Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis

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ABSTRACT. ***Objective.*** Abatacept (ABA) has recently been proposed as second-line treatment in patients with juvenile idiopathic arthritis (JIA)–associated uveitis refractory to anti–tumor necrosis factor-α (anti-TNF) agents, but little is known about its efficacy as a first-line approach. The aim of the present study was to compare the safety and efficacy of ABA as a first-line biological agent (ABA-1) with that of ABA as a second-line treatment after 1 or more anti-TNF agents (ABA-2), in patients with severe JIA-related uveitis.

Methods. In this multicenter study, we collected data on patients with severe JIA-related uveitis treated with ABA as a first-line or second-line biological agent. Changes in frequency of uveitis flares/year and ocular complications before and after ABA treatment, clinical remission, and side effects were recorded.

Results. Thirty-five patients with a mean age of 10.8 years were treated with ABA for a mean period of 19.6 months. In 4 patients, ABA administration was discontinued, owing to inefficacy on arthritis in 3 cases and allergic reaction in 1. Thirty-one patients, 14 in the ABA-1 group and 17 in the ABA-2 group, completed the 12-month followup period; of these, 17 (54.8%) had clinical remission. The mean frequency of uveitis flares decreased from 4.1 to 1.2 in the ABA-1 group ($p = 0.002$) and from 3.7 to 1.2 in the ABA-2 group ($p = 0.004$). Preexisting ocular complications improved or remained stable in all but 5 patients, all in the ABA-2 group. No significant difference was found between the efficacy of the 2 treatment modalities. ABA confirmed its good safety profile.

Conclusion. ABA, used as first-line biological treatment or after 1 or more anti-TNF agents, induces a comparable improvement in severe refractory JIA-related uveitis. (J Rheumatol First Release September 15 2016; doi:10.3899/jrheum.151389)

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Chronic anterior uveitis (CAU), one of the most serious extraarticular manifestations of juvenile idiopathic arthritis (JIA), can cause sight-threatening complications. The first-line treatment of uveitis consists of topical mydriatics and corticosteroid drops, associated with oral steroids and methotrexate (MTX) in the more severe cases. Treatment with other disease-modifying antirheumatic drugs and/or anti-tumor necrosis factor-α (anti-TNF) agents, such as etanercept (ETN), infliximab (IFX), or adalimumab (ADA), has been introduced into clinical practice[1].

Several reports have demonstrated a significant association between ETN, the first anti-TNF agent used for CAU, and the development of new-onset uveitis and/or uveitis relapse[2]. IFX showed a better efficacy on CAU when compared to ETN[3], but serious side effects have been reported[4]. ADA, a fully human anti-TNF agent, is more effective than IFX[5,6]. A large observational study and a recent metaanalysis have shown higher response rates for ADA (67%–87%) in comparison with IFX (43%–72%)[5,7]. However, because all these reports underline that TNF inhibitors are ineffective in around one-third of patients with severe course uveitis, an alternative therapeutic approach has been considered.

Abatacept (ABA), a soluble fusion protein that blocks the CD28 co-stimulatory signal, resulting in T cell inactivation[8], has been shown to be a valid alternative to anti-TNF agents for the treatment of severe JIA-related uveitis[9].

The aim of the present multicenter multinational study was to compare the safety and efficacy of ABA as a first biological agent (ABA-1) with that of ABA used after 1 or more anti-TNF agents (ABA-2), in patients with severe JIA-related uveitis.

MATERIALS AND METHODS

The study series comprised JIA patients with CAU refractory to standard immunosuppressive drugs and/or anti-TNF agents. Patients treated with ABA were evaluated from the start of treatment in 9 pediatric rheumatology centers. Data on uveitis and arthritis activity at baseline and after the initiation of ABA were collected from the patients' clinical records following a standardized protocol. CAU was diagnosed according to the Standardization of Uveitis Nomenclature (SUN) Working Group criteria[10].

