Adalimumab Significantly Reduces the Recurrence Rate of Anterior Uveitis in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To investigate whether use of adalimumab decreases the frequency of attacks of anterior uveitis (AU) in patients with ankylosing spondylitis (AS).

Methods. Consecutive patients with AS, visiting an outpatient clinic and treated for at least 12 weeks with adalimumab, were enrolled. The number of attacks of AU in the year before start and during treatment were assessed by patient history and ophthalmological controls.

Results. In the 77 patients a total of 52 AU attacks occurred in the year before baseline (68 attacks per 100 patient-yrs), whereas during adalimumab treatment 19 attacks were seen (14 per 100 patient-yrs; reduction rate 80%). Twenty-six patients with AU in the year before start of adalimumab treatment had recurrent attacks, with a median number of 2.0 AU attacks per year [interquartile range (IQR) 1.00–3.00], whereas during treatment this decreased to 10 patients with a median number of 0.56 attacks per year (IQR 0.30–0.75). Hence, the number of attacks per year decreased by 72% ($p = 0.000$).

Conclusion. In patients with AS, a significant reduction in the number of AU attacks, as well as in the number of attacks per patient, was observed during adalimumab treatment. (J Rheumatol First Release Aug 1 2014; doi:10.3899/jrheum.131289)

Key Indexing Terms:
UVEITIS ANKYLOSING SPONDYLITIS ADALIMUMAB

Ankylosing spondylitis (AS) is a chronic inflammatory disease that starts at a young age and causes inflammatory back pain, stiffness, and bone deformation of the sacroiliac joints and vertebral spine. Recently, treatment with tumor necrosis factor (TNF)-blocking agents, such as infliximab, etanercept, adalimumab, and golimumab, has proven to be very effective in treatment of spinal inflammation in AS[1,2,3,4].

In AS, in addition to the spine, other organs can be affected, like the eye (anterior uveitis), gut (inflammatory bowel disease), and skin (psoriasis).

Anterior uveitis (AU) is strongly associated with the HLA-B27 antigen. The occurrence of AU is increased in the HLA-B27-positive population, with a lifetime cumulative incidence of 1% compared with 0.2% in the general population[5]. Up to 47% of patients with AU are positive for the HLA-B27 antigen[6]. The mean prevalence of AU in AS was 33% in a systematic literature review, and increased with disease duration[7]. More importantly, AU can be the first presenting symptom of AS[8,9,10]. The attacks of uveitis are usually unilateral and recurrent and cause sudden ocular pain, with redness and photophobia. These attacks might lead to inflammatory debris accumulating in the anterior chamber, which may cause pupillary and lens dysfunction and blurring of vision. Most of the time the uveitis subsides in several weeks, but in some cases glaucoma and severe visual impairment may occur if adequate treatment is delayed[11]. Acute attacks call for urgent treatment by the ophthalmologist with topical (or in some cases even systemic) corticosteroids.

In refractory uveitis (often panuveitis, idiopathic or secondary to an autoimmune disease), infliximab proved to be beneficial, but overall the degree of efficacy of the different TNF-blocking agents for extraspinal manifestations in AS, such as acute AU, varies[12,13,14,15]. Data available at the start of the current study showed a different pattern for infliximab compared with etanercept: etanercept was associated with a smaller reduction in the recurrence rate of the attacks in comparison to infliximab[16,17,18,19].

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However, the majority of these studies in AS were based on retrospective analyses of clinical trials or open-label studies. Moreover, registrations of the attacks were reported by the patients and ophthalmologic controls were not systematically performed.

Therefore, our objective was to examine whether the use of adalimumab decreases the frequency of attacks of AU in patients with AS, who received this treatment for their spinal disease activity. This prospective followup study was carried out in close collaboration with an ophthalmologist who evaluated the patients at several times during the investigation.

