Evidence for Tocilizumab as a Treatment Option in Refractory Uveitis Associated with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To report on experience using the anti-interleukin 6 receptor antibody tocilizumab (TCZ) to treat severe and therapy-refractory uveitis associated with juvenile idiopathic arthritis (JIA).

Methods. Retrospective data were gathered from patients with JIA receiving TCZ treatment for uveitis. JIA and related uveitis data (disease onset, activity, structural complications, and topical and systemic antiinflammatory treatment) were evaluated at the start of TCZ (baseline) and every 3 months during TCZ therapy.

Results. A total of 17 patients (14 women) with active uveitis were included (mean age 15.3 ± 6.9 yrs, mean followup time 8.5 mos). In all patients, uveitis had been refractory to previous topical and systemic corticosteroids, methotrexate (MTX), and other synthetic and biological disease-modifying antirheumatic drugs, including ≥ 1 tumor necrosis factor-α (TNF-α) inhibitor. Uveitis inactivity was achieved in 10 patients after a mean of 5.7 months of TCZ treatment (in 3 of them, it recurred during followup) and persisted in the remaining 7 patients. By using TCZ, systemic corticosteroids or immunosuppressives could be spared in 7 patients. Macular edema was present in 5 patients at baseline and improved in all of them under TCZ treatment. Arthritis was active in 11 patients at the initial and in 6 at the final followup visit.

Conclusion. TCZ appears to represent a therapeutic option for severe JIA-associated uveitis that has been refractory to MTX and TNF-α inhibitors in selected patients. The present data indicate that inflammatory macular edema responds well to TCZ in patients with JIA-associated uveitis. (First Release September 15 2016; J Rheumatol 2016;43:2183–8; doi:10.3899/jrheum.160231)

Key Indexing Terms:
BIOLOGICS JUVENILE IDIOPATHIC ARTHRITIS TOCILIZUMAB
UVEITIS CYSTOID MACULAR EDEMA

Juvenile idiopathic arthritis (JIA) consists of a heterogeneous group of chronic rheumatoid diseases with onset before 16 years of age. Uveitis is observed in about 9%–13% of cases[1,2,3,4,5]. Ocular inflammation may lead to vision-threatening and potentially irreversible ocular complications[5,6]. In a step-by-step approach, topical and/or systemic corticosteroids and synthetic and/or biological disease-modifying antirheumatic drugs (DMARD) are often needed to achieve inactivity of articular and ocular inflammation[7,8]. If ocular inactivity is not achieved with synthetic DMARD (mainly methotrexate), tumor necrosis factor-α (TNF-α) inhibitors are considered as treatment options, with a strong body of

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evidence supporting their efficacy and safety[9,10,11]. Adalimumab is currently the preferred TNF-α inhibitor to treat JIA-associated uveitis; a pooled analysis of results from previous observational studies showed about 87% of children responding (compared with 72% for infliximab and 33% for etanercept)[12]. However, for severe uveitis that is refractory to TNF-α inhibitors or if anti-TNF-α inhibitor antibodies develop, further treatment options are required.

Interleukin 6 (IL-6) is a proinflammatory cytokine that is involved in the proliferation and differentiation of several types of immune cells, including the differentiation of B cells into antibody-producing plasma cells, the development of T helper (Th) 17 cells, and also in the inhibition of the differentiation of regulatory T cells[13,14]. Elevated IL-6 levels have also been found in JIA and correlated with the extent and severity of joint involvement[15]. No such data have been provided for JIA-associated uveitis. The efficacy of IL-6 inhibition in ocular inflammation has been shown in animal models, where IL-6–deficient mice have an impaired Th17 response and lower ocular inflammation scores in experimental autoimmune uveitis[16]. Considering that increased IL-6 levels have not only been found in systemic autoimmune diseases, but also in patients with uveitis[17], the use of a biological that specifically targets the IL-6 receptor (IL-6R) appears to be a promising treatment approach.

