Association Between the Initiation of Anti–Tumor Necrosis Factor Therapy and the Risk of Herpes Zoster

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Importance Herpes zoster reactivation disproportionately affects patients with rheumatoid arthritis (RA). It is unclear whether anti–tumor necrosis factor (anti-TNF) therapy elevates herpes zoster risk.

Objectives To ascertain whether initiation of anti-TNF therapy compared with nonbiologic comparators is associated with increased herpes zoster risk.

Design, Setting, and Patients We identified new users of anti-TNF therapy among cohorts of patients with RA, inflammatory bowel disease, and psoriasis, psoriatic arthritis, or ankylosing spondylitis from 1998 through 2007 within a large US multiinstitutional collaboration combining data from Kaiser Permanente Northern California, Pharmaceutical Assistance Contract for the Elderly, Tennessee Medicaid, and national Medicaid/Medicare programs. We compared herpes zoster incidence between new anti-TNF users (n=33,324) and patients initiating nonbiologic disease-modifying antirheumatic drugs (DMARDs) (n=25 742) within each inflammatory disease cohort (last participant follow-up December 31, 2007). Within these cohorts, we used Cox regression models to compare propensity score–adjusted herpes zoster incidence between new anti-TNF and nonbiologic DMARD users while controlling for baseline corticosteroid use.

Main Outcome Measures Incidence of herpes zoster cases occurring after initiation of new anti-TNF or nonbiologic DMARD therapy.

Results Among 33 324 new users of anti-TNF therapy, we identified 310 herpes zoster cases. Crude incidence rates among anti-TNF users were 12.1 per 1000 patient-years (95% CI, 10.7-13.6) for RA, 11.3 per 1000 patient-years (95% CI, 7.7-16.7) for inflammatory bowel disease, and 4.4 per 1000 patient-years (95% CI, 2.8-7.0) for psoriasis, psoriatic arthritis, or ankylosing spondylitis. Baseline use of corticosteroids of 10 mg/d or greater among all disease indications was associated with elevated risk (adjusted hazard ratio [HR], 2.13 [95% CI, 1.64-2.75]) compared with no baseline use. For patients with RA, adjusted incidence rates were similar between anti-TNF and nonbiologic DMARD initiators (adjusted HR, 1.00 [95% CI, 0.77-1.29]) and comparable between all 3 anti-TNF therapies studied. Across all disease indications, the adjusted HR was 1.09 (95% CI, 0.88-1.36).

Conclusion and Relevance Among patients with RA and other inflammatory diseases, those who initiated anti-TNF therapies were not at higher risk of herpes zoster compared with patients who initiated nonbiologic treatment regimens.

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THE REACTIVATION OF VARICELLA-zoster virus (herpes zoster or shingles) is of substantial public health concern. Its predilection for elderly and immunosuppressed individuals makes it an important cause of morbidity, causing pain, depression, and long-term disability in the form of postherpetic neuralgia. Furthermore, the ability of herpes zoster to cause disseminated complications and death in immunosuppressed individuals is well documented.[1-3] In the United States, herpes zoster incidence rates increase with age and range between 4 per 1000 patient-years in patients aged 50 years and 11 per 1000 patient-years in patients

Author Video Interview available at www.jama.com.

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aged 80 years, with rates highest in women.[4]

For patients with rheumatoid arthritis (RA), the risk of herpes zoster is elevated an additional 2- to 3-fold.[5,6] The contribution of widely used biologic immunosuppressive therapy to this increased risk is not well understood. These therapies, including tumor necrosis factor (TNF) antagonists, are commonly used to treat RA and a variety of other immune-mediated inflammatory diseases and have clearly been associated with an increased risk of tuberculosis and other opportunistic infections.[7,8] However, unlike with tuberculosis, a clear mechanism for TNF antagonism to cause herpes zoster has not been elucidated. Observational studies assessing this have used differing methodology and produced contradictory results to date, with limited ability to evaluate differential risk between TNF antagonist compounds.[9] These gaps in knowledge have large clinical relevance for physicians and patients who use these therapies.

Accordingly, as part of the Safety Assessment of Biologic Therapy, a US multi-institutional initiative to evaluate biologic therapy safety,[10] we assembled a large retrospective cohort combining data from 4 major US databases to describe rates of herpes zoster in various inflammatory diseases. We specifically evaluated in these diseases whether initiation (ie, new use) of anti-TNF therapy is associated with increased herpes zoster risk, and whether the monoclonal antibodies infliximab and adalimumab are associated with greater herpes zoster risk than etanercept.

METHODS

Data Sources and Cohort Formation

We used data from 4 large US automated databases from 1998 through 2007: (1) National Medicaid and Medicare databases (Medicaid Analytic eXtract, 2000-2005; Medicare, 2000-2006; and Medicare Part D, 2006), (2) Tennessee Medicaid (1998-2005), (3) The New Jersey's Pharmaceutical Assistance to the Aged and Disabled, and the Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (1998-2006), and (4) Kaiser Permanente Northern California (1998-2007). We used validated algorithms to identify patients of interest including those with RA, psoriatic arthritis, psoriasis, ankylosing spondylitis, and inflammatory bowel disease (IBD).[10]

This study was approved by the institutional review boards of all the Safety Assessment of Biologic Therapy participating institutions, and a waiver of patient informed consent was granted by these institutional review boards for the purposes of this study. Patients were eligible for inclusion if they had a baseline period of 365 days with continuous enrollment in the respective database preceding the first disease-modifying antirheumatic drug (DMARD) prescription fill. Patients with diagnoses for 2 or more autoimmune diseases or history of herpes zoster prior to first DMARD prescription fill were excluded.

Among potential cohort members, we identified new users of DMARDs, defined as having filled a prescription after 365 baseline days without prescriptions filled for the specific study medication or others in the same group. We defined each patient's index date as the day of first DMARD prescription fill. Study DMARDs were classified in 2 groups: anti-TNF therapy (including infliximab, adalimumab, and etanercept [etanercept was not included for IBD given its nonuse in that disease]) and alternate nonbiologic DMARD regimens. For RA, the alternate regimens were initiation of leflunomide, sulfasalazine, or hydroxychloroquine with use of methotrexate in the previous year. For IBD, the comparison group was initiation of azathioprine or mercaptopurine, whereas for psoriatic arthritis, psoriasis, or ankylosing spondylitis, the comparison was initiation of nonbiologic DMARDs (including methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide).

Follow-up continued through the earliest of the following events: death, loss of enrollment, development of herpes zoster, switch to another DMARD regimen or discontinuation of the current regimen (defined as 30 days without refill of the medication that qualified the individual for cohort entry), or study end. Patients who left the cohort could subsequently contribute new episodes of medication use if selection criteria were fulfilled and could potentially contribute episodes to more than 1 exposure group. The end of follow-up was December 31, 2007, and corresponded with the available dataset, which was truncated at that date. There are no secular changes we are aware of that would change applicability of the analysis. A detailed description of the Safety Assessment of Biologic Therapy methods has been reported elsewhere.[10,11]

Herpes Zoster Case Finding and Rate Calculations

For primary analysis, we defined herpes zoster cases as the presence of either an inpatient or outpatient *International Classification of Diseases, Ninth Revision* (*ICD-9*) code for herpes zoster (053.xx) plus use of an antiviral medication (acyclovir or valacyclovir) within 30 days of the code. We did not have access to direct clinical notes for exam findings by which to judge severity. For secondary analyses, we defined herpes zoster cases using only the *ICD-9* code and did not require antiviral usage. Outpatient and hospital discharge code diagnoses have previously been validated and shown to have high sensitivity and positive predictive values (≥85%) for identification of new cases of herpes zoster disease.[12,13] We calculated crude herpes zoster rates by the underlying inflammatory disease group, as well as within TNF-antagonist and nonbiologic DMARD comparator groups.

Covariates and Propensity Score Calculations

Baseline covariates were measured during the 365-day period prior to index

date and included demographics of age, sex, race, residence (urban or rural), nursing home or community dwelling, area income, and calendar year; generic markers of comorbidities (number of hospitalizations, outpatient and emergency department visits, and number of different medication classes filled); surrogate markers of disease severity (extra-articular disease manifestations, number of intra-articular and orthopedic procedures, number of laboratory tests ordered for inflammatory markers, and use of DMARDs); and other potential risk factors for herpes zoster including history of cancer or diabetes.

