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The Incidence of Uveitis in Ankylosing Spondylitis Patients Undergoing Tumor Necrosis Factor Inhibiting Therapy in Korea

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Objective. The purpose of this study is to evaluate the outcome of uveitis in ankylosing spondylitis (AS) during tumor necrosis factor (TNF)-inhibiting therapy and to compare the incidence rate of uveitis in infliximab, adalimumab, and etanercept.

Methods. A retrospective evaluation was performed in AS patients who had started TNF-inhibiting therapy from June 2003 to June 2011. The clinical characteristics of patients with documented uveitis were evaluated. Results. Among 316 patients treated with TNF inhibitor, 26 patients (8%) had experienced uveitis during TNF-inhibiting therapy. Among them, 15 patients were treated with etanercept, eight with adalimumab, and three with infliximab. The overall incidence rate of uveitis flare during therapy with TNF inhibitor was 46 per 1,000 person-years (pys) (95% confidence interval [CI], 32 to 64). The incidence rate did not differ between TNF inhibitors, with 54/1,000 pys (95% CI, 34 to 81) for etanercept, 46/1,000 pys (95% CI, 21 to 87) for adalimumab, and 22/1,000 pys (95% CI, 5 to 64) for infliximab. Fourteen patients experienced a first episode of uveitis. The overall incidence rate of new onset-uveitis after therapy with TNF inhibitor was 19 per 1,000 pys (95% CI, 10 to 31). The incidence rate for etanercept was 24/1,000 pys (95% CI, 12 to 45); adalimumab, 15/1,000 pys (95% CI, 3 to 45); and infliximab, 7/1,000 pys (95% CI, 0 to 40). There was no statistical difference in the incidence of uveitis flare or the cumulative uveitis-free rate among the three TNF inhibitors. Conclusion. The relative rate of uveitis, including the first episode, was determined using the TNF inhibitor. However, there was no difference in the incidence rate of uveitis among the three TNF inhibitors. (J Rheum Dis 2015;22:288-292)

Key Words. Tumor necrosis factor, Ankylosing spondylitis, Uveitis

INTRODUCTION

Uveitis is the most common extra-articular manifestation occurring in patients with ankylosing spondylitis (AS) [1,2]. Patients with AS have a 20% to 30% chance of developing uveitis during the course of their disease, and 85% of the AS patients who experience uveitis are diagnosed with acute anterior uveitis [1]. It generally affects men and is unilateral, painful, and self-limiting.

Tumor necrosis factor (TNF) inhibitors have been known to be effective agents in treating articular as well as extra-articular manifestations of AS. However, differing from monoclonal antibodies, concerns have been raised that etanercept may have a less protective effect on uveitis flare [3-7]. Although the pathogenic mechanisms have not yet been fully identified, a recombinant soluble receptor to TNF might be related to lack of its effect on uveitis flare or its paradoxically adverse effect of ocular inflammation.

In our study, we investigated the incidence rate of uveitis in AS patients treated with TNF inhibitors in Korea. We also compared the incidence rate of uveitis in patients treated with infliximab, adalimumab, and etanercept.
MATERIALS AND METHODS

We retrospectively reviewed the electronic medical reports (EMR) of 316 AS patients treated with TNF-inhibiting therapy in a tertiary care center in Korea from June 2003 to June 2011. All of the patients had been previously diagnosed as having AS which satisfied the modified New York criteria [8] and had received at least one TNF inhibitor, including etanercept, adalimumab or infliximab, due to the lack of efficacy or the adverse effect of non-steroidal, anti-inflammatory drugs and disease-modifying, anti-rheumatic drugs. This study was approved by the Asan Medical Center Institutional Review Board (IRB 2013-0882).

A previous history of uveitis was evaluated at the first medical examination and it was recorded in the EMR. We defined uveitis patients as those with at least one episode of uveitis diagnosed by an ophthalmologist. Clinical data, including patient age, sex, disease duration, human leukocyte antigen (HLA)-B27 allele, body-mass index, and duration of TNF inhibitor exposure, were collected.

