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Original Article

Risk of Herpes Zoster in Patients with Rheumatoid Arthritis Undergoing Biologic Disease-Modifying Therapy

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Objective. Rheumatoid arthritis (RA) patients suffer from an increased risk of herpes zoster (HZ) partially due to immunosuppressant medications. This study investigated HZ in RA patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs), as compared with conventional DMARDs (cDMARDs). **Methods.** This retrospective case series study assembled record information of 277 RA patients who received bDMARDs after failure of at least one cDMARDs at Seoul National University Hospital between August 2003 and February 2015. Following capture of baseline information and identification of HZ episodes, crude HZ incidence rates per 100 patient-years (95% confidence intervals) were calculated. **Results.** For 718 treatment courses, 277 (38.6%) comprised cDMARDs, 66 (9.2%) infliximab, 175 (24.4%) etanercept, 95 (13.2%) adalimumab, 9 (1.3%) golimumab, 41 (5.7%) rituximab, 31 (4.3%) abatacept, and 24 (3.3%) tocilizumab. There were 37 HZ episodes, 16 during cDMARD treatment courses, and 21 accompanying bDMARDs, two with infliximab, eight with etanercept, five with adalimumab, and three each with rituximab and abatacept. The crude HZ incidence rate per 100 patient-years was 2.4 (1.4～3.9) for cDMARDs, 2.2 (0.3～7.9) for infliximab, 1.8 (0.8～3.6) for etanercept, 3.7 (1.2～8.4) for adalimumab, 3.9 (0.8～11.0) for rituximab, and 8.5 (1.8～23.1) for abatacept. **Conclusion.** We conclude that bDMARDs do not always increase the risk of HZs in RA patients, although HZ rates vary for different bDMARDs. **(J Rheum Dis 2017;24:220-226)**

Key Words. Herpes zoster, Rheumatoid arthritis, Biological therapies, Antirheumatic agents

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease characterized by inflammation and hypertrophy of the synovial lining of joints, mainly associated with T cell-mediated immune responses [1,2]. RA is an immunological disorder that is treated with immunosuppressive and immunomodulatory agents. Previous studies reported that infection-related mortality was increased in RA patients and attributed the increased infection to the immunosuppressive treatment [3-5].

Herpes zoster (HZ) is closely associated with an impaired T-cell immunity against the causative virus [6]. Immunocompromised patients with impaired T-cell immunity, including recipients of organ or hematopoietic stem-cell transplants and those receiving immunosuppressive therapy, are at an increased risk of HZs [7]. HZs occur two to three times more often in RA patients than in the general population, with incidence rates of 0.89 to 1.32 cases per 100 patient-years [8-12]. The reported risk of HZs in biologic disease-modifying antirheumatic drug (bDMARD) users varies. For example, the reported odds ratio of HZs ranged from 0.95 (95% confidence interval [CI], 0.75～1.21) to 2.61 (95% CI, 0.86～7.91) for tumor necrosis factor (TNF) blockers compared with conventional DMARDs (cDMARDs) [13,14]. The risk of HZ in Asian RA patients seems to be higher, considering higher incidence of HZ in Asian RA

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patients in recent tofacitinib trials [15].

However, the effect of bDMARD treatment on the risk of HZs in Asian RA patients has not been reported. Therefore, we decided to investigate the effect of bDMARD use on the incidence of HZs in Korean RA patients. The bDMARDs investigated included TNF blockers, B cell-depleting agents, costimulation inhibitors, and interleukin-6 blockers.

MATERIALS AND METHODS

Subjects

We conducted a medical record review for a retrospective cohort study to investigate the incidence of HZ in RA patients who received bDMARDs at a Seoul National University Hospital between August 2003 and February 2015. All patients received cDMARDs as the initial therapy before the bDMARD treatment. Biologics included infliximab, etanercept, adalimumab, golimumab, rituximab, abatacept, and tocilizumab. We collected baseline characteristics (demographics, disease duration), comorbidities, history of malignancy, laboratory data, including rheumatoid factor and anti-citrullinated protein antibodies, erythrocyte sedimentation rate, C-reactive protein, and cDMARDs at the initiation of each treatment episode. The Institutional Review Board of Seoul National University Hospital approved this study (no. 1505-098-674).