MATERIALS AND METHODS

Consecutive patients with AS (who fulfilled the modified New York criteria, attended the outpatient clinic of the Jan van Breemen Institute Reade, and fulfilled the Assessment in Spondyloarthritis International Society (ASAS) criteria for treatment with a TNF-blocking agent were enrolled[20,21]. They were treated for at least 12 weeks with 40 mg adalimumab every other week, while other medication was continued. The number of attacks of AU in the year before start and during adalimumab treatment was assessed by patient history and ophthalmological controls at baseline and yearly thereafter. The study started August 2006 and followup ended January 1, 2012, or upon discontinuation of adalimumab treatment for any reason. All patients gave written informed consent prior to enrolment, and the local medical ethical committee gave its approval for this study.

Historical data were collected by patient questions on the occurrence of uveitis in the past, and confirmative answers were verified with the medical records of the treating ophthalmologist. Additionally, an examination by our ophthalmologist was performed at baseline and every 12 months during the first 2 years of treatment. In case of a uveitis attack the patient was treated by his or her own ophthalmologist, who was always contacted by our study ophthalmologist afterwards. The number of attacks of uveitis during treatment with adalimumab was compared with the number of attacks in the year before therapy. According to the Standardization of Uveitis Nomenclature (SUN) working group a relapse in < 3 months after discontinuing treatment was defined as chronic uveitis; therefore a maximum of 3 flares per year were counted as separate episodes[22]. Patients with insufficient data (no previous uveitis data or followup data available, or less than 12 weeks followup) were excluded from the analysis.

The patients were assessed by a physician and research nurse at regular intervals. The following measurements and questionnaire data were collected: swollen joint count, spinal measurements [Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global score (BASG), and ASQOL (AS Quality of Life questionnaire)], and the occurrence of extraspinal manifestations (like colitis, psoriasis, and uveitis)[23,24,25,26]. In addition, laboratory tests were performed, e.g., erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Visits took place at screening, baseline (within 2 weeks after screening), after 1, 3, 6, 9, and 12 months during the first year, and every 6 months thereafter.

The primary outcome measure was the occurrence of attacks of AU in the year before baseline and during treatment with adalimumab. The secondary outcome measures were the changes in disease variables and the efficacy of adalimumab on disease activity of AS measured with the ASAS 20%, ASAS 40%, and BASDAI 50% responses during treatment[27].

Statistical analysis. The distribution of continuous variables was tested for normality. Data are represented as mean ± standard deviation (SD), median, and interquartile range (IQR) or percentages. A paired t-test, or when appropriate the Wilcoxon signed-ranks test, was used to determine significant changes from baseline; missing values were excluded in listwise fashion. Binary variables (such as occurrence of uveitis) were analyzed with the McNemar test. P values < 0.05 were considered statistically significant. All analyses were performed using SPSS version 17.0.

RESULTS

A total of 100 consecutive patients with AS were screened for study, of whom 90 were included and 10 were not: 5 patients never started with adalimumab therapy for several reasons, 4 declined to participate in the study and 1 declined due to pregnancy. Out of these 90 patients, 13 were excluded: 2 withdrew consent and 11 patients had incomplete followup (Figure 1). The remaining 77 patients were included in the final analyses. Demographic and disease characteristics at baseline are shown in Table 1. Disease-modifying antirheumatic drugs were used at baseline by 27% of patients (e.g., sulfasalazine or methotrexate) and 21% did not respond to prior anti-TNF treatment (etanercept and in 1 case infliximab; Table 1). The patients were predominantly male (61%) with a median

