

Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis

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Background: The purpose of this study was to investigate the long-term effects of adalimumab, a tumor necrosis factor alpha antagonist, in the treatment of uveitis associated with juvenile idiopathic arthritis.

Methods: Adalimumab was initiated in 94 patients with juvenile idiopathic arthritis to treat active arthritis and/or active associated uveitis. In 18 patients, therapy was discontinued after a short period because of inefficacy or side effects. The activity of uveitis (using Standardized Uveitis Nomenclature [SUN] criteria and clinical examination) and arthritis (number of swollen or active joints) was evaluated at the start and at end of the study.

Results: At the end of the study, uveitis was under good clinical control in two thirds of 54 patients (31% did not need any local treatment and 35% used only 1–2 corticosteroid drops a day), and one third had active uveitis (at least three corticosteroid drops a day). According to SUN criteria, adalimumab treatment for uveitis showed improved activity (a two-fold decrease in uveitis activity) in 28% of patients, with a moderate response in 16 patients, no change in a further 16 patients, and worsening activity (a two-fold increase in uveitis activity) in 13% of patients. The overall proportion of patients with active arthritis decreased. At the beginning of the study, 69% of patients with uveitis had more than two active joints, and at the end of the study only 27% had active joint disease. In 27 patients with juvenile idiopathic arthritis without uveitis on adalimumab, the number of active joints decreased from 93% to 59%. Systemic corticosteroid treatment could be stopped in 22% of patients with uveitis and in 11% of those without uveitis. Most of the patients had received methotrexate, other immunosuppressive therapy, or other biological drugs before initiating adalimumab.

Conclusion: Adalimumab is a valuable option in the treatment of uveitis associated with active juvenile idiopathic arthritis.

Keywords: adalimumab, juvenile idiopathic arthritis, uveitis

Introduction

Anterior uveitis is a serious manifestation of juvenile idiopathic arthritis, with a potential for significant ocular damage and even blindness. Uveitis has been reported in 10%–20% of patients with juvenile idiopathic arthritis, although lower and higher figures have been published.^{1,2} Antinuclear antibody (ANA)-positive girls younger than seven years of age with oligoarthritis are at the greatest risk of developing uveitis.²

The first-line standard therapy for uveitis is topical and systemic corticosteroids, often reinforced by methotrexate as a second-line disease-modifying antirheumatic drug (DMARD). Tumor necrosis factor-alpha (TNF- α) has been shown to play an important role in the development of uveitis.³ TNF- α blockers have been used to treat uveitis and

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juvenile idiopathic arthritis, and especially uveitis associated with juvenile idiopathic arthritis in children who have failed conventional topical and second-line DMARD therapy.^{4,5} A meta-analysis of the impact of anti-TNF therapy on anterior uveitis in ankylosing spondylitis was used to compare the effect of infliximab and etanercept to decrease the number of uveitis flares in 717 patients with ankylosing spondylitis. The flares were less frequent during infliximab than during etanercept treatment.⁶ A Canadian study compared the efficacy of etanercept and infliximab in uveitis among 21 patients with active uveitis at onset of treatment. A better clinical response with fewer ocular complications was seen with infliximab than etanercept.⁷

In a small study from Columbia, ocular inflammation in 13 of 14 children responded to adalimumab (a humanized monoclonal TNF- α antibody).⁸ A better effect of adalimumab for uveitis compared with etanercept was shown in a German study of 18 children and young adults with juvenile uveitis and/or arthritis.^{9,10} In a Finnish retrospective study, of 20 patients with juvenile idiopathic arthritis and chronic uveitis on adalimumab treatment, seven (35%) showed improved activity, one (5%) had worsening activity, and 12 (60%) showed no change.¹¹ A recent Greek study reported a decrease in uveitis flares with adalimumab treatment in three of six patients with juvenile idiopathic arthritis and uveitis.¹² We describe a large retrospective cohort of patients with juvenile idiopathic arthritis and associated uveitis treated with adalimumab for a mean of two years.

