Is Tocilizumab an Effective Option for Treatment of Refractory Uveitis Associated with Juvenile Idiopathic Arthritis?

To the Editor:

Anti-interleukin 6 receptor (anti-IL-6R) antibodies have been effective in experimental models of autoimmune arthritis, encephalomyelitis, and also uveitis[1,2]. Tocilizumab (TCZ; RoActemra®, Hoffmann-La Roche, Basel, Switzerland), a fully humanized anti-IL-6R antibody, has been approved for the treatment of rheumatoid arthritis. Efficacy has also been shown for systemic-onset juvenile idiopathic arthritis (JIA)[3] and vasculitis[4]. To date, however, no reports have appeared concerning its efficacy in JIA-associated uveitis.

In about one-third of JIA patients with uveitis, eye inflammation runs a severe course and vision-threatening complications develop, and immunosuppressive treatment is required[5]. Because some patients do not respond properly to the widely used disease-modifying antirheumatic drugs (DMARD), including tumor necrosis factor-α (TNF-α) inhibitors, there is a significant need for alternative treatment options. We describe our initial experience with TCZ for treatment of JIA-associated uveitis at a tertiary uveitis and pediatric rheumatology referral center.

Three adult patients (mean age 18.3 yrs) with JIA-associated chronic anterior uveitis (mean duration 8 yrs, range 4–13) with insidious onset of flare and the presence of vision-threatening complications (Table 1) were treated with intravenous TCZ 8 mg/kg body weight at 4-weekly intervals[6]. Written informed consent was obtained from patients for off-label use of TCZ. In all patients the disease had been refractory to high dosages of topical corticosteroids and previous systemic corticosteroid treatment and DMARD, including at least 1 TNF-α inhibitor; all were used at conventional medication doses (Table 2). Within the followup period under TCZ treatment (mean followup 9 mo, range 6–12), inactivity of the uveitis (< 0.5 anterior chamber cells[7]) was achieved in Patients 2 and 3 for all eyes with previous activity (Table 2). Uveitis continued in the other patient, requiring a further increase in the dosage of topical steroids. Mean best-corrected visual acuity improved by 1 line in Patient 2 and by 4 lines in Patient 3 during the subsequent followup period under TCZ. No patient developed additional eye complications during the intermediate-term of TCZ treatment; no adverse events were observed related to TCZ. In all 3 patients, arthritis that had been active before TCZ treatment improved during followup[8]. Adalimumab and abatacept were withdrawn before initiating the TCZ treatment. Otherwise, steroids or immunosuppression treatment was not spared in any significant way.

IL-6 is a pleiotropic, proinflammatory cytokine mainly produced by T cells and monocytes/macrophages, inducing proliferation and differentiation of T cells as well as the terminal differentiation of B cells[9]. IL-6 is a key agent generating Th17 cells while inhibiting regulatory T cell generation[10]. Increased serum levels of IL-6 have been found in several systemic autoimmune diseases and also in diverse uveitis entities[11]. In an animal model, IL-6-deficient mice showed an impaired Th17 response and a lower inflammation score in experimental autoimmune uveitis[1]. In our case series, TCZ treatment achieved suppression of uveitis in 2 of 3 patients in whom disease had been refractory to previous DMARD, including at least 1 TNF-α inhibitor. In our cases, all medication was used at conventional doses. Whether further dose escalation (e.g., adalimumab at once-weekly intervals) would have been more effective is unclear.

TCZ may represent a treatment option for otherwise refractory JIA-associated uveitis. Further prospective studies are needed to evaluate the efficacy of this new drug in comparison to other biologicals.

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Table 1. Adult patients with juvenile idiopathic arthritis (JIA)-associated uveitis were treated with tocilizumab when refractory to topical corticosteroids and systemic immunosuppression.

Patient	Age*/sex	ILAR Classification	HLA-B27/ANA/RF	JIA Diagnosis at Age, yrs	Uveitis Diagnosis at Age, yrs	Uveitis Type**	Involved Eyes	Complications
1	18 M	Oligoarthritis, ext.	Neg/pos/neg	4	5	Anterior	Both	Cataract, synechiae, glaucoma
2	18 F	Polyarthritis	Neg/pos/neg	11	11	Anterior	Both	Cataract, synechiae
3	19 F	Polyarthritis	Neg/pos/neg	3	15	Anterior	Left	Cataract, synechiae, macular edema, glaucoma

* At time of starting tocilizumab therapy. ** Standardization of Uveitis Nomenclature classification[7]. ANA: antinuclear antigen; RF: rheumatoid factor; ILAR: International League of Associations for Rheumatology.

Table 2. Response to treatment in adult patients with juvenile idiopathic arthritis (JIA)-associated uveitis treated with tocilizumab (TCZ) when refractory to topical corticosteroids and systemic immunosuppression. Dosages were within generally used ranges, e.g., for methotrexate (MTX) 15 mg/m^2, azathioprine (AZA) 2 mg/kg body weight, adalimumab (ADA) 40 mg biweekly, etanercept (ETA) 0.8 mg/kg body weight weekly, abatacept (ABA) 10 mg/kg body weight monthly.

Patient	Treatment Prior to TCZ	Uveitis Activity† After TCZ	Months Until Inactive	Sparing of Other Immunosuppressives After TCZ**	Steroid Eye Drops Before/ After TCZ (n = times daily)	Uveitis Recurrence After TCZ (followup, mo)	Arthritis Activity†† Prior to TCZ	Arthritis Activity†† After TCZ
1	PRED*, MTX*, ETA, ADA, ABA*	Active	—	No	5/7	Ongoing; 8	Yes	Improved
2	PRED*, MTX*, ETA, ADA*	Inactive	1	No	4/2	No; 12	Yes	Improved
3	PRED*, AZA*, MTX, ETA, ADA*	Inactive	1	No	3/1	No; 6	Yes	Improved

† Uveitis activity determined according to SUN criteria[7]. †† Arthritis activity determined by PedACR30/50/70 criteria[8]. Pred: prednisolone; SUN: Standardization of Uveitis Nomenclature.

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