Within each inflammatory disease cohort, these covariates were included within propensity score calculations to estimate the probability a patient would receive a nonbiologic DMARD regimen. Thus, a propensity score value summarizing covariate information for each new treatment episode was created and used to control for confounding factors between anti-TNF and nonbiologic DMARD users. This score was calculated within each individual database and was grouped into quintiles and nonoverlapping tails between exposure groups were trimmed.[10,11,14]

Patients using oral corticosteroids in the 90 days prior to index date were categorized as baseline corticosteroid users (yes or no). For all baseline corticosteroid users, we calculated a mean daily dose of prednisone equivalents in the 6 months prior to index date: less than 5 mg/d (low dose), 5 to less than 10 mg/d (medium dose), and 10 mg/d or more (high dose).[10,11,15,16]

Evaluation of Herpes Zoster Risk With Anti-TNF Therapy

Within each inflammatory disease group, we used Cox proportional hazards regression models to assess the association between exposure groups and herpes zoster diagnosis.[10,11] Covariates that potentially could confound this association were controlled for by using the propensity score. Because patients could contribute 1 episode or more of new use (with an updated set of covariates), we used the sandwich or Huber/White variance estimator and calculated robust standard errors for all estimates.[17] The proportional hazard assumption was verified for each study exposure. The final disease-specific outcome models for cohort analyses included only the exposure groups, propensity score quintile, and the indicator for baseline glucocorticoid use. We also conducted head-to-head analysis of etanercept vs infliximab, and adalimumab vs infliximab in which similar cohort selection criteria and censoring rules were applied.

All statistical tests were 2-sided, and $P \leq .05$ was considered to indicate statistical significance. All analyses were performed using SAS version 9.3 (SAS Institute Inc).

Subgroup and Sensitivity Analyses

We performed a number of planned subgroup and sensitivity analyses. Within the RA cohort, in which the majority of herpes zoster cases occurred, we compared crude and adjusted herpes zoster incidence rates between exposure groups by database and within a number of prespecified groups including those with diabetes mellitus, chronic obstructive pulmonary disease, and baseline corticosteroid use; similar analyses were conducted in various age strata. Sensitivity analyses restricting follow-up to 3 or 6 months within each disease group were also conducted. We also conducted sensitivity analysis around the issue of baseline corticosteroid exposure. Rather than baseline corticosteroid use, we alternatively considered corticosteroid dose in a time-varying fashion beginning 90 days before and after the index date until censor or study end. Lastly, we conducted a subgroup analysis within the RA cohort restricted only to anti-TNF and nonbiologic DMARD patients who had used methotrexate in the baseline period.[10] No differences in hazard ratios (HRs) were observed in this subgroup analyses (eTable 3).

RESULTS

We identified 407 319 potentially eligible patients with immune-mediated inflammatory disorders in the respective study databases, of which 170 788 patients (42%) were excluded due to having more than 1 auto-immune disease or auto-immune diseases other than RA, IBD, psoriatic arthritis, psoriasis, or ankylosing spondylitis. We identified 59 066 patients who were new users of either anti-TNF therapy or comparator nonbiologic DMARDs, 36 212 patients with RA, 10 717 patients with IBD, and 12 137 patients with psoriatic arthritis, psoriasis, or ankylosing spondylitis (Table 1). Overall, 20% of patients were aged 65 years or older (25% for RA, 7% for IBD, and 14% for psoriatic arthritis, psoriasis, or ankylosing spondylitis). Within each disease group, baseline demographic and covariates were relatively similar between anti-TNF initiators and nonbiologic DMARD users (TABLE 1).

Across all disease indications, there were 310 herpes zoster cases among anti-TNF and 160 among nonbiologic DMARD users, and crude herpes zoster incidence rates per 1000 patient-years of exposure were similar between exposure groups (TABLE 2). Crude herpes zoster incidence rates were highest for the RA group and lowest for the psoriatic arthritis, psoriasis, or ankylosing spondylitis cohort, and within each disease indication, crude incidence was similar between medication exposure groups (Table 2). After adjustment for propensity score quintiles and baseline corticosteroid use, no significant difference in herpes zoster rates was observed within any disease indication (nor across indications) between patients initiating anti-TNF therapy and those initiating new DMARD regimens (Table 2). Higher doses of corticosteroid (mean daily dose of $\geq$ 10 mg) were associated with a significantly increased risk of herpes zoster (HR, 2.13 [95% CI, 1.64-2.75] across all disease indications). The models considering corticosteroid use as a time-varying covariate produced near identical HRs as our primary analysis

(eTable 6, available at www.jama.com).

