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Original Article

Infliximab for juvenile idiopathic arthritis-associated uveitis

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Abstract

Background: Infliximab is a murine–human recombinant antitumour necrosis factor monoclonal antibody recently introduced for the treatment of autoimmune diseases in which tumour necrosis factor is thought to be a key mediator. Its role in the treatment of juvenile idiopathic arthritis-associated uveitis is as yet undefined.

Methods: Six children with juvenile idiopathic arthritis-associated uveitis, inadequately controlled on currently available therapy, were treated with infliximab between September 2002 and November 2004. All children were required to remain on low-dose immunomodulatory treatment in conjunction with the infliximab. A retrospective review of two electronic databases containing details of ophthalmology and rheumatology visits was conducted.

Results: In all six children, institution of infliximab therapy was associated with increased ease of management. Ocular inflammation and intraocular pressure control improved in all. It was also possible to reduce the dose or withdraw some glaucoma, steroid and other immunomodulatory drugs. Two children underwent intraocular surgery without noticeable flare of intraocular inflammation. No patient developed any serious systemic complications attributable to infliximab.

Conclusion: Infliximab may be a useful adjunct to the management of refractory juvenile idiopathic arthritis-associated uveitis. In our series it was associated with improved uveitis control and simplification of drug use as well as possibly improving safety of surgical intervention. This study suggests that its role is likely to be in conjunction with maintenance immunomodulatory treatment to provide more optimal disease control. Controlled studies are required to confirm its efficacy and safety, and the potential breadth of its use in uveitis and related disorders.

Key words: adalimumab, anti-TNF therapy, chronic anterior uveitis, etanercept, infliximab, juvenile idiopathic arthritis.

Introduction

A naturally occurring versatile cytokine, tumour necrosis factor alpha (TNFα) is primarily produced by activated monocytes and macrophages. It has multiple effects on normal and abnormal immune-mediated inflammatory reactions. It affects permeability of epithelial cell barriers, recruitment of inflammatory cells and regulation of adhesion molecules and matrix metalloproteinases. TNFα exists in soluble and transmembrane forms and its effect is triggered by its binding to p55 and p75 membrane receptors.[1]

To date, there are three anti-TNFα agents licensed: infliximab (Remicade, Centocor, Horsham, PA, USA), etanercept (Enbrel, Immunex, Thousand Oaks, CA, USA) and adalimumab (Humira, Abbott Laboratories, Abbott Park, IL, USA). Diseases that appear to respond to anti-TNF therapy with these agents include those with ocular manifestations such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, Crohn's disease and juvenile idiopathic arthritis (JIA).[2–6] As a result, there is increasing interest in the application of these agents for the treatment of refractory autoimmune ocular inflammatory syndromes.

There are differences between the TNFα blockers in efficacy and safety profile. Infliximab is an IgG1 murine–human chimeric antibody, which binds to membrane-bound and soluble TNFα. It also binds complement and has the ability to lyse TNFα-bearing monocytes.[7] In contrast, etanercept, a fusion protein of recombinant human TNF-receptor and human IgG1, forms stable complexes with only trimeric forms of soluble TNFα.[8] Being more potent than etanercept it is possible that infliximab may prove to have greater potential for adverse effects. Infliximab and etanercept also differ in their modes of administration and pharmacokinetics. Infliximab has a half-life of 10.5 days. It is given as an intravenous infusion at intervals of 2 weeks or more. Different

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regimens are under investigation but we are currently administering it at weeks 0, 2 and 6 followed by an infusion every 8 weeks. Etanercept has a half-life of 3 days and is usually given subcutaneously twice a week. Adalimumab is a recombinant, fully humanized IgG1 monoclonal antibody to TNFα, which is given subcutaneously once every other week.