Patients and methods

This study was based on data for 320 patients drawn from the juvenile idiopathic arthritis registry for biologic drugs at the Rheumatism Foundation Hospital, Heinola, Finland, for 2008–2010. Some of these cases belonged to the cohort described earlier by Tynjälä et al.¹¹ From the patient records, we collected baseline demographic data (age, gender, age at disease onset, duration of disease), disease information (juvenile idiopathic arthritis subtype, number of active joints, laboratory values, if available), and treatment data (biologics and concomitant DMARDs, including start and stop dates, as well as reasons for withdrawal). The study was retrospective and evaluated the long-term impact of adalimumab, the monoclonal anti-TNF- α antibody, on juvenile idiopathic arthritis and associated uveitis.

The 2001 revised International League Against Rheumatism classification criteria for juvenile idiopathic arthritis were used in this study.¹³ All diagnoses of juvenile idiopathic arthritis were confirmed by a pediatric rheumatologist

who examined arthritis activity by evaluating the number of swollen or active joints and joints with a limited range of motion at the start of adalimumab therapy and at the end of the study. Inflammatory laboratory markers (erythrocyte sedimentation rate and C-reactive protein), if available, were recorded.

Evaluation of the efficacy of adalimumab on uveitis activity was done using the Standardized Uveitis Nomenclature (SUN) criteria (a two-fold improvement or a two-fold worsening of uveitis, ie, a change in the amount of anterior chamber cells and flare) and clinical examination (evaluating the decrease in activity of inflammation in the eye by biomicroscopy, decrease in amount of anterior chamber cells and flare, and decrease in amount of topical treatment).¹⁴

Remission of juvenile idiopathic arthritis with medication was stated if the patient had no joints with active arthritis and no systemic signs (eg, fever, rash). Erythrocyte sedimentation rate and C-reactive protein needed to be at normal levels. No global assessment of disease activity scores was available in this retrospective series.¹⁵

The clinical response to treatment for uveitis was considered good if there were <3 anterior chamber cells/1 mm slit and there was no need for corticosteroid drops. A moderate response was deemed to be 3–9 anterior chamber cells/1 mm slit and no more than three corticosteroid drops per day. Ineffective treatment was considered to be >10 cells in the anterior chamber and more than three corticosteroid drops per day (beyond which the risk of cataract is increased).

Adalimumab was initiated in 94 patients with juvenile idiopathic arthritis because of active arthritis and/or active associated uveitis. The patients were divided into two groups, ie, 54 patients with juvenile idiopathic arthritis and uveitis and 40 patients with juvenile idiopathic arthritis and without uveitis.

The 54 patients with uveitis were either not responsive to standard immunosuppressive therapy for uveitis or were intolerant to it. Adalimumab was administered at a dose of 24 mg/m² at 14-day intervals subcutaneously, and according to clinical response, up to a frequency of 24 mg/m² at seven-day intervals. In 22 patients with uveitis, adalimumab was the first anti-TNF treatment and was started because of active ocular inflammation.

The results are expressed as the median \pm standard deviation and interquartile range. Statistically significant differences between the groups were evaluated using the Mann–Whitney U test and Chi-squared and Fisher Exact tests, as appropriate.

Table 1 Demographics of 94 patients with juvenile idiopathic arthritis receiving adalimumab

Variable	JIA with uveitis (n = 54)	JIA without uveitis (n = 40)	P value
Female, n (%)	37 (69)	26 (65)	0.72
Age at diagnosis, years, median (IQR)	3 (2, 7)	5 (3, 11)	0.027
Age at end of study, years, median (IQR)	15 (14, 18)	16 (11, 18)	0.67
Course type of arthritis, n (%)			0.003
Oligoarthritis	14 (26)	1 (2)	
Extended oligoarthritis	17 (31)	12 (30)	
Polyarthritis:	20 (27)	24 (60)	
Seronegative	20	22	
Systemic JIA	0 (0)	2 (5)	
Psoriatic arthritis	2 (4)	0 (0)	
Spondyloarthropathy	1 (2)	1 (2)	
HLA B27 present n (%) [†]	12 (32)	13 (50)	0.16
ANA present n (%) [‡]	36 (71)	9 (31)	<0.001

Notes: [†]15 patients with uveitis and 2 without uveitis were missing data for HLA-B27; [‡]1 patient with uveitis and 3 without uveitis were missing data for the ANA studies.