Within the RA cohort, in which most cases occurred, we obtained descriptive data regarding herpes zoster cases that occurred in anti-TNF users. Cases in this group (n=266) occurred in patients of median age 60 years (range, 20-90 years), at a median of 294 days (2-2425 days) after drug start. Among 266 patients who developed herpes zoster while using anti-TNF, 16 (6.0%) required hospitalization, whereas 5 of 90 (5.5%) of those who developed herpes zoster while

Table 1. Baseline Characteristics of Disease-Modifying Antirheumatic Drug New Users by Immune-Mediated Inflammatory Disease Cohort

	No. (%) of Patients					
	Rheumatoid Arthritis		Inflammatory Bowel Disease		Psoriasis, Psoriatic Arthritis, or Ankylosing Spondylitis	
Variables	TNF Antagonists (n = 24 384)	Nonbiologic DMARD (n = 11 828)	TNF Antagonists (n = 3850)	Nonbiologic DMARD (n = 6867)	TNF Antagonists (n = 5090)	Nonbiologic DMARD (n = 7047)
Age, mean (SD), y	57.73 (14.53)	58.47 (14.27)	40.39 (16.13)	40.38 (17.80)	48.82 (15.33)	52.19 (16.82)
Women	20 955 (85.9)	10 205 (86.3)	2559 (66.5)	4330 (63.1)	2854 (56.1)	4331 (61.4)
Race						
White	15 244 (62.5)	7340 (62.0)	3010 (78.2)	5075 (73.9)	3716 (73.0)	4986 (70.7)
Black	3927 (16.1)	1831 (15.5)	586 (15.2)	993 (14.5)	357 (7.0)	576 (8.2)
Other[a]	5212 (21.4)	2659 (22.5)	254 (6.6)	799 (11.6)	1017 (20.0)	1489 (21.1)
Nursing home resident	992 (4.1)	493 (4.2)	99 (2.6)	167 (2.4)	146 (2.9)	334 (4.7)
≥1 Hospitalization at baseline	6995 (28.7)	3305 (27.9)	2133 (55.4)	3387 (49.3)	1042 (20.5)	1613 (22.9)
Charlson-Deyo comorbidity score, mean (SD)[b]	1.72 (1.13)	1.73 (1.17)	0.51 (.95)	0.47 (0.90)	0.74 (1.13)	0.79 (1.18)
≥1 Inflammatory marker tested	8955 (36.7)	4380 (37.0)	1094 (28.4)	2058 (30.0)	1045 (20.5)	1370 (19.4)
Residence (rural)	5773 (23.7)	2835 (24.0)	1030 (26.8)	1491 (21.7)	1180 (23.2)	1651 (23.4)
Area income, mean (SD), US $	40 025.40 (16 905.28)	40 869.18 (18 126.73)	41 814.94 (16 988.80)	45 408.74 (19 972.94)	43 025.17 (18 606.87)	43 879.51 (19 909.48)
Glucocorticoid and prednisone use						
Glucocorticoid and prednisone equivalents, mean (SD), mg						
None	9732 (39.9)	5079 (42.9)	1714 (44.5)	2773 (40.4)	4038 (79.3)	5461 (77.5)
0-< 5	7552 (31.0)	3650 (30.9)	609 (15.8)	973 (14.2)	700 (13.8)	1162 (16.5)
5-10	4604 (18.9)	2045 (17.3)	594 (15.4)	1167 (17.0)	196 (3.9)	153 (2.2)
>10	2495 (10.2)	1056 (8.9)	933 (24.2)	1954 (28.5)	156 (3.1)	275 (3.9)
Any orthopedic surgery	1752 (7.2)	633 (5.4)	66 (1.7)	85 (1.2)	189 (3.7)	177 (2.5)
Any intra-articular injection	8607 (35.3)	3596 (30.4)	198 (5.1)	259 (3.8)	695 (13.7)	817 (11.6)
Comorbidities						
COPD	3241 (13.3)	1584 (13.4)	311 (8.1)	484 (7.0)	502 (9.9)	870 (12.3)
Cerebrovascular disease	947 (3.9)	419 (3.5)	82 (2.1)	118 (1.7)	116 (2.3)	248 (3.5)
Diabetes	4618 (18.9)	2266 (19.2)	336 (8.7)	541 (7.9)	1021 (20.1)	1337 (19.0)
Obesity	2153 (8.8)	1227 (10.4)	276 (7.2)	676 (9.8)	697 (13.7)	953 (13.5)
History of cancer	1795 (7.3)	956 (7.9)	174 (4.4)	352 (4.8)	277 (5.3)	595 (7.4)
≥1 Antibiotic dispensed	16 627 (68.2)	7234 (61.1)	2775 (72.1)	4419 (64.4)	3178 (62.4)	4075 (57.8)
Medication initiated[c]						
Adalimumab	5888 (24.1)		118 (3.1)		294 (5.8)	
Etanercept	10 283 (42.2)				4270 (83.9)	
Infliximab	8212 (33.7)		3732 (96.9)		526 (10.3)	
Hydroxychloroquine		5730 (48.4)				569 (8.1)
Leflunomide		4569 (38.6)				133 (1.9)
Sulfasalazine		1531 (12.9)				858 (12.2)
Mercaptopurine				3475 (50.6)		
Methotrexate						5491 (77.9)
Azathioprine				3392 (49.4)		