To date there are more reports published on the use of etanercept in JIA-associated uveitis (JIA-U) than on infliximab, although this trend is changing. In a trial involving follow up of 16 eyes of nine children, 10 eyes improved and 4 entered remission while on etanercept. One eye experienced an exacerbation of uveitis during treatment.[9] Improvement in responsive eyes was maintained over more than 2 years in patients who continued therapy.[10] Of concern is the development of ocular inflammation while on etanercept. In a retrospective review of 16 patients with inflammatory eye diseases treated with TNFα inhibitors, 4/14 on etanercept and 2/2 on infliximab improved. Five patients on etanercept developed inflammatory eye disease for the first time.[11] Use of etanercept has been associated with irreversible ocular complications.[12] In one case the development of sarcoid necessitated withdrawal of the drug.[13] It is not, however, always necessary to discontinue etanercept as it has been possible in some cases to control ocular inflammation with topical steroids.[14]

Experience on the use of infliximab in autoimmune ocular inflammatory diseases is currently based on case reports and case series of patients with Behcet's disease, ankylosing spondylitis and Crohn's disease.[15–19] In one institution a variety of patients with scleritis, intermediate uveitis and retinal vasculitis were treated with infliximab with good results.[20] Even less is known about the use of infliximab in children with JIA-U. A child with seronegative polyarticular JIA and uveitis previously not responsive to steroid, non-steroidal anti-inflammatory drug, methotrexate or chlorambucil treatment, experienced a remission of uveitis with infliximab.[21] In a series of seven patients with inflammatory eye disease, an adult with JIA-U showed marked improvement of the uveitis in his aphakic, hypotonous only eye.[20] A conference report indicated that over a 6-month period five out of eight children with JIA-U on methotrexate and topical steroids, with or without other drugs, responded to infliximab.[22]

At the 2004 American College of Rheumatology conference, Kahn *et al.* reported on the positive efficacy of high-dose infliximab in 11 children (including five with JIA-U) with refractory uveitis.[23] At the same conference, another report from the Hospital for Sick Children, Toronto showed favourable to good response to infliximab in children with severe JIA-U.[24]

In this report, we review our experience with infliximab in six children with refractory JIA-U.

Methods

Six children with long-standing JIA-U and inadequate control of their intraocular inflammatory disease were started on infliximab infusions between September 2002 and September 2004. All children were required to remain on low-dose immunomodulatory treatment in conjunction with infliximab therapy. An electronic database containing details of all ophthalmic visits during this period, and a similar rheumatology database allowed retrospective review of their records. The ophthalmic database included details of anterior chamber activity graded according to the system of Nussenblatt *et al.*[25]

Standard autoimmune antibodies (ANA, rheumatoid factor, dsDNA, ENA) were measured prior to infliximab therapy. Specific anti-TNFα antibodies are not routinely measured at present. Doses of between 5 and 10 mg/kg were administered at weeks 0, 2 and 4, and thereafter 6–8 weekly. The dose was increased in three patients after 4–8 months as response was considered suboptimal. Infusions were administered as per standard protocol at an increasing rate starting at 15 mL/h for 15 min, 30 mL/h for 15 min, 60 mL/h for 30 min and finally 90 mL/h till completion. The rate was adjusted based on tolerance demonstrated by stability of vital signs measured every 15 min. If there was any evidence of acute infusion reaction the infusion was slowed. Treatment was instituted on an outpatient basis.

Once inflammation was under control, topical steroid treatment was reduced, followed by gradual reduction in systemic immunosuppression to a low, maintenance dose.

MSAccess databases containing details of each visit to the ophthalmologist and rheumatologist were maintained. A retrospective review of the clinical course before and after the initiation of infliximab was conducted.

Results

This cohort of children was started on infliximab infusions specifically for refractory uveitis. Only patient 5 would have warranted use of TNFα blocking agents for arthritis alone according to the Australian Paediatric Rheumatology Group national protocols (http://www.hic.gov.au/providers/forms/pbs/mp/etanercept.htm) (see Table 1 for details of rheumatological disease related to uveitis).

