

Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis

P. Tynjälä^{1,2}, K. Kotaniemi³, P. Lindahl⁴, K. Latva⁵, K. Aalto¹, V. Honkanen¹ and P. Lahdenne¹

Objective. To evaluate the efficacy of adalimumab in juvenile idiopathic arthritis (JIA)-associated uveitis.

Methods. Retrospective observational study of 20 patients with JIA and chronic uveitis on adalimumab treatment. The ocular inflammation and improvement was assessed according to the Standardization of Uveitis Nomenclature criteria.

Results. At the initiation of adalimumab, the mean age of patients was 13.4 yrs and the mean duration of uveitis 8.7 yrs. Seventeen (85%) patients had polyarticular JIA and 19 (95%) had previously been on anti-TNF treatment. The mean duration of adalimumab therapy was 18.7 months. Of the 20 patients, 7 (35%) showed improved activity, 1 (5%) worsening activity and in 12 (60%) no change was observed in the activity of uveitis. Those with improved activity were younger and had shorter disease duration. The mean number of flares/yr decreased from 1.9 to 1.4 during adalimumab treatment. Serious adverse events or side-effects were not observed. Seven patients discontinued adalimumab during the follow-up: six because of inefficacy and one because of inactive uveitis.

Conclusion. Adalimumab is a potential treatment option in JIA-associated uveitis, even in patients non-responsive to previous other anti-TNF therapy.

KEY WORDS: Adalimumab, Anti-TNF treatment, Juvenile idiopathic arthritis, Outcome assessment, Uveitis.

Introduction

Chronic uveitis, which involves the anterior part of the uvea, is associated with juvenile idiopathic arthritis (JIA). In the majority of the patients, uveitis is asymptomatic and diagnosed during 4 yrs following the diagnosis of JIA [1, 2], but uveitis can also precede the onset of arthritis [1, 3]. Chronic uveitis may result in complications such as cataract, glaucoma, band keratopathy, synechiae and cystoid macular oedema [2–4]. Impaired vision and blindness as long-term complications have also been reported [3–6].

In paediatric ophthalmology, JIA-associated refractory chronic uveitis is a challenge for treatment. In an early study of Chylack [6], 41% of children with uveitis did not sufficiently respond to corticosteroids over 6 months and were in the need of additional treatment. Recent studies on conventional DMARDs have suggested efficacy of second-line agents such as methotrexate (MTX) [7–9] or cyclosporin [10] in childhood uveitis. The evidence of the beneficial effect of immunosuppressive treatments in chronic uveitis is based on clinical experience and observational studies.

During the last few years, anti-TNF treatment has shown some promise in the treatment of chronic uveitis, although the results have been somewhat conflicting. Etanercept, a soluble TNF receptor, does not seem to change the outcome of uveitis [11–13], whereas there are a few encouraging reports on infliximab, a chimeric monoclonal TNF- α antibody [14–18]. Very recently, three studies on the treatment of childhood uveitis have suggested a positive effect of adalimumab [19–21]. Concerning RA in adults, adalimumab has been shown to be effective in long-term trials [22]. The results of phase III trials on efficacy of adalimumab in JIA are yet to be published.

Since 2003, we have used adalimumab, a humanized monoclonal TNF- α antibody for JIA and associated uveitis in children who have failed conventional topical and second-line therapy and biological agents. In this study, we evaluated our treatment results on childhood anterior uveitis, and alongside on juvenile arthritis, in 20 consecutive JIA-patients, of whom 95% were unresponsive to previous biological drug therapy.

Patients and methods

Patients and drug therapy

The patient series consisted of JIA patients with chronic anterior uveitis for more than 2 yrs, non-responsive and/or non-compliant to topical therapy and second-line agents. Twenty patients taking adalimumab for at least 3 months who had uveitis with anterior chamber (AC) cell activity or flares during the previous 3 months were included (Table 1). The permission to the retrospective study in two tertiary centres in Finland was given by the Finnish Ministry of Social Affairs and Health. The diagnosis of JIA was based on the ILAR criteria [23]. The decision to use adalimumab was at the discretion of the paediatric rheumatologist. Nineteen (95%) patients had failed previous biological treatment because of inefficacy (11/11 on etanercept, 13/18 on infliximab) or side-effects (5/18 on infliximab) (Table 2). Concomitant MTX was given 10–20 mg/m² up to 35 mg weekly, if side-effects were not limiting the dose given (Table 3). Two patients without DMARDs at the baseline had compliance problems. The patients were initially given a standard dose of adalimumab subcutaneously every 2 weeks (40 mg to 18/20 patients and 20 mg to two patients weighting <30 kg).

Evaluation of uveitis

The ophthalmologist examined the patients every 4–12 weeks. The evaluation included the best-corrected visual acuity (BCVA) (range 0.0–1.0), biomicroscopy of the anterior segment of the eye, evaluation of cells and flare, examination of the posterior parts of the eye by dilated indirect ophthalmoscopy or by a Volk 90D lens and the measuring of ocular pressure by applanation tonometry. The activity of the AC inflammation was evaluated according to the Standardization of Uveitis Nomenclature (SUN) criteria, where the activity of AC inflammation was graded from 0 to 4 (grade/cells in field: 0/<1, 0.5+/1–5, 1+/6–15, 2+/16–25,

¹Department of Pediatric Rheumatology, Hospital for Children and Adolescents, Helsinki University Central Hospital, ²Department of Pediatrics, Lohja Hospital, Lohja, ³Department of Ophthalmology, Rheumatism Foundation Hospital, Heinola, ⁴Department of Ophthalmology, Helsinki University Central Hospital and ⁵Department of Pediatric Rheumatology, Rheumatism Foundation Hospital, Heinola, Finland.

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Correspondence to: P. Tynjälä, Research unit, Hospital for Children and Adolescents, Biomedicum 2 Helsinki, 5th floor, PO Box 448 (Tukholmankatu 8A), 00029 HUS, Finland. E-mail: pirjo.tynjala@hus.fi

TABLE 1. General characteristics in 20 JIA patients with uveitis at the onset of adalimumab

Duration of JIA, mean (range) (yrs)	10.0 (2.5–14.8)
Duration of uveitis, mean (range) (yrs)	8.7 (2.5–14.6)
Age at onset of JIA, mean (range) (yrs)	3.4 (1.1–8.0)
Age at onset of uveitis, mean (range) (yrs)	4.7 (1.3–13.9)
Interval: onset of JIA – onset of uveitis, mean (range) (yrs)	1.2 (–3.5–12.1)
Age at onset of adalimumab, mean (range) (yrs)	13.4 (6.0–19.2)
Age at onset of first biological agent, mean (range) (yrs)	10.5 (3.3–19.2)
ANA positive, <i>n</i> (%)	15 (75)
HLA-B27 positive, <i>n</i> (%) (19 examined)	6 (32)

TABLE 2. Baseline characteristics and previous anti-TNF treatment in 20 JIA patients with uveitis on adalimumab

