CONCISE REPORT

Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis

Pirjo Tynjälä, Päivi Lindahl, Visa Honkanen, Pekka Lahdenne, Kaisu Kotaniemi

Ann Rheum Dis 2007;**66**:548–550. doi: 10.1136/ard.2006.058248

Objective: To evaluate the efficacy of anti-tumour necrosis factor (anti-TNF) treatment in juvenile idiopathic arthritis (JIA)-associated uveitis.

Methods: 24 patients with uveitis taking etanercept and 21 taking infliximab were studied. The endpoint ophthalmological evaluation was at 24 months or at the termination of the first biological agent. The ocular inflammatory activity was graded on the basis of the number of anterior chamber cells.

Results: Of the 45 patients, uveitis improved in 14 (31%), no change was observed in 14 (31%) and the activity of uveitis increased in 17 (38%). Inflammatory activity improved more frequently ($p = 0.047$) in the patients taking infliximab than in those taking etanercept. The number of uveitis flares/year was higher ($p = 0.015$) in the patients taking etanercept (mean 1.4, range 0–3.2) than in those taking infliximab (mean 0.7, range 0–2). Uveitis developed for the first time while taking anti-TNF treatment in five patients—4 taking etanercept (2.2/100 patient-years) and 1 taking infliximab (1.1/100 patient-years).

Conclusions: During anti-TNF treatment, the ophthalmological condition improved in one-third of the patients with uveitis. In chronic anterior uveitis, associated with refractory JIA, infliximab may be more effective than etanercept.

Chronic uveitis is associated with juvenile idiopathic arthritis (JIA) in about 5–30% of patients.[1] The risk of uveitis is suggested to be higher in antinuclear antibody (ANA)-positive young women with oligoarthritis.[1 2] In the long term, approximately one-third of the affected eyes have been reported to have impaired vision and one-tenth to have become blind.[2 3]

If quiescence of inflammation is not obtained, early immunomodulatory therapy is recommended. At least methotrexate (MTX)[4] and ciclosporin[5] have been used to control uveitis. Anti-tumour necrosis factor (TNF) treatment, etanercept[6–8] and infliximab[8–11] have also been used, but their efficacy in JIA-associated chronic uveitis is not yet well known. In Finland, biological agents have been in clinical use for JIA since 1999. We report the effect of infliximab and etanercept on anterior uveitis in 45 children taking anti-TNF treatment.

PATIENTS AND METHODS

Patients

The data on 108 consecutive patients with JIA receiving anti-TNF treatment were collected retrospectively in three tertiary centres. The permission to the multicentre chart review was obtained from the Finnish Ministry of Social Affairs and Health. The diagnosis of JIA was based on the classification criteria of Petty *et al*.[12] Table 1 presents the characteristics of patients with and without uveitis. All patients had JIA, refractory to previous treatment regimens, including combination treatment of disease-modifying antirheumatic drugs (DMARDs) and steroids. Anti-TNF treatment was initiated on 103/108 (95%) patients for arthritis and on 5/108 (5%) for uveitis. Forty-five patients with the onset of non-infectious anterior chronic uveitis either before or during the anti-TNF treatment were included.

Drug therapy

The initial etanercept dose was 0.4 mg/kg twice weekly subcutaneously. The infliximab dose was 3–6 mg/kg intravenously, initially at 2, 4 and 6-week intervals, and later based on the response on arthritis and/or uveitis, every 4–8 weeks. The choice of the biological agent was at the discretion of the paediatric rheumatologist, and was not randomised. At the initiation of anti-TNF treatment, 43/45 (96%) patients were taking MTX, 37/45 (82%) oral prednisolone and 36/45 (80%) combination treatment of more than one DMARD. During the follow-up, DMARDs and prednisolone were tapered down if possible. Concomitant MTX was used with both infliximab and etanercept, the MTX dose being 10–20 mg/m^2 up to 25 mg weekly. All patients with active uveitis had topical corticosteroids.

