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

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Ankylosing spondylitis (AS), a chronic inflammatory rheumatic disease that primarily affects the sacroiliac joints and causes inflammatory back pain, is often accompanied by inflammatory extra-articular manifestations such as Crohn’s disease, psoriasis, and uveitis [1]. In a systematic literature review of extra-articular manifestations in patients with AS, acute anterior uveitis (26%) was more common than psoriasis (9%) or inflammatory bowel disease (7%) [2]. Other studies have estimated that 25% to 50% of patients experience at least one episode of uveitis during the course of AS. Characteristics of uveitis in patients with AS include predominantly acute, unilateral onset; anterior location; strong association with human leukocyte antigen (HLA)-B27 positivity; and tendency to recur, often in the opposite eye. In addition, the incidence of uveitis increases with longer disease duration, ranging from 17% for patients with disease duration < 10 years to 39% for patients with disease duration > 20 years [2].

Uveitis is a painful, often recurrent, and potentially serious inflammation of the eye. It is the most preventable cause of blindness worldwide and also has a negative effect on health-related quality of life. AS patients with extra-articular manifestations utilize more medical resources and incur more health care costs compared with AS patients who do not develop extra-articular manifestations. Complications of inadequately treated uveitis include cataract formation, glaucoma, and maculopathy, all of which can lead to visual acuity loss and ultimately blindness. In patients with spondyloarthropathies, uveitis was associated with reduced visual acuity in 8% of patients; and approximately 50% of patients had at least one recurrent flare [3].

Tumor necrosis factor (TNF) is involved in the pathogenesis of both uveitis and AS. TNF is elevated in the aqueous humor and serum of patients affected by uveitis and the joints of patients with AS. Anti-TNF therapy has been shown to reduce ocular inflammation and preserve vision in patients with sight-threatening uveitis, and there is considerable interest in the use of biologic treatments for uveitis and other ocular inflammatory disorders. The anti-TNF agents adalimumab and infliximab have been shown to reduce uveitis flares in patients with AS [4,5], whereas evidence for the ability of etanercept to prevent uveitis flares is mixed [5,6]. Conversely, uveitis develops in some patients, whose articular symptoms are well controlled with anti-TNF therapy, suggesting that the ocular and articular inflammation develop via different pathways. The degree to which new-onset uveitis occurs in patients receiving anti-TNF therapy has been characterized in a retrospective cohort study, with the majority of cases occurring during therapy with etanercept; of 31 cases of uveitis identified, 19 were in AS, 4 were in psoriatic arthritis, 6 were in rheumatoid arthritis, and 2 were in juvenile idiopathic arthritis. Of the 19 cases associated with AS, that anti-TNF agent at the time of the first onset of uveitis was etanercept in 12 cases, infliximab in 4 cases, and adalimumab in 3 cases; the pattern of results was similar among 121 cases identified in a systematic literature review [6]. In South Korea, Kim et al. [7] re-
ported case series of 16 new-onset uveitis among 363 AS patients receiving TNF inhibitor therapy. Intriguingly, all 16 patients were receiving etanercept and no new-onset uveitis was reported in infliximab or adalimumab patients.

In a previous issue of this journal, Koo et al. [8] demonstrated the relative incidence rate of uveitis, including the first episode while using TNF inhibitors and concluded there was no difference in the incidence rate of uveitis among the three TNF inhibitors. Eight years of follow up, analysis of survival using the Kaplan-Meier method and Cox proportional hazards model are the strong points of this study. And they found the overall incidence rate of new onset uveitis after TNF-inhibiting therapy was 19 per 1,000 person-years (pys). Among three TNF inhibitors, the new onset uveitis for etanercept was 24/1,000 pys, for adalimumab was 15/1,000 pys, for infliximab was 7/1,000 pys, respectively. There must be a tendency or increased hazard ratio in patient who used etanercept was 1.6 to 3.4 than that of infliximab and adalimumab, however, there was statistically no difference of incidence rate in three TNF inhibitors. Also, the cumulative uveitis-free rate in the three TNF inhibitors showed no difference regardless of whether new onset uveitis or pre-existing uveitis flare.

This study has two shortcomings that should be considered. First, this was a retrospective electronic medical record review design in single center. So, relatively small number of patients and loss of follow-up might be influence the incidence rate of uveitis. Also, physician’s preference of selecting TNF inhibitors might be biased to using monoclonal antibody agent to the patients who already have uveitis history, based on previous clinical trial data. Second, causality between specific TNF inhibitor and development of uveitis is not clear. Whether the TNF inhibitor has induced the uveitis or lack of efficacy of the TNF inhibitor couldn’t prevent uveitis flare.

In conclusion, a considerable proportion of the AS patients experienced uveitis flare and approximately half of them developed new onset uveitis even during their treatment with TNF inhibitor. Although there was no statistically different uveitis flare rate among three TNF inhibitors in this study, it might be helpful for patients developing uveitis during soluble TNF receptor agent to change monoclonal TNF antibody agents. Future direction of uveitis incidence study in TNF users needs to be done in large population based prospective registry data, meta-analysis, and network analysis.

**CONFLICT OF INTEREST**

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

**REFERENCES**