Definition of treatment episodes

A treatment episode was defined as a period of either cDMARD or bDMARD administration. A period of cDMARD administration was regarded as a single treatment episode regardless of the types of cDMARDs, whereas a period when bDMARDs were administered was considered a separate episode depending on the types of bDMARDs. The bDMARDs were used as 'first-line', 'switched', or 'restarted' therapy. In this study, we identified 277 RA patients who received biologics, and 718 treatment episodes of cDMARDs and/or bDMARDs.

HZ verification

HZ events in RA patients were identified from medical chart review. HZ was identified through direct diagnosis by the responsible rheumatologist and appropriate drug prescription, patient self-reporting of HZ, or an admission for intravenous anti-viral therapy for HZ treatment. Cases referred to other clinics (dermatologic or ophthalmologic) for the treatment of HZ were also included. We considered that the relationship between HZ and biologics was significant when the HZ events occurred during the biologic treatment or within the recommended dosing intervals after the discontinuance of biologics. The recommended dosing intervals were defined as follows: 30 days for abatacept, golimumab, and tocilizumab; 56 days for infliximab; and 180 days for rituximab [16].

Statistical analysis

We conducted statistical analyses to compare the baseline characteristics of RA patients with the treatment episodes. The crude incidence rates of HZ per 100 patient-years (95% CI) were calculated for each treatment episode. These analyses were performed using SPSS 21.0 (IBM SPSS Inc., Armonk, NY, USA).

RESULTS

Baseline characteristics

Baseline characteristics of study patients are tabulated

Table 1. Baseline characteristics of study patients at the time point of RA diagnosis

Variable	Patient (n = 277)
Age at RA diagnosis (yr)	46.8 (13.6)
Sex (female), n (%)	596 (83.0)
Underlying disease, n (%)	
Diabetes milletus	75 (10.5)
Hypertension	198 (27.7)
Malignancy	32 (4.5)
Laboratory findings*	
RF, titer (IU/mL) (n = 273)	80.4 (99.2)
Anti-CCP antibody, titer (IU/mL) (n = 289)	124.2 (166.8)
ESR (mm/h) (n = 253)	49.4 (34.7)
CRP (mg/dL) (n = 271)	2.4 (4.1)
Conventional DMARD after RA diagnosis, n (%)	
Methotrexate	201 (75.0)
Leflunomide	46 (17.2)
Hydroxychloroquine	126 (47.0)
Sulfasalazine	88 (32.8)
Corticosteroids	215 (80.2)
Prednisolone, dose* (mg/d)	5.4 (4.5)

Values are presented as mean (standard deviation) or number (%). RA: rheumatoid arthritis, RF: rheumatoid factor, CCP: cyclic citrullinated peptide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DMARD: disease-modifying antirheumatic drug. *Corticosteroids calculated by prednisolone equivalent dose.

Table 2. Comparison of characteristics and demographics at the time point of starting between cDMARD and bDMARD treatment period