Tocilizumab (TCZ) is a fully humanized anti-IL-6R antibody. Its efficacy has been shown for the treatment of different autoimmune diseases, including rheumatoid arthritis (RA), JIA, Castleman disease, vasculitis, encephalomyelitis, and also uveitis[16,18,19,20,21,22,23,24,25]. TCZ's efficacy in noninfectious uveitis is currently limited to small case series and reports[26,27,28].

In our cohort study, which was conducted at tertiary uveitis referral centers, we reported our experience with TCZ for the treatment of refractory uveitis in patients with JIA using a standardized protocol with outcome measures provided by the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC)[29].

MATERIALS AND METHODS

The efficacy of TCZ treatment in patients with JIA and associated active uveitis [anterior chamber (AC) cell score ≥ 1+] was evaluated in a multicenter, retrospective analysis. JIA was diagnosed according to the International League of Associations for Rheumatology classification[30], and the Standardization of Uveitis Nomenclature (SUN) classification[31] was used to diagnose and grade the associated uveitis and its activity. An AC cell grade of < 0.5+ was judged as inactive uveitis (SUN). Visual acuity [in logarithm of the minimum angle of resolution (logMAR)] and any uveitis-related intraocular complications were documented. All members of the MIWGUC group were invited to provide their data about the use of TCZ in their patients with JIA-associated uveitis. All patients were seen by pediatric rheumatologists. A complete physical examination and laboratory testing were performed, including antinuclear antibodies, rheumatoid factor, and major histocompatibility antigen HLA-B27. Infections and malignancies were excluded according to current diagnostic recommendations. Any contraindication to the use of TCZ excluded treatment. Visits before TCZ treatment start (baseline) and at 3, 6, 9, and 12 months thereafter were evaluated. Uveitis activity and ocular complications were documented by an ophthalmologist with a standardized case report form[29]. Results were evaluated from slit-lamp examination, applanation tonometry, ophthalmoscopy, and other ancillary tests including optical coherence tomography (OCT) and fluorescein angiography. In unilateral uveitis, only the diseased eyes were analyzed. In bilateral uveitis, the eye with the higher anterior chamber cell grade was selected, and topical corticosteroid dosages of these eyes were considered for the analysis.

Inactive uveitis was the primary outcome measure. Secondary outcomes included sparing of corticosteroid and/or immunosuppressive treatment. Here, the definition by Saurenmann, *et al* was applied, i.e., good response means ≥ 50% decrease in both corticosteroid use and immunosuppressive agent; moderate response means ≥ 50% decrease in either corticosteroid or immunosuppressive agent; and poor response means < 50% decrease in both corticosteroid and immunosuppressive agent[32]. Additionally, topical corticosteroid dosage was analyzed at baseline and during followup. All treatment decisions were made at the discretion of the treating physician. Further, arthritis activity (e.g., number of active joints) was documented at baseline and at 3-month intervals during TCZ treatment[33].

The study design conforms to the standards currently applied in the countries of the participating clinics. Written informed consent had been obtained from the patients and their parents for the off-label use of TCZ. No institutional review board approval or informed consent was required for chart review studies based on fully anonymized data as provided to the study directly by the treating physician. The local ethics committee (Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität, #2016-313-f-S) had confirmed that the study conformed to the standards applied in the countries of origin.

