

Paediatric rheumatology

Anti-adalimumab antibodies in juvenile idiopathic arthritis-related uveitis

S.T. Leinonen¹, K. Aalto², K.M. Kotaniemi¹, T.T. Kivelä¹

¹Department of Ophthalmology; ²Department of Paediatrics, University of Helsinki, Helsinki University Hospital, Finland.

Abstract Objective

To evaluate the association of adalimumab trough levels and anti-adalimumab antibodies with activity of uveitis in juvenile idiopathic arthritis-related uveitis.

Methods

This was a retrospective observational case series in a clinical setting at the Department of Ophthalmology, Helsinki University Hospital, Finland in 2014–2016. Thirty-one paediatric patients with chronic anterior juvenile idiopathic arthritis-related uveitis in 58 eyes and who had been on adalimumab ≥ 6 months were eligible for the study. Uveitis activity during adalimumab treatment, adalimumab trough levels and anti-adalimumab antibody levels were recorded.

Results

Anti-adalimumab antibody levels ≥ 12 AU/ml were detected in nine patients (29%). This level of anti-adalimumab antibodies was associated with a higher grade of uveitis ($p < 0.001$), uveitis that was not in remission ($p = 0.001$) and with lack of concomitant methotrexate therapy ($p = 0.043$). In patients with anti-adalimumab antibody levels < 12 AU/ml, higher serum trough levels did not associate with better control of uveitis ($p = 0.86$).

Conclusion

Adalimumab treatment might be better guided by monitoring anti-adalimumab antibody formation in treating JIA-related uveitis.

Key words

paediatric, uveitis, juvenile idiopathic arthritis, anti-drug antibodies, adalimumab

Sanna T. Leinonen, MD
Kristiina Aalto, MD, PhD
Kaisu M. Kotaniemi, MD, PhD
Tero T. Kivelä, MD, PhD

Please address correspondence
and reprint requests to:

Dr Sanna Leinonen,
Department of Ophthalmology,
University of Helsinki,
Helsinki University Hospital,
Haartmaninkatu 4 E, PL 220,
FI-00029 HUS, Helsinki, Finland.
E-mail: sanna.leinonen@hus.fi

Received on July 28, 2016; accepted in
revised form on December 14, 2016.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2017.

Introduction

In chronic anterior juvenile idiopathic arthritis (JIA)-related uveitis, the likelihood of adverse visual prognosis increases in a dose-dependent manner with increasing anterior chamber cell count, whereas immunomodulatory therapy reduces the risk of low vision (1). Remission at 0 cells /1 mm² in the anterior chamber (Standardisation of Uveitis Nomenclature, SUN 0) or no more than 1–5 cells /1 mm² (SUN 0.5+, mild uveitis) should be pursued to improve the long-term visual outcome (1, 2). If uveitis is not under control with corticosteroid and non-biologic disease-modifying anti-rheumatic drug (DMARD) therapy, biologic treatment such as adalimumab should be considered (3, 4) balancing the potential benefits against the absence of long-term safety reports on treating children with biologic treatment. Tolerability of biologic treatment has been acceptable in patients with JIA (5).

JIA-related uveitis patients treated with adalimumab achieve uveitis remission rates as high as 67% (6). Adalimumab trough levels of ≥ 7 –8 µg/ml are reported to be sufficient for JIA patients (7). Adalimumab serum levels that are therapeutic when managing JIA-related uveitis are presently unknown, however. Immunogenicity of adalimumab, which leads to anti-adalimumab antibody (AAA) formation, is one cause of treatment failure. Antibody formation reduces both adalimumab serum levels and the efficacy of treatment by increasing adalimumab clearance, by neutralising the drug effect, or by both mechanisms (8, 9). AAAs are found in 16–26% of adalimumab treated JIA patients; less frequently among patients receiving concomitant methotrexate (8–12). AAAs have been associated with low adalimumab trough levels and more frequent uveitis: 6/8 of paediatric rheumatic patients had active uveitis with AAAs ≥ 12 AU/ml and 3/17 without them (13).