Variable	cDMARDs period (n=277)	bDMARDs (post-cDMARDs period)								
		Total bDMARDs (n=441)	Anti-TNF α antibodies* (n=170)	Infliximab (n=66)	Adalimumab (n=95)	Golimumab (n=9)	Etanercept (n=175)	Rituximab (n=41)	Abatacept (n=31)	Tocilizumab (n=24)
Age (yr)	49.7 (12.7)	52.9 (13.2)	53.4 (13.0)	56.2 (12.4)	51.4 (13.3)	53.7 (10.7)	51.8 (12.8)	55.1 (12.4)	51.8 (14.3)	54.6 (18.0)
Sex (female), n (%)	229 (82.7)	367 (83.2)	145 (85.3)	57 (86.4)	80 (84.2)	8 (88.9)	144 (82.3)	34 (82.9)	26 (83.9)	18 (75.0)
Treatment duration (yr)	2.4 (2.3)	1.8 (1.9)	1.4 (1.5)	1.4 (1.4)	2.5 (2.3)	1.4 (1.6)	1.2 (1.4)	1.9 (1.6)	1.1 (1.2)	0.8 (0.5)
Laboratory findings										
ESR (mm/h)	49.4 (34.7)	56.5 (28.7)	54.1 (26.8)	55.2 (28.4)	54.5 (26.5)	41.5 (11.3)	57.8 (28.7)	71.5 (32.3)	43.5 (23.7)	54.4 (30.0)
CRP (mg/dL)	2.4 (4.1)	2.6 (2.8)	2.2 (2.5)	2.4 (2.6)	2.2 (2.4)	0.6 (0.86)	2.9 (3.1)	3.9 (3.6)	1.8 (1.9)	2.0 (1.8)
Concomitant cDMARD, n (%)										
Methotrexate	201 (75.0)	289 (65.5)	123 (72.4)	50 (75.8)	68 (71.6)	5 (55.6)	113 (64.6)	25 (61.0)	15 (48.4)	12 (50.0)
Leflunomide	46 (17.2)	28 (6.4)	14 (8.2)	8 (12.1)	6 (6.3)	0 (0)	10 (5.7)	3 (7.3)	1 (3.2)	0 (0)
Hydroxychloroquine	126 (47.0)	41 (9.3)	12 (7.1)	7 (10.6)	5 (5.3)	0 (0)	24 (13.7)	3 (7.3)	2 (6.5)	0 (0)
Sulfasalazine	88 (32.8)	40 (9.1)	9 (5.3)	4 (6.1)	5 (5.3)	0 (0)	22 (12.6)	8 (19.5)	1 (3.2)	0 (0)
Prednisolone	215 (80.2)	378 (85.7)	147 (86.5)	63 (95.5)	80 (84.2)	4 (44.4)	149 (85.1)	37 (90.2)	27 (87.1)	18 (75.0)
Prednisolone, dose† (mg/d)	5.4 (4.5)	5.3 (3.3)	5.2 (3.1)	6.1 (2.8)	4.7 (3.0)	2.1 (3.4)	5.0 (3.0)	6.7 (4.4)	5.7 (4.2)	4.7 (3.5)

Values are presented as mean (standard deviation) or number (%). n: the number of treatment episodes receiving cDMARD and/or bDMARD therapies. cDMARD: conventional disease-modifying antirheumatic drug, bDMARD: biologic disease-modifying antirheumatic drug, TNF: tumor necrosis factor, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. *Anti-TNF α antibodies including infliximab, adalimumab, and golimumab. †Oral corticosteroid calculated by predinisolone equivalent dose.

in Table 1. A total of 277 RA patients were enrolled in this study, 83.0% of which were female. The median age (±standard deviation, SD) at RA diagnosis was 46.8 (±13.6) years, and the median disease duration was 9.5 (±5.7) years. The 718 treatment episodes of cDMARDs and bDMARDs were identified. The treatment episode profiles for each biologic were as follows: 277 (38.6%) episodes for cDMARDs, 66 (9.2%) for infliximab, 175 (24.4%) for etanercept, 95 (13.2%) for adalimumab, 9 (1.3%) for golimumab, 41 (5.7%) for rituximab, 31 (4.3%) for abatacept, and 24 (3.3%) for tocilizumab. Comparison of characteristics according to cDMARD and bDMARD (post-cDMARDs) treatment episodes are summarized in Table 2.

Crude incidence rates of HZ

A total of 37 HZs were confirmed during 1,470 patient-years of follow-up analyses. In these HZ events, 16 occurred during cDMARD treatment courses, and 21 occurred during bDMARD treatments (2 during infliximab, 8 during etanercept, 5 during adalimumab, and 3 each during rituximab and abatacept). The crude incidence rate for HZ are shown in Table 3. The crude incidence rate was 2.5 per 100 patient-years (95% CI, 1.8～3.5) in total, with 2.4 (95% CI, 1.4～3.9) for cDMARDs, 2.2 (95% CI, 0.3～7.9) for infliximab, 1.8 (95% CI, 0.8～3.6) for etanercept, 3.7 (95% CI, 1.2～8.4) for adalimumab, 3.9 (95% CI, 0.8～11.0) for rituximab, and 8.5 (95% CI, 1.8～23.1) for abatacept.

