Tumor Necrosis Factor-α Blocker in Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Second-line Agents: Results of a Multinational Survey

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ABSTRACT. Objective. Uveitis occurs in 10%–15% of patients with juvenile idiopathic arthritis (JIA). If topical treatment fails, second-line agents are used to control the disease. However, some patients need the addition of tumor necrosis factor-α (TNF-α) antagonist (anti-TNF). We organized a cross-sectional cohort to investigate use and efficacy of anti-TNF treatment in patients with JIA-associated uveitis.

Methods. The international pediatric rheumatology community was queried about the use and efficacy of anti-TNF in treatment of JIA-associated uveitis using an E-mail survey.

Results. Of the 33 responding centers following 884 patients with uveitis, only 15 centers, following 404 patients, were using anti-TNF for this indication. A total of 47 patients with JIA-related uveitis treated with anti-TNF because of an insufficient response to previous therapy were reported. The mean age of the patients was 12.5 years. The mean duration from onset of uveitis to start of anti-TNF treatment was 45.1 months. Three different anti-TNF agents were used: etanercept in 34 cases, infliximab in 25 cases, and adalimumab in 3 cases. In 12 of the 34 patients etanercept was inefficacious and patients were switched to infliximab. The final response was rated according to a composite index as 53%/12%/32%, and according to physician rating as 47%/12%/38% representing good, moderate, and poor, respectively, in the etanercept group; and 70%/30%/0% and 68%/24%/0% in the infliximab group. All 3 patients taking adalimumab were responders. Infliximab was statistically significantly more efficacious for the treatment of JIA-associated uveitis than etanercept (chi-square p = 0.004).

Conclusion. Anti-TNF seems to be an effective treatment for refractory JIA-associated uveitis. In this cohort infliximab was more efficacious than etanercept. (First Release Mar 1 2007; J Rheumatol 2007;34:1146–50)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
TUMOR NECROSIS FACTOR-Α ANTAGONIST
MULTINATIONAL SURVEY
UVEITIS
TREATMENT

Uveitis occurs in around 10%–15% of patients with juvenile idiopathic arthritis (JIA), and is still one of the most frequent reasons for acquired blindness in the western world. Topical eyelrops are the first line of therapy, but only around 40% of patients respond to such treatment. Nonresponders require a second-line agent to prevent the eye damage. A variety of immunomodulatory agents are used to control active uveitis associated to JIA, but methotrexate remains the most commonly used drug. A smaller percentage of patients will not respond to a second-line agent, and need the addition of a tumor necrosis factor-α inhibitor (anti-TNF-α) to control the disease.

To date, only case reports and a small controlled study have been published on the effectiveness of anti-TNF in treatment of JIA-associated uveitis. In a recently presented abstract, superiority of infliximab over etanercept treatment was described. This was followed by 2 other studies showing similar results.

We conducted a multinational survey to investigate the use and effectiveness of anti-TNF in the treatment of JIA-associated uveitis in a cross-sectional cohort.
RESULTS
Thirty-three centers responded, following 884 patients with JIA-associated uveitis. However, only 15 centers, following 404 (45%) patients with uveitis, were using anti-TNF-α in 47 (5.3%) refractory cases. Thirty-one of the 47 patients were female. The mean age of patients at the time of last followup was 12.5 years. The mean time from diagnosis of JIA to onset of uveitis was 17 months. Uveitis was diagnosed and classified according to the local ophthalmologist of the participating pediatric rheumatologic center as anterior in 36 (77%), intermediate in 4 (9%), and posterior in 2 (4%) patients. Panuveitis occurred in 5 (10%) of the cases. The 47 patients had 81 involved eyes. Before initiation of anti-TNF therapy, 23 patients (49%) had undergone eye surgery and 32 (65%) had visual impairment. In the other 35% of patients the visual acuity was not reported. Forty-two of the 81 eyes (52%) had a diagnosis of cataract or posterior synechiae, and 25 (31%) glaucoma. In all cases the reason for starting anti-TNF-α was an insufficient response to local therapy in combination with at least one second-line agent in sufficient dose and length of therapy as judged by the ophthalmologist and by the pediatric rheumatologist. The mean time between the onset of uveitis and start of the second-line agent was 17 months. The second-line agent was methotrexate in 43 patients (mean dose 17.28 mg/m² body surface area), cyclosporin A in 15, mycophenolate mofetil in 4, azathioprine in 4, cyclophosphamide in 3, sulfasalazine in 2, hydroxychloroquine in 2, and leflunomide in one patient. The mean interval between initiation of sec-

<table>
<thead>
<tr>
<th>Response</th>
<th>Etanercept, n = 34</th>
<th>Infliximab, n = 25</th>
<th>Adalimumab, n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>53/47</td>
<td>70/68</td>
<td>100</td>
</tr>
<tr>
<td>Moderate</td>
<td>15/15</td>
<td>30/32</td>
<td>0</td>
</tr>
<tr>
<td>Poor</td>
<td>32/38</td>
<td>0/0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Application of the anti-TNF agents.
32% and 38%. The rating for infliximab similarly was according to the composite index and physician’s opinion: good in 70% and 68%, moderate in 30% and 32%, poor in 0% and 0%. The response as rated by the physician (Table 1) who completed the survey differed only slightly from the composite index. In 3% of the etanercept treated patients and in 8% of the infliximab treated patients the reporting physicians did not give their personal judgment for the response. Three patients switched from infliximab to adalimumab because of insufficient response: all 3 responded to adalimumab (Figure 1); these patients received primarily infliximab as anti-TNF agent. Overall, it was possible to reduce use of local glucocorticoid eyedrops at time of the last followup below the initial dose by ≤ 50% in 9 (26%) cases, > 50% in 11 (31%) cases, and this therapy was stopped in 15 cases (43%). It was possible to reduce systemic glucocorticoids at the time of last followup from the initial dose by ≤ 50% in 3 cases (9%), > 50% in 8 (23%) cases, and therapy was stopped in 24 cases (69%). Second-line agents at the time of last followup were reduced by ≤ 50% in 7 cases (20%), > 50% in 9 (26%) cases, and were stopped in 7 cases (20%). Most centers did not change the dosage of second-line agents, even if patients responded well to anti-TNF-α treatment (Table 2).

We further investigated prognostic variables regarding response to anti-TNF therapy; the numbers of operations on the eyes in the patients with good response to therapy were as follows: 6 of 14 (43%) in the etanercept group and 9 of 18 (50%) in the infliximab group; 2 of 4 (50%) in the group with moderate response to etanercept and 5 of 8 (62.5%) in the group with moderate response to infliximab; and 6 of 12 (50%) in the group with no response to etanercept. The mean time duration until initiation of the anti-TNF treatment was 51.8 months in patients with good response and 45.8 months in patients with moderate or poor response to the therapy. The numbers of patients with good response according to subtype of uveitis were 30 of 36 with anterior uveitis, one of 2 with intermediate uveitis, 2 of 4 with posterior uveitis, and 3 of 5 with panuveitis.

**DISCUSSION**

In this cross-sectional survey we observed effectiveness of anti-TNF-α treatment in about two-thirds of preselected patients, who did not respond sufficiently to previous second-line agents, despite receiving sufficient dosages. Interestingly, only 15 of the 33 responding centers applied anti-TNF as a treatment option, although the numbers of patients with uveitis were similar in the centers. The anti-TNF treatment was started quite late in the disease course, with a mean duration of 52 months since the onset of uveitis. In the patients with good response, the duration from diagnosis of uveitis to initiation of TNF-α therapy was longer than in the other patients. It could be speculated that the patients with moderate and poor response had an even more severe disease course. The mean duration of 17 months from diagnosis of uveitis to the initiation of a second-line agent is already quite long. We may speculate whether earlier initiation of a second-line agent and earlier initiation of anti-TNF therapy could have avoided the significant damage to the eyes. At the time of initiation of anti-TNF-α treatment more than half of the involved eyes (42/81) already had complications such as cataract or synechiae, and the numbers of operated eyes and eyes with increased intraocular pressure were high. It has been shown that part of these complications evolve in a time-dependent manner during the course of uveitis and reduction of the cumulative local glucocorticoid therapy may be able to reduce the number of cataracts and number of patients with increased intraocular pressure. We did not observe a difference in the response according to previous surgeries performed on an individual eye.

The final response was rated according to the composite index and the personal judgment of the physician who completed the survey (Table 1). The rating did not differ significantly between the 2 evaluation methods. We used these criteria, first suggested by Saurenmann, et al13, because there are no existing international criteria for remission of JIA-associated uveitis17. The responses to the 3 anti-TNF agents that were applied differed, although the adalimumab-treated group in this cohort was too small to make any judgment. Infliximab appeared to be more effective than etanercept. The patients with good response in the infliximab compared to the etanercept group according to the composite index were 70% and 53%, respectively. Comparing the number of nonresponders in the etanercept (38%) and infliximab (0%) groups, there is a statistically significant difference (chi-square p = 0.004). The differences observed in responses to the various anti-TNF agents are in accord with the observations of Saurenmann, et al13 showing a significantly higher good response to infliximab (61.5%) than to etanercept (13.3%). Data from the German etanercept registry18 showed insufficient control of uveitis by etanercept in a prospective cohort of patients treated with etanercept for their JIA-associated arthritis, whereas the arthritis was well controlled. The single published small controlled trial found no difference between etanercept and placebo in the control of JIA-associated uveitis12, but these findings represented a very small number of patients. No placebo-controlled data exist regarding the efficacy of infliximab and adalimumab for the treatment of JIA-associated uveitis.

Our survey of efficacy of the different anti-TNF agents represents results from daily clinical practice, but the study is limited by the cross-sectional design that does not allow for

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**Table 2. Reduction of concomitant medications.**

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Steroid Eyedrops</th>
<th>Systemic Steroids</th>
<th>Second-line Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50%</td>
<td>9</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>11</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Stopped</td>
<td>15</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>


control with another anti-TNF agent or patients without anti-
TNF therapy and the same severity of JIA-associated uveitis. 
Also, because of the survey design, we were not able to col-
lect more detailed ophthalmologic data on response and 
improvement of the uveitis.

It was possible to stop use of systemic steroid treatment in 
51% of the patients and use of local eyedrops in 32% during 
the anti-TNF treatment; this is an important point because 
continuous local and systemic glucocorticoid treatment has 
significant morbidity, and especially in pediatric patients the 
decreased growth velocity represents a severe morbidity of 
continuous glucocorticoid treatment. The majority of physi-
cians contributing to this study did not change the dose of the 
second-line agent. It is known from studies in the treatment of 
JIA that the combination of methotrexate and etanercept or 
adalimumab is more effective to control arthritis than anti-
TNF-α monotherapy.

Only 2 (4%) patients in our cohort had to stop the anti-TNF 
treatment because of adverse events; this number is lower than 
that reported in the phase III study of etanercept or infliximab 
for JIA12. Three (6%) patients in our cohort were able to dis-
continue anti-TNF treatment because of remission of the 
uveitis.

Anti-TNF-α seems to be an effective treatment option for 
JIA-associated uveitis that is otherwise resistant to therapy; 
infliximab seems to be more efficacious than etanercept for 
treatment of JIA-related uveitis; patients with insufficient 
response to one TNF-α blocker may profit from switching to 
another agent of this class. Earlier use of anti-TNF-α agents 
and changing the type of anti-TNF-α agent in case of nonre-
response might be an effective therapeutic strategy to prevent 
ocular damage caused by uveitis.

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