Ophthalmological evaluation

The endpoint evaluation of ocular activity was performed at 24 months for anti-TNF treatment or, if the anti-TNF treatment was discontinued earlier, at the time of the discontinuation of the first biological agent. The examination included the best-corrected visual acuity (range 0.0–1.0), biomicroscopy of the anterior segment of the eye, and evaluation of cells and aqueous flare. The posterior parts of the eye were examined by dilated indirect ophthalmoscopy or by a Volk 90 D lens. Ocular pressure was measured by applanation tonometry when possible. Uveitis was classified according to the recommendations of the International Uveitis Study Group.[13] The ocular complications (cataract, glaucoma, cystoid macular oedema and band keratopathy) were registered. The activity of uveitis was graded from 0 to 3 based on the number of anterior chamber cells per field (0, <3 cells; 1, 3–10 cells; 2, 11–30 cells; and 3, >30 cells), modified from the recommendations of Rao *et al*[14] and Nussenblatt *et al*.[15] Ocular improvement was defined as a reduction of inflammation by at least one grade. A treatment failure was defined as increased inflammation by at least one grade, worsening of visual acuity, development of ocular complications or a first course of uveitis during biological drug treatment.

Statistical analysis

The differences between the category variables in patients with or without uveitis were tested with the χ^2 test or Fisher's exact test. In a case of non-normality, Mann–Whitney U test was used and in a case of normality, Student's t test was used. The

Abbreviations: ANA, antinuclear antibody; DMARD, disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis; MTX, methotrexate; TNF, tumour necrosis factor

Table 1 Characteristics of patients with juvenile idiopathic arthritis with and without uveitis

	Uveitis	Without uveitis	p Value
n (%)	47 (44)	61 (56)	
Gender, male/female (%)	8/39 (17/83)	17/44 (28/72)	NS
Type of JIA, n (%):			
Oligoarthritis	3 (6.4)	0	NS
Extended oligoarthritis	11 (23.4)	11 (18)	NS
Seronegative polyarthritis	29 (61.7)	38 (62.3)	NS
Seropositive polyarthritis	0	5 (8.2)	NS
Systemic arthritis	1 (2.1)	5 (8.2)	NS
Enthesitis-related arthritis	3 (6.4)	1 (1.6)	NS
Psoriatic arthritis	0	1 (1.6)	NS
ANA-Ab positive, n (%)	30 (63)	18 (29)	<0.001
HLA-B27 positive, n (%)	15 (33)	23 (37)	NS
Mean (range) age of onset of JIA, years	2.8 (0.8–9)	4.8 (0.9–13.3)	<0.001
Mean (range) age at initiation of BA, years	9.8 (3.3–15.8)	10.3 (3–15.9)	NS
Mean (range) duration of JIA, years	7 (1.1–13.7)	5.5 (0.3–11.6)	0.028

ANA-Ab, antinuclear antibody; BA, biological agents; HLA-B27, human leucocyte antigen B27; JIA, juvenile idiopathic arthritis, NS, non-significant.

difference in the ocular outcome between infliximab and etanercept was assessed by Fischer's exact test.

RESULTS

Characteristics of the patients with uveitis

At the initiation of anti-TNF treatment in 1999–2001, 40/108 (37%) of the patients had uveitis and at the end of the follow-up in 2005, 47/108 (44%) had ongoing uveitis or a history of uveitis. Forty-five patients were included in the final analysis (table 2), because in two patients the first flare of uveitis was discovered after the discontinuation of anti-TNF treatment. The mean age at the onset of uveitis was 5.6 (range 1.3–16.9) years, and 34/45 (76%) patients had bilateral uveitis. The mean interval between the onset of juvenile arthritis and uveitis was 2.8 (range −3.6 to 14.7) years. In 7/45 (16%) patients, uveitis was diagnosed before symptoms of arthritis. The mean duration of uveitis at the initiation of anti-TNF treatment was 4.3 (range −4.2 to 13.3) years.