Clinical characteristics of HZs

The clinical characteristics and number of biologics used during HZ cases in RA patients who were receiving or had received bDMARDs were summarized in Table 4. The mean patient's age was 55.4 (±12.5) years, and 95.2% of the patients were female. Twelve (57.1%) HZ cases occurred during initial biologics use, eight (38.1%) cases during secondary biologics use, and one (4.8%) case during tertiary biologic treatment. The number of biologics previously used was not related to HZ.

Outcome of HZs

Of the 37 HZ cases, only one, who had received rituximab treatment, developed an HZ during hospitalization. The other cases developed HZs at home, which led to mild shingles and recovery without complication after treatment with an oral anti-viral agent at an outpatient clinic. There were no cases of severe HZs that would require hospitalization or result in death.

DISCUSSION

The incidence rates of HZs in RA patients in this study were 2.5 per 100 patient-years in the entire patient cohort, 2.4 per 100 patient-years in patients exposed to cDMARDs, and 2.6 per 100 patient-years in those exposed to bDMARDs. The incidence of HZs did not increase with bDMARD exposure, but the rates varied depending on the biologics used.

The incidence of HZs in RA patients is higher than in the general population [8,17]. However, it is still controversial whether the use of bDMARDs is a contributing factor. To date, the risk of HZ in bDMARD users has not been investigated in Asian populations, where tofacitinib

Table 3. Crude incidence rates of herpes zoster events per 100 patient-years

Treatment	Observed patient-years	HZ cases	Crude incidence rates (95% CI)
cDMARDs (n=277)	662.1	16	2.4 (1.4～3.9)
bDMARDs (n=441)	808.1	21	2.6 (1.6～4.0)
Anti-TNF α antibodies* (n=170)	236.9	7	2.9 (2.2～6.0)
Infliximab (n=66)	89.8	2	2.2 (0.3～7.9)
Adalimumab (n=95)	135.9	5	3.7 (1.2～8.4)
Golimumab (n=9)	11.2	0	0.0 (0～28.5)
Etanercept (n=175)	440.3	8	1.8 (0.8～3.6)
Rituximab (n=41)	77.1	3	3.9 (0.8～11.0)
Abatacept (n=31)	35.5	3	8.5 (1.8～23.1)
Tocilizumab (n=24)	18.3	0	0.0 (0～18.5)

n: the number of treatment episodes receiving cDMARDs and/or bDMARDs therapies. HZ: herpes zoster, CI: confidence interval, cDMARDs: conventional disease-modifying antirheumatic drugs, bDMARD: biologic disease-modifying antirheumatic drug, TNF: tumor necrosis factor. *Anti-TNF α antibodies including infliximab, adalimumab, and golimumab.

Table 4. Clinical characteristics of herpes zoster cases in bDMARD users

Patient no.	Age (yr)	Sex	Disease duration at HZ occurrence (yr)	Biologics	MTX (mg/wk)	PD* (mg/d)	N'th biologics at HZ occurrence	Total number of biologics use
1	39	F	7.2	ETA	10	1.25	1	2
2	78	F	9.0	ADA	12.5	0	2	4
3	54	F	1.4	RTX	0	5	2	2
4	45	F	4.4	ADA	15	0	1	3
5	52	F	7.3	ABT	15	0	2	3
6	57	F	9.1	IFX	15	2.5	1	1
7	50	F	18.3	ETA	17.5	2.5	1	2
8	56	F	7.8	RTX	0	5	2	2
9	37	F	14.8	ETA	15	5	1	1
10	41	F	12.4	ETA	0	0	1	1
11	42	F	12.7	ETA	0	0	1	1
12	51	F	1.1	ADA	15	5	1	2
13	59	F	2.2	ETA	0	5	1	1
14	66	M	2.1	ETA	10	2.5	1	1
15	74	F	12.1	IFX	15	5	2	2
16	75	F	18.0	ADA	12.5	5	1	1
17	42	F	8.3	ETA	0	2.5	2	2
18	56	F	13.3	ABT	0	0	2	2
19	65	F	22.2	RTX	12.5	5	3	3
20	73	F	3.1	ABT	0	5	2	2
21	51	F	2.1	ADA	15	1.5	1	1

bDMARD: biologic disease-modifying antirheumatic drug, HZ: herpes zoster, MTX: methotrexate, PD: prednisolone, M: male, F: female, ETA: etanercept, ADA: adalimumab, RTX: rituximab, ABT: abatacept, IFX: infliximab. *Oral corticosteroid calculated by predinisolone equivalent dose.

users are more susceptible to HZ [15]. The crude incidence rate of HZs in RA patients was 2.5 per 100 patient-years in this study and higher than those in other ethnic RA patients, which was reported as 0.8 to 1.6 per 100 patient-years [13,18,19]. The current study thus revealed that the incidence rate of HZ is higher in Korean RA patients than in the general population or other ethnic groups.

