Abatacept in the Treatment of Severe, Longstanding, and Refractory Uveitis Associated with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** Abatacept (ABA), a selective T cell costimulation modulator that binds to CD80 and CD86 on antigen-presenting cells, was investigated for its antiinflammatory effect in treating severe chronic uveitis associated with juvenile idiopathic arthritis (JIA).

Methods. Our retrospective study was conducted by members of the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC). Patients with JIA who are receiving ABA treatment for active uveitis were included. In all patients, uveitis had been refractory to previous topical and systemic corticosteroids, immunosuppressives, and at least 1 tumor necrosis factor–α inhibitor. A standardized protocol was used to document uveitis (MIWGUC) and arthritis. Baseline visit and visits at 3, 6, 9, and 12 months before and after ABA start were evaluated. Primary outcome measure was defined as achievement of uveitis inactivity; secondary outcome measures were tapering of corticosteroid and/or immunosuppressive treatment, and occurrence of complications.

Results. In all, 21 patients (16 female) with active uveitis (n = 21) and arthritis (n = 18) were included (mean age 11.8 ± 3.6 yrs). In 7 of 18 patients with active arthritis at baseline, inactivity was achieved following ABA treatment. Uveitis inactivity was achieved in 11 patients, but recurred later in 8 of them, and remained active in another 10 cases. Systemic corticosteroids or immunosuppression were tapered in 3 patients, but uveitis recurred in all of them during further followup. Ocular complications secondary to uveitis were present in 17 patients at baseline, while 3 patients developed new ocular complications during followup.

Conclusion. A sustained response to ABA was uncommon in patients with severe and refractory uveitis. (First Release Feb 1 2015; J Rheumatol 2015;42:706–11; doi:10.3899/jrheum.140410)

Key Indexing Terms:
ABATACEPT BIOLOGICALS JUVENILE IDIOPATHIC ARTHRITIS UVEITIS

Juvenile idiopathic arthritis (JIA) is an inflammatory rheumatic disease with onset before 16 years of age[1]. Uveitis develops in about 8-13% of children[2,3,4]. In about one-third of patients, ocular inflammation leads to vision-threatening complications[4,5,6]. Therefore, immunosuppressive treatment is recommended in severe cases to achieve uveitis inactivity and to reduce the risk of vision loss[7,8,9]. Nowadays, if inactivity cannot be achieved with classic disease-modifying antirheumatic drugs (DMARD), biologics offer new therapeutic options. In uveitis associated with JIA, the tumor necrosis factor-α (TNF-α) inhibitors infliximab and adalimumab may be effective;

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however, data from randomized prospective clinical trials are not yet available[7,10,11]. Currently, adalimumab is the preferred TNF-α inhibitor for these patients[7,11].

Because some patients do not respond adequately to DMARD or TNF-α inhibitors, alternative treatment options are needed. Among the newer biologics, abatacept (ABA) prevents full T cell activation[12,13,14]. ABA is a fully humanized, soluble recombinant fusion protein, consisting of cytotoxic T lymphocyte antigen 4, linked to a modified Fc domain of human immunoglobulin 1. A significant clinical and functional benefit of ABA has been reported in patients with rheumatoid arthritis (RA) who did not respond adequately to TNF-α inhibitor treatment[13,15]. In addition, ABA provided clinically significant and longterm efficacy in patients with JIA[16,17,18]. ABA has been approved in the United States and Europe as a second-line treatment for RA as well as for JIA with a polyarticular course. Previous case reports regarding ABA treatment in uveitis associated with JIA have given encouraging results[14,19,20,21].

Our present study comprises the largest multinational cohort study to analyze the efficacy of ABA in uveitis associated with JIA. It was conducted at tertiary uveitis referral centers using a standardized protocol with outcome measures established by the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC)[22].

MATERIALS AND METHODS

A multicenter, retrospective analysis was performed of the efficacy of ABA treatment in patients diagnosed with JIA according to the International League of Associations for Rheumatology classification[1] and associated active uveitis (JIAU; anterior chamber cell grade ≥ 1+[22,23]). All members of the MIWGUC group were invited to participate in the study; those with personal experience with ABA for the treatment of JIAU provided their respective data to the study. Only patients with uveitis manifestation before the age of 16 years and who started ABA treatment before the age of 18 years were included. The study design conforms to the standards currently applied in the countries of the participating clinics. No institutional review board approval or informed consent is required for chart review studies based on anonymized data provided by the treating physician.

ABA was instituted between 2009 and 2011 in patients with active uveitis refractory to systemic corticosteroid and immunosuppressive treatment. All patients were clinically monitored by a pediatric rheumatologist and received a complete physical examination assessing the number of involved joints and routine laboratory tests for antinuclear antibody, rheumatoid factor (RF), and HLA-B27. Patients with infections or malignancies were excluded. The epidemiological data, course of visual acuity, and presence of uveitis complications were recorded before and after ABA was instituted. Visits at 3, 6, 9, and 12 months before and after baseline (ABA start) were evaluated. A standardized system for documenting uveitis activity and secondary complications was used, and data were recorded on a standardized case report form provided to all study participants[22]. Briefly, uveitis was graded according to anterior chamber cells, where an anterior chamber cell grade of < 0.5+ was defined as inactive disease[22,23]. Patients were followed up at 3-month intervals, preferably up to 12 months. Ophthalmological documentation included determination of best-corrected visual acuity (logMar), slit-lamp examination, applanation tonometry, and ophthalmoscopy. Uveitis complications (e.g., glaucoma, cataract, band keratopathy, optic disc edema, macular edema, epiretinal membrane, and vitreous haze) were documented at baseline and at the 3-month followup visits during ABA treatment.

The primary outcome measure was defined as achievement of uveitis inactivity. Percentages of visits with active uveitis in the year before and after ABA institution were compared. A secondary outcome measure was tapering of corticosteroid and/or immunosuppressive treatment, according to previous publications: good response, ≥ 50% decrease in both corticosteroid use and immunosuppressive agent; moderate response, ≥ 50% decrease in either corticosteroid or immunosuppressive agent; and poor response, < 50% decrease in both corticosteroid and immunosuppressive agent[24]. Concomitant use of corticosteroids and immunosuppressives was documented (treatment decisions were at the discretion of the treating physician). Additionally, topical corticosteroid dosage was documented at baseline and at the end of followup. Arthritis activity was determined during ABA treatment[25]. A further secondary outcome measure was occurrence of complications during followup.

RESULTS

Included in this study were 21 patients who had uveitis associated with JIA (Münster, n = 9; Milan, n = 4; Helsinki, n = 4; Paris, n = 3; and Heidelberg, n = 1), with a mean age of 11.8 ± 3.6 years and a mean duration of arthritis of 8.1 ± 3.9 years. The demographic data at baseline are shown in Tables 1 and 2. JIA subtypes were classified as extended (n = 9) or persistent oligoarthritis (n = 7) and RF-negative polyarthritis (n = 5). All patients had severe, chronic uveitis (all with insidious onset of flare), with a mean duration of uveitis of 7.5 ± 4.0 years. In all patients, high dosages of topical (e.g., prednisolone acetate 1%, up to hourly) and systemic corticosteroids (prednisone equivalent ≥ 1 mg/kg body weight) had been used temporarily (in general, 4–6 weeks) prior to ABA. However, recurrences of uveitis occurred with subsequent tapering of medication or at maintenance dosages. The disease reactivated with topical (≤ 3 drops/day) and systemic corticosteroids (≤ 0.15 mg/kg) combined with DMARD and biologics, including at least 1 TNF-α inhibitor (Table 3). At baseline, a considerable number of patients were receiving topical (90.5%) and systemic (61.9%) corticosteroids.

A total of 21 patients attended the 3-month followup

Table 1. Patient characteristics. All patients had severe juvenile idiopathic arthritis–associated uveitis refractory to corticosteroids and systemic immunosuppression (n = 21 patients).

Age, yrs (mean ± SD)*	11.8 ± 3.6
Male/female (n)	5/16
ILAR classification, n/%	
Persistent oligoarthritis	7/33.3
Extended oligoarthritis	9/42.9
Polyarthritis	5/23.8
ANA+, n/%	18/85.7
HLA-B27+, n/%	2/9.5
RF+, n/%	0/0
Age at JIA diagnosis, yrs (mean ± SD)	3.7 ± 2.6
Age at uveitis diagnosis, yrs (mean ± SD)	4.3 ± 3.2
Duration of uveitis, yrs (mean ± SD)	7.5 ± 4.0

* Age at time of starting abatacept therapy. ANA: antinuclear antigen; RF: rheumatoid factor; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic arthritis.

Table 2. Ophthalmological baseline findings for patients with refractory uveitis associated with juvenile idiopathic arthritis–associated uveitis (n = 21 patients). Data are no. patients/% unless otherwise specified.

Uveitis type*	
Anterior	19/90.5
Panuveitis	2/9.5
Involved eyes	
Unilateral/bilateral	4/17
BCVA, mean (range), logMar	0.46 (0–1.52)
BCVA ≤ 20/200 on worse eye	4/19.0
Secondary complications	
Patients without complications	4/19.0
Patients with complications	17/81.0
Cataract	16
Band keratopathy	11
Synechiae	14
Ocular hypertension	2
Glaucoma	3
Macular edema	4
Epiretinal membrane	2
Optic disc edema	4
Phthisis	1
Retinal detachment	1

* Standardization of Uveitis Nomenclature Working Group classification[23]. BCVA: best-corrected visual acuity.

visit, 20 patients the 6-month followup visit, 14 the 9-month followup visit, and 12 the 12-month followup visit. Persistent uveitis activity was documented in all patients during a period of at least 3 months prior to instituting ABA despite aggressive treatment with corticosteroids and DMARD. An overview of immunosuppressive treatments at baseline is provided in Table 3. Vision-threatening complications before initiating ABA treatment were present in 17 patients (Table 2). Anterior chamber assessment at baseline revealed a cell grade of 1+ cells in 11 patients, 2+ in 7 patients, and 3+ in another 3 patients, respectively (in bilateral uveitis, the eye with the higher anterior chamber cell grade was selected). ABA was administered at a dosage of 10 mg/kg (up to a maximum of 750 mg) by 30-min intravenous infusion at weeks 0, 2, and 4, and was then continued monthly.

Following ABA treatment, uveitis inactivity (defined as anterior chamber cell grade < 0.5+) was achieved in 2 of 21 patients at 3 months, in 7 of 20 patients at 6 months, in 8 of 14 patients at 9 months, and in 5 of 12 patients at 12 months. Whereas uveitis inactivity was observed in 11 patients during at least 1 followup visit after initiating ABA (52.4%), uveitis had recurred in 8 of them during subsequent visits

Table 3. Patients with active juvenile idiopathic arthritis–associated uveitis (n = 21) were treated with abatacept (ABA) when disease was refractory to topical corticosteroids and systemic immunosuppression. Comparison of systemic and topical treatment before and after ABA. Tapering of systemic corticosteroids and/or immunosuppressives was defined according to Saurenmann, *et al*[24].

Pt.	Treatment Prior to ABA	Baseline Treatment	Tapering of Systemic Corticosteroids and/or Immunosuppressives after ABA	Steroid Eyedrops Before/after ABA (no. times daily; +: periocular corticosteroid application)
1	PSL, MTX, ETA	MTX, ETA	No	0/1
2	PSL, MTX, CSA, IFX, ADA, IFN	PSL, MTX, CSA, ADA	Moderate	2/5 (+)
3	PSL, MTX, ARA, ADA	PSL, MTX, ARA, ADA	No	3/5
4	PSL, MTX, CSA, ARA, ETA, ADA, RTX	MTX, CSA, ARA	No (rescue: PSL, RTX)	7/12 (+)
5	PSL, MTX, AZA, ADA	PSL, AZA, ADA	No	12/3 (+)
6	PSL, MTX, ADA	PSL, MTX, ADA	Moderate (rescue: IFX)	4/3
7	PSL, MTX, ADA	MTX, ADA	No (rescue: PSL)	4/0 (+)
8	PSL, MTX, ADA	MTX, ADA	No	0/3
9	PSL, MTX, AZA, ARA, MMF, ETA, ADA	PSL, MTX, ADA	No	5/3
10	PSL, MTX, CSA, ADA	PSL, MTX	No	4/0
11	PSL, MTX, CSA, ADA	PSL, MTX, CSA	Good	4/0
12	PSL, MTX, AZA, CSA, ETA, IFX, ADA	PSL, MTX, CSA	No	4/0
13	PSL, MTX, CSA, IFX	PSL, MTX, CSA	No	4/4
14	PSL, MTX, CSA, IFX, ADA	PSL, MTX, CSA	No	4/0
15	PSL, MTX, ETA, IFX, ADA, GOL	MTX, GOL	No	3/0
16	PSL, MTX, IFX, ADA	MTX	No	2/3
17	PSL, MTX, MMF, IFX, ADA	MTX	No	4/8
18	PSL, MTX, CSA, IFX	CSA, IFX	No (rescue: ADA)	5/2
19	PSL, MTX, IFX, ADA	PSL, MTX, IFX	No	1/3
20	PSL, MTX, ETA, IFX	PSL, MTX	No	2/1
21	PSL, MTX, ETA, IFX, ADA	PSL, MTX, IFX	No	4/0

Dosages were within the generally used ranges, e.g., for methotrexate (MTX) 15 mg/m^2 weekly, azathioprine (AZA) 2 mg/kg body weight daily, cyclosporine (CSA) 3 mg/kg body weight daily, mycofenolate mofetil (MMF) 500–2000 mg daily, arava (ARA) 10–20 mg daily, etanercept (ETA) 0.8 mg/kg body weight weekly, infliximab (IFX) 5–6 mg/kg body weight bimonthly, adalimumab (ADA) 24 mg/m^2 biweekly, rituximab (RTX) cycle 375 mg/m^2, golimumab (GOL) 30 mg/m^2 monthly, interferon-α2 (IFN) 1.5–3 Mio IU weekly. PSL: prednisolone.