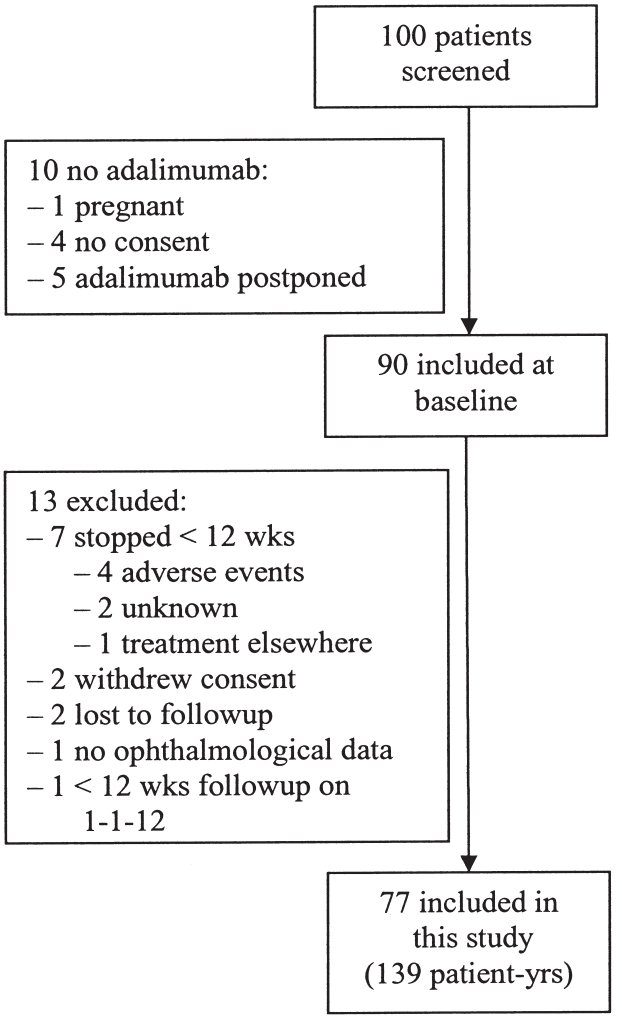

Figure 1. A total of 100 consecutive patients with ankylosing spondylitis (AS) were screened for study; 90 were included and 10 were not.

Table 1. Demographic and disease characteristics of patients with ankylosing spondylitis (AS) at baseline (n = 77) and during followup with adalimumab treatment. Mean values (standard deviation) or median (interquartile range, IQR) are shown, as appropriate.

Characteristic	Baseline	12 Weeks	52 Weeks
Male, n (%)	47 (61)		
Age, yrs, mean (SD)	45 (10)		
White, n (%)	53 (75)		
Duration of inflammatory back pain, median yrs (IQR)	17 (10–25)		
Disease duration (diagnosis), median yrs (IQR)	7 (2–15)		
Years since first uveitis, median (IQR)	11 (4–23)		
Anterior uveitis ever, n (%)	33 (43)		
Anterior uveitis last year, n (%)	26 (34)		
HLA-B27 present, n (%) (n = 75)	57 (76)		
Psoriasis, n (%)	5 (6)		
Inflammatory bowel disease, n (%)	9 (12)		
Use of NSAID at baseline, n (%)	65 (84)		
Use of DMARD at baseline, n (%)**	21 (27)		
Use of prednisone, n (%)	4 (5)		
Previous use of other anti-TNF therapy***	16 (21)		
BASDAI, mean (SD)	5.5 (2.1)	3.8 (2.5)*	3.7 (2.4)*
BASFI, median (IQR)	4.7 (2.7–6.6)	3.6 (1.1–5.4)*	2.9 (0.9–5.6)*
BASG, mean (SD)	6.6 (2.1)	4.9 (2.4)*	4.0 (2.5)*
BASMI, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
ASQOL, median (IQR)	9.0 (5.8–13.0)	6.5 (2.0–10.0)*	4.0 (2.0–9.0)*
No. patients with at least 1 swollen joint (SJC-72) (%)	18 (25)	6 (9)*	3 (6)*
ESR, median mm/h (IQR)	14 (7–31)	6 (3–15)*	6 (2-14)*
CRP, median mg/l (IQR)	4 (2–13)	1 (1–4)*	1 (1–3)*
No. ASAS-20% responders (%)		25 (56)	20 (53)
No. ASAS-40% responders (%)		1 (2)	3 (8)
No. BASDAI-50% responders (%)		31 (55)	19 (41)

*p < 0.05 followup towards baseline. **DMARD: In most cases sulfasalazine (n = 10) or methotrexate (n = 8). ***Previous use of other anti-TNF agent: etanercept (n = 15), infliximab (n = 1). NSAID: nonsteroidal antiinflammatory drug ; DMARD: disease-modifying drug; BASDAI: Bath AS Disease Activity Index (0–10); BASFI: Bath AS Functional Index (0–10); BAS-G, Bath AS Global Score (0–10); BASMI, Bath AS Metrology Index (0–10); ASQOL, AS Quality of Life (0–18); SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASAS: Assessment in Spondyloarthritis International Society; TNF: tumor necrosis factor.

disease duration of 7 years. The prevalence of HLA-B27 antigen was 76%, and 33 patients (43%) had experienced at least 1 attack of uveitis.

Comparison between patients with and those without uveitis showed that among patients who had experienced at least 1 attack of uveitis, the prevalence of the HLA-B27 antigen was significantly higher: 29/33 (94%), compared with those who never had uveitis: 28/44 (64%) (p = 0.003). The median BASMI was lower in the patients with uveitis-ever (score 1.0; IQR 1.0–2.5) compared to the rest of the patients (score 3.0; IQR 1.5–5.0) (p = 0.007). The median disease duration of patients with uveitis-ever (12.0 yrs; IQR 2.8–19.8) was longer than that in patients who never had uveitis (7.0 yrs; IQR 1.5–12.5), but this difference was not significant (p = 0.069). No other significant differences were seen between patients with and those without uveitis-ever in other patient or disease characteristics (data not shown).

In total, 67 of the 77 patients (87%) were seen by the ophthalmologist at baseline and 44 (57%) during followup; the other data were retrieved from hospital charts and protocol visits to the research physician. The median followup period (i.e., duration of treatment) was 1.74 years (IQR 0.83–2.84), with a total of 139 patient-years. Three subjects had symptomatic uveitis at baseline. Ophthalmological examinations in patients without symptoms did not reveal any uveitis.

Out of the 77 patients at baseline, 51 (66%) had no attacks of uveitis in the year before treatment, nor during treatment. No patient developed uveitis for the first time during adalimumab treatment. Seven patients (9%) were classified as having chronic uveitis, but during adalimumab treatment chronic uveitis did not occur.

In all patients, the total number of uveitis attacks was 52 in the year before baseline (i.e., 68 attacks per 100 patient-yrs), whereas during adalimumab treatment 19 attacks were seen (14 per 100 patient-yrs; reduction rate 80%). Uveitis attacks were treated with topical steroids.

Among the 26 (34%) patients with uveitis in the year before treatment, 10 had flares of uveitis during treatment and 16 had no uveitis (Figure 2). This indicates a 62% decrease in the number of patients with uveitis attacks (p < 0.0001). The patients with chronic uveitis responded as well as the other uveitis patients: 27% of the patients with uveitis

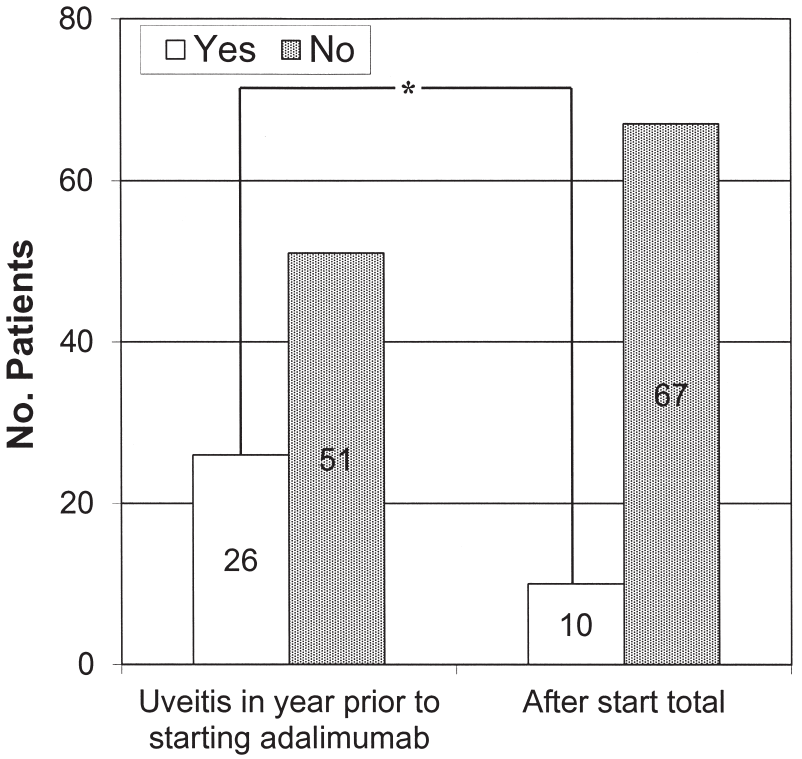

Figure 2. Among 26 patients with uveitis in the year before treatment, 10 had flares during treatment and 16 had no uveitis. *p < 0.0001.

in the year before baseline had chronic uveitis and 2 of these had uveitis after start of adalimumab (20% of all patients with uveitis during therapy).

The 26 patients with uveitis in the year before start of adalimumab experienced recurrent attacks, with a median number of 2.0 uveitis attacks per year (IQR 1.00–3.00), whereas during treatment this dropped to 10 patients, with a median number of 0.56 attacks per year (IQR 0.30–0.75). Hence, the number of attacks per year dropped by 72% ($p < 0.0001$).

The 26 patients with uveitis in the year before therapy had 200 flares per 100 patient-years before therapy and during adalimumab had 19 flares in 61 patient-years (31 flares per 100 patient-years; reduction rate 84%; Table 2).

Disease measures at followup are shown in Table 1. In general, improvement was seen in measures for disease activity, functionality, and quality of life. These improvements were statistically significant, except for the BASMI. The percentages of patients with ASAS 20% and BASDAI 50% response were 56 and 55, respectively, at Week 12 and 53 and 41, respectively, at Week 52. At Week 52 complete datasets were available for 47 patients.

Discontinuation of therapy and adverse events. Twenty-eight (36%) of the patients stopped adalimumab therapy, usually because of inefficacy (17 patients, 61% of dropouts) or adverse events (3 patients, 11%). Other reasons for dropping out were as follows: moving out of area (2), withdrawal of informed consent (1), and other reasons (5). No patient discontinued because of an AU episode. The median followup period of the dropouts was 0.82 years (IQR 0.37–1.48).

A total of 268 adverse events (AE), mostly mild, were observed among 67 (87%) patients, of whom 43 (64%) were still on drug and 24 (36%) had stopped. Infection was the most common AE observed (69 times). One patient was hospitalized (due to local skin infection), and in 13 cases antibiotics were given. No patient died during adalimumab treatment.

DISCUSSION

The number of attacks of uveitis in patients with AS before and during adalimumab treatment revealed a significant decrease in the number of patients with uveitis (62%) during treatment, as well as a decrease in the number of attacks per patient (72%), even in patients with chronic uveitis. No patient developed uveitis for the first time during adalimumab treatment. The majority (87%) of patients remained free of uveitis attacks for the entire followup period. A significant improvement of disease activity (ASAS 20% response in 56% of patients) was seen as well, which is similar to the results of placebo-controlled trials with anti-TNF agents[3,4].

Patient characteristics of those who experienced uveitis and those who did not have any attack did not differ, except

Table 2. Number of anterior uveitis (AU) attacks/100 patient-years and reduction during anti-tumor necrosis factor (anti-TNF) therapy compared to placebo, i.e., year before therapy in this study compared with other studies. Duration of followup in patient-years and mean patient-years/patient.