Our hypothesis was that failure to maintain remission of uveitis with adalimumab in paediatric patients with JIA-related uveitis is associated with anti-adalimumab antibody formation.

Methods

Patients were eligible for inclusion in our retrospective case series in a clinical setting if they had chronic anterior JIA-related uveitis, were 16 years old or younger and had received regular adalimumab for ≥ 6 months by the time of serum adalimumab measurements in 2014–2016. Forty-three adalimumab treated JIA-uveitis patients were identified in the patient database of the Helsinki University Hospital. Thirty-one patients fulfilled the eligibility criteria. The following data were recorded: age at onset of uveitis, age at onset of JIA diagnosed by a paediatric rheumatologist, anti-rheumatic medication, uveitis activity during adalimumab treatment (14), adalimumab serum trough level and anti-adalimumab antibody level. Blood samples for measuring the serum adalimumab trough level were drawn a maximum of 24 hours before the next scheduled adalimumab administration. The ethics committee of the Helsinki University Hospital approved this study and its design complies with the Declaration of Helsinki. A retrospective study model requires an ethical evaluation of the study, and the data are de-identified for analysis, but no patient consent form is needed. For statistical analysis, Stata, version 13 (StataCorp) was used. The eye with higher grade of uveitis was chosen from patients with bilateral uveitis. Distributions of continuous variables were compared using Mann-Whitney U-test and singly ordered contingency tables using Kruskal-Wallis test. Spearman correlation was used to compare adalimumab doses, SUN-grades and trough levels. Non-parametric test for trend was used to compare continuous variables between ordered groups (15). Predictors of AAA >12 AU/ml were modelled by multiple logistic regression. All tests were two-sided and $p < 0.05$ was considered significant.

In our hospital, the starting dose of adalimumab in JIA-related uveitis is 24 mg/m² every other week. If $>SUN 0.5+$ uveitis prevails on adalimumab, the dose is increased. Maximum single dose is 40 mg. Methotrexate is routinely combined with adalimumab, but if the patient does not tolerate methotrexate, it is substitut-

Competing interests: none declared.

ed with other DMARDs. Adalimumab therapy is terminated when it is deemed inefficient (14) even if adalimumab trough level is ≥ 7 $\mu\text{g/ml}$. Adalimumab therapy is terminated also when serum adalimumab is low (<0.5 $\mu\text{g/ml}$) and at the same time AAA level is ≥ 12 arbitrary units (AU)/ml. If the AAA level is ≥ 12 AU/ml, but the adalimumab trough level is ≥ 0.5 $\mu\text{g/ml}$, adalimumab dose is increased and the drug is continued provided that uveitis activity remains mild ($\leq \text{SUN } 0.5+$). When adalimumab therapy is discontinued because of treatment failure another biologic drug is chosen for patients with more active uveitis.

Results

Adalimumab serum levels and AAA levels were measured in 31 paediatric patients with JIA-related uveitis (58 eyes with uveitis; Table I). No adalimumab-related adverse effects occurred among these patients during the study period. Remission of uveitis was achieved and maintained in 15 patients, 9 patients had mild uveitis and 7 patients had at least one eye with more active uveitis while on adalimumab. AAA levels ≥ 12 AU/ml were found in 9 patients (29%; 95% CI, 12–46) after a median of 3.1 years on adalimumab treatment. AAA levels ≥ 12 AU/ml were associated with higher grade of uveitis ($p < 0.001$, non-parametric test for trend), low adalimumab trough levels ($p < 0.001$, Fisher's exact test), and lack of methotrexate treatment ($p = 0.043$). Concomitant methotrexate (mean dose, 13mg; 95% CI, 12–15; range, 7.5–20) was given to 25 adalimumab treated patients. Methotrexate had been discontinued before adalimumab treatment in four patients after liver enzyme elevations and in two patients with intolerable nausea. AAA levels were ≥ 12 AU/ml in 4 of 6 patients without and in 5 of 25 patients with concomitant methotrexate (Table I). Higher methotrexate dose was not associated with either lower AAA levels ($p = 0.73$, Mann-Whitney U-test) or activity of uveitis ($p = 0.16$, Spearman correlation). Patients with AAA levels ≥ 12 AU/ml were younger at disease presentation (Table I). In logistic regression analysis, there was an association between