When comparing the three TNF inhibitors, the chi-square test or Kruskal-the Wallis test was performed. The incidence rates of uveitis were calculated as the number of events or patients per 1,000 person-years (pys) of follow-up with a 95% confidential interval (CI) in the infliximab, adalimumab, and etanercept groups. To estimate the difference in the uveitis risk in the three groups, a survival analysis was performed using the Kaplan-Meier method and Cox proportional hazards model. The log-rank test was used to compare survival curves. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Predictive Analytics Software SPSS Statistics ver. 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among the 316 AS patients treated with TNF inhibitor, 42 patients (13%) experienced uveitis before TNF-inhibiting therapy. Table 1 shows a comparison of the infliximab, adalimumab, and etanercept groups. Infliximab was used for 85 patients, adalimumab for 148 patients, and etanercept for 142 patients. Male predominance and high HLA-B27 positivity were similar in all of the groups. As each TNF inhibitor was approved by Korean National Health Insurance at points in time, the exposure duration differed in each group.

In patients treated with infliximab and adalimumab, the number of patients who experienced uveitis was decreased following their treatment, although not in those treated with etanercept. The overall incidence rate of uveitis flare in all TNF inhibitors was 46 per 1,000 pys (95% CI, 32 to 64). The incidence rate for etanercept was...
Figure 1. Cumulative uveitis-free survival rate after tumor necrosis factor (TNF) inhibitors (A) in all patients and (B) in patients who had never experienced uveitis before TNF-inhibiting therapy.
pared to AS patients in general, who usually have a 20% to 30% chance of developing uveitis [1]. However, some studies have reported that etanercept did not reduce the incidence of uveitis differently from that of TNF monoclonal antibodies. Guignard et al. [11] reported a difference in the efficacies of the three TNF inhibitors in 46 spondyloarthropathy patients who had at least one uveitis flare. They suggested that etanercept did not reduce the number of flares, whereas infliximab and adalimumab greatly reduced the number of flares. However, it has also been seen in AS clinical trials that etanercept is effective for lowering the uveitis flare rate in AS patients [12].

Our study showed that developing a uveitis flare and the new onset of uveitis did not statistically differ in the three TNF inhibitors. However, five of our patients who were previously treated with etanercept were switched to infliximab or adalimumab alternatively after their uveitis flare, and after which they experienced no subsequent flare. Considering the results of previous reports related to TNF inhibitor and uveitis, these clinical experiences support the supposition that etanercept might be less effective for treating uveitis compared to the other TNF inhibitors.

Etanercept is a soluble TNF receptor molecule, whereas infliximab and adalimumab are monoclonal antibodies. Because their mechanisms of antagonizing TNF-α differ, there are pharmacodynamic and pharmacokinetic differences between the TNF inhibitors that may potentially contribute to their action in different disease states [4,13,14]. This evidence suggests that the monoclonal antibodies may be more appropriate than etanercept for treating EAM, including uveitis [15]. Although our study showed that there was no difference in the uveitis flare among the three TNF inhibitors, changing from etanercept to a monoclonal antibody, including infliximab and adalimumab, could be effective for preventing uveitis flare in patients experienced uveitis before.

In conclusion, a considerable proportion of the AS patients experienced uveitis flare and approximately half of them developed new uveitis onset even during their treatment with the TNF inhibitor. Although there was no difference in the uveitis flare in the three TNF inhibitors in our study, it might be helpful for patients developing uveitis during etanercept therapy to change to monoclonal antibodies.

**Table 2. Cox proportional hazard analysis for uveitis of ankylosing spondylitis patients treated with infliximab, adalimumab, or etanercept**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infliximab (n = 85)</th>
<th>Adalimumab (n = 148)</th>
<th>Etanercept (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR developing uveitis during TNFi therapy</td>
<td>Reference</td>
<td>2.0 (0.5 ∼ 7.8)</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR developing uveitis during TNFi therapy*</td>
<td>Reference</td>
<td>1.8 (0.4 ∼ 7.9)</td>
</tr>
<tr>
<td></td>
<td>HR of new onset of uveitis</td>
<td>Reference</td>
<td>2.8 (0.3 ∼ 28.2)</td>
</tr>
<tr>
<td></td>
<td>Adjusted HR of new onset of uveitis*</td>
<td>Reference</td>
<td>0.9 (0.1 ∼ 12.3)</td>
</tr>
</tbody>
</table>

CI: confidence interval, HR: hazard ratio, TNFi: tumor necrosis factor inhibitor. *Adjusted for ankylosing spondylitis disease duration and duration of TNFi exposure.

**CONCLUSION**

In conclusion, a considerable proportion of the AS patients experienced uveitis flare and approximately half of them developed new uveitis onset even during their treatment with the TNF inhibitor. Although there was no difference in the uveitis flare in the three TNF inhibitors in our study, it might be helpful for patients developing uveitis during etanercept therapy to change to monoclonal antibodies.
CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES