterior chamber cells, optic neuritis, and CME in the left eye. He remains in remission for 6 years, after 3 infliximab infusions one month apart with concomitant azathioprine, which continues to date.

Cases 4-11: relapsing ocular disease

Case 4. A 54-year-old man with a 4-year BD history treated with azathioprine, methotrexate and steroids for bilateral relapsing panuveitis (3 attacks) developed a fourth acute relapse with grade 1 anterior chamber cells, retinal vasculitis, optic neuritis, and CME (VA was

Table II. Characteristics of ocular inflammation and visual acuity at baseline and end of follow-up of 11 BD patients who achieved long-term ocular remission after successful short- term Infliximab treatment for sight-threatening attack.

			Baseline	Follow-up end (years)
Characteristics of ocular attack (number of patients)				
	First attack		**3 patients**	N/A
	Relapsing disease		8 patients	N/A
	Unilateral		3	N/A
	Bilateral		8	N/A
	Panuveitis		5	0
	Cystoid macular oedema		7	0
	Retinal vasculitis		7	0
	Optic neuritis		6	0
	Scleritis		1	0
	Anterior chamber cells	0	4	0
		1+	5	0
		3+	2	0
Visual acuity	Case 1	Left	CF	0.9 (7.3)
		Right	0.6	0.8 (7.3)
	Case 2	Left	CF	1 (6.5)
		Right	1	1 (6.5)
	Case 3	Left	CF	1(6)
		Right	0.9	1 (6)
	Case 4	Left	0.5	0.6 (10.2)
		Right	0.6	0.8(10.2)
	Case 5	Left	0.2	0.3 (9.6)
		Right	0.2	0.3 (9.6)
	Case 6	Left	0.2	0.6 (14.5)
		Right	1	1 (14.5)
	Case 7	Left	1	1 (11.6)
		Right	0.6	1 (11.6)
	Case 8	Left	0.5	0.9 (14.8)
		Right	0.7	0.9 (14.8)
	Case 9	Left	0.4	0.5 (15.6)
		Right	1	0.8 (15.6)
	Case 10	Left	1	1 (9.4)
		Right	0.7	1 (9.4)
	Case 11	Left	1	0.5 (3.7)
		Right	0.4	0.5 (3.7)

0.5 and 0.6). He remains in remission for 10.2 years, after 3 infliximab infusions one month apart with concomitant azathioprine and cyclosporine-A, both of which continue to date.

Case 5. A 43-year-old woman with a 7-year BD history treated with azathioprine and cyclosporine-A for bilateral relapsing panuveitis (5 attacks) developed a sixth acute relapse with grade 3 anterior chamber cells, retinal vasculitis, optic neuritis, and CME (VA was 0.2 in both eyes). She remains in remission for 9.6 years, after 3 infliximab infusions one month apart with concomitant azathioprine and cyclosporine-A, both of which continue to date.

Case 6. A 61 year-old man with a 1-year BD history treated with cyclosporine and steroids for ocular involvement (1 attack) developed a second attack of unilateral posterior uveitis (VA of 0.2) with grade 1 anterior chamber cells, accompanied with scleritis. He remains in remission for 14.5 years, after 3 infliximab infusions one month apart with concomitant azathioprine which discontinued, being in any drug free remission for 8 years.

Case 7. A 33-year-old woman with a 1-year BD history treated with azathioprine, colchicine and steroids developed a second unilateral posterior uveitis attack with grade 1 anterior chamber cells and retinal vasculitis; VA was 0.6. She remains in remission for 11.6 years, after 3 infliximab infusions one month apart with concomitant azathioprine which discontinued, being in any drug free remission for 8 years.

Case 8. A 24-year-old man with a 10-year BD history treated with azathioprine, cyclosporine-A, colchicine and corticosteroids experienced the fifth ocular attack, *i.e*. bilateral posterior uveitis with retinal vasculitis, optic neuritis and CME, without anterior chamber cells (VA was 0.5 and 0.7). He remains in remission for 14.8 years, after 3 infliximab infusions one month apart with concomitant azathioprine which discontinued, being in any drug free remission for 10 years.

Case 9. A 58-year-old man, with a 2-year BD history treated with azathioprine and steroids experienced the 3rd relapse of bilateral posterior uveitis with optic neuritis and CME, without anterior chamber cells (VA was 0.4 and 1). He remains in remission for 15.6 years, after 3 infliximab infusions one month apart with concomitant azathioprine which discontinued, being in any drug free remission for 8 years

Case 10. A 32-year-old man with BD treated with azathioprine and oral steroids experienced a relapse of his ocular inflammation with bilateral posterior uveitis with retinal vasculitis without anterior chamber cells (VA 1 t and 0.7). He remains in remission for 9.4 years, after a single infliximab infusion and azathioprine, which continues to date.

Case 11. A 32-year-old man, with 1-year BD history treated with azathioprine and steroids developed a second bilateral posterior uveitis attack; VA was 1 and 0.4. He remains in remission for 3.7 years, after a single infliximab

infusion with concomitant azathioprine, which discontinued, being in any drug free remission for 2 years.

Discussion

The empiric use of anti-TNF agents in BD with vital organ involvement has been well established in the past years (5, 7, 8). Since a 2-year successful anti-TNF treatment given in such patients can induce sustained BD remission for many years after treatment cessation (15), we aimed to retrospectively examine the long-term outcome after successful short-term infliximab therapy for ocular involvement.

We were able to identify 11 of 12 patients, with a total of 19 eyes affected, who received successful short-term infliximab therapy and achieved ocular remission sustained for up to 15.6 years. It should be mentioned however, that some of the patients included were aged over 40 years at baseline; since BD manifestations usually resolve with time except for oral ulcers, it is possible that their favourable disease course rather reflected age-related remission. The last patient, a 24-year-old man with a 2-year history of BD (orogenital ulcers, pseudofolliculitis, and posterior uveitis) treated with cyclosporine-A and oral steroids, was treated with infliximab for a bilateral ocular attack with retinitis, retinal vasculitis and 5+ anterior chamber cells with hypopyon (VA 0.5 and CF). Although he responded completely to 3 monthly infliximab infusions, he relapsed 6 months later and was re-treated successfully with continuous infliximab treatment.

Notably, infliximab was given in 9 patients for relapsing ocular disease previously treated with corticosteroids, azathioprine and/or cyclosporine-A, as well as a first-line therapy in the 3 remaining patients. This heterogeneity is due to the fact that infliximab was given as first line therapy after 2008, according to the EULAR recommendations for the management of BD published that year (17). Moreover, although one of the former patients with relapsing disease (case 11) presented in 2015, we decided to initially treat him with azathioprine because he had milder ocular inflammation, but he subsequently received infliximab at his first sight-threatening relapse.

In our recent study describing patients with BD who received infliximab therapy for a median of 2 years, long-term remission after treatment cessation was common (15). The differential treatment pattern for these patients versus the patients described herein, *i.e.* many repetitive infliximab infusions *versus* only up to three infusions, is due to the following reasons: firstly, the lack of experience, in addition to logistic reasons, for some years after 2001, when our first 5 patients treated with a single infliximab infusion were published (6), prevented us from prescribing long-term therapy at that time. Secondly, some of our patients refused to continue infliximab therapy and preferred conventional immunosuppressive drugs following their rapid and complete ocular response to infliximab. Thirdly, long-term empiric infliximab therapy was given in patients who did not achieve an immediate "full house" remission, *i.e.* resolution of retinitis, retinal vasculitis and/or macular oedema, as the most refractory manifestation (18), after the first infliximab infusion.

BD patients treated long-term with TNF inhibitors may relapse within the first year following anti-TNF treatment withdrawal (15); notably, those patients who remain ocular disease-free had significantly shorter disease duration at infliximab initiation than those who relapsed. Taken together with the results presented herein, we propose that infliximab as a first-line therapy should be promptly administered to every patient with ocular BD for rapid remission of ocular inflammation and preservation of visual acuity. In case of a complete and rapid resolution of ocular inflammation, infliximab treatment can be discontinued after two additional infliximab monthly infusions to stabilize the response. Following cessation, a closely monitoring is needed and continuous anti-TNF therapy should be considered in case of relapse, with an attempt to discontinue using a step-down approach in patients with sustained remission after a period of about 2 years (15). Whether there are specific baseline clinical characteristics indicative of continuous anti-TNF therapy, is not clear at present and should be investigated further.

Key messages

- Short-term infliximab therapy of BD-associated uveitis may lead to sustained remission.
- Three monthly infliximab infusions should be considered for every BD patient with sight threatening uveitis.
- Close monitoring is needed following infliximab cessation for continuous re-treatment upon relapse.

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