Briefly, uveitis was graded according to anterior chamber cells, an anterior chamber cell grade of < 0.5+ being defined as inactive disease[10]. Uveitis flare was defined as a 2-degree increase of the level of inflammation (anterior chamber cells). Clinical remission on medication (CRM) was defined as the absence of flares for more than 6 months while taking systemic treatment, without or with minimal topical treatment (corticosteroid and/or mydriatic-cycloplegic eye drops ≤ 1/day). Structural complications of uveitis and visual acuity outcomes were also recorded according to standardized methods[11]. Complicated uveitis was defined as the occurrence of 1 or more structural complications such as posterior synechiae (involving at least 1 iris quadrant), band keratopathy (BK), cataract, cystoid macular edema (CMO), or ocular hypertension (OH).

Ophthalmological evaluation frequency ranged from once a week to once a month, depending on the uveitis course. Clinical data, collected at baseline and during the followup, included number of uveitis flares, new onset or worsening of preexisting ocular complications, and ABA-related adverse events. A comparison was made between the frequency of uveitis flares during the 12-month period before the introduction of ABA and those occurring during the 12-month period of treatment.

Arthritis course was evaluated by clinical assessment, performed at baseline and during followup, at regular intervals of 3-4 months or sooner if needed.

Standard immunosuppressive drugs had been administered at the dosage conventionally used for pediatric rheumatic diseases.

MTX (10–20 mg/m^2/week) and low-dose steroids (up to 0.2 mg/kg/day), if present at baseline, were maintained or tapered during the study period when possible. Only patients with at least 1 year of followup were included in the study.

The study protocol was submitted to the local ethics committee, but approval was deemed not necessary because only de-identified data were collected by the data manager (FZ), and ABA was used following the criteria of good clinical practice of treating and preventing severe ocular complications in patients with JIA refractory to immunosuppressive drugs and at least 1 anti-TNF agent.

In the ABA-1 group, ABA was used as a first-line biologic agent for uveitis refractory to at least 6 months' MTX treatment, in agreement with the national Russian Federation regulations.

Statistical analysis. Demographic, clinical, and laboratory data of patients included in the study were examined on a descriptive basis and expressed as the mean ± SD, median, frequency, and percentages. The Mann-Whitney U test was used to compare continuous variables, and the chi-square test and Fisher's exact probability test were used to test for differences between categorical variables. For the comparison between results in the first and in the last examination of the same patient within the first year of followup, the Wilcoxon rank sum test for paired data was used. The analysis of time to uveitis flare was undertaken in each treatment group according to the Kaplan-Meier procedure and compared by log-rank test.

For all statistical tests, a p value < 0.05 (2-tailed test) was taken to indicate a significant difference. All data were processed using the statistical software PASW Statistic 18.0 (IBM-SPSS Inc.).

RESULTS

Thirty-five patients with JIA-related uveitis entered the study (33 females, 2 males). All were white, with a mean age of 4.8 years at uveitis onset (1.3–14.3), a mean age of 10.8 years at treatment start (3.1–23.8), and 7.7 years of uveitis duration (1–17.7).

In all cases, a step-up treatment approach for CAU had been followed. Topical steroids and cycloplegic ophthalmic drops had been initially administered. Systemic corticosteroids (oral or intravenous) and immunosuppressive agents [MTX as first choice, followed by cyclosporine (1 patient) or mycophenolate mofetil (2 patients)] were used for more severe or relapsing cases. TNF-α antagonists (ETN, IFX, ADA) or ABA were used as adjunctives in refractory cases.

ABA was administered for a mean period of 19.6 months (6–38 months). During the first year of followup, 4 patients stopped ABA treatment either for arthritis inefficacy (3 patients) or because of an allergic reaction (1 patient). Thirty-one patients, all oligoarticular, with at least 12 months' followup were therefore eligible for the study. Table 1 summarizes the clinical and demographic characteristics of the patients. In 14 patients, ABA was introduced early as the first-line biologic agent (ABA-1). In 17 patients, ABA was introduced as a second-line biologic (ABA-2). Five patients had been previously treated with ETN for aggressive arthritis, and were then switched to IFX, ADA, or both in succession,

Table 1. Baseline demographic and clinical characteristics of the patients. Data are number (%) unless otherwise indicated.

