Subcutaneous Tocilizumab May Be Less Effective than Intravenous Tocilizumab in the Treatment of Juvenile Idiopathic Arthritis–associated Uveitis

To the Editor:

Tocilizumab (TCZ) is a fully humanized, monoclonal, anti-interleukin-6R antibody shown by clinical trials to be a safe and effective treatment for patients with rheumatoid arthritis (RA) or systemic-onset or polyarticular juvenile idiopathic arthritis (JIA).\(^1\)\(^2\)\(^3\) TCZ seems to be an effective agent to treat JIA-associated uveitis, and several case reports have described a good efficacy profile in patients with refractory JIA-associated uveitis.\(^4\)\(^5\) Interim outcomes of the STOP-Uveitis clinical trial were presented by Nguyen, \textit{et al}, showing that TCZ has a good safety and efficacy profile in noninfectious uveitis.\(^6\) For several years, TCZ has also been available in a subcutaneous (SC) formulation, and switching from intravenous (IV) to SC administration may provide greater flexibility and quality of life to patients who follow TCZ treatment. Several clinical trials have shown the safety and efficacy profile of TCZ-SC to be comparable to that of TCZ-IV.\(^7\) Switching from TCZ-IV to SC was shown to be generally successful and sustained over time.\(^8\) A recent study analyzed clinical data from 58 patients with RA who switched from TCZ-IV to TCZ-SC, suggesting that the switch in real-world settings is effective and can be considered for convenience.\(^9\) In that study, only the disease activity of high-body-weight patients showed a tendency to worsen after switching. At present, TCZ-SC is being tested in patients with JIA in 2 ongoing phase Ib clinical trials (NCT01904292 and NCT01904279, www.clinicaltrials.gov) and in 1 phase II clinical trial, currently recruiting in the UK, investigating the efficacy of TCZ-SC in JIA-associated uveitis that is refractory to anti-tumor necrosis factor (www.isrctn.com/ISRCTN95363507). To our knowledge, there are no reports on the results of switching from TCZ-IV to TCZ-SC in patients with JIA.

We describe 4 patients with long-term JIA and associated chronic anterior uveitis (CAU) who had good and sustained clinical response with TCZ-IV and who experienced early flares after switching to TCZ-SC. Our study received ethics approval from the Clinical Research Ethics Committee of Vall d’Hebron University Hospital and Research Institute.

Table 1 describes the clinical characteristics of these patients at baseline. Three of the patients (patients 1, 3, 4) experienced bilateral CAU and patient 2, unilateral CAU. In these patients, TCZ was switched from IV to SC mainly for patient convenience. All patients were in clinical remission on TCZ-IV treatment, had a stable clinical situation, and had been receiving TCZ-IV for an average of 3.4 years (range, 2.5–4.8 years) before switching. Three of the patients (patients 1, 2, 3) received a TCZ-IV dosage of 8 mg/kg/4 weeks, whereas patient 4 received 8 mg/kg/2 weeks of TCZ-IV. Three of these patients (patients 1, 2, 3) did not experience disease flare during TCZ-IV treatment, and only 1 (patient 4) had a mild uveitis flare that was promptly controlled with corticosteroid eyedrops. Patients 1 and 3 had experienced a severe CAU course in the past, presenting chronic severe ocular complications and severe visual impairment as a consequence of the disease course. In one of these patients (patient 3), the eye examination was hindered by synchiae, media opacity, and calcifications, but the ophthalmologist reported improvement during TCZ-IV treatment. In addition, 2 of them (patients 1, 2) required several surgical procedures for joint complications before starting TCZ-IV treatment.

Three of our 4 patients (patients 1, 3, 4) started TCZ-SC at doses of 162 mg/week. One of our patients (patient 2) weighed 32 kg and started TCZ-SC adjusted to body surface area at 108 mg/week, as usual in clinical practice. All patients experienced disease relapse a few months after TCZ-SC was started (Table 1)\(^10\)\(^11\) and had no changes in concomitant medications while receiving TCZ-IV or TCZ-SC. In all cases, TCZ-SC was discontinued owing to a lack of efficacy: 3 of them (patients 2, 3, 4) for ocular flare and 2 (patients 1, 3) for joint flare. One of the patients (patient 3) who experienced joint flare also had the most severe ocular condition, and simultaneously with the joint symptoms, experienced vitreous hemorrhage, an eye complication that could be interpreted as related to ocular inflammation. The patients did not experience any other adverse event while receiving TCZ-SC treatment.

All 4 patients with JIA who switched to TCZ-SC while in remission with TCZ-IV treatment experienced a flare (ocular and/or joint) in the first few months after TCZ-SC initiation. Our observation suggests that the results previously observed in patients with RA cannot be extrapolated to patients with JIA. The pathogenesis of ocular involvement in JIA is not yet fully understood.

### Table 1. Demographics and main clinical characteristics of patients with juvenile idiopathic arthritis (JIA).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>ILAR Classification</th>
<th>HLA-B27</th>
<th>Age at JIA Diagnosis, yrs</th>
<th>Age at Uveitis Onset, yrs</th>
<th>Duration of Uveitis, yrs</th>
<th>Secondary Ocular Complications and Procedures</th>
<th>Previous DMARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/F</td>
<td>Undiffer.</td>
<td>Pos/Pos/Neg</td>
<td>8.5</td>
<td>5.2</td>
<td>27.9</td>
<td>Cataract; glaucoma; synchiae; left macular edema; right hypotonic maculopathy. Surgery: bilateral cataract extraction, vitreectomy and lensectomy; left Ahmed valve implantation</td>
<td>MTX, LFN, MMF, gold salts, CSA, ETN, ADA, RTX, IFX, ABA</td>
</tr>
<tr>
<td>2</td>
<td>25/F</td>
<td>Psoriatic</td>
<td>Pos/Neg/Pos</td>
<td>1.5</td>
<td>14.8</td>
<td>11.2</td>
<td>No</td>
<td>MTX, LFN, MMF, gold salts, CSA, AZA, HCQ, IVIG, ETN, ADA, CZP</td>
</tr>
<tr>
<td>3</td>
<td>18/F</td>
<td>Oligoarticular extended</td>
<td>Pos/Neg/Neg</td>
<td>2</td>
<td>3.2</td>
<td>14.7</td>
<td>Cataract; glaucoma; band keratopathy; synchiae; intracocular calcifications; chronic hyphema; multiple sub-Tenon triamcinolone injection. Surgery: bilateral cataract extraction, left retinal detachment repair</td>
<td>MTX, LFN, MMF, CSA, TAC, HCQ, IVIG, ETN, ADA, IFX, ABA, ANK</td>
</tr>
<tr>
<td>4</td>
<td>14/F</td>
<td>Psoriatic</td>
<td>Pos/Neg/Neg</td>
<td>1.9</td>
<td>4.7</td>
<td>9.3</td>
<td>No</td>
<td>MTX, LFN, ADA</td>
</tr>
</tbody>
</table>

understood. Therefore, we could speculate that ocular disease is more readily controlled with TCZ-IV than with TCZ-SC because of high blood levels achieved during the first few days after IV infusion, which would help control ocular inflammation. Further studies with patients with JIA are needed to determine the efficacy of TCZ-SC.

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