Abbreviations: COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.
[a] Other race includes Hispanics, Asian/Pacific islander, Native American, unknown.
[b] The Charlson-Deyo comorbidity index provides an estimate of the disease severity and comorbidities for a given patient. Lower values correspond with low comorbidity or disease severity.
[c] Medication initiation data were collected for specific treatments in each inflammatory disease; blank cells reflect an absence of data.

using nonbiologic DMARDs were hospitalized.

Subgroup and Sensitivity Analyses

Secondary analysis using our alternate case-finding algorithm (*ICD9-CM* diagnosis code alone without medications used to treat herpes zoster) revealed rates of herpes zoster 20% to 30% higher than our primary analysis within each disease group, and adjusted HRs for rate comparisons between exposure groups were similar to our findings from our primary analysis (eTable 7). When follow-up was truncated at either 3 or 6 months using either case definition for herpes zoster, results were similar to those from our primary analyses (eTables 4a and 4b). For the RA group, we also extended follow-up time for the Medicare/Medicaid portion of our cohort until the end of 2008, and herpes zoster crude incidence rates per 1000 patient-years were observed to be similar in each group (HR, 12.6 [95% CI, 10.2-15.5] for anti-TNF initiators and HR, 12.4 [95% CI, 11.0-13.8] for nonbiologic initiators; adjusted HR, 0.95 [95% CI, 0.74-1.21]) (eTable 1). Among patients with RA starting nonbiologic DMARDs, herpes zoster crude incidence rates were similar between hydroxychloroquine, leflunomide, and sulfasalazine initiators (eTable 2).

We explored potential interactions between drug exposure and underlying chronic disease, age, and propensity score quintile. Although absolute herpes zoster rates varied according to various comorbidities and age, within each strata (eg, diabetes vs no diabetes), the adjusted herpes zoster incidence associated with anti-TNF therapy was not significantly elevated in any subgroup and no interactions were noted between subgroups (TABLE 3, eTable 5).

We evaluated drug-specific risk within the RA group in which the majority of cases occurred, allowing for such analysis. Within the RA cohort,

Table 2. Crude Incidence and Adjusted Hazard of Herpes Zoster Among New Users of Anti−Tumor Necrosis Factor Therapy or Nonbiologic Disease-Modifying Antirheumatic Drugs