	ABA-1, n = 14	ABA-2, n = 17	p
Sex (F:M)	1 :2	17:0	0.196
Age at treatment start, yrs, mean (SD), range	8.7 (3.4), 3.1–14.6	12.6 (4.9), 5.0–23.8	0.015
Age at uveitis onset, yrs, mean (SD), range	4.8 (3.3), 1.3–13.6	4.2 (2.0), 2.0–9.5	> 0.999
Uveitis duration at ABA start, yrs, mean (SD), range	3.8 (3.2), 1–10.8	7.4 (5.2), 1.4–17.7	0.007
Uveitis relapses 12 mo pre-ABA, mean (SD), range	4.1 (2.3), 1.0–8.0	3.7 (3.0), 1.0–12.0	0.387
Complicated uveitis*	7/14 (50.0)	10/17 (58.8)	0.785
Previous anti-TNF-α treatments			
Etanercept	—	5 (29.4)	—
Infliximab	—	11 (64.7)	—
Adalimumab	—	17 (100)	—
Corticosteroids/DMARD (MTX)	8	10	0.925
Only DMARD (MTX, CSA, MMF)	6	7	

* Complicated uveitis: the occurrence of 1 or more structural complications such as posterior synechiae (involving at least 1 iris quadrant), band keratopathy, cataract, cystoid macular edema, or ocular hypertension. ABA: abatacept; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; MTX: methotrexate; MMF: mycofenolate mofetil; CSA: cyclosporine.

as a result of the worsening of uveitis. In 12 patients uveitis was refractory to IFX and ADA. In one of these patients, IFX had been interrupted because of the onset of optic neuritis.

Uveitis severity at the time of treatment initiation was comparable in the 2 groups, ABA-1 and ABA-2, in terms of mean number of uveitis flares/year (p = 0.387) and number of complicated uveitis cases (p = 0.785). Conversely, the mean age of the patients and the mean duration of CAU at treatment start were both significantly different in the 2 cohorts (p = 0.015 and p = 0.007, respectively; Table 1).

After 12 months of ABA treatment, 17 patients (54.8%) achieved CRM. A slightly higher frequency of CRM was observed in the ABA-1 group (57.1%) than in the ABA-2 group (52.9%), but the difference was not statistically significant (p = 0.478).

The mean frequency of uveitis flares during the 12 months before and after ABA treatment initiation significantly decreased both in ABA-1, from 4.1 (median = 3.0) to 1.2 (median = 1.0, p < 0.01), and in ABA-2, from 3.7 (median = 3.0) to 1.2 (median = 1.0, p < 0.01; Table 2). The efficacy was comparable in the 2 groups as shown by the Kaplan-Meier survival estimates of the time to uveitis relapse (p = 0.101, log-rank test; Figure 1). The efficacy of ABA was greater after the first 6 months of treatment — only 9/24 uveitis flares (37.5%) occurred during the second semester.

Best corrected visual acuity (using logMAR chart) also improved from 0.42 to 0.38 (not significant). The preexisting structural complications (BK, cataract, CMO-related residual abnormalities) significantly hampered complete recovery.

Ocular complications, present in both groups at baseline, consisted mainly of posterior/anterior synechiae (n = 10), cataract (n = 14), BK (n = 8), CMO (n = 4), OH (n = 3), and papillitis (n = 1). At the end of the followup period, pre-existing ocular complications remained unchanged in the 7 ABA-1 patients, but progressed in number in 5 ABA-2 patients, who experienced new-onset CMO (n = 2), vitritis (n = 2), and a combination of synechiae, cataract, and glaucoma (n = 1; Table 2). This worsening, although noticeable, did not attain statistical significance. Of note, among 18 patients who were taking low-dose corticosteroids at baseline (prednisone mean 0.15 mg/kg/day, range 0.05–0.2), 5 (27.8%) were able to either discontinue the treatment (3 patients) or halve the daily dosage (2 patients), while the remaining patients continued with the same dose. None of the 13 patients without corticosteroids at baseline (6 in ABA-1 and 7 in ABA-2) needed to start them during the study period. All patients taking MTX at baseline continued with this treatment during the followup.

