

Infliximab for the treatment of refractory scleritis

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ABSTRACT

Background Scleritis is a potentially blinding inflammatory disorder. Standard care consists of systemic corticosteroids and immunosuppressants. The authors describe a series of 10 patients suffering from scleritis treated with the TNF inhibitor infliximab because this scleritis was refractory to standard therapy.

Methods The authors reviewed the medical records of patients with scleritis at the Massachusetts Eye Research and Surgery Institution, treated with infliximab. All cases had non-infectious scleritis refractory to traditional immunomodulatory therapy and received 5 mg/kg of infliximab at 4–8-weekly intervals. The main outcome measures evaluated were clinical response, reduction in concomitant immunomodulatory therapy and adverse effects. Inflammation control and visual acuity were assessed using life-table methods.

Results A favourable clinical response to infliximab was seen in 100% of the patients, with six (60%) of them achieving remission and cessation of concomitant immunosuppression. A clinical response to infliximab therapy occurred within 13.24 weeks on average. Based on clinical response, the authors found that repeat monthly infusions were required to maintain remission. One (10%) patient developed a lupus-like reaction necessitating discontinuation of infliximab.

Conclusion Infliximab may be considered in the treatment of non-infectious scleritis refractory to other treatment.

BACKGROUND

Scleral inflammation is associated with systemic autoimmune disorders in 50% of cases, and is often associated with significant morbidity.¹ Ocular complications include keratitis, uveitis, and glaucoma with anterior scleritis and exudative detachments or other posterior segment complications with posterior scleritis.^{1–2} Immunosuppressive therapy has proved to be successful in the treatment of autoimmune disorders.^{3–4} Infliximab, a humanised, chimeric monoclonal antibody directed against the proinflammatory cytokine tumour necrosis factor α (TNF- α), has been approved and marketed for the treatment of rheumatoid arthritis and Crohn disease.^{5–6} While there have been reports of the efficacy of infliximab in the treatment of uveitis, there is little known about the efficacy and tolerability of infliximab for the treatment of scleritis. We review our experience with this drug in the treatment of scleritis refractory to conventional treatment.

METHODS

The medical records of 10 patients with scleritis who received infliximab (Remicade, Centocor,

Horsham, Pennsylvania) from September 2003 to October 2007 were reviewed. All of the patients were seen by the same physician (CSF). Scleritis was defined as oedema in the episcleral and scleral tissues with both superficial and deep episcleral vessel injection accompanied by pain and tenderness to palpation. It was classified as anterior (diffuse, sectoral or necrotising) or posterior, as proposed by Watson and Hayreh.⁷ Posterior scleritis was diagnosed on the basis of clinical and ultrasonography findings. Scleritis was graded and scored according to the grading system defined by Foster and Vitale—sclera injection and inflammation 0 to 4 in 0.5 gradations; these findings were documented by drawings, photography or both.

Treatment with infliximab was considered on an off-label basis after failure of alternative immunosuppression. Infliximab was initiated as 5 mg/kg infusions over 120 min (180 min for the first infusion). A loading dose was infused at zero and 2 weeks, and then maintenance therapy was administered at intervals of approximately 1 month. The intervals between infusions and dose of infliximab were adjusted depending on disease activity and tolerance of the medications. Ophthalmic assessment was performed every 4–6 weeks. Serum biochemical and haematological profiles were monitored at each clinic visit. Remission was defined as control of inflammation while on infliximab therapy without use of corticosteroid therapy.

Outcome variables evaluated included inflammation recurrence, treatment response and decrease in ocular and systemic adjuvant therapy.

Statistical analysis was performed using PROC LIFETEST in PC_SAS (version 6.08; SAS Institute, Cary, North Carolina). Because eyes were not examined independently and because disease progression and response to therapy are highly correlated between eyes, the data for left and right eyes were analysed separately.

RESULTS

The clinical data for each patient are summarised in table 1. The ocular diagnoses included diffuse scleritis (n=4), nodular scleritis (n=2), sclerouveitis (n=2) and scleritis associated with keratitis (n=2).

Seven patients had underlying systemic diagnoses, which included rheumatoid arthritis, Crohn disease and Behçet disease.

