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Risk and severity of herpes zoster in patients with rheumatoid arthritis receiving different immunosuppressive medications: a case–control study in Asia

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ABSTRACT

Objective: Increasing evidence indicates that the risk of herpes zoster (HZ) is elevated in rheumatoid arthritis (RA). Little is known about the epidemiology of HZ in patients with RA in Asia. The aim of this study was to determine the risk factors and outcomes of HZ among patients with RA.

Design: A case–control study.

Setting: A medical centre in Asia.

Participants: A total of 9025 newly diagnosed and eligible patients with RA (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 714.0) during the period 2001–2014. Among them, 275 (3.05%) were newly diagnosed with HZ (ICD-9-CM code 053.0) after the RA identification. As the control group, patients with RA without HZ were matched for age, gender and RA disease duration at the time of HZ infection with the RA-HZ case group at a ratio of 4:1, and a total of 1100 control subjects were selected.

Outcome measures: We estimated ORs using conditional logistic regression to investigate the risk and severity of HZ among patients with RA receiving different immunosuppressive medications.

Results: Exposure to corticosteroids (≥10 mg/day adjusted OR (aOR)=2.30, 95% CI 1.25 to 4.22, p=0.01), anti-tumour necrosis factor biologicals (aOR=2.07, 95% CI 1.34 to 3.19, p=0.001) and conventional synthetic disease-modifying anti-rheumatic drugs (methotrexate (aOR=1.98, 95% CI 1.43 to 2.76, p<0.001) and hydroxychloroquine (aOR=1.95, 95% CI 1.39 to 2.73, p<0.001)) was associated with an increased HZ risk in patients with RA. The association between the use of corticosteroids and HZ risk was dose-dependent (p_{trend}<0.001). Time-to-HZ diagnosis among patients with RA receiving biological medications was significantly shorter than that in patients not receiving biological medications. A higher proportion of severe HZ and ophthalmic involvement was found in patients with RA receiving biologicals.

Conclusions: There was an increased risk of HZ in patients with RA taking specific immunosuppressive medication. Biologicals used were associated with severe HZ occurrence. Therefore, it is important to closely monitor and prevent severe HZ complications during specific immunosuppressive therapy.

Strengths and limitations of this study

- This is the first case–control study to investigate an association between immunosuppressive drugs and herpes zoster (HZ) among patients with rheumatoid arthritis (RA) in Asia and the relationship between biologicals and severe HZ.
- The use of long-term medical records: a 14-year follow-up period (2001–2014) enhanced the statistical power and accuracy of this study.
- The present study was conducted at a single medical centre and cannot reflect the complete characteristics of HZ in patients with RA.
- The matched control cohort may have a selection bias. Nevertheless, we analysed data from a clinical information database and reviewed medical care records to identify patients with RA with HZ.

INTRODUCTION

Herpes zoster (HZ) is a significant global health burden and results from reactivation of the latent varicella-zoster virus (VZV) within the sensory ganglia.[1] Approximately 50% of persons living until the age of 85 years will develop HZ.[2] Ageing, female gender, ethnicity and depression were potential risk factors for HZ.[3] In addition, cellular immune dysfunction in certain diseases (eg, HIV infection and non-Hodgkin's lymphomas) is another factor triggering HZ.[4]

Complications occur in almost half of the older persons with HZ, including postherpetic neuralgia (PHN), ophthalmic HZ, meningoencephalitis and secondary bacterial infection.[5] PHN is the most common

debilitating complication, a neuropathic pain syndrome that persists or develops after the dermatomal lesions have cured.[6] PHN may impair the elderly patient's functional status by interfering with basic activities of daily life, resulting in an increased annual medical care cost.[7] In addition, ocular nerve and other organ involvement with HZ may occur, often with severe sequelae.[6]

The Consortium of Rheumatology Researchers of North America registry data showed that VZV infection was the most frequent opportunistic infection in patients with rheumatoid arthritis (RA).[8] Several studies in western countries demonstrated that patients with RA have an increased risk of HZ compared with the general population, which may be due to RA-related immune dysfunction or the immunosuppressive effects of therapeutic agents.[9–12] Among patients with RA in the USA or Europe, those treated with anti-tumour necrosis factor (anti-TNF) biologicals, disease-modifying antirheumatic drugs and/or corticosteroids appeared to be at higher risk.[11–15] The HZ incidence was higher in Asia (Japan: 4.15 per 1000 person-years; Taiwan: 4.89–5.67 per 1000 person-years) than in the USA (3.2–3.7 per 1000 person-years) and Europe (3.7 per 1000 person-years).[16] In Japan, the HZ incidence in patients with RA was higher than that in the general population (9.1 vs 4.15 per 1000 person-years).[17] However, the association between HZ and immunosuppressive medications in Asian patients with RA is still uncertain and little is known about clinical outcomes of HZ in patients with RA after treatment with different immunosuppressive medications. Therefore, we conducted a case–control study using a medical clinical information database to analyse the epidemiology, risk factors and outcomes of HZ in patients with RA with different immunosuppressive medications admitted to one medical centre in Taiwan during the period 2001–2014.

