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 uveitis1,2. 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 vasculitis4. 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 immuno-suppressive treatment is required5. 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 intervals6. 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 cells7) 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 followup8. Adalimumab and abatacept were withdrawn before initiating the TCZ treatment. Otherwise, steroids or immuno-suppression 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 cells9. IL-6 is a key agent generating Th17 cells while inhibiting regulatory T cell generation10. Increased serum levels of IL-6 have been found in several systemic autoimmune diseases and also in diverse uveitis entities11. In an animal model, IL-6-deficient mice showed an impaired Th17 response and a lower inflammation score in experimental autoimmune uveitis11. 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 immuno-suppression.

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

* At time of starting tocilizumab therapy. ** Standardization of Uveitis Nomenclature classification7. 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 immuno-suppression. Dosages were within generally used ranges, e.g., for methotrexate (MTX) 15 mg/m², 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.

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

† Uveitis activity determined according to SUN criteria7. †† Arthritis activity determined by PedACR30/50/70 criteria8. Pred: prednisolone; SUN: Standardization of Uveitis Nomenclature.
REFERENCES


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