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 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 immunosuppressive treatment (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 followup5. 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 cells8. IL-6 is a key agent generating Th17 cells while inhibiting regulatory T cell generation9. Increased serum levels of IL-6 have been found in several systemic autoimmune diseases and also in diverse uveitis entities10. 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 immunosuppression.

<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, macular edema, glaucoma</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 immunosuppression. 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† Before TCZ</th>
<th>Months Until Inactive</th>
<th>Sparing of Other Immunosuppressives After TCZ**</th>
<th>Steroid Eye Drops Before/After TCZ</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.
Reference:


