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MAJOR ARTICLE

Herpes Zoster Risk Factors in a National Cohort of Veterans with Rheumatoid Arthritis

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(See the editorial commentary by Cohen on pages 1372–4)

Background. Herpes zoster occurs more commonly in patients taking immunosuppressive medications, although the risk associated with different medications is poorly understood.

Methods. We conducted a retrospective cohort study involving 20,357 patients who were followed in the Veterans Affairs healthcare system and treated for rheumatoid arthritis from October 1998 through June 2005. Cox proportional hazards regression was used to determine risk factors for herpes zoster and herpes zoster–free survival. Chart review was performed to validate the diagnosis of herpes zoster.

Results. The incidence of herpes zoster was 9.96 episodes per 1000 patient-years. In time-to-event analysis, patients receiving medications used to treat mild rheumatoid arthritis were less likely to have an episode of herpes zoster than patients receiving medications used to treat moderate and severe rheumatoid arthritis ($P < .001$). Independent risk factors for herpes zoster included older age, prednisone use, medications used to treat moderate and severe rheumatoid arthritis, malignancy, chronic lung disease, renal failure, and liver disease. Among patients receiving tumor necrosis factor–α antagonists, etanercept (hazard ratio, 0.62) and adalimumab (hazard ratio, 0.53) were associated with a lower risk of herpes zoster. There was excellent agreement between the *International Classification of Diseases, Version 9, Clinical Modification* diagnosis of herpes zoster and diagnosis by chart review ($\kappa = 0.92$).

Conclusions. Risk factors for herpes zoster included older age, prednisone use, medications used to treat moderate and severe rheumatoid arthritis, and several comorbid medical conditions. These results demonstrate that the Department of Veterans Affairs' national administrative databases can be used to study rare adverse drug events.

Herpes zoster (HZ), a reactivation of latent varicella-zoster virus infection, causes substantial morbidity, especially among elderly and immunocompromised patients [1]. Established risk factors for HZ include older age and immunosuppressive medications [2–4]. Other potential risk factors, including female sex [3, 5, 6], malignancy [7, 8], kidney disease [6, 8], and AIDS [9], have been identified by some studies but not others.

Although it has been established that immunosuppressive medications contribute to excess risk of HZ, the comparative risk of HZ among different immunosuppressive medications is unclear. Enhanced understanding of the risk of HZ associated with different classes of immunosuppressive medications may provide clinicians with useful information as they prescribe immunomodulatory drugs to individual patients. This newfound knowledge may also influence the evaluation and implementation of HZ immunization strategies in patients prior to their receipt of immunosuppressive medications.

Adverse drug events, such as infection after immunosuppression, are between the fourth and sixth most common cause of death in the United States [10]. Under the Food and Drug Administration's current drug approval process, premarketing clinical trials for a new drug typically include 500–3000 exposed patients. This

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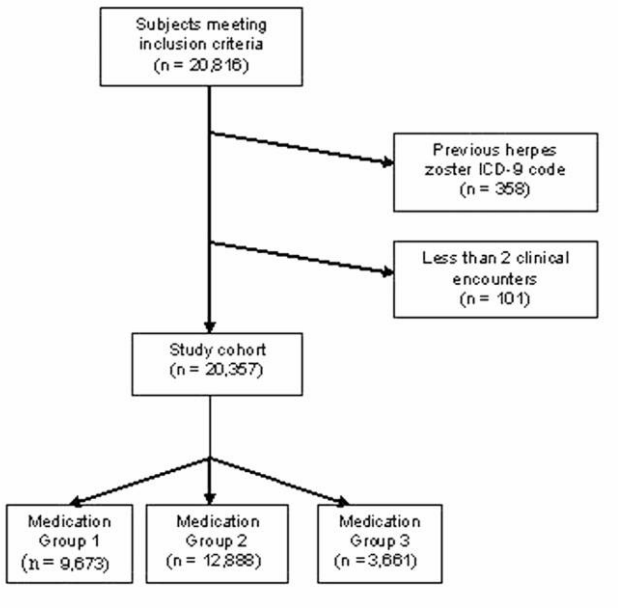