All six patients had a history of multiple uveitis flares with poor baseline control despite the use of standard immunosuppressive regimen. Treatment prior to commencement of infliximab was dependent on individual tolerance of drugs (Table 1), but in general included the drugs commonly used to treat resistant uveitis and inflammatory arthritis (methotrexate, cyclosporin, mycophenolate mofetil and intravenous and oral steroids). The main reason for considering infliximab therapy was that, after multiple manipulations of their drug regimens to attain one that they would tolerate, their uveitis was still inadequately controlled. Five of the six children had experienced problems with intraocular pressure control, which was thought to be related mainly to steroid use prior to the initiation of infliximab treatment. These children either had ocular hypertension (raised intraocular pressure with no demonstrable optic disc changes), or glaucoma (raised intraocular pressure with progressive cupping of the optic disc). At the time of pressure problems most

Table 1. Demographics and rheumatological clinical details of five resistant JIA-U patients treated with infliximab

Patient no.	1	2	3	4†	5	6
Current age	7 years 6 months	11 years 6 months	13 years 7 months	17 years	8 years 6 months	11 years 4 months
Sex	Female	Male	Female	Female	Female	Female
Age of onset of JIA‡	2 years	5 years 5 months	6 years 3 months	2 years 1 month	1 years 1 month	1 year 5 months
JIA onset type	Oligoarthritis	Oligoarthritis	Oligoarthritis	Oligoarthritis	Oligoarthritis	Oligoarthritis
Anti-nuclear antibody status	Positive	Positive	Positive	Positive	Negative	Positive
Rheumatoid factor	Negative	Negative	Negative	Negative	Negative	Negative
HLA-B27	Not done	Positive	Negative	Positive	Negative	Negative
Time diagnosis arthritis to eye disease	At onset	4 months	10 months	4 years 4 months	2 months	3 years 5 months
Therapy for arthritis	NSAIDs	Intra-articular steroids NSAIDs	NSAIDs	Intra-articular steroid NSAIDs	Intra-articular steroids NSAIDs	Intra-articular steroid NSAIDs
Arthritis response to Rx	Good	Good	Good	Partial	Good	Good
Course post infliximab	Already controlled	Already controlled	Already controlled	Improved	Already controlled	Already controlled
Course/pattern of JIA‡	Extended oligoarthritis	Oligoarthritis (remission)	Oligoarthritis (remission)	Extended oligoarthritis	Oligoarthritis (remission)	Oligoarthritis (remission)

†After initial negative uveitis screening patient 4 was lost to review at another institution for 2.5 years and presented 4 years 4 months after onset with severe complicated bilateral anterior uveitis. ‡In all cases, diagnosis of JIA was within 3 months of onset of symptoms attributable to disease. JIA-U, juvenile idiopathic arthritis-associated uveitis; NSAIDs, non-steroidal anti-inflammatory drugs.

were too young to enable us to perform reliable visual field testing.

Prior to treatment all patients had been on continuous topical steroids in conjunction with systemic medication. Following initiation of treatment all patients experienced reduced anterior chamber cellular activity within weeks and needed fewer and shorter courses of topical steroids after starting infliximab (see Table 2 for details of ocular history and Table 3 for details of drug use). Patients 3 and 6 were easily controlled with negligible activity. Patients 1 and 2 who had surgery while on infliximab as well as patient 4 who has remained difficult to control, are discussed in detail below. Patient 5 had a long history of uveitis exacerbation during childhood illnesses. Her uveitis flared (3+ cells) during an upper respiratory tract infection and at the time of a dental abscess. The attacks settled easily with short tapering courses of topical steroid treatment. In patients 1 and 3 slightly increased cellular anterior chamber activity was noted after the fourth week following infusion while on the lower dose of infliximab. This resolved rapidly after the subsequent infusion and for this reason no change in the topical steroid dose was necessary.

Patient 1 with ANA-positive JIA-U had previously undergone cataract surgery in the UK with incomplete clearance of soft lens matter. After complete uveitis control on infliximab she was able to undergo further intraocular surgery with standard short-course oral and topical steroid cover without significant exacerbation of the quiescent uveitis. Her intraocular pressure in the other eye, which had steroid/uveitis-induced glaucoma, remained unacceptably high despite improved uveitis control and reduced steroid dose. She underwent successful Molteno implant surgery with little postoperative inflammation and a few months later, cataract extraction with Acrysof intraocular lens implantation. She is now bilaterally pseudophakic and has recently undergone uneventful Nd:YAG capsulotomy in the right eye. After being on infliximab for 18 months her uveitis began to flare (up to 3+ cells) approximately 4 weeks after infliximab infusions. Flares were treated with short tapering courses of topical steroid. After increasing the dose of infusions this pattern ceased and her uveitis is currently quiet.

Patient 2 is ANA (and incidentally HLA B27)-positive with oligoarticular JIA. Although he is HLA B27-positive his systemic and ocular disease pattern has fitted better in the oligoarticular JIA group than with HLA B27 type disease, for which reason he has been managed as such. He presented with chronic bilateral anterior uveitis poorly responsive to steroid and immunosuppressive treatment. Infliximab therapy was started with good response. Visually significant cataracts eventually developed. Excellent control of his uveitis allowed intraocular surgery to proceed with implantation of an Acrysof lens. He is now bilaterally pseudophakic with vision of 6/6 in both eyes. He received a standard short course of perioperative topical and oral steroid cover and his mild postoperative uveitis settled within 2 months.

Patient 4 had compliance issues throughout her disease course, related to adverse social circumstances. Even when compliant, however, her response to treatment had been suboptimal, with only brief periods of good uveitis control. After an initial good response to the addition of infliximab she stopped her maintenance therapy. She then experienced multiple flares with severe arthritis and hypopyon uveitis. Following reintroduction of maintenance mycophenolate with better compliance and increased dose of infliximab (7.5 mg/kg) her ocular and systemic inflammation came under good control. This patient also developed systemic lupus erythematosus (SLE) type autoantibodies but no clinical evidence of autoimmune disease. Her ANA titre increased from 1:160 to 1:2560 and dsDNA converted from negative to 47 IU. After restarting mycophenolate her ANA fell to 1:1260 and dsDNA to 9 IU (all patients have autoantibodies measured before and 12 monthly during infliximab therapy).

No serious side-effects of treatment were experienced. Patient 3 developed itching, sneezing and rhinorrhoea as a result of the infliximab infusion. This has been easily controlled by pretreating with oral antihistamines. The same patient developed an attack of staphylococcal folliculitis, which responded to topical treatment. Patient 5 developed widespread pityriasis versicolor, which also settled with topical treatment.

Discussion

Apart from a few conference reports on infliximab therapy in children with uveitis, our series is the first study to report the use of infliximab in JIA-U. In our small group of six patients with 3–26 months follow up, infliximab appears to have made a significant contribution to improved uveitis management. Inflammation is better controlled, glaucoma has become easier to manage and patients are experiencing a reduction in side-effects of ocular and systemic medication. No significant safety concerns have become apparent and tolerance of the infusions and 6–8 weekly hospital visits has been good. For this reason we feel that formal clinical trials are definitely warranted.

Our experience with two paediatric surgical cases whose ocular inflammation remained well controlled postoperatively on infliximab illustrates a possible special indication for use of the drug. To date we are not aware of any other patients who have undergone surgical intervention under these circumstances.

We note with interest the view of Honkanen *et al.* that intervals of 4 weeks between infusions might be more effective than 6 weeks.[22] In our experience some patients failed to come under satisfactory control or else developed recurrence of mild uveitis activity after week 4 while on 'lower' dose infliximab (5 mg/kg). In no case was the inflammation sufficient to warrant change of therapy. Decreased dose intervals as suggested in Honkanen *et al.*'s report might be a means of preventing this phenomenon. Our approach, which we believe is equally effective was, however, to increase the dose of infliximab (up to 10 mg/kg) and maintaining 6–8 week treatment intervals. This reduced the frequency of admissions to hospital. A similar approach has also been noted for

Table 2. Details of uveitis and therapy prior to and during infliximab use

Patient no.	1	2	3	4	5	6
Type of uveitis	Chronic, anterior, bilateral	Chronic, anterior, bilateral	Chronic, anterior, bilateral	Chronic, anterior, bilateral	Chronic, anterior, unilateral	Chronic, anterior, bilateral
Complications of uveitis prior therapy	Cataract, glaucoma	Cataract, ocular hypertension	Cataract, ocular hypertension	Cataract, glaucoma	Nil	Cataract, ocular hypertension
Uveitis therapy prior to infliximab[†]	MTX	MTX, CyA	Pred, MMF, CyA	MTX, MMF, CyA, Pred oral/IV	MTX	Pred, MTX, CyA
Age at first infliximab dose	5 years 5 months	10 years 1 month	11 years 6 months	14 years 10 months	7 years 6 months	11 years 3 months
No. infusions to date	21	14	17	21	9	3
Side-effects associated with infliximab	Nil	Nil	Pruritis,[‡] staphylococcal folliculitis	Nil	Pityriasis	Nil
Concurrent immuno-modulation	MTX decreased (dose reduction by 50% over time)	MTX stopped. CyA decreased by 30% (month 2)	CyA stopped (month 5). MMF decreased 50% from month 5. Pred stopped (month 7)	Non-compliant MMF (from month 5). Restarted month 9	MTX reducing dose	CyA
Uveitis cellular activity prior to infliximab	0–3+	0–2+	0–3+	0–3+	0–3+	0–3+
Uveitis cellular activity on infliximab (see text for details)	0 baseline mild flares with URTI (3+ post-Molteno)	0 baseline (2+ post-phaco)	0	0 (hypopyon initially when non-compliant)	0 baseline mild flares with URTI	0
Glaucoma treatment immediately prior to infliximab	Intermittent α-agonist, β-blocker and CAI	Intermittent α-agonist, β-blocker and CAI	Intermittent α-agonist, β-blocker and CAI	Intermittent α-agonist and β-blocker, CAI, Molteno implant R	Nil	Nil
Glaucoma treatment post infliximab	R Molteno implant (month 7). No glaucoma drugs since month 7	None since month 3	None since month 5	None since Molteno implant	Nil	Nil
Surgery since infliximab	L washout of soft lens matter. R Molteno implant. R cataract surgery	L and R cataract surgery				

[†]All patients had extensive topical steroid treatment. [‡]Responds to oral antihistamine preload. CAI, carbonic anhydrase inhibitor; CyA, cyclosporin A; L, left; MFM, mycophenolate mofetil; MTX, methotrexate; Pred, prednisolone; R, right; URTI, upper respiratory tract infection.

Table 3. Systemic therapy prior to and after starting infliximab therapy

Patient no.	1	2	3	4	5	6
Prior to infliximab (IFX) therapy						
Oral prednisolone (Pred)	Used for preoperative cover only	Varying doses to 1 mg/kg	Varying doses up to 1 mg/kg	Varying doses up to 1 mg/kg	Intermittent short courses, up to 1 mg/kg with a tapering schedule	Up to 0.75 mg/kg max. 15 mg orally for 2.5 years prior to IFX
Methotrexate (MTX)	0.8 mg/kg for arthritis and uveitis (max. 10 mg) for 18 months	Up to 10 mg (0.4 mg/kg) from May 2000 continuous	Increasing doses up to 1 mg/kg (15 mg) for 2 years	From June 1998 up to 0.5 mg/kg (max. 15 mg) until December 1999	From April 2002 max. dose 15 mg (1 mg/kg)	For 2 years increasing to 0.5 mg/kg (max. 15 mg)
Cyclosporin A (CyA)	Considered but not started	Added at 5 mg/kg (125 mg/day) from June 2002 for 14 months prior to IFX	Added at 5 mg/kg and (MTX stopped after 4 months overlap) CyA continued until IFX	Started June 1999 at 3 mg/kg increased to 5 mg/kg until December 2002		Following MTX for 12 months (4 months overlapping) at max. of 4 mg/kg
Mycophenolate mofetil (MMF)		Started April 2000 30 mg/kg and continued ever since at 500 mg b.d.	From July 2000 until present in up to 40 mg/kg (max. 2 g/day)			
Other			Sulphasalazine from 1995 to 1998			
After infliximab therapy						
Oral prednisolone (Pred)	Stopped	Stopped	Stopped	Short courses required but not continuous	Stopped	Stopped
Methotrexate (MTX)	Reduced to 7.5 mg (0.35 mg/kg)	Stopped	Stopped several years before IFX	Stopped before IFX	Reduced to 7.5 mg (0.3 mg/kg)	NA
Cyclosporin A (CyA)	NA	Reduced to 3 mg/mg (100 mg)	Stopped	Stopped	NA	Reduced by 25% to 75 mg/day
Mycophenolate mofetil (MFM)	NA	NA	Dose now down to 13 mg/kg	Current dose 500 mg b.d.	NA	NA