Patient no.	Age (yrs)	Gender (M/F)	Type of JIA	Duration of Uv (yrs)	Previous BA: IFX (mg/kg) (interval, w)	Reason to discontinue IFX/ETA	Reason for ADA
1	6	F	Oligo	3	IFX (6–4)	in: Uv	Uv
2	8	F	Poly	6	IFX (7–4)	in: Uv	Uv
3	11	F	Poly	8	ETA	in: Uv	Uv
					IFX (3–5)	in: Uv	
4	12	F	Poly	6	IFX (3–4)	in: Uv	Uv
5	16	F	Poly	3	IFX (4–6)	in: Uv	Uv
6	8	F	Poly	6	ETA	in: Uv & Art	Uv & Art
					IFX (3–4)	in: Uv & Art	
7	13	F	Ext-o	11	IFX (3–4)	adr	Uv & Art
					ETA	in: Uv & Art	Art
8	14	F	Ext-o	10	ETA	in: Uv & Art	Uv & Art
					IFX (NA)	in: Uv & Art	Art
9	14	F	Poly	13	ETA	in: Uv & Art	Uv & Art
					IFX (3–7)	adr	Art
10	14	M	Poly	12	IFX (NA)	in: Uv & Art	Uv & Art
11	15	F	Ext-o	14	IFX (3–6)	adr	Uv & Art
12	15	F	Ext-o	10	IFX (4–6)	in: Uv & Art	Uv & Art
13	16	F	Syst	10	ETA	in: Uv & Art	Uv & Art
					IFX (3–4)	adr	Art
14	17	M	Ext-o	11	IFX (3–4)	in: Uv & Art	Uv & Art
15	17	F	Ext-o	15	IFX (3–8)	adr	Uv & Art
					ETA	in: Uv & Art	Art
16	19	M	Poly	8	–	–	Uv & Art
17	11	F	Poly	7	IFX (5–6)	in: Uv & Art	Art
					ETA	in: Uv & Art	
18	13	F	Poly	7	ETA	in: Uv & Art	Art
					IFX (5–6)	in: Uv & Art	
19	13	M	ERA	3	ETA	in: Uv & Art	Art
20	14	F	Ext-o	12	ETA	in: Uv & Art	Art
					IFX (4–6)	in: Uv & Art	

Uv: uveitis; BA: biological agents; IFX: infliximab; ETA: etanercept; w: weeks; NA: not available; ADA: adalimumab; Art: arthritis; Oligo: oligoarthritis; Poly: polyarthritis; Ext-o: extended oligoarthritis; ERA: enthesitis-related arthritis; Syst: systemic arthritis; adr: adverse drug reaction; in: inefficacy.

3+/26–50, 4+/>50) [24]. An improved activity was defined as either a two-step decrease in the level of inflammation or a decrease to inactive (grade 0) and a worsening of the inflammation as either a two-step increase in the level of inflammation or an increase to the maximum grade (4+). If one eye improved, but the other eye worsened, the interpretation was increased activity. The flare in uveitis was defined as an episode with worsening activity in the AC inflammation during the follow-up. The number of flares were assessed from 1 yr before adalimumab to baseline and from baseline to the end of the follow-up. Additionally, the change in the activity was calculated separately for each eye with uveitis. For comparative purposes, we also evaluated AC inflammation with another method, modified from the recommendations of Rao *et al.* [25] and Nussenblatt *et al.* [26], where the activity of uveitis was graded from 0 to 3 (grade/cells: 0/<3, 1/3–10, 2/11–30, 3/>30) [17]. In this method, an ocular improvement was defined as a reduction of inflammation by one grade and a treatment failure as increased inflammation by one grade.

Evaluation of the activity of JIA

The paediatric rheumatologist examined the patients every 12–18 weeks, depending on the activity of the disease. On each visit,

the number of active and swollen joints as well as ESR and laboratory tests (haematological and serum chemical analysis) for drug safety were assessed. Physician global assessment of disease activity, parent/patient assessment of overall well-being and functional ability in Childhood Health Assessment Questionnaire (CHAQ) were evaluated in each patient on regular basis. Improvement of arthritis was assessed using the ACR Pediatric 30, 50 and 70 criteria [27]. The data on six ACR Pediatric core set response variables were obtained retrospectively from the patient charts or from the national register of biological agents (ROB-FIN) [28] that includes a separate register for juvenile patients. The national ethics committee granted the approval for this study and the patients and/or their guardians gave their informed consent to obtain the data.

Statistical analysis

The differences between the number of uveitis flares/yr and disease activity parameters (ESR, CRP, number of active joints, etc.) before and during adalimumab therapy were compared using two-tailed non-parametric tests, Wilcoxon's signed-rank test for continuous variables and McNemar's test for dichotomous variables. Spearman's correlation test was used to assess the correlation coefficient (r_s) between the favourable response or change in the number of uveitis flares/yr and JIA-related parameters. Linear and logistic regression analysis was performed to estimate predictors or determine variables that may correlate independently with the change in the number of flares and the favourable outcome, respectively. The differences between the patient characteristics on adalimumab with good or poor outcome were compared with Mann–Whitney U-test (continuous variables) or Fisher's exact test (category variables). The 5% significance level was used in all tests.

Results

Patient characteristics

The main indication for adalimumab treatment was uveitis in five (25%) patients, active uveitis plus arthritis in 11 (55%) and arthritis in four (20%) patients (Table 2). All patients had a JIA-associated bilateral anterior chronic uveitis. The mean duration of the adalimumab therapy was 18.7 months (range 4.5–35.6 months). The first biological drug in 19 (95%) patients was started for a mean of 38 months earlier (range 16–67 months). Eighteen patients (90%) had been taking infliximab prior to adalimumab therapy.

Activity of uveitis

Based on the SUN criteria [24], 7/20 (35%) of the patients had improved activity and one (5%) had worsening activity. There was no significant change in the activity of uveitis in 12 (60%) patients (Table 3). The single patient with worsening activity of uveitis had also an active arthritis at the end of the follow-up. The indication to adalimumab therapy had no significant effect on the outcome of uveitis, and the outcome was not associated with the change in the number of active joints. The seven patients with improved activity were younger (mean age 11.0 vs 14.7 yrs, $P=0.046$) and their duration of JIA was shorter (7.4 vs 11.3 yrs, $P=0.019$). Additionally, they had smaller active joint count at the baseline (1.7 vs 4.9 joints, $P=0.041$), but not at the end of the follow-up (0.7 vs 2.6 joints, $P=0.086$). There were no differences in the use of DMARDs or corticosteroids between the well-responding patients and the non-responders. A negative association was found between the favourable outcome and duration of JIA ($r_s=-0.52$, $P=0.019$), active joint count at the baseline ($r_s=-0.534$, $P=0.015$) and the active joint count at the follow-up ($r_s=-0.47$, $P=0.036$).

TABLE 3. Treatment effect and concomitant medication in 20 JIA patients with uveitis on adalimumab

Patients no.	Dose (mg/kg) – interval (w) of A	F/U (m)	Therapy at start ^a	Therapy at 12 months ^a	Therapy at end of F/U ^a	Flares/yr before	Flares/yr on A	AC score ^b OD/OS before A	AC score ^b OD/OS at end of F/U
1	1.5–2	26	T, P 0.8, M 5	T, M 20	T, M 20	2	2.3	0.5+/0.5+	0.5+/0
2	1.4–2	12	T, M 15	T, M 15	T, M 15	2	2.0	0.5+/2+	0.5+/0.5+
3	1.1–2	28	T, L 10	T, L 10	T, L 10	5	0.4	3+/3+	0.5+/0.5+
4	1.0–2	6	T, M 7.5	–	T, M 10	2	4.3	0/2+	0/3+
5	0.8–2	27	T, M10	T, M 10	T, L 20	1	1.4	3+/0	3+/0
6	1.3–2	27	T, P 0.1, M 15	T, M 15	T, M 15	1	0	0.5+/0.5+	0.5+/0
7	1.1–2	8	T, P 0.1, M 5, C 150	–	T, P 0.1, M 5	12	11.7	3+/3+	3+/3+
8	0.9–1	8	T, P 0.2, L 20, C 125	–	T, P 0.2, L 20, C 125	3	0	0/0	0/0
9	0.7–1	14	T, P 0.2, M 30, C 100	T, P 0.2, M 30	T, P 0.2, M 30	0	1.7	1+/1+	0.5+/0.5+
10	0.4–1	7	T, P 0.1, M 35, C 100	–	T, P 0.1, M 25	1	1.6	1+/0	0/0
11	0.5–2	28	T, P 0.3, M 15, C 100	T, P 0.1, M 15	T, M 10	2	1.3	2+/0	1+/0.5+
12	0.7–2	23	T, P 0.2, M 20, GH	T, S 1000, M 10, L 20	T, S 2000M 10	2	2.1	1+/0.5+	1+/1+
13	0.8–1	5	T, P 0.4, L 10, GH	–	T, P 0.6, Ig, L 10, GH	1	0	0/1+	0/1+
14	0.6–2	30	T, P 0.3, L 20	T, L 20	T, L 20	1	0.8	0/3+	0/0.5+
15	0.7–1	14	T, M 13, Az 150	T, M 13, Ig, Az 150	T, M13, Ig, Az 150	3	0	2+/0.5+	1+/0.5+
16	0.5–2	7	T	–	T	0	0	3+/0.5+	3+/0.5+
17	1.0–2	14	T, H 150	T, H 150	T, H 200	1	0	0.5+/1+	0.5+/0.5+
18	1.0–2	24	T, P 0.2, GH	T, M 30, GH	T, M 30, GH	0	0	0/0.5+	0/0.5+
19	0.9–2	21	–	T, P 0.3, M 20	M 10	0	0	0.5+/0.5+	0/0.5+
20	0.8–2	31	T, P 0.4 L 20, GH	T, P 0.2, L 20	T, L 20	1	0.4	1+/0	3+/0