METHODS

Study setting, patients and data source

This case–control study was conducted at Taichung Veterans General Hospital (TCVGH), a medical centre in Taiwan. We searched the clinical database in accordance with case definitions to identify newly diagnosed and eligible patients with RA with HZ during the period January 2001 to December 2014. As the control group, patients with RA without HZ were matched for age, gender and RA disease duration at the time of HZ infection with the RA-HZ case group at a ratio of 4:1. The HZ infection date was in the index date for cases and their matched controls. Comorbidities and medication use were measured during the 365-day period prior to the index date.[15] We evaluated clinical symptoms, outcomes, complications and medication used by reviewing the medical records of patients with RA with HZ and control cohorts. The data from the patient records/information were forms of secondary information that were de-identified in an anonymous format prior to analysis. This study was conducted in compliance with the Declaration of Helsinki, has been approved by the Institutional Review Board of TCVGH (CE15001B) and the requirement of patient informed consent was waived. The methods were carried out in accordance with the approved guidelines.

Definitions

The identification of patients with different diseases in this study was primarily done using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The diagnosis of RA (ICD-9-CM codes 714.0) was made according to the 1987 American College of Rheumatology criteria[18] and on more than one occasion in either the inpatient or outpatient record. The criteria were verified by using the National Health Insurance Research Database's Registry of Catastrophic Illness Patient Database (RCIPD). Patients with RA started biological therapy according to the guidelines of the British Society for Rheumatology.[19 20] The ICD-9-CM code of HZ was 053.0. The diagnosis of HZ was required to have been made after the RA identification index date. Baseline clinical HZ outcome measures (eg, hospitalisation, complication, death) were obtained within 6 months or longer from the initial HZ diagnosis index date. The definition of each comorbidity was based on the ICD-9-CM codes, including hypertension (HT, ICD-9-CM code 401.9), diabetes mellitus (DM, ICD-9-CM code 250), chronic kidney disease (CKD, ICD-9-CM code 585) and HIV disease (ICD-9-CM codes 042–044).

In this study, RA treatments were subdivided into three medication groups in accordance with the immunosuppressive drugs used: (1) anti-TNF biologicals, including adalimumab, etanercept and golimumab; (2) non-anti-TNF biologicals, including rituximab, tocilizumab and abatacept; (3) non-biologicals, including corticosteroids, hydroxychloroquine, sulfasalazine, methotrexate, leflunomide and non-steroid anti-inflammatory drugs. Immunosuppressive medication exposure analysis was conducted to study the drugs-used status before 365 days of the initial HZ diagnosis index date.[15] For examining anti-TNF use, current use was defined as end of exposure ≤6 months prior to the index date.[21] For infused biological agents (eg, abatacept, rituximab and tocilizumab), we assigned exposure as 30 days for abatacept and tocilizumab, and 180 days for rituximab, based on the recommended dosing frequency. Patients using oral corticosteroids in the 90 days prior to the index date were categorised as baseline corticosteroid users.[15] For all baseline corticosteroid users, we calculated a mean daily dose of prednisone equivalents in the 6 months prior to the index date.[15] Severe HZ was defined as the requirement for intravenous antiviral treatment, or ophthalmic HZ. The study end point was defined as the onset of new HZ during the 14-year follow-up period (2001–2014).

Statistical analysis

The data are presented as the means±SDs for the continuous variables, and proportions for the categorical variables. Descriptive statistics were used to analyse the patients' demographic and clinical characteristics. Student's t test and the χ^2 test were used for univariate comparisons when appropriate. A p value of <0.05 was considered statistically significant. We used conditional logistic regression to estimate the crude and adjusted ORs and 95% CIs to quantify associations between HZ and exposure to specific immunosuppressive drugs. The multivariable model was adjusted for covariates possibly associated with HZ, including other immunosuppressive medication use and comorbidities (eg, HT, CKD and DM). A time-to-event analysis was performed using the log-rank test. Analyses were performed using the SPSS (IBM SPSS V.22.0; International Business Machines Corp, New York, USA). All tests were two-tailed with a type 1 error (α) rate of 5%.

RESULTS

Characteristics of study cohort

A total of 9025 newly diagnosed and eligible patients with RA were identified at TCVGH during the period 2001–2014. Among them, 275 (3.05%) were newly diagnosed with HZ after the RA identification. To evaluate the risk of HZ in patients with RA, those without HZ (the control group) were matched for age, gender and RA index date with the HZ group at a ratio of 4:1, and a total of 1100 control subjects were selected. The characteristics of the enrolled participants are summarised in table 1.

Approximately 67.3% (n=185) of patients with RA with HZ were aged over 50 years and 78.2% (n=215) were female. The prevalence of comorbidities, including HT, CKD and DM (p<0.05), was higher in patients with RA with HZ compared with the controls. In this study, none of the patients with RA had HIV disease. Significantly higher proportions of non-steroid anti-inflammatory drugs (77.1% vs 49.6%, table 1), conventional synthetic disease-modifying anti-rheumatic drugs (eg, methotrexate (53.8% vs 19.6%), hydroxychloroquine (74.5% vs 39.5%) and sulfasalazine (49.1% vs 19.1%)), corticosteroids (88.0% vs 40.9%) and anti-TNF biologicals (20.0% vs 6.2%) were used in RA with HZ cases. The average time of RA disease duration at the time of HZ diagnosis is 10.0±4.7 years (range 0.1–15.0 years) (figure 1A).

Table 1 Baseline characteristics (N=1375)

	HZ case (n=275) n (%)	Control (n=1100) n (%)	p Value
Age at entry, years			
Mean±SD	55.3±12.7	55.3±12.7	1.00
RA disease duration	10.0±4.7	10.1±4.7	0.704
Year			
20–49	90 (32.7%)	360 (32.7%)	
50–64	123 (44.7%)	492 (44.7%)	
≥65	62 (22.5%)	248 (22.5%)	
Gender			0.86
Female	215 (78.2%)	868 (78.9%)	
Male	60 (21.8%)	232 (21.1%)	
BMI, kg/m^2	23.7±4.4	24.0±4.1	0.535
Smoking history	29 (10.5%)	85 (7.7%)	0.163
CRP, mg/dL	1.75±0.58	0.98±0.47	**0.04**
Comorbidity			
HT	96 (34.9%)	235 (21.4%)	**<0.001**
CKD	52 (18.9%)	118 (10.7%)	**<0.001**
DM	42 (15.3%)	114 (10.4%)	**0.03**
Malignancies	8 (2.9%)	50 (4.5%)	0.30
Medication used			
NSAID	212 (77.1%)	546 (49.6%)	**<0.001**
Methotrexate	148 (53.8%)	216 (19.6%)	**<0.001**
Hydroxychloroquine	205 (74.5%)	435 (39.5%)	**<0.001**
Sulfasalazine	135 (49.1%)	210 (19.1%)	**<0.001**
Leflunomide	13 (4.7%)	24 (2.2%)	**0.03**
Corticosteroids	242 (88.0%)	450 (40.9%)	**<0.001**
Anti-TNF biologicals*	55 (20.0%)	68 (6.2%)	**<0.001**
Non-anti-TNF biologicals†	15 (5.5%)	42 (3.8%)	0.29

Bold text indicates that a p value of <0.05 and considered statistically significant.
*Including adalimumab, etanercept and golimumab.
†Including rituximab, tocilizumab and abatacept.
BMI, body mass index; CKD, chronic kidney disease; CRP, C reactive protein; DM, diabetes mellitus; HT, hypertension; HZ, herpes zoster; NSAID, non-steroid anti-inflammatory drugs; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