Abbreviations: ANA, antinuclear antibody; HLA, human leukocyte antigen; IQR, interquartile range; JIA, juvenile idiopathic arthritis.

Results

The main characteristics of the 94 patients receiving adalimumab at the beginning of the study are shown in Table 1. The number of girls was slightly higher among the patients with uveitis (69%) than those without it (65%). The median age at onset of arthritis was lower in the patients with uveitis (median 3.0 years, interquartile range 2–7 years) than that of patients without uveitis (median 5.0 years, interquartile range 3–11 years), but the difference was not statistically significant. Patients with uveitis were more often ANA-positive ($P < 0.001$).

The majority of patients with uveitis had oligoarthritis (26%) or extended oligoarthritis (31%). Among the patients without uveitis, the arthritis subtype was more aggressive; one patient had oligoarthritis, 12 had extended oligoarthritis, 22 had seronegative polyarthritis, two had seropositive polyarthritis, two had systemic onset arthritis, and one had spondyloarthropathy.

Adalimumab was stopped in 18 patients (five with associated uveitis) after a short period because of inefficacy or side effects, except for one patient who went to remission. At the end of the study, uveitis was under good clinical control in two thirds of patients, ie, 31% did not need any local treatment for uveitis and 35% used only 1–2 corticosteroid

drops per day. One third of the patients still had active uveitis and used at least three corticosteroid drops per day.

According to the SUN criteria, the response to adalimumab treatment was improved in 28% of patients, and worsened (two-step change in the amount of inflammation in the anterior chamber) in 13% of patients (Tables 2 and 3). Taking into account the 16 patients with uveitis whose response to adalimumab was moderate, an overall positive effect of adalimumab was seen in 57% of the patients with uveitis.

After 24 months of treatment with adalimumab, the proportion of patients with active arthritis decreased from 69% to 27% in the patients with uveitis, and from 93% to 59% in those without uveitis (Table 4). Systemic corticosteroid treatment could be stopped in 22% of patients with uveitis and in 11% of those without uveitis ($P = 0.222$, data not shown).

Binocular visual acuity in the patients with juvenile idiopathic arthritis and uveitis was good in all but one patient who was legally blind because of severe early-onset chronic uveitis associated with juvenile psoriatic arthritis. Twenty-eight children (52%) with juvenile idiopathic arthritis developed complications of uveitis, comprising five children who had incipient cataract, 21 who had undergone cataract surgery (intraocular lens implantation in 20 cases), five with

Table 2 Clinical control of uveitis in 54 patients treated with adalimumab

Effect of treatment on local uveitis	Patients n (%)
No corticosteroid drops	17 (31)
1–2 corticosteroid drops/day	19 (35)
≥3 corticosteroid drops/day	18 (33)

Table 3 Efficacy on uveitis according to Standardized Uveitis Nomenclature criteria in 54 patients*

Response to treatment	Patients, n (%)
Improved activity	15 (28)
Moderate response	16 (30)
No change	16 (30)
Worsening activity	7 (13)

Note: *Adalimumab was stopped in 5 patients.

Table 4 Effect of adalimumab on arthritis, and number of patients on adalimumab therapy at end of study

Patients on adalimumab therapy at end of study with signs of inflammation and swollen/active joints	Patients with uveitis (n = 49)	Patients without uveitis (n = 27)	P value
At start of adalimumab, n (%)	34 (69)	25 (93)	0.023
At end of study	13 (27)	16 (59)	0.005

secondary glaucoma (Molteno implantation in three), and three with uveitis complicated by cystoid macular edema.