The mean patient age was 51.1 ± 11.4 (range 35 to 70). The mean number of infliximab infusions was 16.2 ± 6.0 (range 7 to 24), and the mean follow-up time while on infliximab was 16.4 months (range 6–48). Nine patients received infliximab primarily for treatment of scleritis, whereas patient no 6 received infliximab primarily for control of uveitis associated with scleritis.



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Table 1 Clinical data of patients treated with infliximab

No	Ocular diagnoses	Systemic diagnoses	Therapy before infliximab	Current therapy	No of infusion(s)	Follow-up (months)	Visual acuity before infliximab	Visual acuity after infliximab	Inflammation before infliximab therapy	Inflammation after infliximab therapy (at last visit)	Status at last follow-up
1	Sclerouveitis OU, CMO OU, OAG OU	Crohn disease	Sirolimus, CHLOR, CYCLO, MMF	INF, MMF, Sirolimus	24	27	OD 20/20, OS 20/25	OD 20/20, OS 20/40	1 injection OU	Quiet OU	Responder, unable to reduce concurrent IMT
2	Scleritis OU	Crohn disease, RA	CHLOR, MMF, AZA, Pred	INF	15	22	OU 20/15	OU 20/15	Quiet OU	Quiet OU	Responder, able to discontinue all IMT
3	Scleritis OU	RA	AZA, CYCLOP, MTX	Lost to follow-up, MMF at last visit	12	24	OU 20/20	OU 20/20	1 injection OU	Quiet OU	Responder, control of inflammation with INF but developed lupus-like reaction
4	Scleritis with PUK OU	Crohn disease, RA	intravenous MP	INF, MTX, Methylprednisolone	20	21	OD 20/25, OS 20/20	OU 20/20	2 injection OD, 1 injection OS	Quiet OU	Partial responder, required concurrent antimetabolite and steroid therapy
5	Scleritis OU	Crohn disease	intravenous MP, Pred	INF	21	20	OU 20/20	OU 20/20	1 injection OU	Quiet OU	Responder, able to discontinue methylprednisolone infusions
6	Sclerouveitis OU	RA	MTX, Pred	INF, MTX, Pred	16	14	OU 20/20	OU 20/20	1 injection OU	Quiet OU	Responder, unable to reduce concurrent IMT
7	Nodular scleritis OU	None	MMF, CYCLO	INF	13	13	OU 20/20	OU 20/20	Quiet OU	Quiet OU	Responder, able to discontinue all IMT
8	Scleritis OU	None	MMF, CYCLO, MTX	INF	8	6	OU 20/40	OD 20/60, OS 20/20	2 injection OU, 1 injection OS	Quiet OU	Responder, able to discontinue all IMT
9	Nodular scleritis OU	None	MTX, CYCLO	None	24	48	OU 20/20	OU 20/20	2 injection OU, 1 injection OS	Quiet OU	Responder, able to discontinue all IMT (discontinued INF use because of remission)
10	Scleritis OS	Behçet disease	Pred, Celecoxib, MMF, MTX, intravenous MP, Chlor, Napr	INF, Napr	7	6	OU 20/40	OD 20/60, OS 20/20	2 injection OD, 1 injection OS	Quiet OU	Responder, able to discontinue all IMT; use of concomitant naproxen required

AZA, azathioprine; CHLOR, chlorambucil; CMO, cystoid macular oedema; CYCLO, cyclophosphamide; INF, infliximab; intravenous MP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MTX, methotrexate; Napr, naproxen; OAG, open-angle glaucoma; OD, right eye; OS, left eye; OU, both eyes; PUK, peripheral ulcerative keratitis; RA, rheumatoid arthritis.

The medications in table 1 reflect all IMT regimes used prior to infliximab therapy. Lifetime tables for control of inflammation are reported in table 2, and visual acuity in table 3.

Case reports

Patient 1 had a long history of Crohn disease with bilateral sclerouveitis, cystoid macular oedema and open-angle glaucoma. This patient had initially been treated with chlorambucil which had been discontinued due to leucopenia, and subsequently with mycophenolate mofetil with sirolimus, which proved inadequate for control of ocular inflammation. A marked clinical improvement occurred within days of the first infliximab infusion. Mycophenolate mofetil and sirolimus were coadministered to maintain remission of inflammation. The patient underwent bilateral glaucoma surgeries and unilateral cataract surgery while on this combination with no reactivation of scleritis post-operatively.