Table 2. Change of uveitis severity after treatment with abatacept (ABA) used as first-line or second-line agent. Data are mean (SD) for uveitis flares and n (%) for number of complications.

	Pretreatment	Post-treatment	p
ABA-1, n = 14			
Uveitis flares	4.1 (2.3)	1.2 (0.44)	< 0.01
No. complications	7 (50.0)	7 (50.0)	> 0.999
ABA-2, n = 17			
Uveitis flares	3.7 (3.0)	1.2 (0.43)	< 0.01
No. complications	10 (58.8)	15 (88.2)	0.063
Overall, n = 41			
Uveitis flares	3.9 (2.6)	1.2 (0.42)	< 0.01
No. complications	17 (41.5)	22 (53.7)	0.063

Arthritis went into clinical remission in 11/18 patients (61.1%; 5/11 ABA-1 and 6/7 ABA-2). In the remaining 7 patients, the median number of active joints decreased from

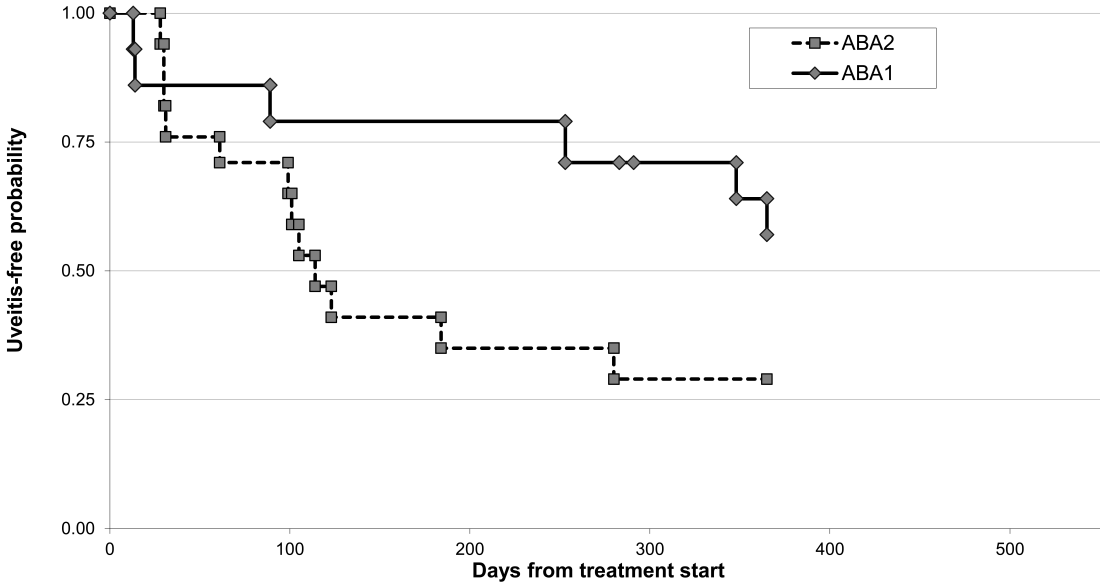

Figure 1. Kaplan-Meier survival estimates of the time to uveitis relapse in ABA-1 and ABA-2 groups (p = 0.101, log-rank test). ABA: abatacept.

10.1 to 7.0. No patient without articular involvement at baseline (3 in ABA-1 and 10 in ABA-2) developed arthritis during the followup.

Two patients (6.4%) experienced adverse events (1 post-infusion headache, 1 weight gain). No infusion reactions or other drug-related adverse events were reported in the remaining patients.

DISCUSSION

Several reports have shown that anti-TNF agents (IFX and ADA) represent effective treatment for severe JIA-related uveitis in patients who do not respond to first-line immunosuppressive drugs such as MTX or cyclosporine[1].

A large observational study and a metaanalysis have shown a high response rate for both of these anti-TNF agents, although in around one-third of the patients, resistance or loss of efficacy have been reported[5,6,7,12].