^aDMARDs mg, prednisolone mg/kg/alternate day, ^bAnterior chamber cells score (0=cells <1, 0.5+=cells 1–5, 1+=cells 6–15, 2+=cells 16–25 and 3+=cells 26–50). A: adalimumab; F/U: follow-up (months); Uv: uveitis; OD: right eye; OS: left eye; Art: arthritis; Drug therapy; Az: azathioprine; C: cyclosporin A; H: hydroxychloroquine; Ig: intravenous gammaglobulin monthly; L: leflunomide; M: methotrexate weekly; P: oral prednisolone; T: topical steroids; S: salazopyrin; GH: growth hormone.

The 20 JIA patients had uveitis in 40 eyes. When the ocular inflammation activity was assessed separately in each eye, improvement was observed in 8 (20%) eyes, worsening in one (2.5%) and in 32 (77.5%) the activity did not change. Alternatively, based on our formerly used method [17] modified from Rao *et al.* [25] and Nussenblatt *et al.* [26], uveitis improved in 11/20 (55%) patients, no change was observed in 3 (15%), and in 6 (30%) the activity of uveitis worsened.

The mean number of uveitis AC flares/yr decreased from 1.9 (range 0–12) before adalimumab to 1.4 (range 0–11.7) during adalimumab treatment. This change was not significant ($P=0.186$ in Wilcoxon's test) in the whole group of 20 patients, but closer to true significance in 15 patients with positive ANA ($P=0.076$) and in 13 HLA-B27-negative patients ($P=0.084$). However, when transformation into dichotomous variables was performed with a cutpoint of one flare/yr, the decrease in the number of flares during the adalimumab therapy was significant ($P=0.039$ in McNemar's test) in all patients, especially in ANA-positive patients ($P=0.016$), but not in HLA-B27-negative ones ($P=0.219$). There was no relationship between the change in the number of uveitis flares/yr and any other variable assessed: age, duration of JIA, duration of uveitis, type of JIA, gender, change in the number of DMARDs, change in oral corticosteroid doses, change in the number of active joints or the overall activity of JIA (measured by CRP and ESR) in the correlation tests.

To explore the predictors for the change in the number of flares during adalimumab therapy, all JIA-related variables mentioned above were entered into linear regression analysis. All the statistically significant models gave low explanation rates (data not shown). We also performed logistic regression analysis to explore the uveitis-related covariates (e.g. duration of JIA, age, treatment time, change in corticosteroid doses, number of DMARDs and active joint count) possibly confounding with the favourable outcome, but no significant relationships were found in any models.

The uveitis was inactive throughout the study period in one (5%) patient with topical steroids (patient no. 8, Table 3). In one patient (patient no. 10), uveitis became inactive in both eyes during the therapy and in three patients (patients no. 1, 6 and 19) one eye became inactive. All except one (patient no. 19) continued topical steroids.