Most of the patients had been previously treated with more than one DMARD as monotherapy or as part of combination therapy (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, cyclosporin A, mycophenolate mofetil). At the end of the study, only four of 54 patients with juvenile idiopathic arthritis and uveitis remained on adalimumab monotherapy, and the rest were on combination therapy with prednisolone (n = 9), methotrexate (n = 34), leflunomide (n = 9), cyclosporin A (n = 7), azathioprine (n = 1), sulfasalazine (n = 4), or hydroxychloroquine (n = 2). The numbers of patients with uveitis on an anti-metabolite and on systemic steroids at baseline and at the end of the study are shown in Table 5. Prednisolone therapy could be stopped in 22% of patients with uveitis. Of these patients, 29 had not responded to previous anti-TNF agents (etanercept or infliximab). Twenty-five patients were receiving adalimumab every fortnight at the end of the study, and 24 patients were receiving it weekly. The main clinical reason for weekly treatment was activity of uveitis.

Discussion

Adalimumab is a valuable option in the treatment of uveitis associated with refractory juvenile idiopathic arthritis. Our study was retrospective, but is one of the largest done in patients with treatment-resistant childhood uveitis treated with adalimumab.

Table 5 Number of patients with uveitis on an antimetabolite and systemic steroids at baseline and at end of study

	Treatment at baseline in patients with uveitis (n = 54)	Treatment at end of study JIA with uveitis (n = 54)
Prednisolone	20	9
Methotrexate	47	34
Hydroxychloroquine	5	2
Cyclosporin A	10	7
Azathioprine	2	1
Leflunomide	13	9
Sulfasalazine	8	4

Abbreviation: JIA, juvenile idiopathic arthritis.

At the end of this study, disease activity improved in 15 of 54 patients with uveitis on adalimumab therapy (31% of those continuing with adalimumab), and disease activity worsened in seven patients (13%) according to SUN criteria. However, improvement of uveitis was seen altogether in 31 out of 54 patients (57%), because in another 16 patients with uveitis the response for uveitis was moderate, but did not reach the two-fold change. In 16 cases, no change was seen according to SUN criteria. Clinical evaluation gave better results (improvement of uveitis in 66% of patients), because the use of SUN criteria in the evaluation of juvenile idiopathic arthritis-associated uveitis is difficult. The amount of anterior chamber cells is often quite small when the eye disease is still active. The two-fold difference is hard to achieve, because changes are quite small. In many cases, clinical evaluation by an experienced ophthalmologist may be better. The rate of favorable outcome was somewhat higher in previous studies with smaller numbers of patients, in which the activity of uveitis improved in 35% (seven of 20 patients) according to a report by Tynjälä et al and in 89% according to a report by Biester et al.^{9,11}

The type of arthritis was more severe in patients without uveitis. Any significant risk factors according to the type of arthritis were noted in this study. Both persistent and extended oligoarthritis groups were equally represented among the patients with juvenile idiopathic arthritis associated with uveitis. Interestingly, in a study from the UK consisting of 23 patients with juvenile idiopathic arthritis and uveitis, an association between patients with extended oligoarthritis and uveitis was noted, and patients with extended oligoarthritis also had a shorter interval from diagnosis of arthritis to development of uveitis.¹⁶ Five patients with juvenile idiopathic arthritis and uveitis had discontinued adalimumab therapy due to adverse events or inefficacy.

Our study was performed in clinical practice conditions, with a long period of follow-up by one ophthalmologist. Adalimumab was a good option in the treatment of patients with juvenile idiopathic arthritis and associated uveitis, often in combination with methotrexate and/or other DMARDs.

Disclosure

The authors report no conflicts of interest in this work.

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