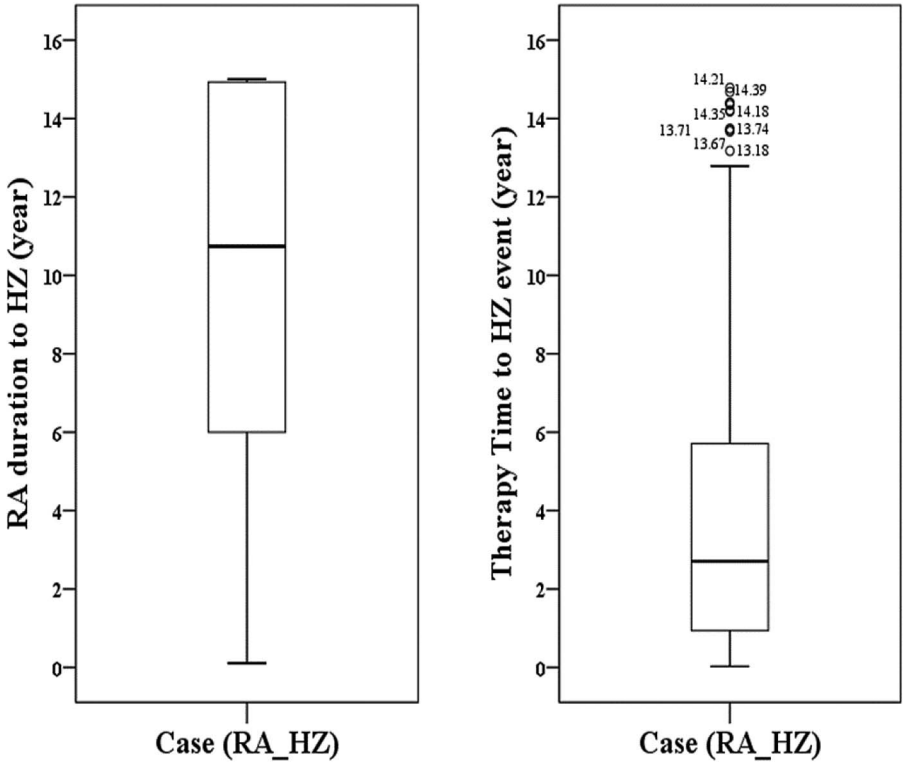


Figure 1 (A) The distribution of rheumatoid arthritis (RA) disease duration at the time of herpes zoster (HZ) diagnosis. (B) The distribution of immunosuppressive drug exposure time at the time of HZ diagnosis.

Risk of HZ in patients receiving different immunosuppressive medications

After full adjustment, methotrexate (adjusted OR (aOR) =1.98, 95% CI 1.43 to 2.76, p<0.001), hydroxychloroquine (aOR=1.95, 95% CI 1.39 to 2.73, p<0.001), sulfasalazine (aOR=1.75, 95% CI 1.27 to 2.43, p<0.001) and corticosteroids (<5 mg/day aOR=1.28, 95% CI 1.17 to 1.47, p<0.001; 5 to <10 mg/day aOR=1.73, 95% CI 1.34 to 2.32, p<0.001; ≥10 mg/day aOR=2.30, 95% CI 1.25 to 4.22, p<0.001) were associated with an increased risk of HZ (table 2). In addition, a dose-dependent association was observed between corticosteroids and a greater OR for HZ (p_{trend}<0.001) after adjustment for comorbidities (HT, CKD and DM) and other immunosuppressive medication use.

Current anti-TNF biologicals users had significantly increased risk of HZ compared with non-users (aOR=2.07, 95% CI 1.34 to 3.19, p=0.001) (table 2). However, there was no significantly increased risk of HZ in patients with RA who received non-anti-TNF biologicals (aOR=1.05, 95% CI 0.54 to 2.03, p=0.88). Among anti-TNF biological users, more patients with RA with HZ had received adalimumab compared with the control cohort (10.9% vs 2.2%, p<0.001) (see online supplementary table). An increased risk of HZ in adalimumab users was detected (crude OR=5.49, 95% CI 3.15 to 9.56, p<0.001).

The proportion of severity and complications of HZ in patients receiving different immunosuppressive medications