Study	No. AU Attacks/ 100 Patient-yrs During Placebo	No. AU Attacks/ 100 Patient-yrs During Anti-TNF	Reduction, %	Followup, Patient-yrs (No. patients)	Mean Patient-yrs/ Patient
Braun[1], 2005	16	ETN 8	49	430 (297)	1.4
(RCT + OL phase)		IFX 3	78	146 (90)	1.6
Sieper[28], 2010 (RCT + OL phase)	19	ETN 12	38	1137 (1074)	1.1
	Before anti-TNF				
Rudwaleit[30], 2009	15	ADA 7	51	363 (1250)	0.3
Current study	68	ADA 14	80	139 (77)	1.8

RCT: randomized controlled trial; OL: open-label phase; ETN: etanercept; IFX: infliximab; ADA: adalimumab.

for the prevalence of HLA-B27 antigen, which was significantly higher among the patients who had experienced at least 1 attack of uveitis. This observation is in accord with previous studies, which show a strong association between uveitis and HLA-B27[5,28]. The lower median BASMI in the patients with uveitis-ever is probably due to chance, as all other disease measures were not different. A longer disease duration in patients who had ever had uveitis could be expected, but this difference did not reach statistical significance in our patients[7].

In contrast with other studies in AS, information about uveitis in our study was obtained at visits to the ophthalmologist at baseline and during followup. Because the visit to the ophthalmologist could not be combined with the other protocol visits, not all patients were seen by the ophthalmologist. However, it is not likely that this had a significant influence on our results as (1) this was particularly the case in those who never had eye problems, and (2) in case of an attack of uveitis, patients were always seen by their attending ophthalmologist and this was verified by our (study) ophthalmologist.

The rates of uveitis per 100 patient-years in our study are compared with other studies that investigated this topic in Table 2. In 2 studies the incidence of uveitis during placebo and during anti-TNF therapy was determined from several clinical trials of etanercept and infliximab, including open-label extension studies[28,29]. In an open-label uncontrolled study the rate of uveitis during adalimumab treatment was compared with the incidence reported during the year before treatment[30]. In all studies the rate of uveitis during anti-TNF treatment was lower compared to that of the placebo period or the year before therapy. The 80% reduction in recurrence rates of uveitis during adalimumab treatment in our study was higher in comparison with the other studies, which varied from 78% for infliximab, to 38%–49% with etanercept, and 68% with adalimumab (Table 2).

Differences in reduction of uveitis between these studies could be explained by differences in duration of followup. In our study the mean number of patient-years per patient was 1.8 years versus 0.3 years in the study of Rudwaleit, *et al*[30]. In some patients the efficacy of the anti-TNF treatment could last some months, an observation that might be overlooked in studies with shorter followup period.

Another difference is that a high percentage of our patients (n = 33, 43%) had experienced uveitis at some time before treatment, whereas in most AS studies the prevalence of AU ranged between 25% and 40% among patients[11]. Comparing the rates of uveitis flares/100 patient-years (Table 2) also shows a higher number (n = 68) in our study compared with the lower rates before treatment or during placebo in patients of other studies (which described 15 to 19 flares/100 patient-yrs). Obviously, the absolute numbers of patients with uveitis during therapy cannot be compared with other studies, but the rates of reduction can. We observed a high rate of reduction of uveitis, even in our patients with a high incidence of uveitis or chronic uveitis.

In addition, we cannot exclude that the high percentage of uveitis at baseline in our study might be due to a selection bias, because of preferential prescription of adalimumab in cases of a history of uveitis during the period of our study. On the other hand, comparing the frequency of earlier treatment with another anti-TNF therapy in this study (21%) with that of another study (26%), the study populations appear to be comparable[30].

The prevalence of uveitis in AS increases with longer disease duration[7]. However, the high prevalence of uveitis recorded in our study cannot be explained by longer disease duration compared to other studies. In contrast, the median disease duration in our study was 7 years (IQR 2–15), compared to a mean duration of 9.5–11 years in other studies[28,30].

Interestingly, in our study no patient developed AU for the first time during adalimumab treatment, but other studies have described that a first attack of uveitis may occur during therapy with several TNF-blocking agents[30,31,32].

We observed a significant and substantial reduction of the rate of recurrence of attacks of acute anterior uveitis during adalimumab treatment in patients with AS, even in patients with chronic uveitis. The majority (87%) of patients remained completely free of uveitis attacks for the entire followup period.

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