Before the initiation of anti-TNF treatment, there were no significant differences between the ocular complications in etanercept or in infliximab treatment groups, except for six patients in the infliximab treatment group, and no patients in the etanercept group had glaucoma ($p = 0.007$). There were no differences between etanercept and infliximab groups in visual acuity either at the baseline ($p = 0.81$) or at the end of the follow-up ($p = 0.90$). The onset of JIA was at a younger age in patients receiving etanercept (mean 2.3 years) than in patients receiving infliximab (mean 3.5 years, $p = 0.016$). In other variables such as duration of disease, duration of uveitis, onset of uveitis, gender, number of DMARDs at the baseline, endpoint evaluation time, presence of ANA or human leucocyte antigen-B27, there were no differences between the treatment groups.

Activity of uveitis during anti-TNF treatment

Inflammatory activity improved more frequently ($p = 0.047$) in the patients taking infliximab than in those taking etanercept (table 3). In 24 patients taking etanercept, the mean number of flares/year was 1.35 (range 0–3.2) and in 21 patients taking infliximab, 0.68 (range 0–2.02). The difference between the flares during etanercept and infliximab treatment was significant ($p = 0.015$). There was no correlation either with the dose or the frequency of infliximab infusions and the ophthalmological outcome.

Table 2 Ocular characteristics in 45 patients with uveitis during anti-tumour necrosis factor treatment

Ocular characteristics	At baseline	At 24 months
Mean (range) visual acuity	0.91 (0.2–1)	0.93 (0.1–1)
Cystoid macular oedema, n (%)	5 (11)	8 (18)
Cataract, n (%)	18 (40)	25 (56)
Glaucoma, n (%)	6 (13)	13 (29)
Band keratopathy, n (%)	5 (11)	7 (16)

Five patients had their first course of uveitis during anti-TNF treatment and concomitant MTX, four taking etanercept and one taking infliximab. The patient taking infliximab had the first course of uveitis 50 months after the initiation of infliximab. At the time, the infliximab dose was low (2.4 mg/kg) and after doubling the dose, the ocular inflammation resolved in 10 months. Four patients taking etanercept had their first episode of uveitis at 8, 13, 30 and 45 months. During the follow-up, one patient had a remission in uveitis at 10 months and one at 5 years, but two still had active uveitis after 4 years. The mean occurrence of new cases of uveitis during infliximab was 1.1 cases/100 patient-years (95% CI 0.03 to 5.54) and that during etanercept was 2.2 (95% CI 0.59 to 6.13), the difference being insignificant ($p = 0.6$).

Side effects and adverse events

Of the 45 patients with uveitis, anti-TNF treatment was discontinued owing to side effects or adverse events in two patients taking etanercept (one patient with rash and recurrent skin infection and one with ocular complication; retinal ablation) and in four patients taking infliximab (three patients with infusion reactions and one with increases in ANA and DNA antibodies with concomitant alopecia). In four patients taking etanercept and four taking infliximab, the treatment was discontinued because of lack of efficacy. Two patients with inactive disease including inactive uveitis were able to discontinue infliximab treatment, and remained in clinical remission taking DMARDs for 5.2 and 0.5 years. In 4/24 (16.6%) patients, the adverse events during etanercept treatment were classified as severe: pneumonia, unspecified abdominal infection, sight-threatening macular oedema and retinal ablation. In 3/21 (14.3%) patients taking infliximab, the adverse events were severe: peritonsillar abscess, pansinuitis and alopecia with highly increased ANA and DNA antibodies. No life-threatening adverse drug reactions were seen in any of these patients with uveitis taking anti-TNF treatment.