Adalimumab dosing and other medications

During adalimumab therapy, four patients had a flare of arthritis and a weekly 40 mg dose of adalimumab was used for several weeks to several months, yet without improvement in uveitis or arthritis. Two of these patients (patients no. 8 and 13) discontinued adalimumab due to inefficacy, one (patient no. 15) continued with the weekly 40 mg dose until the end of the follow-up and one (patient no. 9) switched back to standard dose because of recurrent upper respiratory infections. In one patient (patient no. 10) after starting a weekly 40 mg dose because of unilateral uveitis flare, the uveitis became inactive.

Altogether seven (35%) patients discontinued adalimumab during the follow-up, six of them because of inefficacy. One had active uveitis, one a flare in arthritis and four had activity both in uveitis and arthritis. One patient (Patient no. 2) on concomitant MTX discontinued adalimumab because of subsiding uveitis and inactive arthritis. In this patient, after 4 months the arthritis was still in remission, but the findings of uveitis were back (AC cells 1+/1+).

During adalimumab therapy, seven (35%) patients were able to discontinue systemic prednisolone (Table 3). In the whole group of patients, the mean daily dose of prednisolone decreased from 0.1 mg/kg (range 0–0.4) to 0.03 mg/kg (range 0–0.3) ($P=0.057$). Only five (25%) patients had systemic prednisolone at the end of the follow-up. One patient (patient no. 13) had to increase prednisolone dose due to sight-threatening macular oedema and active arthritis. During the follow-up, four (20%) patients were able to switch combination DMARDs to single therapy. In three of the four patients, both the activity of uveitis and arthritis further decreased.

Ophthalmological complications

At the onset of adalimumab, 10 (50%) patients had a complicated uveitis (cataract, glaucoma, cystoid macular oedema, band keratopathy and/or secondary cataract). Ten patients had undergone ocular surgery before and three were operated during adalimumab therapy (Table 4). One patient (patient no. 14) had an acute attack of ocular hypertension, hypopyon, decrease in BCVA from 0.8 to 0.4 and was operated (cyclophotocoagulation with diode laser). One patient with a consistently active bilateral

TABLE 4. Ocular complications and surgery before and during adalimumab in 20 patients with JIA-associated uveitis

Complication	Before A	During A	Surgical treatment, n (patient no.)
Cystoid macular oedema, n (%)	8 (40)		
Glaucoma, n (%)	10 (50)	1 (5)	Molteno tube implantation 5 (9,11,13,16,19) Trabeculectomy 3 (1,10,16) Cyclophotocoagulation 1 (14) Deep sclerectomy 1 (20)
Band keratopathy, n (%)	8 (40)		
Complicated cataract, n (%)	11 (55)	2 (10)	Cataract extraction 6 (1 × 2, 6, 8, 11, 14, 20) Anterior vitrectomy 5 (1, 9, 13, 14, 20) Phagoemulsification and IOL implantation 3 (9, 10, 13) Lens extraction 3 (8, 11) Posterior capsulotomy 3 (9, 13, 20) IOL implantation 2 (14, 20) YAG-laser iridotomy 1 (14) YAG-laser capsulotomy 1 (6) Vitrectomy 1 (13)
Secondary cataract, n (%)		1 (5)	Excision of secondary cataract 1 (1)

IOL: Intra-ocular lens; A: adalimumab.

TABLE 5. The frequency and percentage of patients with adverse events and side-effects in 20 patients with JIA-associated uveitis on adalimumab treatment

Adverse drug reaction	No. of events	No. of patients (%)	Events/patient-yr
Upper respiratory infection	11	11 (55)	0.35
Sinusitis (antibiotics required)	7	3 (15)	0.23
Local skin reaction	5	5 (25)	0.16
Headache	5	4 (20)	0.16
Herpetic infections	4	2 (10)	0.13
Bacterial skin infection (antibiotics required)	4	2 (10)	0.13
Conjunctivitis	2	1 (5)	0.06
Secondary adrenal insufficiency	2	2 (10)	0.06
Mildly elevated serum transaminases	2	2 (10)	0.06
Otitis media (antibiotics required)	1	1 (5)	0.03
Candida vaginitis	1	1 (5)	0.03
Gastritis	1	1 (5)	0.03
Psychiatric disorders	1	1 (5)	0.03

uveitis had a unilateral increase in cataract formation (patient no. 7). In another patient (patient no. 5) with active uveitis, cataract was found for the first time during adalimumab therapy. One patient (patient no. 13) had an increase of macular oedema with BCVA decreasing from 0.1 to 0.05. No relationship between the change in the activity of uveitis and the surgical procedures existed.