NA, not applicable.

its efficacy in a trial of its use in rheumatoid arthritis. Notably in this trial simultaneous use of methotrexate significantly improved the effectiveness and duration of infliximab's effect.[26] The dose of infliximab (3 mg/kg) was initially chosen based on the recommendations for inflammatory arthritis disorders (rheumatoid arthritis). As more information has become available it is clear in resistant disease that 5–10 mg/kg may be required and is effective where the lower doses are not as effective or effective at all. In most cases we moved to 5–6 mg/kg if there was no response after three to four doses at the lower level. Based on current efficacy data no increase beyond 10 mg/kg was considered.

The relapse of ocular and systemic disease in our non-compliant patient, along with the development of new autoantibodies, highlights the need for simultaneous low-dose immunosuppression during treatment with infliximab (usually recommended to be methotrexate). The clinical significance of these autoantibodies, which appear to occur more commonly when infliximab use is not accompanied by methotrexate use,[3] is as yet unknown. In addition to the possible risk of antibody formation, infliximab alone may be insufficient therapy for severe JIA-U. Preliminary evidence suggests that infliximab works synergistically with drugs such as methotrexate.[26] In trials of infliximab therapy for Crohn's disease, development of antibodies occurred less commonly in patients in whom concurrent steroid and immunosuppressives were used.[27]

As it contains 30% mouse protein, infliximab is immunogenic and may induce human antichimeric antibodies (HACAs).[28] Depending on the assay used, HACAs have been detected in 15–40% of infliximab-treated patients. High-titre HACAs have been associated with the loss of efficacy and serum-sickness-like hypersensitivity reactions.[29] However, use of adalimumab may circumvent these problems. A pilot study showed improved efficacy and increased tolerance to adalimumab in patients who were allergic to infliximab.[30] At present we are not routinely screening these children for this antibody.

In our series the single acute reaction to the infusion was in line with a reported incidence of reactions of approximately 5% during administration of the current formulation of infliximab.[31] The acute reaction is similar to that seen with intravenous immunoglobulin infusions and is likely to be multifactorial but does not appear to be an IgE-mediated Type I hypersensitivity reaction alone. Such reactions may include headache, fever, flushing, chills, pruritus, urticaria, chest symptoms, nausea and vomiting, myalgia, erythema, abdominal discomfort, nasal congestion, sneezing, hyper or hypotension, sore throat or lassitude. Chiefetz *et al.* present a useful protocol for management of acute or delayed mild, moderate or severe reactions, which includes measures ranging from slowing the infusion, to use of paracetamol and diphenhydramine, to administration of adrenaline and steroids as necessary.[31]

Increasing use of TNFα antagonists is resulting in more reports of adverse events. These include decreased resistance to intracellular infections such as tuberculosis as well as opportunistic infections such as pneumocystis carinii, blood dyscrasias, demyelinating syndromes and development of lupus-like reactions.[32] Although the data suggest that these adverse events are linked to TNFα blockade, the severity and risks may not be the same for all blocking agents currently in use. To date, these side-effects have rarely been reported in children, possibly because experience with them is still in its infancy. It is recommended that tuberculosis is excluded prior to infliximab therapy in high-risk patients.[33,34]

The present expense of infliximab will continue to limit its use to the most difficult cases. In our setting the current cost of infliximab alone (excluding hospital expenses) is AU$1015.81 per 100 mg with our doses ranging from 100 to 400 mg each. If administered at 0, 2, 6 weeks and then 6–8 weekly intervals, approximately nine doses are given in the first year, that is, 9 × AU$1000–4000, which amounts to AU$9000–36 000 per year.

Although we acknowledge the limitations of our small case series, we believe that infliximab offers a significant alternative in the treatment of refractory JIA-U and its use in this setting is certainly worthy of formal investigation. Caution is warranted given the limited experience of its use in children. We believe it should be used in conjunction with low-dose immunosuppressive therapy.

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