DISCUSSION

This study suggests that the anti-TNF treatment has beneficial effects in JIA-associated uveitis and that infliximab may be more effective than etanercept in controlling ocular

Table 3 Activity of uveitis during etanercept and infliximab treatment at the end of the follow-up compared with the baseline in 45 patients with juvenile idiopathic arthritis

Response of uveitis	Etanercept	Infliximab	Total
Treatment failure, n (%)	13 (54.2)	4 (19)	17 (37.8)
No change, n (%)	6 (25)	8 (38.1)	14 (31.1)
Improved activity, n (%)	5 (20.8)	9 (42.9)	14 (31.1)

inflammation. Our findings are in line with previous observational studies.[8–11] Interestingly, during the 2-year follow-up, the frequency of long-term complications of uveitis seemed to increase despite decreased ocular inflammatory activity. This might reflect the long duration of uveitis even before effective treatment. In this cohort of patients with refractory JIA, uveitis was associated with polyarthritis more frequently than in population-based JIA series.[1]

In severe cases of anterior uveitis, ocular inflammation inevitably results in a chronic course of the disease, ocular complications and eventually impaired vision. The longer the progression of the disease, the poorer the outcome. Although we still lack more specific treatment, anti-TNF treatment seems to be a promising approach. In the future, the optimal dose, frequency and timing of infliximab infusions or alternative immunomodulatory treatments need to be studied in a randomised prospective trial.

Authors' affiliations

Kaisu Kotaniemi, Department of Opthalmology, Rheumatism Foundation Hospital, Heinola, Finland
Pirjo Tynjälä, Visa Honkanen, Pekka Lahdenne, Department of Pediatric Rheumatology, Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland
Päivi Lindahl, Department of Ophthalmology, Helsinki University Central Hospital, Helsinki, Finland

Competing interests: None declared.

Correspondence to: Dr P Tynjälä, Research Unit, Hospital for Children and Adolescents, Biomedicum 2 Helsinki, 5th Floor, PO Box 448 (Tukholmankatu 8A) Helinski, 00029 HUS, Finland; pirjo.tynjala@hus.fi

Accepted 22 October 2006
Published Online First 26 October 2006

REFERENCES

1 **Kotaniemi K**, Kautiainen H, Karma A, Aho, K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. *Ophthalmology* 2001;**108**:2071–5.
2 **Rosenberg AM**. Uveitis associated with juvenile idiopathic arthritis: envisioning the future. *J Rheumatol* 2002;**29**:2253–5.
3 **Ozdal PC**, Vianna RN, Deschenes J. Visual outcome of juvenile rheumatoid arthritis-associated uveitis in adults. *Ocul Immunol Inflamm* 2005;**13**:33–8.
4 **Foeldvari I**, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005;**32**:362–5.
5 **Kilmartin DJ**, Forrester JV, Dick AD. Cyclosporin A therapy in refractory non-infectious childhood uveitis. *Br J Ophthalmol* 1998;**82**:737–42.
6 **Smith JA**, Thompson DJ, Whitcup SM, Suhlir E, Clarke G, Smith S, *et al*. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18–23.
7 **Schmeling H**, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2005;**44**:1008–11.
8 **Saurenmann RK**, Levin AV, Rose JB, Parker S, Rabinovitch T, Tyrrel PN, *et al*. Tumour necrosis factor α inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006;**45**:982–9.
9 **Richards JC**, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Exp Ophthalmol* 2005;**33**:461–8.
10 **Rajaraman RT**, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology* 2006;**113**:308–14.
11 **Kahn P**, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006;**113**:864.
12 **Petty RE**, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, *et al*. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;**31**:390–2.
13 **Bloch-Michel E**, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol* 1987;**103**:234–5.
14 **Rao NA**, Forster DJ, Spalton DJ. The uvea. Uveitis and intraocular neoplasms, Vol 2. In: Podos and Yanoff, eds, *Anterior uveitis*. New York: Gover Medical Publishing, 1992:1–19.
15 **Nussenblatt RB**, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. In: Nussenblatt RB, Whitcup SM, Palestine AG, eds. *Examination of the patient with uveitis*. 2nd edn. St Louis: Mosby, 1996:58–68.