Exposures	No. of Events	Person-Years of Exposure	Crude Incidence Rate (95% CI)[a]	Adjusted Hazard Ratio (95% CI)[b]
Rheumatoid arthritis[c]				
Nonbiologic DMARD	90	7100	12.7 (10.3-15.6)	1 [Reference]
New users of TNF antagonists	266	22 019	12.1 (10.7-13.6)	1.00 (0.77-1.29)
Baseline glucocorticoid use (prednisone equivalents), mg/d				
None	124	11 671	10.6 (8.9-12.7)	1 [Reference]
0-< 5	111	8917	12.4 (10.3-15.0)	1.19 (0.92-1.54)
5-<10	61	5609	10.9 (8.5-14.0)	0.99 (0.72-1.35)
≥10	60	2922	20.5 (15.9-26.4)	1.87 (1.37-2.57)
Inflammatory bowel disease[c]				
Azathioprine or mercaptopurine[d]	43	4556	9.4 (7.0-12.7)	1 [Reference]
New users of TNF antagonists	26	2292	11.3 (7.7-16.7)	0.79 (0.41-1.53)
Baseline glucocorticoid use (prednisone equivalents), mg/d				
None	21	2706	7.8 (5.1-11.9)	1 [Reference]
0-< 5	7	846	8.3 (3.9-17.4)	0.93 (0.38-2.31)
5-<10	7	1133	6.2 (2.9-13.0)	0.87 (0.37-2.03)
≥10	34	2164	15.7 (11.2-22.0)	1.99 (1.12-3.52)
Psoriasis, psoriatic arthritis, or ankylosing spondylitis[c]				
Nonbiologic DMARD	27	3931	6.9 (4.7-10.0)	1 [Reference]
New users of TNF antagonists	18	4081	4.4 (2.8-7.0)	0.63 (0.28-1.43)
Baseline glucocorticoid use (prednisone equivalents), mg/d				
None	28	6262	4.5 (3.1-6.5)	1 [Reference]
0-< 5	9	1146	7.9 (4.1-15.1)	1.70 (0.77-3.72)
5-<10	5	354	14.1 (5.9-33.9)	3.33 (1.27-8.72)
≥10	3	250	12.0 (3.9-37.3)	3.32 (0.98-11.16)
Across all disease indications				
Nonbiologic DMARD	160	15 586	10.3 (8.8-12.0)	1 [Reference]
New users of TNF antagonists	310	28 392	10.9 (9.8-12.2)	1.09 (0.88-1.36)
Baseline glucocorticoid use (prednisone equivalents), mg/d				
None	173	20 639	8.4 (7.2-9.7)	1 [Reference]
0-<5	127	10 909	11.6 (9.8-13.9)	1.37 (1.08-1.72)
5-<10	73	7096	10.3 (8.2-12.9)	1.18 (0.89-1.56)
≥10	97	5335	18.2 (14.9-22.2)	2.13 (1.64-2.75)

Abbreviations: DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.
[a] Crude incidence rates per 1000 person-years of exposure.
[b] Adjusted for propensity score quintile and mean daily prednisone dose in 6 months prior to index.
[c] Number of participants for each exposure group are given in Table 1.
[d] Infliximab or adalimumab only.

crude incidence rates were highest among those starting infliximab (13.6 per 1000 patient-years) and lowest for those starting adalimumab (10.0 per 1000 patient-years); however, there was no significant difference between rates after adjustment for baseline steroid usage and propensity score quintile (TABLE 4). Furthermore, a higher proportion of infliximab users used concomitant methotrexate at baseline and after index date compared with those using etanercept or adalimumab (TABLE 5).

COMMENT

Within the Safety Assessment of Biologic Therapy consortium, we performed a large cohort study examining herpes zoster rates within inflammatory disease groups. Our results suggest that patients initiating anti-TNF drugs are at similar risk of herpes zoster as patients who initiate nonbiologic medications, and that herpes zoster risk is similar among different anti-TNF compounds. Within the RA cohort, herpes zoster risk was associated with increasing age, female sex, overall health status, and higher-dose corticosteroid use.

Our study adds to several other large population-based studies that have evaluated the relative risks of herpes zoster with anti-TNF and nonbiologic DMARD therapy in patients with RA, but our methodology differed in important ways from these other studies. First, to our knowledge our study is the largest RA cohort in which herpes zoster risk has been evaluated. Our cohort, more than 35 000 individuals, is several fold

Table 3. Crude Incidence and Adjusted Hazard of Herpes Zoster in Patients With Rheumatoid Arthritis Stratified by Baseline Demographics and Medical Comorbidities