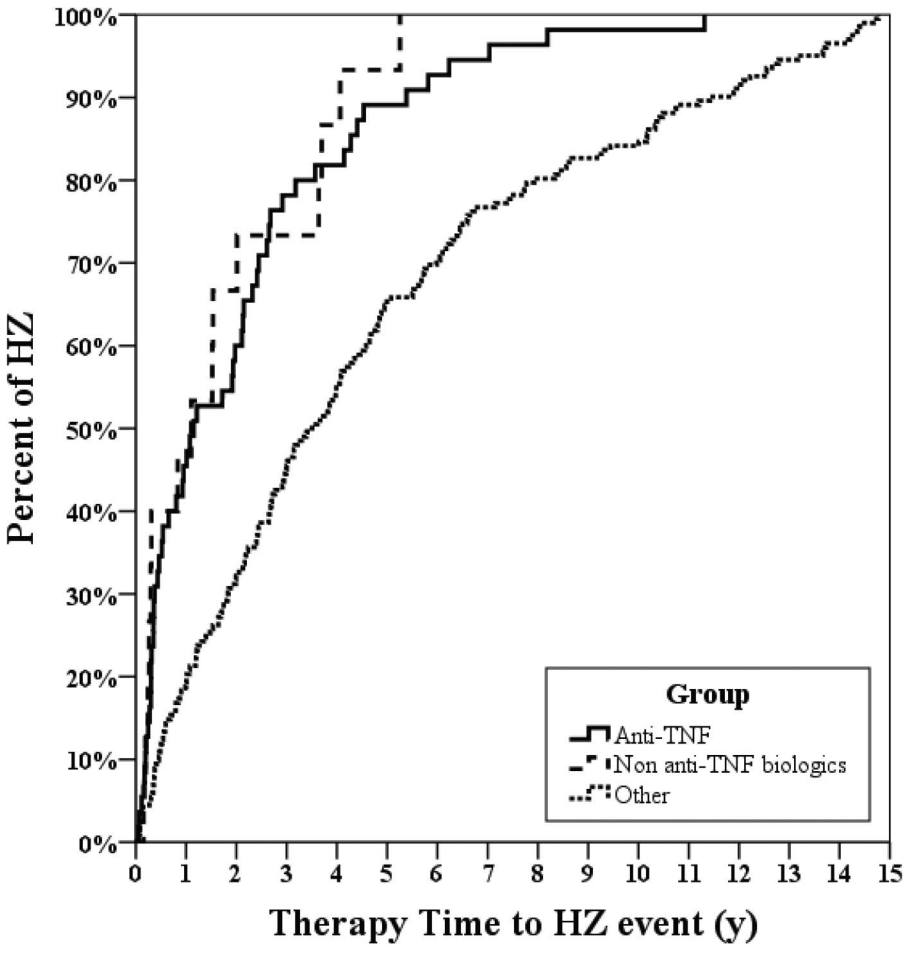
In this study, the average time of drug exposure at the time of HZ diagnosis is 4.0±3.8 years (range 0.1–14.8 years) (figure 1B). All HZ cases who had drug exposure time more than 13 years (circle symbol, n=8, figure 1B) were receiving non-biologicals therapy. We further analyse the immunosuppressive drug exposure time-to-HZ diagnosis among patients with RA receiving different immunosuppressive medication (figure 2). The results showed that patients in biologicals medication groups had a shorter time period for HZ occurrence than those in the non-biologicals group. HZ occurrence time was significantly different between the biologicals and non-biologicals medication groups (p<0.001), but there was no significant difference between the anti-TNF biologicals and non-anti-TNF biologicals groups (p=0.41). The average time between the onset of RA identification and HZ occurrence was 4.0±3.8 years (range 0.1–14.8 years, table 3); and 75 (27.3%) patients were diagnosed with HZ within 1 year after RA identification. The time-to-HZ was the shortest in the non-anti-TNF biologicals group (1.7±1.3 years, p<0.001, table 3), followed by the anti-TNF biologicals group (2.3 ±2.0 years, p<0.001) and the non-biologicals group (4.6 ±4.0 years).

In this study, 154 (56.0%) patients with RA with HZ were treated with oral antiviral medications, and 31 (11.3%) received intravenous acyclovir (table 3). Eighty patients with RA with HZ (80/275, 29.1%) had HZ complications, the most common of which was HZ neuralgia (73/275, 26.5%), followed by ophthalmic HZ (7/275, 2.5%). Among seven cases of RA with ophthalmic HZ, three patients had received non-anti-TNF biologicals (2 rituximab and 1 tocilizumab) medication (p<0.001).

Table 2 ORs for the risk of HZ according to anti-rheumatic medication used in patients with rheumatoid arthritis

	HZ case (n=275)	Control (n=1100)	Crude OR (95% CI)	p Value	Adjusted* OR (95% CI)	p Value
NSAID						
Non-current use	63 (22.9%)	554 (50.4%)	1.0 (ref.)		1.0 (ref.)	
Current use	212 (77.1%)	546 (49.6%)	3.41 (2.52 to 4.63)	**<0.001**	1.28 (0.89 to 1.84)	0.18
Methotrexate						
Non-current use	127 (46.2%)	884 (80.4%)	1.0 (ref.)		1.0 (ref.)	
Current use	148 (53.8%)	216 (19.6%)	4.77 (3.61 to 6.31)	**<0.001**	1.98 (1.43 to 2.76)	**<0.001**
Hydroxychloroquine						
Non-current use	70 (25.5%)	665 (60.5%)	1.0 (ref.)		1.0 (ref.)	
Current use	205 (74.5%)	435 (39.5%)	4.48 (3.33 to 6.03)	**<0.001**	1.95 (1.39 to 2.73)	**<0.001**
Sulfasalazine						
Non-current use	140 (50.9%)	890 (80.9%)	1.0 (ref.)		1.0 (ref.)	
Current use	135 (49.1%)	210 (19.1%)	4.09 (3.09 to 5.41)	**<0.001**	1.75 (1.27 to 2.43)	**<0.001**
Leflunomide						
Non-current use	262 (95.3%)	1076 (97.8%)	1.0 (ref.)		1.0 (ref.)	
Current use	13 (4.7%)	24 (2.2%)	2.22 (1.12 to 4.43)	**0.02**	1.12 (0.54 to 2.32)	0.76
Corticosteroids						
None	33 (12.0%)	650 (59.1%)	1.0 (ref.)		1.0 (ref.)	
<5 mg/day	61 (22.2%)	148 (13.5%)	8.12 (5.13 to 12.86)	**<0.001**	1.28 (1.17 to 1.47)	**<0.001**
5 to <10 mg/day	151 (54.9%)	263 (23.9%)	11.31 (7.56 to 16.92)	**<0.001**	1.73 (1.34 to 2.32)	**<0.001**
≥10 mg/day	30 (10.9%)	39 (3.5%)	15.15 (8.39 to 27.35)	**<0.001**	2.30 (1.25 to 4.22)	**0.01**
p_{trend}				**<0.001**		**<0.001**
Anti-TNF biologicals†						
Non-current use	220 (80.0%)	1032 (93.8%)	1.0 (ref.)		1.0 (ref.)	
Current use	55 (20.0%)	68 (6.2%)	3.79 (2.58 to 5.57)	**<0.001**	2.07 (1.34 to 3.19)	**0.001**
Non-anti-TNF biologicals‡						
Non-current use	260 (94.5%)	1058 (96.2%)	1.0 (ref.)		1.0 (ref.)	
Current use	15 (5.5%)	42 (3.8%)	1.45 (0.79 to 2.66)	0.23	1.05 (0.54 to 2.03)	0.88

Bold text indicates that a p value of <0.05 and considered statistically significant.
*Adjusted by comorbidities (HT, CKD and DM) and other anti-rheumatic medication use.
†Including adalimumab, etanercept and golimumab.
‡Including rituximab, tocilizumab and abatacept.
CKD, chronic kidney disease; DM, diabetes mellitus; HT, hypertension; HZ, herpes zoster; NSAID, non-steroid anti-inflammatory drugs; TNF, tumour necrosis factor.



Test method	P for log rank	Pair comparison		
		(Anti-TNF, Non anti-TNF biologics)	(Anti-TNF, Other)	(Non anti-TNF biologics, Other)
Log Rank test	**<0.001****	0.41	**<0.001****	**<0.001****

Figure 2 Drug exposure time-to-HZ diagnosis among patients with RA receiving different immunosuppressive medication treatments. HZ, herpes zoster; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Table 3 The proportion of severity and complications of HZ in patients with rheumatoid arthritis

			Medication group							
	All		Anti-TNF biologicals*			Non-anti-TNF biologicals†			Non-biologicals	
	(N=275)		(N=55)			(N=15)			(N=205)	
Variable	n	Per cent	n	Per cent	p Value‡	n	Per cent	p Value‡	n	Per cent
Time-to-HZ event (years)										
Mean±SD	4.0±3.8		2.3±2.0		**<0.001**	1.7±1.3		**<0.001**	4.6±4.0	
Antiviral treatment										
Oral	154	56.0	37	67.3	0.086	8	53.3	0.798	109	53.2
Intravenous§	31	11.3	14	25.5	**<0.001**	6	40.0	**<0.001**	11	5.4
HZ complication										
HZ neuralgia	73	26.5	20	36.4	0.092	4	26.7	0.943	49	23.9
Ophthalmic HZ	7	2.5	1	1.8	0.625	3¶	20.0	**<0.001**	3	1.5

Bold text indicates that a p value of <0.05 and considered statistically significant.
*Including adalimumab, etanercept and golimumab.
†Including rituximab, tocilizumab and abatacept.
‡Compared with the non-biologicals group.
§Including adalimumab (11), etanercept (3), rituximab (4), tocilizumab (2), and non-biologicals (11).
¶Rituximab (2), tocilizumab (1).
HZ, herpes zoster; TNF, tumour necrosis factor.

DISCUSSION

We performed a case–control study using a hospital-based clinical information database to investigate the association of immunosuppressive medication with HZ. Among 9025 newly diagnosed patients with RA during the period 2001–2014, we noted an increased risk of HZ in those receiving immunosuppressive medication to treat RA disease. The use of corticosteroids showed a strong dose-dependent association with HZ (p_{trend}<0.001). Patients with RA taking specific non-biological medications (eg, methotrexate aOR=1.98, hydroxychloroquine aOR=1.95, and sulfasalazine aOR=1.75) were similar or slightly less prone to develop HZ than patients taking anti-TNF biological medications (aOR=2.07). Furthermore, patients in biologicals medication groups had a shorter time period for HZ occurrence than those in the non-biologicals group (p<0.001). A higher incidence of severe HZ (11.3%) was found in our RA cohort. The use of biologicals was associated with an increased risk of severe HZ and ophthalmic involvement.

Serious infections are a major concern in patients with RA and result in increased mortality.[22] An increased risk of infections in patients with RA may be associated with RA-related immunological dysfunctions, immunocompromising comorbidities and immunosuppressive agent-related immunosuppressive effects.[23 24] Several comorbidities (eg, HT, CKD, DM and malignancy) have been shown to lead to an increased risk of developing HZ in patients with RA, which associated with disease-related immunocompromisation or therapeutic treatment, causes a reduction in cellular immunity.[25–27] In this study, our patients with RA with HZ also had a higher prevalence of HZ-related comorbidities (eg, HT, CKD and DM, p<0.05) as did other population-based studies in western countries.[10 25] Previous published literature had shown that HT, CKD and DM were associated with increased risk HZ,[28] which may be due to disease-related immune dysfunction or the effects of therapeutic agents.

Glucocorticoids are potent immunosuppressive drugs that are widely used in rheumatic diseases care.[29] Dixon *et al*[30] showed that glucocorticoids therapy is associated with serious infection risks in older patients with RA, which particularly in current and recent doses have the greatest impact on infection risk.[31] Our results showed an increased risk of HZ in patients with RA using corticosteroids (<5 mg/day aOR=1.28 vs ≥10 mg/day aOR=2.30, p_{trend}<0.001); this was consistent with previous studies in western countries.[10–15] We thought the risk of HZ should be associated with the severity of the RA disease and glucocorticoids-related immunosuppressive effects. In addition to corticosteroids, we also found that several non-biological medications (eg, methotrexate aOR=1.98, hydroxychloroquine aOR=1.95, and sulfasalazine aOR=1.75) were associated with the risk of HZ in patients with RA; this had also been noted in studies in the USA and Europe.[10–14]

In addition, our results showed that the use of anti-TNF biologicals in patients with RA was associated with an increased risk of HZ (aOR=2.07, 95% CI 1.34 to 3.19) compared with non-users. Since TNF plays a critical role in the control of viral infection, the depletion of TNF by treatment with anti-TNF biologicals might facilitate the development or reactivation of viral infection.[31 32] Furthermore, the drug exposure time-to-HZ in patients receiving anti-TNF biological medications was shorter than that in those using non-biological medications (2.3±2.0 vs 4.6±4.0 years, p<0.001). Our data showed that the risk of HZ was greatest soon after initiating anti-TNF therapy. A similar result has also been found in the UK.[14]

Among anti-TNF biologicals users, a higher ratio of patients with RA with HZ received adalimumab compared with control subjects (10.9% vs 2.2%, p<0.001). In addition, we found an increased risk of HZ in adalimumab users (crude OR=5.49, 95% CI 3.15 to 9.56, p<0.001), compared with non-users (see online supplementary table). Another study in Germany also found that only treatment with monoclonal anti-TNF antibodies (adalimumab or infliximab) was associated with an increased risk of HZ in patients with RA (HR=1.82, 95% CI 1.05 to 3.15, p=0.03); there was no association with the TNF receptor fusion protein (etanercept) (HR=1.36, 95% CI 0.73 to 2.55, p=0.33).[14] Since immunosuppression-related cellular immunity decline is known to trigger reactivation of VZV, we thought some characteristics of adalimumab (eg, high TNF binding avidity, slow dissociation and long serum half-life)[33] might explain the higher risk of HZ in patients with RA receiving adalimumab, compared with those receiving etanercept. In addition, golimumab was not available until mid-2012 in Taiwan. Therefore, the numbers of golimumab user was less than etanercept, which may cause that patients prescribed golimumab seem not have higher risk compared with etanercept in this study. The confirmation is required from further large and long-term studies.

In accordance with intravenous antiviral medications used for HZ, it is worth noting that our results showed that the incidence of severe HZ was higher compared with a previous RA cohort study in the USA (11.3% vs 4.6%).[12] Most patients with RA with HZ complications were aged more than 50 years (93.8%) and female (83.8%), which was consistent with the results in the general population.[6 34] Regarding the complications of HZ, the incidence of PHN was higher in our RA cohort compared with patients with RA in the USA (26.5% vs 19.1%).[12] In addition, our results showed that the incidence of severe HZ was higher in patients with RA receiving biologicals, compared with those in the non-biologicals group (anti-TNF, 25.5% vs 5.4%, p<0.001; non-anti-TNF, 40.0% vs 5.4%, p<0.001). Serious morbidity and mortality from VZV infection has been reported in patients receiving anti-TNF biologicals therapy in the USA, Europe and Korea.[35] Most cases were receiving

infliximab, followed by etanercept and adalimumab.[35] A study in Israel found anti-TNF biologicals to be associated with an increased HZ risk (HR=2.73, 95% CI 1.58 to 4.70), as well as related to PHN occurrence (HR=2.95, 95% CI 0.41 to 21.06).[36] In Taiwan, infliximab is not approved. In this study, the incidence of PHZ tended to increase with anti-TNF biologicals treatment, compared with non-biologicals treatment (36.4% vs 23.9%), but this increase was not statistically significant (p=0.092). We thought that the decrease in statistical power might be associated with the small case numbers in this study, and confirmation is required from further larger studies. In addition to PHN, ophthalmic HZ is another common HZ complication. Until now, most published ophthalmic HZ studies are case reports[37] and little is known about the risk factors of ophthalmic HZ in patients with RA. Our results demonstrated a trend towards a higher proportion of ophthalmic HZ in patients receiving therapy with non-TNF biologicals (rituximab/tocilizumab), compared with non-biologicals (20.0% vs 1.5%, p<0.001). The above observations suggest a higher risk of severe HZ in patients with RA receiving biological therapy.

This study has several limitations. First, the immunosuppressive medication-related individual rheumatic disease activity data was lacking. In our databases, a total of 52 HZ cases had a measurement of 28-joint disease activity score (DAS28) at the time of HZ, and the average of the score was higher (4.54±1.27) and had an active status. In addition, a significantly higher C reactive protein (CRP) was shown in HZ cases (1.75±0.58 mg/dL), compared with that in controls (0.98±0.47 mg/dL, p=0.04). On the basis of our results, we thought uncontrolled RA disease itself would render one more prone to HZ. In addition, the British Society for Rheumatology guidelines requested that patients with RA had a DAS28>5.1 (severe RA) then started biological therapy.[20] In this study, among 70 HZ cases with biologicals treatment, only 53 (75.7%) were first-time used, while the other 17 (24.3%) were had other biologics use history. Therefore, we thought that patients with more severe RA may be more likely to use biologicals and a higher dosage of corticosteroids for more intensive therapy. Therefore, we estimated the severity of RA maybe as a risk factor for HZ. Further studies are required to confirm. Second, the validation of antiviral treatment in the outpatients department cannot be fully confirmed. Although only 185 (67.3%) of the patients with RA with HZ received antiviral therapy, most patients without an antiviral treatment record in our database received HZ medication in nearby clinics. Therefore, we may have underestimated the risk of HZ. In addition, the real vaccination information is not available completely. In Taiwan, zoster vaccine was available since October 2013. In our database, there were only two patients in the control group who had zoster vaccination. All HZ cases had not had zoster vaccination before HZ. Third, this study was conducted at a single medical centre and included a small number of cases; consequently, it is likely that the study cannot reflect the complete characteristics of HZ in patients with RA. However, to the best of our knowledge, this is the first long-term case–control study to describe an association between immunosuppressive drugs and HZ in Asian patients with RA after controlling for several potential confounders, and the first study to investigate the relationship between biologicals and severe HZ in Asia. Finally, the matched control cohort may have a selection bias. Nevertheless, we analysed data from a clinical information database and reviewed medical care records to identify patients with RA with HZ, so we believe that it is only slightly affected by selection and recall biases. The major strength of this study is the use of long-term medical records. A 14-year follow-up period (2001–2014) enhanced the statistical power and accuracy of this study. We believe this study provides useful information that can help increase the awareness of physicians in assessing the possibility and outcomes of HZ in patients with RA during the period of specific immunosuppressive medication therapy.

In conclusion, although it is difficult to distinguish the risks conferred by immunosuppressive drugs from disease activity among patients with RA, our data showed an increased risk of HZ in patients with RA with several immunosuppressive medications, particularly when using corticosteroids. The incidence of severe HZ among patients with RA in Asia was higher than that in the USA (11.3% vs 4.6%). Biologicals were associated with severe HZ occurrence and the risk of HZ was greatest soon after initiating biologicals therapy. A higher incidence of HZ complications in patients with RA was found in this study. Therefore, it is important to closely monitor the occurrence of HZ in patients with RA during immunosuppressive therapy and start immediate efficient antiviral treatment to prevent the development of severe complications.

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