Other side-effects and adverse events

The total adalimumab exposure during the study was 31 patient-yr. Serious or life-threatening adverse events or side-effects were not observed. Altogether 30 infections (0.97/patient-yr) were recorded, most commonly upper respiratory infections (Table 5). None of the infections were defined as severe, nor required intravenous antibiotics. Two patients needed oral anti-retroviral treatment: one patient with varicella without complications, and one patient with two recurrent herpes zoster episodes. One patient had a series of upper respiratory infections with sinusitis and was finally operated (antroostomy). Another patient had

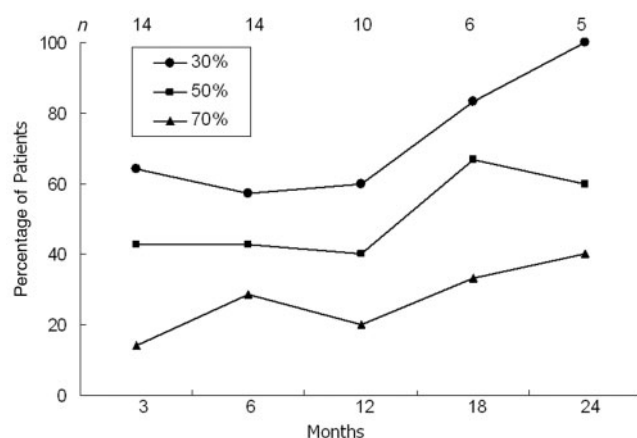


FIG. 1. The proportion (%) of ACR Pediatric 30, 50 and 70 responses in 14 patients with JIA-associated uveitis and active arthritis. The patients were treated with adalimumab for 6–24 months. The number (n) of patients at each time point is depicted at the top of the graph.

prolonged abdominal pain that was diagnosed as gastritis on gastroduodenoscopy.

Efficacy of adalimumab on juvenile arthritis

At the initiation of adalimumab therapy, 14/20 (70%) patients with uveitis had active joints and elevated ESR and CRP. Their mean observation period on adalimumab was 17.1 months (range 6–36 months). After the follow-up, 6/14 (43%) patients had inactive arthritis and normal ESR and CRP. Of these patients, ACR Pediatric 30 response was observed in 9/14 (64%), 8/14 (57%), 6/10 (60%), 5/6 (83%) and 6/6 (100%) at 3, 6, 12, 18 and 24 months, respectively (Fig. 1). The mean number of active joints decreased from 6 to 3 ($P=0.002$) during the follow-up. The mean decrease in ESR was from 27 to 15 mm/h ($P=0.131$) and the mean decrease in CRP was from 11 to 9 mg/l ($P=0.586$). The decrease in CHAQ, physician or parent/patient global assessment was not significant (data not shown). In these 14 patients, differences in the outcome of arthritis were not explained by age, duration of JIA, type of JIA, ANA- or HLA-B27 type, gender, number of DMARDs, dose of corticosteroids or onset of JIA.

The number of JIA patients with inactive disease [24, 29] increased during adalimumab treatment. If inactivity of AC cells (grade 0/0) in addition to inactive arthritis was required for inactive disease, there was one (5%) such patient in our series before adalimumab and two (10%) after the therapy. If the ocular activity of 'trace' cells (grade 0.5+/0.5+) was used as a cutpoint, there were 5/20 (25%) patients with inactive disease before and 11/20 (55%) after adalimumab treatment.

Discussion

This study shows that adalimumab is a potential treatment option for JIA-associated uveitis. Notably, 95% of the patients had insufficient response to previous local therapy in combination with second-line agents plus anti-TNF therapy indicating that the present series represent a patient cohort with refractory course of uveitis. Nevertheless, during adalimumab therapy the activity of uveitis improved in 35% of the patients. The patients with favourable response were younger, had shorter duration of JIA and smaller active joint count at the baseline.

In the present study, ophthalmological outcome did not seem to be as favourable as in three other retrospective series. Biester *et al.* [19] described an improvement of uveitis in 89% of the patients,

when their favourable response was based on the number of relapses. These patients were older at the onset of uveitis and arthritis compared with our cohort, and the age at the initiation of adalimumab was not clearly defined. Vazquez-Cobian *et al.* [20] showed improved activity in 81% of the eyes, which is considerably more frequently than improvement in 20% of the eyes in the present study. Their patients were younger than ours, the underlying conditions were somewhat different and the definition of improvement was not as stringent as in our series. A favourable response in three patients with uveitis taking adalimumab was reported in a recent survey, which, however, lacked detailed ophthalmological data [21]. In that study, all three patients had failed on infliximab prior to adalimumab [21]. Most probably, differences in patient characteristics and response criteria may explain the lower rate of favourable outcome in our study compared with previous studies.

The majority of our patients (90%) had previously failed on infliximab either because of inefficacy or side-effects. This is clearly different from the series of Biester *et al.* [19], where 28% of the patients were infliximab failures. However, the doses of infliximab that were recommended in the early years (since 1999 3–5 mg/kg) were probably suboptimal for the treatment of uveitis. In a recent publication [16], high doses of infliximab up to 10–20 mg/kg have been used successfully on refractory uveitis. However, formal efficacy and safety analyses of high-dose infliximab treatment have not been published yet. Moreover, the higher cost of the high-dose infliximab may limit its wider use.

When evaluating the activity of uveitis, we tested both the recently published SUN criteria [24] and modified criteria from Rao *et al.* [25] and Nussenblatt *et al.* [26] previously used by us [17]. The results between these two methods did not seem to differ appreciably, although the proportion of patients without a change in the activity of uveitis was higher when assessed by SUN criteria. This is probably due to the requirement of two-step change in the activity of uveitis. On the other hand, this requirement may diminish the confounding effect of spontaneous fluctuation in the number of AC cells to the results. To facilitate comparison of different studies in the future, it would be necessary to agree on common response criteria.

The efficacy of adalimumab in JIA, assessed by ACR Pediatric criteria, has not yet been established in a prospective fashion. In a recent retrospective study by Biester *et al.* [19], adalimumab induced inactive arthritis in 63% of the patients. The present results are in line with these results. Although based on retrospective analysis, the efficacy of adalimumab in JIA seems to correspond to that of other TNF modulators [30].

The number of observed side-effects and adverse events was an estimate due to retrospective nature of the study. As in previous studies, serious side-effects and adverse events were absent [19, 20]. Because all hospitalizations and severe or life-threatening conditions are documented in the patient charts, this part of the data can be considered reliable. In adult studies, adalimumab has demonstrated an acceptable safety profile and the rate of serious infections has also been low; 0.02/patient-yr [22]. Adalimumab seems to cause less hypersensitivity reactions than infliximab, at least with the doses given in our patient cohort.

At the moment there is no optimal therapy for chronic JIA-associated uveitis. If ocular inflammation is not controlled by topical steroids, treatment should be intensified with immunosuppressive drugs and in most severe cases with biological agents. Unfortunately, optimal timing of the second- and third-line therapy is currently not well known. On the other hand, the longer the uveitis is undertreated, the worse seem to be the complications in frequency and severity. Our current sequence of treatment in refractory JIA-associated uveitis is MTX on top of topical steroids and in non-responsive cases, infliximab. The present study

suggests that adalimumab may be an equal treatment option. Prospective studies would be necessary to further evaluate efficacy and safety of biological drugs in JIA-associated uveitis.

Rheumatology key messages

- Adalimumab was beneficial and well tolerated in one-third of patients with JIA-associated uveitis unresponsive to previous anti-TNF therapy.
- The patients with favourable response were younger and had shorter duration of JIA.

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