(Table 4). In contrast, 10 patients did not respond to ABA treatment and showed uveitis activity during the entire followup. When comparing the uveitis course before and after ABA institution, uveitis was active in 83.3% versus 72.8% of visits, respectively ($p > 0.05$). New onset of ocular complications secondary to uveitis was observed in 3 patients under ABA (patient 4, optic disc edema; patient 10, cataract, epiretinal membrane; patient 17, macular edema), whereas in 5 patients, preexisting cataract had progressed (patient 4, 5, 7, 16, and 17). In 1 patient, optic disc edema developed in the other eye (patient 10). During ABA treatment, optic disc edema resolved in 3 patients (patients 5, 6, and 12) and macular edema resolved in 1 (patient 12).

Tapering systemic corticosteroids or immunosuppressive treatment was possible in 3 patients (good tapering: 1 patient, moderate tapering: 2 patients; Table 3). However, uveitis recurred in all of them during the course of the followup period after tapering the concomitant corticosteroids or immunosuppressives. The dosage of topical corticosteroids could be tapered in 10 patients during treatment with ABA (uveitis relapsed in 8 of them during further followup), while in another 10 patients topical corticosteroids needed to be increased or periocular triamcinolone (subtenon or orbital floor injections in 4 patients) needed to be injected to control uveitis activity during followup. In 1 patient, the topical therapy remained unchanged at the end of the study.

Best-corrected visual acuity did not change significantly (Wilcoxon test, $p = 0.83$), from a mean of 0.46 logMar (0–1.52) at baseline to 0.53 logMar (0–3.00) at the end of followup in the study eyes.

A total of 18 patients presented with active arthritis at baseline; in 7 of them articular inactivity was achieved by the end of followup (Table 4). In another 2 patients with joint inactivity at baseline, arthritis remained inactive during the study. No adverse events were reported that were due to ABA treatment.

DISCUSSION

In the last few years, the role of T cells in endogenous uveitis and JIA has been demonstrated[26,27,28,29]. Blocking the interaction between T cells and antigen-presenting cells by interfering with the CD80/86 and CD28 costimulation has previously been shown to reduce inflammation in experimental autoimmune uveitis (EAU)[30,31], a model reflecting features of posterior uveitis in adults. Treatment strategies are mostly derived from clinical experience in adults and from well-established uveitis animal models, such as for EAU.

Because ABA is successfully used as a second-line treatment in JIA[13,16,17,18], it would also be highly desirable to evaluate its efficacy for associated uveitis. However, only a few smaller case series with a total of 12 patients have been published to date in which the value of the drug in uveitis associated with JIA was assessed[14,19,20,21]. In 7 patients with JIA and refractory uveitis, a decrease of uveitis flares after instituting ABA was reported by Zulian, *et al*[14]. Kenawy, *et al* presented 2 children with refractory uveitis who responded well to ABA[21]. Elhai, *et al* observed uveitis quiescence after ABA infusions in 2 patients with JIA[20], and a rapid decrease of ocular inflammation with ABA treatment was reported by Angeles-Han, *et al* in a child with refractory psoriatic arthritis and uveitis[19]. It is not clear how many other patients had been treated with ABA for JIAU with less favorable results that were not reported. In our study of 21 patients with JIA-associated uveitis, disease inactivity was achieved in 11 patients (52.4%; Table 4). But relapses developed in 8 of them during the subsequent course of the 12-month followup period, while in the other 3 patients, inactivity was maintained until the end of followup. After instituting ABA, a slightly lower rate of clinical visits with active uveitis was observed. This suggests a potential benefit for this group of patients with severe and refractory uveitis, where other treatment options are limited.