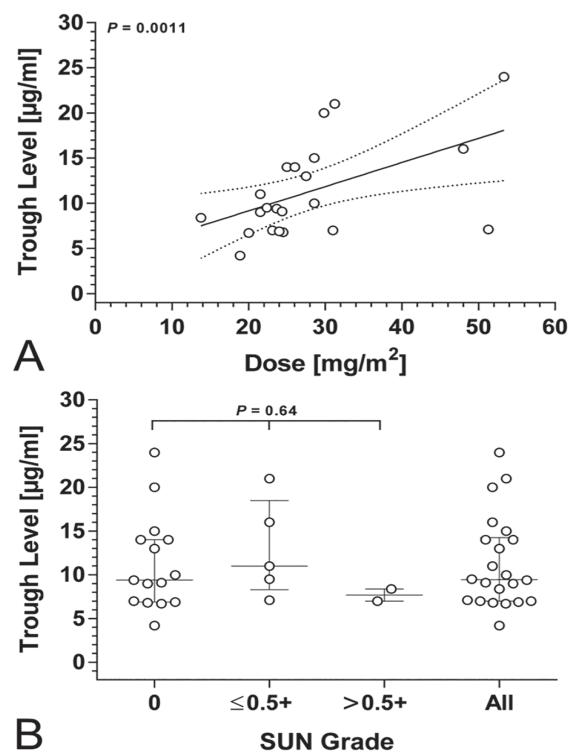
Table I. Characteristics of the 31 adalimumab treated juvenile idiopathic arthritis-related uveitis patients.

	Anti-adalimumab antibodies ≥ 12 AU/ml (n=9)		Anti-adalimumab antibodies < 12 AU/ml (n=22)		p-value
	Median	Range	Median	Range	
Age at onset of uveitis, years	3.1	1.8–5.6	5.6	1.6–14.2	0.010*
Age at onset of JIA, years	1.9	0.9–4.2	3.8	1.0–14.0	0.017*
Age at adalimumab measurements, years	9.3	3.7–14.9	9.8	4.4–16.8	0.36*
Duration of adalimumab treatment, years	3.1	0.5–5.2	1.7	0.5–7.3	0.43*
Adalimumab dose, mg/m^2 in 2 weeks	26	20–50	25	14–53	0.74*
Adalimumab trough level, $\mu\text{g/ml}$	<0.01	<0.01 to 4.0	9.4	4.2–24.0	<0.001 *
SUN	1.0	<0.5 to 3	0	0–1	<0.001 ‡
Remission, %	0		68		0.001**
Methotrexate, %	29		91		0.043**

JIA: juvenile idiopathic arthritis; SUN: Standardisation of Uveitis Nomenclature; *Mann-Whitney U; ‡ non-parametric test for trend; **Fisher's exact test.

Fig. 1.

A. Adalimumab serum trough levels and adalimumab doses among patients with <12 AU/ml of anti-adalimumab antibodies. **B.** Adalimumab serum trough levels and uveitis activity among patients with <12 AU/ml of anti-adalimumab antibodies. Scatterplot of (A) adalimumab serum trough levels against adalimumab dose (Spearman correlation) and (B) according to Standardisation of Uveitis Nomenclature (SUN) grades (nonparametric test for trend for patients with anti-adalimumab antibody levels of less than 12 arbitrary units/ml). The line in (A) is from linear regression with 95% confidence intervals. The long bar in (B) is the median and the short bars represent the interquartile range.



AAA levels ≥ 12 AU/ml and earlier onset of JIA (OR 0.50, 95% 0.25–0.99, $p = 0.046$) and uveitis (OR 0.51, 95% CI 0.28–0.94, $p = 0.0030$) but not between AAA levels ≥ 12 AU/ml and antinuclear antibodies (ANA) $>1:160$ (OR 2, 95% CI 0.38–10.5, $p = 0.41$). AAA level ≥ 12 AU/ml was not associated with duration of adalimumab treatment ($p = 0.43$, Mann-Whitney U-test) or younger age ($p = 0.36$) at the adalimumab measurement time.

Patients with AAA levels ≥ 12 AU/ml

Seven patients had a low serum adali-

mumab level (median <0.01 $\mu\text{g/ml}$, range from <0.01 $\mu\text{g/ml}$ to 0.2 $\mu\text{g/ml}$) and their adalimumab therapies were terminated. Three of them had mild uveitis and they were continued on topical corticosteroids, non-biologic DMARDs, or both with no increase in uveitis activity during the following 12 months. Four patients had more active uveitis and were given other TNF inhibitors.

One patient with an adalimumab trough level of 4.0 $\mu\text{g/ml}$ (AAA level of 19 AU/ml) and mild uveitis was given weekly adalimumab and achieved remission

with adalimumab trough level of 8.4 µg/ml. One patient with an adalimumab trough level of 3.4 µg/ml (AAA level of 62 AU/ml) had mild uveitis until her treatment was discontinued elsewhere whereafter the uveitis flared up.

Patients with AAA levels <12 AU/ml

Remission of uveitis was preferentially observed among patients with AAA levels <12 AU/ml as compared to higher levels ($p=0.001$, Fisher's exact test). Among the 22 patients with AAA levels <12 AU/ml, adalimumab dose (median, 25 mg/m²; range: 14–53) was associated with the trough level ($p=0.0032$ Spearman correlation; Fig 1A). The median trough level was 9.4 µg/ml (range: 4.0–24.0 µg/ml), being 9.3 µg/ml (range: 4.0–24.0) among those in remission, 11.0 µg/ml (range: 7.1–21.0) among those with SUN 0.5+ uveitis and 7.0 and 8.4 g/ml among 2 patients with a more active uveitis ($p=0.86$, non-parametric test for trend; Fig 1B). Presence or absence of methotrexate treatment was not associated with adalimumab trough levels ($p=0.23$, Mann-Whitney U-test) or activity of uveitis ($p=0.63$, non-parametric test for trend). Methotrexate dose was not associated with adalimumab trough levels ($p=0.89$, Spearman correlation) or activity of uveitis ($p=0.25$, non-parametric test for trend).

Discussion

Anti-adalimumab antibody levels ≥ 12 AU/ml, which were detected in 9 of our 31 JIA-related uveitis patients, were associated with higher grade of uveitis, failure to achieve remission of uveitis and with lack of concomitant methotrexate therapy. The association between methotrexate and AAAs has been reported earlier (8–12), and AAA levels ≥ 12 AU/ml have been associated with more frequent uveitis among 25 paediatric rheumatic patients (13). An association between the adalimumab dose and its trough level was found among the patients with AAA levels <12 AU/ml. Adalimumab trough levels did not associate with the activity of uveitis among patients with AAA levels <12 AU/ml. We are thus unable to suggest any threshold for therapeutic

adalimumab trough level to control JIA-related uveitis.

Younger age at JIA and uveitis presentation was associated with AAA levels ≥ 12 AU/ml. To our knowledge, no other studies on the association of anti-drug antibodies and age at JIA or uveitis onset have been published to date. Patients with antinuclear antibody titres >1:160 were younger at the onset of JIA and uveitis in our study and in previous studies (16). Higher pretreatment ANA levels have been shown to associate with anti-infliximab antibodies in treating psoriasis (17). Increasing ANA titres can occur during JIA treatment independently of anti-rheumatic treatment (18). Among our patients, no association was found between ANA titres >1:160 at disease presentation and anti-adalimumab antibodies. Pretreatment ANA titres were not measured, however. More studies are needed to test if younger age at JIA presentation and higher ANA titers associate with anti-drug antibody formation.