Patient Age, y	No. of Patients	No. of Events	Person-Years of Exposure	Crude Rate per 1000 Person-Years (95% CI)[a]	Adjusted Hazard Ratio (95% CI)[b]
<50					
Methotrexate exposure	3212	13	1731	7.5 (4.4-12.9)	1 [Reference]
New users of TNF antagonists	7014	47	5903	8.0 (6.0-10.6)	1.39 (0.70-2.77)
≥50					
Methotrexate exposure	8942	77	5369	14.3 (11.5-17.9)	1 [Reference]
New users of TNF antagonists	17 591	219	16 116	13.6 (11.9-15.5)	0.94 (0.70-1.24)
<60					
Methotrexate exposure	6276	35	3597	9.7 (7.0-13.6)	1 [Reference]
New users of TNF antagonists	13 102	114	11 546	9.9 (8.2-11.9)	1.09 (0.73-1.63)
≥60					
Methotrexate exposure	5878	55	3503	15.7 (12.1-20.5)	1 [Reference]
New users of TNF antagonists	11 503	152	10 474	14.5 (12.4-17.0)	0.93 (0.66-1.31)
No baseline history of COPD					
Methotrexate exposure	10 539	75	6164	12.2 (9.7-15.3)	1 [Reference]
New users of TNF antagonists	21 329	224	19 465	11.5 (10.1-13.1)	0.96 (0.72-1.28)
Baseline history of COPD					
Methotrexate exposure	1615	15	936	16.0 (9.7-26.6)	1 [Reference]
New users of TNF antagonists	3276	42	2554	16.4 (12.2-22.3)	1.21 (0.65-2.27)
No baseline history of DM					
Methotrexate exposure	9846	69	5907	11.7 (9.2-14.8)	1 [Reference]
New users of TNF antagonists	19 950	214	18 208	11.8 (10.3-13.4)	1.09 (0.81-1.47)
Baseline history of DM					
Methotrexate exposure	2308	21	1192	17.6 (11.5-27.0)	1 [Reference]
New users of TNF antagonists	4655	52	3812	13.6 (10.4-17.9)	0.74 (0.43-1.27)
Female sex					
Methotrexate exposure	10 476	78	6047	12.9 (10.3-16.1)	1 [Reference]
New users of TNF antagonists	21 133	237	18 778	12.6 (11.1-14.3)	0.94 (0.72-1.24)
Male sex					
Methotrexate exposure	1678	12	1053	11.4 (6.5-20.1)	1 [Reference]
New users of TNF antagonists	3272	29	3241	8.9 (6.2-12.9)	1.46 (0.66-3.23)
No steroid use in 90 d[c]					
Methotrexate exposure	6066	28	2511	11.1 (7.7-16.1)	1 [Reference]
New users of TNF antagonists	11 021	74	7043	10.5 (8.4-13.2)	0.78 (0.52-1.17)
Steroid users[c]					
Methotrexate exposure	6088	62	4588	13.5 (10.5-17.3)	1 [Reference]
New users of TNF antagonists	13 584	192	14 977	12.8 (11.1-14.8)	1.17 (0.83-1.65)

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; TNF, tumor necrosis factor.
[a] Crude incidence rates per 1000 person-years of exposure.
[b] Adjusted for propensity score quintile and mean daily prednisone dose in 6 months prior to index.
[c] Adjusted for propensity score quintile only. Steroid use (yes/no) in 90 days before index date.

larger than the other 2 major cohort studies addressing this topic.[18,19] Second, our study is one of the few to evaluate using a design in which only new users of TNF antagonists were compared with patients initiating new nonbiologic DMARDs. This study design is optimal in evaluating drug risks given the absence of prevalent users who are less likely to have complications of their therapies (ie, survivor bias).[18] Furthermore, unlike some prior studies, we used propensity scores to control for differences between the treated cohorts that might have influenced selection of DMARD therapy.

