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Editorial

Association between Treatment with Biologic Agents and the Incidence of Herpes Zoster in Rheumatoid Arthritis

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Herpes zoster (HZ), caused by reactivation of the varicella-zoster virus (VZV) in the dorsal root ganglia, is characterized by a vesicular dermatomal rash and long-term disability in the form of postherpetic neuralgia. The lifetime risk of developing HZ is 10%～20% in general population. The major risk factor is age, since VZV-specific cell-mediated immunity declines with aging [1]. High risk for developing HZ is also observed among people with a compromised immune status, such as leukemia, bone marrow transplantation, human immunodeficiency virus infection, or autoimmune diseases [2,3].

Increased risk of developing HZ is also well known in patients with rheumatoid arthritis (RA). This may be due to the dysregulation of immune system by the disease itself, and/or due to the immunosuppressive medications for the treatment of RA, such as disease-modifying anti-rheumatic drugs (DMARDs) [4]. Several studies have been performed in order to investigate the association between the risk of developing HZ and biologic DMARDs (bDMARDs), such as anti-tumor necrosis factor (TNF) inhibitors [4-8]; however, the nature of this association remains controversial.

Smitten et al. [4] reported that the current use of anti-TNF inhibitors was associated with an increased risk of developing HZ (odds ratio [OR]=1.54, 95% confidence interval [CI]=1.04～2.29), using data for the 122,272 RA patients obtained from a large database of the United States. Strangfeld et al. [5] studied the German Rheumatoid Arthritis oBservation of Biologic Therapy (RABBIT) registry and revealed that of the 86 reported cases of HZ, 62/3,266 patients received the anti-TNF inhibitors and 24/1,774 patients received conventional DMARDs (cDMARDs). The crude incidence rate per 1,000 patient-years was 11.1 for treatment with the monoclonal antibodies, 8.9 for etanercept, and 5.6 for cDMARDs, which suggested that the anti-TNF monoclonal antibodies may be associated with an increased risk of developing HZ (statistically significant compared with cDMARDs). García-Doval et al. [6] examined the rate of hospitalization with primary diagnosis of HZ and primary varicella infection, using a Spanish registry of rheumatic disease patients treated with biologic agents (BIOBADASER database). They reported that the rate of hospitalization due to HZ was nine-fold higher in the RA patients treated with anti-TNF inhibitors as compared to that in the general Spanish population (32 per 100,000 patient-years [95% CI=14～78] vs. 3.4 per 100,000 person-years [95% CI=3.2～3.5]).

In contrast, McDonald et al. [7] conducted a retrospective study involving 20,357 RA patients in a national cohort of US war veterans. They observed 96 cases of HZ in 3,661 patients (2.6%) receiving anti-TNF inhibitors and 617 HZ cases in 22,561 patients (2.7%) receiving cDMARDs, which indicated no difference in HZ risk between the treatment groups. Winthrop et al. [8] utilized data for RA patients from 4 large US automated databases and reported that those who initiated the anti-TNF therapies were not at higher risk of HZ compared to the patients who initiated non-biologic treatment regimens (adjusted hazard ratio [HR]=1, 95% CI=0.77～1.29).

In the previous issue of the *Journal of Rheumatic Diseases*, Kwon et al. [9] reported that among the Korean RA patients, bDMARDs did not increase the risk of developing HZ compared to cDMARDs (crude incidence rate, 2.6

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[95% CI=1.6～4] vs. 2.4 [95% CI=1.4～3.9]), although the number of patients and observed patient-years was low for treatment with several biologic agents. The authors also documented the differences in the risk of developing HZ by various bDMARDs, and demonstrated that the crude incidence rate was the highest for treatment with abatacept (8.5 per 100 patient-years) followed by rituximab (3.9 per 100 patient-years), anti-TNF monoclonal antibodies (2.9 per 100 patient-years), etanercept (1.8 per 100 patient-years), and tocilizumab (0 per 100 patient-years). Each bDMARD has a different mechanism of action and may have a different effect on T cell functioning for inducing VZV-specific cell-mediated immunity [10]. However, the association between the risk of developing HZ and bDMARDs remains inconclusive. McDonald et al. [7] reported that RA patients treated with infliximab showed a higher incidence rate of HZ than those treated with etanercept or adalimumab. Using multivariate analysis, Strangfeld et al. [5] reported that the incidence rate of HZ in the monoclonal antibody-treated patients was significantly higher (HR=1.82, 95% CI=1.05～3.15) compared to that in the etanercept-treated patients. However, Yun et al. [11] studied the association between the risk of developing HZ and bDMARD treatment in RA patients using the US Medicare data and reported that neither the crude incidence rate nor the adjusted hazard ratio differed significantly among the biologic agents.

Generally, HZ can be prevented by vaccination. Thus, the knowledge that certain biologic agents increase the risk of developing HZ is important. Currently, for RA patients aged 60 years or more, the American College of Rheumatology recommends the administration of a live attenuated HZ vaccine, prior to the initiation of treatment with biologic agents [12]. In many cases, biologic agents are used in RA patients who are under the age of 60 years. However, knowledge about the safety and efficacy of HZ vaccination in these patients is lacking. And increased rates of HZ were observed in RA patients (particularly among the Asian patients) treated with tofacitinib, a targeted synthetic DMARD [13]. Therefore, further studies should be undertaken to evaluate the efficacy of HZ vaccination among a large number of Korean RA patients, belonging to various age groups and receiving various immunosuppressants (including tofacitinib).

CONFLICT OF INTEREST

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

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