Our results are consistent with the hypothesis that adalimumab treatment might be better guided by monitoring AAA formation in patients with JIA-related uveitis who are 16 years old or younger. Prospective studies are needed to test the hypothesis and to determine a generally applicable therapeutic dose and trough level of adalimumab in managing patients with JIA-related uveitis.

References

- GREGORY AC, KEMPEN JH, DANIEL E, THORNE JE; SYSTEMIC IMMUNOSUPPRESSIVE THERAPY FOR EYE DISEASES COHORT STUDY RESEARCH GROUP: Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the SITE study. *Ophthalmology* 2013; 120: 186–92.
- THORNE JE, WORETA F, KEDHARA SR, DUNN JP, JABS DA: Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. *Am J Ophthalmol* 2007; 143: 840–6.
- HEILIGENHAUS A, MICHELS H, SCHUMACHER C *et al.*: Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012; 32: 1121–33.
- TAPPEINER C, KLOTSCHKE J, SCHENCK S *et al.*: Temporal change in prevalence and complications of uveitis associated with juvenile idiopathic arthritis: data from a cross-sectional analysis of a prospective nationwide study. *Clin Exp Rheumatol* 2015; 33: 936–44.
- KLOTSCHKE J, NIEWERTH M, HAAS JP *et al.*: Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). *Ann Rheum Dis* 2015; 73 (Suppl. 2).
- KOTANIEMI K, SÄILÄ H, KAUTIAINEN H: Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. *Clin Ophthalmol* 2011; 5: 1425–9.
- KINGSBURY DJ, BADER-MEUNIER B, PATEL G, ARORA V, KALABIC J, KUPPER H: Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years. *Clin Rheumatol* 2014; 33: 1433–41.
- WANG SL, HAUENSTEIN S, OHRMUND L *et al.*: Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013; 5: 39–44.
- GARCÉS S, DEMENGEOT J, BENITO-GARCIA E: The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 2013; 72: 1947–55.
- IMAGAWA T, TAKEI S, UMEBAYASHI H *et al.*: Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan. *Clin Rheumatol* 2012; 31: 1713–21.
- LOVELL DJ, RUPERTO N, GOODMAN S *et al.*: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008; 359: 810–20.
- SKRABL-BAUMGARTNER A, ERWA W, MUNTEAN W, JAHNEL J: Anti-adalimumab antibodies in juvenile idiopathic arthritis: frequent association with loss of response. *Scand J Rheumatol* 2015; 44: 359–62.
- MURIAS S, ALCOBENDAS R, PASCUAL-SALCEDO D, REMESAL A, PERALTA J, MERINO R: Anti-adalimumab antibodies in paediatric rheumatology patients: a pilot experience. *Rheumatology* 2014; 53: 2124–6.
- JABS DA, NUSSENBLATT RB, ROSENBAUM JT; STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005; 140: 509–16.
- CUZICK J: A Wilcoxon-type test for trend. *Stat Med* 1985; 4: 87–90.
- RAVELLI A, VARNIER GC, OLIVEIRA S *et al.*: Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 267–75.
- HOFFMANN JH, HARTMANN M, ENK AH, HADASCHIK EN: Autoantibodies in psoriasis as predictors for loss of response and anti-infliximab antibody induction. *Br J Dermatol* 2011; 165: 1355–8.
- HÜGLE B, HINZE C, LAINKA E: Development of positive antinuclear antibodies and rheumatoid factor in systemic juvenile idiopathic arthritis points toward an autoimmune phenotype later in the disease course. *Pediatr Rheumatol Online J* 2014; 12: 28.