RESULTS

Patients and baseline data. A total of 17 patients (mean age 15.3 ± 6.9 yrs, range 7–30 yrs; Table 1) with JIA-associated (mean age at JIA onset 3.1 ± 2.1 yrs, range 3 mos to 8 yrs) chronic anterior uveitis (mean age at uveitis onset 4.3 ± 2.6 yrs, range 1–10 yrs) were treated with intravenous TCZ (8 mg/kg body weight) at 4-week intervals[34]. The median time between uveitis onset and starting TCZ was 10 years (minimum 3.9, maximum 27). At baseline, bilateral uveitis activity was found in a total of 13 patients (26 eyes). In all patients, uveitis had been refractory to previous topical and systemic corticosteroid treatment and DMARD, including at least a combination of 1 conventional immunosuppressive drug and 1 TNF-α inhibitor (Table 1). All drugs were used at conventional medication doses. The previous biological DMARD were withdrawn before instituting TCZ. Biological DMARD were not added and concomitant nonbiological DMARD were not increased during the TCZ treatment period. In TCZ nonresponders, TCZ was discontinued and the DMARD treatment was then modulated to manage the disease. Topical corticosteroids were used in 14 patients (82.4%, mean 2.8 drops/day, range 0–5) and systemic corticosteroids were given to 7 patients at baseline (41.2%, mean dosage 3.0 mg/day, range 0–20). A total of 13 patients (76.5%) had documented vision-threatening complications before initiating TCZ treatment (e.g., cataract, n = 10; macular edema, n = 5; glaucoma, n = 4; epiretinal membrane, n = 3; Table 1). At baseline, slit-lamp examination revealed an anterior chamber cell grade of 1+ cells in 10 patients, 2+ in 3 patients, and 3+ in another 4 patients (in bilateral uveitis,

Table 1. Patient characteristics at TCZ start. All patients had severe JIA-associated uveitis refractory to corticosteroids and systemic immunosuppression (n = 17 patients). Values are n (%) unless otherwise specified.

Characteristics	Values
Age, yrs, mean ± SD*	15.3 ± 6.9
Male:female, n	3:14
Age at JIA diagnosis, yrs, mean ± SD	3.1 ± 2.1
Age at uveitis diagnosis, yrs, mean ± SD	4.3 ± 2.6
ILAR classification	
Persistent oligoarthritis	5 (29.4)
Extended oligoarthritis	4 (23.5)
Polyarthritis	7 (41.2)
Undifferentiated	1 (5.9)
ANA+	16 (94.1)
HLA-B27+	2 (11.8)
RF+	0 (0)
Uveitis type: anterior, no. patients (%)	17 (100)
Secondary ocular complications	
Patients with complications, no. patients (%)	13 (76.5)
Cataract	10 (58.8)
Band keratopathy	9 (52.9)
Synechia	7 (41.2)
Ocular hypertension	4 (23.5)
Glaucoma	4 (23.5)
Macular edema	5 (29.4)
Epiretinal membrane	3 (17.6)
Optic disc edema	4 (23.5)
Ocular hypotony or phthisis	2 (11.8)
Retinal detachment	1 (5.9)
Amblyopia	1 (5.9)
Active arthritis	11 (64.7)
Treatment history before baseline, patients	
Methotrexate	16 (94.1)
Cyclosporine	5 (29.4)
Mycophenolate mofetil	5 (29.4)
Leflunomide	1 (5.9)
Azathioprine	7 (41.2)
Infliximab	13 (76.5)
Adalimumab	7 (41.2)
Etanercept	2 (11.8)
Rituximab	1 (5.9)
Golimumab	7 (41.2)
Treatment at baseline, patients	
Topical corticosteroids	14 (82.4)
Systemic corticosteroids	7 (41.2)
Methotrexate	10 (58.8)
Cyclosporine	2 (11.8)
Leflunomide	4 (23.5)
Infliximab	2 (11.8)
Adalimumab	4 (23.5)
Abatacept	3 (17.6)

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

the eye with the higher anterior chamber cell grade was selected).

Achievement of uveitis inactivity with TCZ. A total of 17 patients were exposed to TCZ for a total of 144 months, which corresponded to 12 patient-years of TCZ. Following TCZ treatment (mean followup time 8.5 mos, range 3–12 months), uveitis inactivity was achieved in 4 out of 17 patients (23.5%) at 3 months, in 5 out of 14 patients (35.7%) at 6 months, in 5 out of 9 patients (55.6%) at 9 months, and in 4 out of 8 patients (50.0%) at 12 months. In 5 patients, TCZ was discontinued (2 patients after 3 mos and 3 patients after 6 mos) because of the lack of efficacy. Whereas uveitis inactivity was observed in 10 patients for at least 1 followup visit (≥ 3 mos) after initiating TCZ, uveitis had recurred in 3 of them during subsequent visits (Table 2). In contrast, 7 patients did not respond to TCZ treatment and showed persisting uveitis activity during the entire followup. In these 7 patients, ocular activity had improved in 4 patients and worsened in 1, whereas in 2 patients no relevant change was observed (< 2 steps) according to the SUN definition.

Ocular complications. New ocular complications were observed in 4 patients during the TCZ treatment (cataract, n = 2; band keratopathy, n = 1; posterior synechia, n = 1; ocular hypertension, n = 1; glaucoma, n = 1; Table 2). Cystoid macular edema was present in 5 patients at baseline, and resolved in all of them following TCZ treatment, as observed by fundoscopy, and OCT or fluorescein angiography (Table 2).

Visual acuity. Best-corrected visual acuity (BCVA) did not change significantly from a mean of 0.59 ± 0.72 logMAR at baseline to 0.60 ± 0.69 logMAR at the end of followup in the study (paired Student t test, p = 0.84). In 2 patients (11.8%), visual acuity improved from baseline to the end of followup. BCVA ≤ 20/50 (≥ logMAR 0.4) was found in 57.1% at baseline and also in 57.1% at the end of followup, whereas BCVA ≤ 20/200 (≥ logMAR 1.0) was documented in 21.4% at baseline and in 14.3% at the end of followup (Fisher's exact test, p > 0.05 each). Further, in the 5 eyes with cystoid

Table 2. Effect of tocilizumab on intraocular inflammation in treatment-refractory chronic uveitis in juvenile idiopathic arthritis (n = 17). Sparing of systemic corticosteroids and/or immunosuppressives was defined according to Saurenmann, *et al*[32]. Values are n (%) unless otherwise specified.

Variables	Values
Active uveitis at baseline, no. patients	17
Ocular quiescence at any time during followup	10 (58.8)
Mean duration until quiescence, mos	5.7
Recurrences after achieving quiescence	3 (30)
Sparing of systemic corticosteroids and/or immunosuppressives	
Good	2 (11.8)
Moderate	11 (64.7)
Poor	4 (23.5)
Patients with new complications	4 (23.5)
Cataract	2 (11.8)
Band keratopathy	1 (5.9)
Posterior synechia	1 (5.9)
Ocular hypertension	1 (5.9)
Glaucoma	1 (5.9)
Improvement of preexisting macular edema	5 (100)
Inactivity of arthritis	6 (54.5)

macular edema, mean BCVA did not change significantly between baseline and the end of followup (1.16 ± 0.92 vs. 1.19 ± 0.89 logMAR, paired Student t test, p = 0.37).

Sparing of corticosteroids and conventional immunosuppressive drugs. Any other biological medication used at baseline was withdrawn before instituting TCZ. Sparing of systemic corticosteroids or immunosuppressive treatment was reported in 13 out of the 17 studied patients (good sparing: 2 patients, moderate sparing: 11 patients; Table 2). However, in 6 out of the 13 patients in whom a reduction or stop of corticosteroids or immunosuppressive drugs was attempted, uveitis recurred (n = 3) or worsened (n = 3). Therefore, systemic corticosteroids or immunosuppressives could be spared in 7 patients. Upon TCZ treatment, the topical corticosteroids could be tapered down from baseline (mean 2.8 drops/day) to 3-month visit (mean 2.3 drops/day), 6-month visit (mean 1.8 drops/day), 9-month visit (mean 1.5 drops/day), and 12-month visit (mean 1.4 drops/day).

Arthritis. A total of 11 patients presented with active arthritis at baseline. In 6 of the patients (54.5%), arthritis inactivity was achieved with TCZ by the end of followup.

DISCUSSION

TCZ has been approved for the treatment of refractory RA in many countries, and also for systemic and polyarticular JIA[24,25,35,36].

Elevated IL-6 levels have been found in ocular fluids of patients and animals with uveitis[37,38]. Further, IL-6 blockade resulted in suppression of Th1 and Th17 cell induction and their downregulation[39]. In animal models for uveitis, IL-6 inhibition reduced the risk of disease development[16].

So far, only limited data are available on the use of IL-6–blocking agents in uveitis in humans. Muselier, *et al* reported on ocular quiescence in 2 and resolution of cystoid macular edema in 1 of the 2 patients studied (birdshot uveitis, n = 1; idiopathic panuveitis, n = 1)[40]. A positive treatment effect on uveitis has also been described in case reports of patients with Behçet disease[41] and Cogan syndrome[42]. Achievement of ocular quiescence has also been reported in 2 out of 3 patients with TCZ treatment for refractory JIA-associated uveitis[26]. Others have described favorable TCZ effects on refractory uveitis (total of 5 patients; JIA-associated uveitis, n = 1) and associated secondary cystoid macular edema, with resolution of cystoid macular edema in all of their patients[27,43]. In addition, the longterm efficacy and safety of TCZ for refractory uveitis-related macular edema has been reported in 11 eyes from 7 patients (JIA-associated uveitis, n = 3)[28]. Currently, a randomized interventional study is being performed of the safety, tolerability, and bioactivity of TCZ for adult patients with non-infectious uveitis (STOP-UVEITIS Study, clinicaltrials.gov identifier NCT01717170), and open-label trials are in progress for the assessment of TCZ efficacy and safety in the management of treatment refractory JIA-associated uveitis (clinicaltrials.gov identifier NCT01603355 and APTITUDE trial, ISRCTN identifier NCT01603355).

In our retrospective study on TCZ, inactive uveitis was achieved in 7 out of 17 patients. Considering that all of these patients had a severe course of persisting uveitis being refractory to at least 1 synthetic and 1 or more biological DMARD, TCZ holds promise as a rescue drug. In agreement with previous observations, it might be speculated that early use of TCZ in patients with refractory uveitis may reduce disease[27,43].

Our data also confirm the findings of previous publications on the positive effect of TCZ on uveitic macular edema[27,28,43,44]. Indeed, high levels of IL-6 in inflamed tissue lead to an excess of vascular endothelial growth factor, and therefore to an increased vascular permeability[45]. This observation might explain the favorable effect of therapeutic IL-6 blockage on macular edema.

Our study reports a multicenter experience of tertiary uveitis centers adhering to the proposed outcome measures provided by the multinational interdisciplinary working group for uveitis in childhood (MIWGUC). All participating centers used a standardized documentation system for reporting uveitis activity and secondary complications, which strengthens the study[29]. Further analysis is required for supporting the benefit of TCZ treatment in JIA-associated uveitis. Our current study consists of the observations made in a highly selected group of patients with severe and refractory uveitis not responding to other immunosuppressives and biological treatments and who showed a high frequency of secondary complications already at study inclusion. The response rate to TCZ might be considerably higher if patients without severe and refractory uveitis were included. The mean visual acuity did not increase despite obvious improvement in macular edema, which was probably related to irreversible structural damage caused by chronic macular edema. No TNF-α inhibitor-naive patients were included in our study because the use of TCZ was only considered after failure of 1 TNF-α inhibitor. However, treating severe JIA-associated uveitis with TCZ as the first biological DMARD might be an interesting approach for the future, especially for patients with secondary macular edema. As to the rarity of disease, our study included only a small sample. The followup time is short and thus information is lacking on the longterm effect of TCZ on the course of uveitis and its probable harmful complications. The absence of a control group in our study is a further limitation. Although the patients were followed up in an interdisciplinary fashion and the undesirable side effects enumerated, no severe adverse events requiring discontinuation of TCZ were documented for the study group.

TCZ may be a treatment option in patients with severe and refractory JIA-associated uveitis. Further prospective studies with larger patient numbers and longer followup are needed to evaluate the efficacy of this drug in JIA-associated uveitis.

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