In these patients with severe refractory JIA-related uveitis, ABA has been shown to be a possible valid alternative[9]. This biologic agent proved to be effective in patients with refractory rheumatoid arthritis (RA)[13] and polyarticular JIA[14]. More recently, a small pilot study reported a case series of 7 patients with longstanding uveitis, refractory to immunosuppressive therapy and to 2 or more anti-TNF treatments, who were successfully treated with ABA[9]. Further case reports confirmed these preliminary results[15,16,17].

The present series consisted of 31 patients with JIA-related uveitis who were refractory to standard immunosuppressive treatment. When used as first-line treatment, ABA showed a good efficacy; 57% were in complete remission after 12 months of treatment. These results are comparable with those obtained with anti-TNF agents. Two studies reported a good response rate of uveitis (57% and 76%) in patients with JIA treated with ADA[18,19]. However, in neither study was it possible to extract specific outcomes in the subset of patients who received ADA as first-line biological treatment. In a recent metaanalysis including 5 studies on ADA, improvement in intraocular inflammation was reported in 87% of 31 patients treated with this biologic agent, but again, the number of biologic-naive patients was not specified and data on remission were available for only a few cases[7].

The only available study in which ADA was used as first-line biological treatment for more than 12 months in a small cohort of 15 patients reported remission in 60% of cases[6]; this remission rate is comparable to that (57%) found in our present study.

When ABA was used as second-line biologic treatment, more than half of the patients in our series responded to treatment. This result, although relevant, is inferior to that previously reported, in which 6 out of 7 patients responded to treatment after a mean followup of 9 months[9]. The larger sample size and longer followup in our present study might explain the difference in outcomes. A poorer performance of ABA as a second-line biological agent for CAU has been reported recently by a multicenter retrospective study[20]. Of 12 patients treated with ABA for longstanding refractory uveitis for at least 12 months, only 3 (25%) reached a stable CRM. Conversely, from our study, the followup was shorter (12 months for just 12 patients) and the disease was more aggressive (81% presenting ocular complications at baseline and 38% having been treated with more than 2 biological agents and several immunosuppressive drugs before starting ABA).

Another interesting finding of our study was that ABA was also effective in reducing the number of uveitis flares both in ABA-1 from 4.1 to 1.2/year and in ABA-2 from 3.7 to 1.2/year. A better performance of ABA was observed after the first 6 months of treatment; only one-third of flares occurred during the second treatment period (Figure 1). Although we do not have a clear explanation for this, we believe that some patients might require treatment for 4 to 6 months before responding, as reported in JIA[21]. This hypothesis is also borne out by data from adult RA trials, in which a longer treatment duration was associated with progressive improvement in response[22,23].

Interestingly, we found no significant difference between the ABA-1 and ABA-2 groups in terms of response rate, as shown by the Kaplan-Meier survival estimates of the time to uveitis relapse (Figure 1). This is different from what we observed with ADA, where a greater efficacy was observed when it was used as the first biologic agent rather than after the failure of another[24]. Of note, ABA seems to be more effective in preventing uveitis complications when used at an earlier stage of disease, as observed in the ABA-1 group.

Two-thirds of patients with active arthritis at baseline presented CRM, a result comparable to that observed in the registration trial in which the response rate (American College of Rheumatology 30) was 65%[14]. Although the response rate was higher in the ABA-2 group (85% vs 45%), this difference did not attain statistical significance.

The safety profile of ABA was very good: only 2 patients had minor adverse events, consisting of postinfusion headache and weight gain.

A few caveats should be considered before drawing conclusions from our study. The retrospective nature of the study and the possibility of unknown confounders because of the study setting, with different patient cohorts from 3 countries, should be considered and can only in part be offset by the standardized way by which the patients were followed and treated. The definition of improvement, taken from the SUN criteria[10] and not validated for use in children, may represent an additional limitation. However, as yet, they are the only standardized measures available for assessing differences in uveitis inflammation, and therefore are the only means available for comparing different treatment groups.

ABA represents a valid therapeutic approach for the treatment of severe JIA-related uveitis, whether used as either first-line biological agent or after failure of anti-TNF agents.

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