Under ABA treatment, tapering systemic corticosteroids and/or immunosuppressive agents was attempted in 3 patients; however, further uveitis relapses occurred in all of them. We attempted to taper topical steroids in 10 patients, but uveitis relapsed in 8 of them. The different outcome in our study as compared to the previous case reports may to some extent be due to the tapering regimen of concomitant steroids and immunosuppressives. The ability of a drug being evaluated to maintain inactive disease in the face of tapering corticosteroids and/or immunosuppressives is one of the major outcome measures provided by the Standardization of Uveitis Nomenclature Working Group[23]. Additionally, use of the strict outcome measures for JIA-associated uveitis, which were recently established[22], might also have influenced our results. It must also be considered that the patients included in our study and treated at tertiary uveitis referral centers represent a small subset of severe cases of JIAU that have been refractory to multiple treatment approaches with DMARD, at least 1 TNF-α inhibitor, and in most cases also a second biologic. All patients were treated with ABA for active uveitis, and 85.7% also had active arthritis at baseline. The question of whether systemic corticosteroids are required for the treatment of arthritis remains unanswered in our study.

Although all patients had common characteristics (severe, chronic, and refractory uveitis), differences in treatment prior to ABA and the retrospective character of our study constitute limitations and should be taken into consideration when interpreting the results. The outcome measure of inactivity may be biased by the chance of (transient) inactivity occurring anyway in this group of patients. Therefore comparison of visits with activity in the year before and after treatment start allows assessment of a potential treatment effect, with the limitations of such a

Table 4. Response of uveitis and arthritis activity to abatacept (ABA) treatment in patients with severe uveitis associated with juvenile idiopathic arthritis (n = 21 patients).

Pt.	Uveitis Activity after ABA	Months until Uveitis Inactivity	Uveitis Recurrences after Achieving Inactivity	Arthritis Activity* prior to ABA	Arthritis Activity* at End of Followup	Followup, mos
1	Inactive	6	Yes	Yes	Inactive	12
2	Inactive	6	Yes	Yes	Active	12
3	Inactive	6	Yes	Yes	Active	12
4	Active	—	Ongoing	Yes	Active	6*
5	Active	—	Ongoing	Yes	Inactive	12
6	Inactive	6	Yes	Yes	Active	9**
7	Inactive	9	No	Yes	Inactive	12
8	Active	—	Ongoing	Yes	Active	6**
9	Inactive	3	Yes	Yes	Active	6**
10	Inactive	6	Yes	Yes	Active	12
11	Inactive	9	Yes	Yes	Inactive	12
12	Inactive	9	No	Yes	Active	12
13	Active	—	Ongoing	Yes	Active	6**
14	Inactive	6	No	Yes	Inactive	12
15	Inactive	3	Yes	Yes	Active	9**
16	Active	—	Ongoing	No	Inactive	6**
17	Active	—	Ongoing	No	Inactive	12**
18	Active	—	Ongoing	Yes	Inactive	6**
19	Active	—	Ongoing	Yes	Inactive	3
20	Active	—	Ongoing	Yes	ND	12
21	Active	—	Ongoing	ND	ND	12

Uveitis activity determined according to Standardization of Uveitis Nomenclature Working Group criteria[23]. * Arthritis activity determined by American College of Rheumatology Pediatric30/50/70 criteria[25]. ** Premature study end because of treatment failure. ND: no data.

retrospective approach. The achievement of persistent inactivity may be biased by changes in concomitant treatment after inactivity has been observed, and is another limitation to consider when interpreting our results. All centers adhered to the MIWGUC group and used a standardized system for documenting uveitis activity and secondary complications, allowing good comparability of clinical data. Our study patients had a very severe course of uveitis prior to ABA, with a high rate of secondary complications at baseline. Progression of preexisting cataract (n = 5 patients) might be due to uveitis activity and the use of corticosteroids (in the 5 patients with cataract progression, corticosteroids were used at a mean systemic dosage of 6.2 mg/day and at a mean topical dosage of 4.5 drops/day).

A previous longterm ABA trial showed that some patients require treatment for > 3–4 months to achieve a response and that the level of response may even increase with a longer duration of therapy[18]. Indeed, except for 1 patient, the others in our study had been treated with ABA for at least 6 months. We cannot exclude that a higher response rate might have been observed with a longer duration of ABA treatment. Further, patients with JIA who have not taken TNF-α inhibitors probably respond better to ABA, at least regarding the achievement of arthritis inactivity[18,32]. We treated a selection of patients with JIA with a longstanding history of uveitis in whom disease was refractory to prior TNF-α inhibitor treatment, which may explain the low response rate.

In our study, arthritis inactivity was achieved by the end of followup in 7 of 18 patients in whom activity was present at baseline (39.9%). Therefore, our results are in line with published data regarding the efficacy of ABA for arthritis in patients with JIA[18].

A sustained response to ABA was uncommon and was seen in < 15% of patients with severe and refractory uveitis. Controlled trials are required to determine the role of ABA in the treatment of uveitis associated with JIA.

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