Figure 1. Flow diagram for study of patients in the Veterans Affairs health care system treated for rheumatoid arthritis, October 1998–June 2005. Data from different discrete time periods within a single patient record could be included in different medication groups if the patient's medication group number increased over time. A patient could be in only 1 medication group at any point in time.

allows identification of common adverse drug events but not rare ones [11]. Current systems for detection and investigation of rare adverse drug events in the United States are inadequate [12]. A 2007 report by the Institute of Medicine emphasized the need to improve postmarketing surveillance of adverse drug events by increasing the number and quality of programs that use data from large automated healthcare databases [13]. The Department of Veterans Affairs (VA) national administrative databases present an ideal opportunity to characterize and investigate rare adverse drug events. In this study, we used the VA's national administrative databases to examine HZ risk, risk factors, treatments, and outcomes in a large national cohort of veterans with rheumatoid arthritis (RA), with a particular focus on the contribution of different classes of immunosuppressive medications to the risk of HZ.

METHODS

This study was approved by the institutional review boards of the participating institutions.

Databases

The Austin Automation Center is the VA's centralized repository of administrative data. We obtained all inpatient and outpatient *International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM)* diagnosis codes, encounter data, and demographic data from the inpatient and outpatient data sets of the Austin Automation Center. We obtained inpatient and outpatient pharmacy data on our patients from the VA's Pharmacy Benefits Management database. Data from the Austin Automation Center and the Pharmacy Benefits Management database were merged into a single database by means of common unique identifiers.

Study Sample

The study period was 1 October 1998–30 June 2005. The study sample included all veterans who had an *ICD-9-CM* code diagnosis of RA during the study period and who, after a ⩾4-month history of receiving medications from the VA during the study period, subsequently received a first prescription for a disease-modifying antirheumatic drug (DMARD).

We excluded patients who had a diagnosis of HZ at any time prior to receiving a DMARD or who did not have ⩾2 separate outpatient or inpatient clinical encounters during the study period.

Patient records were censored at the end of the last prescribed medication course, the last clinical encounter, or the first occurrence of HZ, whichever came last. Thus, recurrent HZ was excluded from our analyses. Uncensored patients were followed up through 31 December 2006.

Definitions

RA. On the basis of an algorithm validated by Singh et al [14], the diagnosis of RA required both occurrence of an *ICD-9-CM* code for RA on ⩾1 occasion in either the inpatient or outpatient record and the receipt of a prescription for a DMARD on ⩾1 occasion. See the appendix (online only) for *ICD-9-CM* codes accepted for definition of RA.

Medication group. RA treatments were subdivided into medication groups on the basis of their place in the armamentarium of RA therapeutics. Group 1 (treatment of mild disease) included hydroxycholoroquine, sulfasalazine, auranofin, injectable gold, and penicillamine. Group 2 (treatment of moderate disease) included methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine, and anakinra. Group 3 (treatment of severe disease) included the tumor necrosis factor (TNF)–α antagonists (etanercept, infliximab, and adalimumab), which are typically used after failure to respond adequately to medications in groups 1 and 2. Though treatment of RA is highly individualized, existing RA treatment guidelines support this classification system [15, 16].

DMARD. DMARDs were defined as all medications in medication groups 1, 2, and 3.

Patient-time in medication group. Time zero was defined as the date of the first prescription for a medication in a given medication group. The patient continued in that medication group until a medication from a higher-numbered medication

group was prescribed or until censorship. Data from different discrete time periods within a single patient record could be included in different medication groups if the patient's medication group number increased over time. A patient could be in only 1 medication group at any point in time.

HZ. The first occurrence in the study period of an *ICD-9-CM* code accepted for the definition of HZ (appendix [online only]) after ⩾1 clinical encounter in the study period without such an *ICD-9-CM* code.

Hospitalization for HZ. Hospitalization for which an *ICD-9-CM* code for HZ is in the field indicating the diagnosis primarily responsible for hospitalization.

HZ complications. See the appendix (online only) for accepted *ICD-9-CM* codes.

HZ treatments. Oral acyclovir, valacyclovir, famciclovir, and intravenous acyclovir were defined as HZ treatment if they were prescribed within 90 days before or after HZ diagnosis.

Comorbid medical conditions. We used *ICD-9-CM* code definitions developed by Elixhauser et al.[17] for use with administrative data. Our variable for malignancy was a composite of ICD-9-CM codes that were used to define metastatic cancer, solid tumor without metastases, and lymphoma [17].

Validation

The accuracy of *ICD-9-CM* diagnosis of HZ was measured against the gold standard, medical record review by a physician. For the patients in our cohort from the St. Louis VA Medical Center, medical records were randomly selected for review using a random number generator. Of 101 patients with an HZ diagnosis code, 50 were reviewed, and of 3860 patients without an HZ diagnosis code, 150 were reviewed. Medical record review was performed by 1 author (J.R.M.), by means of a methodology described in the appendix (online only).

Data Analyses

The incidence of HZ was calculated as the number of events per 1000 patient-years. For descriptive and bivariate analysis, dichotomous variables were analyzed using the χ^2 test and Fisher's exact test, where appropriate. Continuous variables were analyzed using the Student's t test. A 2-sided P value of <.05 was considered to be statistically significant. The risk of outcomes was described using hazard ratios and 95% confidence intervals (CIs). Time-to-event analysis was performed using Cox proportional hazards regression. In regression modeling, membership in each medication group was modeled as a time-dependent dummy variable to account for the change in medication groups over time. Each drug was modeled separately and adjusted for age, sex, race, and time-dependent comorbid diagnoses. The race variable as it was recorded in the Austin Automation Center has been shown to correlate poorly with patient self-report [18]. Despite this limitation, we obtained this variable and included it in our analyses in order to control for it. Comorbidities were treated as time-dependent variables. For validation of the HZ diagnosis, agreement between *ICD-9-CM* code and the gold standard was calculated using the κ statistic. All analyses were performed using SAS software, version 6.12 (SAS Institute). The time-to-event graph was created using R software, version 2.5.1 (R Foundation).

RESULTS

There were 20,816 patients who met our inclusion criteria. After applying exclusion criteria, our study cohort consisted of 20,357 patients with >26 million patient-days (figure 1).

Patient demographic characteristics, comorbid medical conditions, and RA treatments are shown in table 1. Of the 20,357 patients, there were 5771 (28.4%) with malignancy; the most common type of malignancy was prostate cancer (1674 [29% of malignancies]). The frequency of malignancy in our sample is consistent with the frequency seen in other administrative data sets [17], after considering the additional cases found when outpatient claims data are added [19]. Only 2451 (12.0%) of the patients had none of the examined comorbid conditions.

There were 713 episodes of HZ in the study cohort, with an overall incidence of 9.96 episodes per 1000 patient-years. The incidence of HZ was significantly higher in medication group 2, compared with that of medication group 1 (11.18 vs. 8.00 per 1000 patient-years; $P < .001$), and the incidence of HZ was significantly higher in medication group 3, compared with that of medication group 1 (10.60 vs. 8.00 episodes per 1000 patient-years; $P < .001$). The incidence was similar between medication groups 2 and 3. In time-to-event analysis (figure 2), patients in each of medication groups 2 and 3 had shorter HZ-free survival than group 1. HZ-free survival was significantly different between medication groups ($P < .001$).

In the study cohort, 471 (66.1%) of the 713 patients with HZ were treated with oral antiviral medications, and 33 (4.6%) received intravenous acyclovir (table 2). Hospitalization for HZ occurred in 35 (4.9%) of the patients, and the incidence was similar between medication groups.

Independent risk factors for HZ included older age, prednisone, medications in groups 2 and 3, malignancy, chronic lung disease, renal failure, and liver disease (table 3). The hazard ratio of group 2 medications was similar to the hazard ratio of group 3 medications (1.34 vs. 1.38; $P = .67$).

There were 96 patients with incident HZ among the 3661 patients who were prescribed TNF antagonists. Of these 96 patients, 59 were receiving etanercept, 33 infliximab, and 4 adalimumab at the time of the HZ episode. Among the TNF antagonists, etanercept (hazard ratio, 0.62; 95% CI, 0.40–0.95) and adalimumab (hazard ratio, 0.53; 95% CI, 0.31–0.91) were associated with a lower risk of HZ, compared with infliximab (table 4).

Table 1. Demographic and clinical characteristics of patients with rheumatoid arthritis in retrospective cohort study.

Variable	All (N = 20,357)	Medication group		
		Group 1 (n = 9673)	Group 2 (n = 12,888)	Group 3 (n = 3661)
Age, mean (SD) years	62.92 (12.4)	61.9 (12.8)	63.7 (12.0)	59.3 (11.6)
Male sex, no. (%)	18,477 (90.8)	8616 (89.1)	11,764 (91.3)	3333 (91.0)
Race, no. (%)				
White	13,639 (67.0)	6311 (65.2)	8696 (67.5)	2565 (70.1)
Black	2280 (11.2)	1320 (13.6)	1299 (10.1)	324 (8.9)
Other	1079 (5.3)	512 (5.3)	651 (5.1)	223 (6.1)
Unknown	3359 (16.5)	1530 (15.8)	2242 (17.4)	549 (15.0)
Medication, % of patients (no. of months, median [IQR])				
Prednisone	59.8 (26 [15–47])	34.5 (13 [5–30])	62.7 (18 [6–28])	55.0 (20 [8–33])
Hydroxychloroquine	46.0 (27 [10–43])	72.8 (19 [8–38])	28.7 (19 [7–35])	22.0 (15 [5–29])
Sulfasalazine	26.8 (14 [5–28])	39.7 (12 [5–26])	17.3 (13 [6–26])	17.0 (12 [5–29])
Auranofin	0.6 (16 [4–28])	1.0 (14 [5–27])	0.3 (15 [6–29])	0.2 (12 [4–26])
Injectable gold	0.4 (13 [6–23])	0.8 (11 [4–21])	0.1 (14 [6–22])	0.2 (11 [7–24])
Penicillamine	0.3 (11 [4–19])	0.5 (12 [4–21])	0.1 (10 [5–22])	0.1 (8 [4–18])
Methotrexate	54.6 (27 [15–48])	0	83.7 (24 [14–51])	51.5 (23 [12–52])
Azathioprine	5.1 (13 [4–30])	0	7.2 (14 [5–26])	4.9 (13 [4–31])
Leflunomide	13.7 (20 [6–40])	0	19.8 (18 [5–36])	19.8 (22 [6–37])
Cyclosporine	1.9 (11 [3–22])	0	2.7 (13 [4–20])	1.3 (9 [4–19])
Cyclophosphamide	1.8 (7 [2–13])	0	2.7 (8 [3–15])	0.6 (8 [3–13])
Anakinra	0.5 (6 [2–12])	0	0.5 (7 [2–14])	1.5 (6 [3–11])
Etanercept	12.4 (16 [6–33])	0	0	68.9 (16 [6–33])
Infliximab	4.0 (14 [5–30])	0	0	22.0 (14 [5–30])
Adalimumab	5.8 (9 [4–18])	0	0	32.4 (9 [4–18])
Comorbidities,[a] no. (%)				
Hypertension	19,284 (94.7)	6949 (71.8)	9634 (74.8)	2701 (73.8)
Diabetes mellitus	7825 (38.4)	2656 (27.5)	4044 (31.4)	1125 (30.7)
Malignancy	5771 (28.3)	2056 (21.3)	2983 (23.1)	732 (20.0)
Chronic lung disease	10,163 (49.9)	3617 (37.4)	5099 (39.6)	1447 (39.5)
Congestive heart failure	3726 (18.3)	1285 (13.3)	1987 (15.4)	454 (12.4)
Cardiac arrhythmia	5408 (26.6)	1804 (18.6)	2871 (22.3)	733 (20.0)
Renal failure	2106 (10.3)	730 (7.5)	1076 (8.3)	300 (8.2)
Liver disease	1582 (7.8)	808 (8.4)	512 (4.0)	262 (7.2)
AIDS	102 (0.5)	46 (0.5)	38 (0.3)	18 (0.5)
None of the above	2451 (12.0)	869 (9.0)	1166 (9.0)	416 (11.4)
Episode of HZ, no. (%) of patients	713 (3.5)	208 (2.2)	409 (3.2)	96 (2.6)
No. of patient-years	71,607.4	25,986.2	36,595.1	9053.5
Episodes of HZ per 1000 patient-years	9.96	8.00	11.18	10.60

NOTE. Because of group switching over time, group sums may exceed total N and statistical comparisons between groups were not performed. HZ, herpes zoster; IQR, interquartile range.

[a] Diagnosed prior to or during group time.

A medical record review to validate the *ICD-9-CM* code for HZ demonstrated that 45 of the 50 patients with an HZ *ICD-9-CM* code had an acute episode of HZ in the 90 days prior to receiving the code, for a positive predictive value of 90%. All 5 of the patients who did not have an acute episode of HZ in the prior 90 days had had HZ in the past. One (0.7%) of the 150 patients without an HZ *ICD-9-CM* code had an episode of acute zoster during the study period, for a negative predictive value of 99.3%. The κ statistic for agreement between the *ICD-9-CM* code diagnosis and the medical record diagnosis was 0.92, indicating excellent agreement.

DISCUSSION

For this large sample of patients with RA in the VA health care system, we analyzed HZ-free survival as well as outcomes, treat-

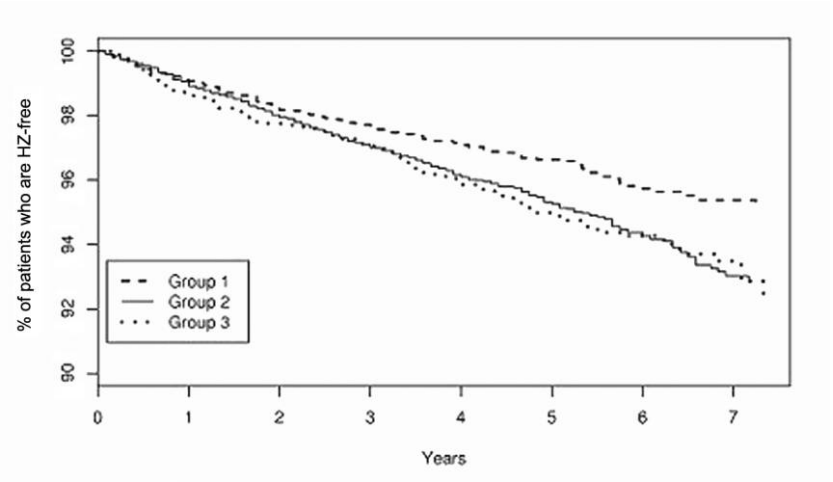

Figure 2. Graph of time-to-event analysis indicating herpes zoster (HZ)–free survival for patients in 3 medication groups. After adjusting for demographic data and comorbid medical conditions, time-to-HZ was different among groups 1, 2, and 3 ($P < .001$).

ments, and risk factors for HZ. While the occurrence of HZ in a patient with RA is relatively uncommon, we were able to identify 713 such occurrences among 20,357 patients, in >71 thousand patient-years, even after applying stringent inclusion criteria designed to ensure the quality of our data and the validity of our conclusions. We demonstrated in this population that the risk of HZ while taking TNF antagonists is similar to the risk while taking group 2 medications, and that the risk associated with infliximab exceeds the risk associated with other TNF antagonists.

HZ incidence was highest among patients taking group 2 and 3 medications, and the risk was similar between the 2 groups. Prior studies have conflicting results in this area. Listing et al. [20] studied 1529 patients with RA receiving DMARDs and demonstrated that the risk of herpes virus infections was similar among patients receiving TNF antagonists and those receiving other DMARDs. The small study size (only 17 episodes of HZ were seen) made it unlikely that significant differences would be detected. Wolfe et al. [4] studied 10,614 patients with RA and found that cyclophosphamide, azathioprine, prednisone, leflunomide, and some nonsteroidal anti-inflammatory drugs were risk factors for HZ, but that TNF antagonists and methotrexate were not. However, data on both medication exposure and HZ incidence were collected by self-administered patient questionnaires, which are likely to be less temporally accurate than electronic prescription and diagnosis data. In addition, our study included more than twice as many patient-years as this study. Smitten et al. [21] studied a database of >160,000 commercially insured patients and found that biologic DMARDs were associated with a higher risk of HZ than other DMARDs; however, this study did not differentiate between groups of nonbiologic DMARDs and did not include several covariates known to impact HZ risk.

The incidence of HZ in our sample (9.96 episodes per 1000 patient-years) was similar to the incidence seen in other studies. Donahue et al. [22] and Insinga et al. [23] found incidences of 2.2 and 3.2 episodes per 1000 patient-years, respectively, in administrative databases sampling the general US population, not specifically selected for RA. Studies examining cohorts of patients with RA found incidences similar to ours: a study using an administrative database of commercially insured RA patients in the United States found an incidence of 9.83 episodes per 1000 patient-years [23], and a study using a registry of patients with RA identified an incidence of 13.2 episodes per 1000 patient-years [4]. The higher incidence of HZ in the latter study may be explained by a higher rate of infliximab use among patients in that study or by overestimates of HZ based on patient self-report. Although it is possible that inaccuracies in diagnosis coding explain the difference, our validation results suggest that our incidence estimate is robust for this population.

We found that older age and certain comorbid medical conditions (malignancy, chronic lung disease, renal failure, and liver disease) were independent risk factors for HZ. Older age and cell-mediated immune defects are well-described risk factors for HZ [2–4]. Prior studies have described malignancy [7, 8], renal disease [6, 8], and chronic lung disease [24] as HZ risk factors. Female sex was not found to be an HZ risk factor in our study. Some prior studies have identified female sex as a risk factor [3, 5, 6], possibly due to sex-specific patterns of healthcare utilization [24]. Our results may differ because of the inclusion of previously ignored covariates or differences in sex-specific healthcare utilization between female veterans and nonveterans, or because the low proportion of women in our sample (9.5%) made that part of our analysis relatively underpowered.

Among patients receiving TNF antagonists, adalimumab and

Table 2. Treatments and outcomes for patients with rheumatoid arthritis and herpes zoster (HZ).

Variable	All (n = 713)	Medication group			P	
		Group 1 (n = 208)	Group 2 (n = 409)	Group 3 (n = 96)	Group 2 vs. Group 1	Group 3 vs. Group 1
Antiviral treatment						
Oral	471 (66.1)	136 (65.4)	268 (65.5)	67 (69.8)	>.5	>.1
Intravenous	33 (4.6)	2 (1.0)	28 (6.8)	3 (3.1)	<.001[a]	>.1
HZ complication						
HZ meningitis	3 (.4)	1 (0.5)	2 (0.5)	0 (0)	>.1	>.5
Other HZ nervous system complication	136 (19.1)	43 (20.7)	76 (18.6)	17 (17.7)	>.5	>.5
Ophthalmic HZ	48 (6.7)	15 (7.2)	28 (6.8)	5 (5.2)	>.5	>.1
Other HZ complication	45 (6.3)	13 (6.3)	28 (6.8)	4 (4.2)	>.5	>.1
Hospitalization for HZ	35 (4.9)	6 (2.9)	25 (6.1)	4 (4.2)	>.5	>.1

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Statistically significant association.

etanercept use were significantly associated with a lower risk of HZ. This finding is consistent with those of previous studies, which show higher rates of a composite endpoint of infection [22] as well as tuberculosis and other granulomatous infections [25] among patients who received infliximab, compared with patients who received etanercept. There are several differences in the properties of TNF antagonists that may explain differences in infection risk. In contrast to etanercept, infliximab binds to both soluble and transmembrane forms of TNF, induces apoptosis of monocytes and T cells, and induces expression of different leukocyte genes [25–27].

This study has significant strengths. The large size and national scope of this database allows not only the capture of a large number of rare events but also the application of strict inclusion criteria to maximize the quality of the data. We limited our sample to patients with multiple VA clinical encounters, ⩾4 months of drug prescriptions excluding DMARDs prior to DMARD initiation, and no HZ diagnosis prior to first DMARD prescription. Our data spans an 8-year period, allowing for the identification of events that occur long after drug initiation. Because our patients comprise a real-world cohort that was not subject to the eligibility criteria often present in randomized controlled trials of therapeutic agents, our data are generalizable to similar real-world populations.

Our study is limited by the fact that we did not include medication dose in our analysis. Duration, however, was taken

Table 3. Multivariate risk factors for herpes zoster (HZ) among patients with rheumatoid arthritis.

Variable	HZ (n = 713)	No HZ (n = 19,644)	Hazard ratio (95% CI)
Age, mean (SD) years	63.7 (11.5)	62.9 (12.5)	1.01 (1.01–1.02)[a]
Male sex	643 (90.2)	17,843 (90.8)	0.79 (0.61–1.02)
Prednisone use	512 (71.8)	12,895 (65.6)	1.41 (1.19–1.67)[a]
Medication group, no. of patients			
Group 1	208	9463	Reference
Group 2	409	12,479	1.34 (1.13–1.59)[a]
Group 3	96	3565	1.38 (1.08–1.77)[a]
Hypertension	528 (74.1)	14,928 (76.0)	1.06 (0.89–1.26)
Diabetes mellitus	214 (30.0)	6131 (31.2)	1.03 (0.87–1.21)
Malignancy	173 (24.3)	4742 (24.1)	1.24 (1.04–1.48)[a]
Chronic lung disease	306 (42.9)	8016 (40.8)	1.28 (1.10–1.49)[a]
Renal failure	69 (9.7)	1792 (9.1)	1.52 (1.18–1.97)[a]
Liver disease	46 (6.5)	1293 (6.6)	1.36 (1.00–1.85)[a]
AIDS	6 (0.8)	83 (0.4)	1.94 (0.87–4.36)[a]
None of the above	66 (9.3)	1820 (9.3)	…

NOTE. Data are no. (%) of patients, unless otherwise indicated. CI, confidence interval; SD, standard deviation.

[a] Statistically significant association.

Table 4. Risk factors for herpes zoster (HZ) among patients receiving tumor necrosis factor–α antagonists (medication group 3).

Variable	HZ (n = 96)	No HZ (n = 3565)	Hazard ratio (95% CI)
Age, mean (SD) years	58.5 (12.0)	57.8 (11.7)	1.01 (0.99–1.03)
Male sex	86 (89.6)	3247 (91.1)	0.74 (0.37–1.45)
Medication,[a] % of patients (no. of months, median [IQR])			
Prednisone	62.5 (10 [4–26])	54.7 (30 [13–53])	1.08 (0.69–1.70)
Hydroxychloroquine	16.7 (13 [7–25])	22.1 (27 [10–45])	0.70 (0.41–1.21)
Sulfasalazine	8.3 (11 [3–22])	17.3 (19 [6–42])	0.44 (0.21–0.91)[b]
Auranofin	0	0.2 (10 [3–56])	NC
Injectable gold	0	0.3 (17 [10–25])	NC
Penicillamine	0	0.1 (9 [8–37])	NC
Methotrexate	54.2 (12 [6–24])	51.0 (32 [17–53])	1.13 (0.75–1.70)
Azathioprine	6.3 (23 [9–42])	4.8 (11 [3–28])	1.06 (0.46–2.40)
Leflunomide	21.9 (9 [3–18])	19.7 (21 [7–41])	0.95 (0.58–1.56)
Cyclosporine	1.0 (1 [1–1])	1.3 (7 [2–24])	NC
Cyclophosphamide	1.0 (5 [5–5])	0.6 (7 [2–14])	NC
Anakinra	1.0 (1 [1–1])	1.5 (5 [2–13])	NC
Etanercept	64.6 (11 [5–29])	69.0 (16 [6–33])	0.62 (0.40–0.95)[b]
Infliximab	33.3 (8 [3–27])	21.7 (14 [5–30])	1.32 (0.85–2.03)
Adalimumab	16.7 (5 [4–10])	32.8 (9 [4–18])	0.53 (0.31–0.91)[b]
Comorbidities			
Hypertension	71 (74.0)	2630 (73.8)	1.31 (0.81–2.12)
Diabetes mellitus	30 (31.3)	1095 (30.7)	1.12 (0.71–1.76)
Malignancy	18 (18.8)	714 (20.0)	1.17 (0.69–1.99)
Chronic lung disease	33 (34.4)	1414 (39.7)	0.91 (0.58–1.41)
Renal failure	15 (15.6)	295 (8.3)	0.76 (0.30–1.93)
Liver disease	7 (7.3)	255 (7.2)	1.37 (0.62–3.01)
AIDS	0 (0)	18 (0.5)	NC
None of the above	13 (13.5)	403 (11.3)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. CI, confidence interval; IQR, interquartile range; NC, not calculated because of small numbers; SD, standard deviation.

[a] Received while in medication group 3.

[b] Statistically significant association.

into account in our survival models. With 14 different DMARDs plus prednisone in our study, the inclusion of dose variability in the analysis would have added significant complexity to the interpretation of the study and detracted from our primary aims. Our population was >90% male, and thus our results may not be generalizable to a female population. Although administrative data are imperfect sources of clinical information, they are very useful for large scale epidemiologic research. The validity of different *ICD-9-CM* codes varies widely [28, 29]. Our validation demonstrates that the diagnosis of HZ in our data is accurate, and our approach to RA diagnosis has also been shown to be accurate in prior studies [14].

RA severity can impact risk of infection [30]. We did not evaluate the impact of RA severity on HZ risk, because there is no accepted tool for measuring RA severity from administrative data. One study evaluating the relative contributions of RA treatment and RA severity to infection risk found that approximately one-third of the excess risk of infection was related to RA severity, and two-thirds was related to treatment [22]. Thus, the excess infection seen in the higher medication groups was likely caused in part by medication and in part by RA severity.

A varicella-zoster virus vaccine that prevents HZ is currently available in the United States and is recommended for use in individuals who are $\geq$60 years of age. Because of the risk of disseminated disease caused by the live attenuated vaccine strain of the virus, it is not recommended for patients receiving higher-dose immunosuppressive therapy, although the Advisory Committee on Immunization Practices has recently advocated the safety of the vaccine in selected patients receiving lower-dose corticosteroids and some DMARDs and $\geq$14 days prior to planned immunosuppression [2, 31, 32]. However,

clinical data supporting these recommendations are sparse, and our results on the comparative risk of infection among treatment types may inform future efforts to target this vaccine to populations most likely to benefit.

This study describes the risk of HZ associated with specific medications used to treat RA. These data may inform clinical decision-making in prescribing treatment for RA as well as future HZ vaccine testing and targeting in immunosuppressed populations. Our data show that the administrative databases of the Department of Veterans Affairs can be a useful source of data for the identification and analysis of rare adverse drug events.

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