The effects of anti-TNF agents on the risk of HZs in RA patients are controversial. Strangfeld et al. [18] reported that the use of anti-TNF α antibodies adalimumab and infliximab might be associated with an increased risk of HZ, in contrast to the therapy involving the receptor fusion protein etanercept. Serac et al. [20] concluded that the risk of HZs in anti-TNF α antibody users was significantly higher than in those undergoing a soluble-receptor treatment. According to Yun et al. [16], HZ incidence rate was highest in certolizumab users (2.45 per 100 person-years) and lowest in golimumab users (1.61 per 100 person-years). However, Winthrop et al. [13] suggested that anti-TNF therapies do not increase the risk of HZs to a greater degree than non-biologic treatment regimens and that no significant differences exist for infliximab, adalimumab, and etanercept exposures. In our study group, the HZ incidence rate among anti-TNF α inhibitor (infliximab, adalimumab, and golimumab) users was 2.9 per 100 patient-years, which was comparable to the cDMARDs period and the HZ incidence rate was lower in soluble-receptor protein (etanercept) users (1.8 per 100 patient-years).

The incidence rates of HZ were higher in rituximab (3.9 per 100 patient-years) and abatacept (8.5 per 100 patient-years) period compared to cDMARDs period. Several studies have been reported that rituximab induces T cell depletion, mainly of CD4+ T cells in patient with RA [21,22]. Based on these results, decreased of CD4+ T cell counts after rituximab therapy would be made and consequently might affect to RA patients to be more vulnerable to HZ. In this study, the HZ incidence rate in the abatacept group was higher than in a previously analyzed Caucasian group (2.8%) [23]. Although this high incidence rate may arise from low sample numbers, the suppression of T cells might be responsible. Abatacept can suppress T cell activation by blocking cos-

timulation through CD28. A recent report on the increased incidence of HZs in tofacitinib users in the Asian population is consistent with this finding [15]. Tofacitinib, an oral Janus kinase inhibitor, can suppress T cell function by blocking T cell activation signals [24]. Interestingly, the incidence of HZs was higher in tofacitinib cases in Asian populations compared with the Caucasian population [15]. Therefore, the Korean population may be more susceptible to HZs due to T cell-related functional differences.

We did not observe any HZs in patients treated with golimumab and tocilizumab. This can be attributed to the low number of patients but can also result from the characteristics of these drugs. Accordingly, Schiff et al. [25] reported that the incidence of HZs was very low during a combined treatment of tocilizumab and cDMARDs, equaling 0.3 per 100 patient-years (4 out of 1,870 cases). HZ incidence was also reported to be very low in golimumab cases (1.61 per 100 patient-years) [16]. Larger cohort studies verifying our findings and investigating the underlying mechanisms are warranted.

This study comprises the first report investigating the incidence of HZs in bDMARD users in Korea. Since it comprises a one-center cohort, we were able to collect detailed information on the enrolled patients during a long-term follow-up period. However, the relatively low number of patients, especially those administered the newer classes of bDMARDs, is a limitation of this study. Not all HZs may have been captured since the incidence of HZ events was identified solely through medical record review. Another limitation of the study is that bDMARD treatment was administered following cDMARD treatment in all of the patients. Since age is one of the important risk factors in HZs, the true effect of bDMARDs may have been overestimated, compared with cDMARDs. However, the risks of HZs during bDMARD treatment were not higher than those during cDMARD treatment.

CONCLUSION

In conclusion, compared with cDMARD exposure, bDMARD exposure is not always associated with an increased risk of HZs in RA patients, although HZ rates are different for different bDMARDs.

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CONFLICT OF INTEREST

Eun Bong Lee has acted as a consultant to Pfizer. Other authors has nothing to declare.

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