Patient 2 with Crohn disease initially presented with right eye (OD) pain, redness and photophobia. The patient was diagnosed to have nodular scleritis and was treated with subconjunctival triamcinolone acetonide 4 mg and oral Prednisone on a gradual taper. After an initial improvement, the symptoms recurred 2 months following steroid taper. There was no clinical improvement with oral diclofenac, and the patient developed fatigue and leucopenia following treatment with mycophenolate mofetil, which was therefore discontinued. Chlorambucil along with topical prednisolone acetate eye-drops were instituted, but the patient continued to have pain in the right eye and developed new symptoms in the left eye (OS). Chlorambucil 6 mg/day was started because of prior failed treatments with good clinical response, though the dosage needed to be reduced to 2 mg every alternate day due to leucopenia. This dosage proved to be inadequate for control of ocular inflammation, and a decision to add infliximab was made. The patient's leucocyte count initially rose but subsequently fell on this regime, necessitating discontinuation of chlorambucil. Infliximab was withheld, as the liver function tests were noted to be abnormal. The patient was evaluated and diagnosed as having rheumatoid arthritis with possible autoimmune hepatitis. Liver biopsy was inconclusive, and infliximab therapy was resumed. The ocular inflammation and arthritis-related symptoms are currently in control with 4-weekly infusions of infliximab.

Patient 3 had a history of rheumatoid arthritis-associated bilateral diffuse anterior scleritis treated with azathioprine and chlorambucil in the past and uncontrolled while on subcutaneous methotrexate. The patient responded well to monthly infusions of infliximab with resolution of ocular and joint-related symptoms. After 12 infusions, the patient developed a rash with antinuclear antibody (ANA) titres of 1:640 and skin biopsy-proven systemic lupus erythematosus (SLE). Infliximab was therefore discontinued. On treatment with mycophenolate

Table 3 Life table estimate of visual acuity change

Follow-up (months)	Minus 1 line		Minus 2 lines		Plus 1 line		Plus 2 lines	
	OD	OS	OD	OS	OD	OS	OD	OS
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.20	0.20	0.00	0.00
6	0.11	0.00	0.00	0.00	0.20	0.20	0.00	0.00
12	0.11	0.00	0.00	0.22	0.20	0.20	0.00	0.00

OD, right eye; OS, left eye.

mofetil, the patient developed nausea, fatigue and gastritis, and raised erythrocyte sedimentation rate with normal blood counts and liver function tests. We suspected a reactivation of SLE, and the patient was referred for evaluation but subsequently lost to follow-up.

Patient 4 was diagnosed as having rheumatoid arthritis and Crohn disease with bilateral diffuse scleritis and unilateral peripheral ulcerative keratitis. The patient reported recurrent episodes of scleritis while on oral diclofenac and topical prednisolone acetate necessitating frequent intravenous corticosteroid infusions. In an attempt to achieve control with a steroid-sparing regime, 4-weekly infusions of infliximab were started. Suboptimal resolution of symptoms led us to add weekly subcutaneous methotrexate (20 mg) injections. After 4 months, resolution of inflammation was achieved and has been maintained since. The patient has been controlled on this regime in the absence of systemic or topical corticosteroids.

Patient 5, with Crohn disease and bilateral sclerouveitis with interstitial keratitis, was inadequately controlled with oral prednisone and topical prednisolone acetate. An intravenous course of methylprednisone for 3 days was administered, with topical prednisolone acetate eye-drops, concomitant to a regime of 4-weekly infliximab while tapering off the oral prednisone. Following a mild reactivation of inflammation (trace injection OU) noted after 9 months of treatment, during a reportedly stressful period, the patient is currently well controlled on monthly infliximab infusions.

Patient 6, on subcutaneous methotrexate for rheumatoid arthritis, had a history of bilateral sclerouveitis. Methotrexate had recently been increased to 25 mg/week with the addition of oral prednisone 5 mg for control of her joint symptoms. Despite this therapy, the patient's symptoms persisted and were accompanied by an increase in ocular pain. We noted scleral inflammation and anterior uveitis OS. Topical prednisolone was started along with infliximab, in addition to prior therapy. While the ocular pain and scleritis resolved, the patient noted repeated reactivation of anterior uveitis on this regime necessitating episodic topical prednisolone acetate to keep the associated anterior uveitis in check.

Patient 7 had bilateral nodular scleritis, uncontrolled initially on mycophenolate mofetil and subsequently on cyclophosphamide. The patient was started on monthly infliximab infusions. The infusions had to be temporarily withheld due to development of herpes zoster 3 months after initiating infliximab, which was treated with oral valacyclovir. Infliximab therapy was resumed after a month and took 9 months for achieving control of inflammation with the concomitant use of diflunisal.

Patient 8 developed bilateral diffuse anterior scleritis which had in the past been unresponsive to a combination of subcutaneous methotrexate with oral prednisone 5 mg. Following this, replacement of methotrexate with mycophenolate mofetil was attempted in vain. Ciclosporin A had been added and later

Table 2 Life-table estimate of relapse occurrence

Follow-up month	Relapse rate
0	0
3	0.0
6	0.11
9	0.22
12	0.34
15	0.63
18	0.63
21	0.63

withdrawn due to raised liver enzymes. Subsequent therapy had included intravenous methyl prednisone, regional triamcinolone acetonide and oral prednisone. A month later, ocular symptoms recurred, and we instituted a regime of intravenous methotrexate 50 mg with methylprednisone 1000 mg while we obtained insurance approval for infliximab therapy. The patient responded well to infliximab infusions administered 4-weekly with control of ocular inflammation, except for one episode of reactivation following a missed dose of infliximab. While on infliximab, the patient underwent cataract surgery with no reactivation of inflammation postoperatively, and is currently well controlled on this regime.

Patient 9 had a history of bilateral nodular scleritis unresponsive initially to methotrexate and later cyclophosphamide. The patient responded well to infliximab therapy, initially at 4-weekly intervals. Topical prednisolone acetate was tapered over the initial 3 months. After 1 year of monthly infliximab 400 mg infusions, we gradually reduced the dosage and were eventually able to wean the patient off infliximab over a period of 2.5 years. The patient is off all systemic and topical medication with no activation of inflammation.

Patient 10 had a history of unilateral anterior scleritis OS, dependent on corticosteroid therapy. The patient was HLA-B51-positive and was diagnosed as having Behçet disease, using the 1990 International criteria. The patient was initially unsuccessfully treated with oral celecoxib, mycophenolate mofetil and subsequently methotrexate. The patient achieved symptomatic relief with subcutaneous methotrexate and oral prednisone but needed to change therapy to chlorambucil due to side effects. With this new agent, we were able to discontinue oral prednisone, but the patient developed leucopenia and unresolving pharyngitis. Two months later, the patient presented with uncontrolled ocular inflammation and joint pain, for which three infusions of 50–100 mg intravenous methotrexate combined with 1 g of intravenous methyl prednisolone were administered while obtaining insurance approval for infliximab therapy. The patient was initially treated with 300 mg infusions every 4 weeks and was steroid-free, and without inflammation, for 4 months. Joint pain and mouth ulcers resolved after initiation of infliximab. The patient missed one infusion and developed mild eye pain and injection that resolved with combined infusion of infliximab 300 mg and 1 g of methylprednisolone. The patient did not need additional steroid therapy after this episode and reports no side effects while on infliximab. The patient is currently well-controlled on 6-weekly infliximab infusions.

DISCUSSION

Infliximab, a monoclonal antibody to TNF- α , is a novel immunomodulatory agent which has proven to be effective in a number of autoimmune diseases, in particular Crohn disease, rheumatoid arthritis, psoriasis and systemic vasculitis.^{5 6 8 9} Its use in the treatment of scleritis has been reported in a small number of patients.^{10 11} This report describes a relatively large case series of patients with scleritis to be treated with infliximab.

A favourable response to infliximab was seen in 90% of the patients, with six (60%) of them achieving remission and cessation of concomitant immunosuppression. A clinical response to infliximab therapy occurred within 13.24 weeks on average. Based on clinical response, we found that repeat monthly infusions were required to maintain remission.

Eight (80%) patients continue to receive infliximab therapy on a regularly scheduled basis. The appropriate length of treatment for these patients is unclear and may be indefinite. Life-table

analysis further supports the efficacy of infliximab for controlling ocular inflammation.

One patient (patient 9) with idiopathic nodular scleritis had inflammation resolution after 24 infusions and has remained relapse-free without IMT for 27 months. While biological therapies such as infliximab are generally felt not to be curative, it is possible some patients may achieve durable remission without the need for ongoing treatment.

One patient (patient 4) who initially had inflammation recurrence while receiving infliximab therapy required the addition of methotrexate with good inflammation control thereafter. In two patients (patients 1 and 6) we were unable to reduce concomitant immunomodulatory therapy. In five patients (patients 2, 7, 8, 9 and 10), we were able to stop concomitant systemic immunomodulatory medication with successful control of inflammation.

One patient (patient 6) had persistent uveitis with resolution of scleral inflammation while on infliximab, necessitating the use of prednisolone acetate topically.

Two patients underwent cataract or glaucoma surgery with no exacerbation of scleritis postoperatively. In each instance, ocular surgery was timed to occur within a week of infliximab administration. Postoperative topical medications were as prescribed after routine ocular surgeries.

Two patients developed streptococcal upper respiratory infection while on infliximab, necessitating cessation of therapy until resolution with antibiotics was achieved.

In contrast with the recent finding of a relatively high rate of adverse events in a prospective trial of infliximab therapy,¹² our review included only one adverse event necessitating therapy discontinuation. Other studies have shown low rates of adverse events similar to those in our report. Drug-induced lupus reaction is the one significant adverse event that we observed; this has been previously reported in the ophthalmic and rheumatological literature with use of infliximab.¹³ All the reported cases of lupus-like syndrome have improved with therapy discontinuation. Another patient (patient 2) developed possible autoimmune hepatitis which was not confirmed, and liver function was subsequently normal after resuming therapy with infliximab. Autoimmune hepatitis has been noted to occur with a lupus-like reaction to infliximab.¹⁴

Five of our patients are continuing to receive infliximab therapy without any concomitant IMT. Typically, patients are maintained on low-dose immunosuppressive therapy to prevent antibody production to infliximab. The patients who opted for monotherapy were all informed of possible risks. Their desire to avoid immunosuppressive therapy and their good inflammation control while taking infliximab led them to make this choice. All these patients have maintained an excellent response to infliximab therapy, having received between two and 22 infusions. Monotherapy may be offered to patients with scleritis and may be efficacious over the long term.

In our experience, the optimal maintenance infliximab dosing interval for patients with scleritis is shorter than the 8 weeks that has been reported for patients with diseases such as Crohn disease,¹⁵ and is usually 4 weeks. We have found that every-month dosing in these patients is well tolerated and eliminates 'escape' of inflammation between treatments.

Infliximab is a highly targeted therapy with a rapid action that avoids many of the adverse effects associated with other immunosuppressive agents. Furthermore, immunosuppressants that target T cell activation, such as ciclosporin A and mycophenolate mofetil, may act synergistically with infliximab, because they target the T cell effector response through

a different mechanism. Disadvantages of infliximab therapy include short duration of effect and its high cost.

All 10 of these patients with scleritis had inflammation control while taking infliximab and may be a subgroup of patients who respond well to infliximab therapy and who are more likely to achieve remission. A larger randomised trial would be necessary to further test this hypothesis.

This report demonstrates the efficacy of TNF α blockade with infliximab in treatment-resistant scleritis. This study, however, is limited by its retrospective nature, lack of a control group, relatively small number of patients and limited follow-up period for some patients. Further clinical studies, in particular randomised clinical trials, are needed to investigate the potential impact of anti-TNF- α therapy in scleritis.

Competing interest None.

Ethics approval Ethics approval was provided by the institutional review board of the Massachusetts Eye and Ear Infirmary.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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