In prior studies, the answer to whether anti-TNF therapy increases the risk of herpes zoster has been conflicting. In a nested case-control study, Smitten et al[5] found herpes zoster risk to be slightly elevated in patients with RA using biologic DMARDs (odds ratio, 1.54) or traditional DMARDs (odds ratio, 1.37) compared with no DMARD therapy. A large cohort study conducted within the German biologics register RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy) reported outcomes in more than 5000 patients documenting 86 herpes zoster episodes for crude incidence rates of 11.1 per 1000 patient-years for monoclonal antibody, 8.9 for etanercept, and 5.6 for conventional DMARDs, whereas in multivariate analysis, herpes zoster risk was significantly higher in patients using monoclonal antibodies (infliximab and adalimumab were evaluated together) compared with nonbiologic DMARDs.[19] No increased risk was observed for those using etanercept. In stark contrast, a large cohort study among 20 000 patients with RA within the US Veterans Affairs (VA) health system documented significant protective associations for etanercept (HR, 0.62) and adalimumab (HR, 0.53), and a nonsignificant risk elevation for infliximab (HR, 1.32).[18]

Overall, these 2 large cohort studies described similar, although slightly lower, rates of herpes zoster in TNF-antagonist using patients with RA (approximately 10 per 1000 person-years) as found within our study; however, herpes zoster rates in comparator groups were very different across these studies. Compared with the RABBIT study, herpes zoster rates among the patients with RA in our study are nearly double in the nonbiologic DMARD groups despite the cohorts having similar age and sex constructs. The reason for this is unclear. Interestingly, the RABBIT study used similar methods to ours (new user design and propensity score stratification) but the use of concomitant corticosteroids at baseline in both nonbiologic (77%) and biologic (86%) treated patients in their study was higher than in ours (57% nonbiologic,

Table 4. Crude Herpes Zoster Incidence Rates and Adjusted Hazard of Herpes Zoster Among Patients With Rheumatoid Arthritis Stratified According to Tumor Necrosis Factor Antagonist Exposure

	Infliximab (n = 8087)	Etanercept (n = 10 138)	Adalimumab (n = 6711)
Herpes zoster cases	124	105	42
Person-years of exposure	9086	8513	4218
Crude incidence rate (95% CI)[a]	13.6 (11.4-16.3)	12.3 (10.2-14.9)	10.0 (7.4-13.5)
Adjusted hazard ratio (95% CI)[b]	1 [Reference]	1.09 (0.82-1.45)	0.82 (0.55-1.22)

[a] Crude incidence rates per 1000 person-years of exposure.
[b] Adjusted for propensity score quintile adjustment and baseline glucocorticoid use.

Table 5. Concomitant Methotrexate and Prednisone Therapy at Index Date and Thereafter Stratified by Exposure Group and Immune-Mediated Inflammatory Disease Cohort

	Concomitant Methotrexate and Prednisone Use Among New DMARD Exposure Groups, %							
	Infliximab		Adalimumab		Etanercept		Nonbiologic DMARD	
	Prednisone	Methotrexate	Prednisone	Methotrexate	Prednisone	Methotrexate	Prednisone	Methotrexate
RA, No. of patients	8212		5889		10 283		11 828	
Exposure date, d								
Index	51.8	50.3	56.6	43.4	57.6	39.7	56.1	66.4
180	45.5	46.9	49.1	42.3	48.1	35.9	52.6	50.9
365	43.9	48.0	45.5	43.9	46.5	37.0	51.0	50.4
IBD, No. of patients	3808		121				7267	
Exposure date, d								
Index	52.3	2.5	60.3	14.1			67.9	0.5
180	33.9	4.3	55.9	2.9			41.5	0.4
365	29.9	7.1	44.4	11.1			35.9	0.2
Ankylosing spondylitis, psoriasis, or psoriatic arthritis, No. of patients	541		302		4361		8068	
Exposure date, d								
Index	37.7	42.0	38.1	31.8	46.4	19.8	51.9	76.8
180	28.9	42.0	26.5	32.5	33.5	11.7	39.2	78.4
365	26.7	38.1	27.4	29.0	31.8	13.4	39.9	74.0

Abbreviations: IBD, inflammatory bowel disease; RA, rheumatoid arthritis.

60% biologic), and differential use of corticosteroid (including higher doses of corticosteroid that are more frequently used in Germany),[20] or other concomitant immunosuppressives (eg, methotrexate) after DMARD initiation could have contributed to differences in findings between the 2 studies. Furthermore, our study population contained a large number of Medicare and Medicaid recipients who might have had higher baseline herpes zoster risk due to comorbidities and other unknown factors. Comparison of our study with the VA cohort study is problematic given the large percentage of male patients within that study. Women are known to be at higher herpes zoster risk (a phenomenon not well understood), and this difference in underlying cohorts likely explains the lower herpes zoster rates observed in the VA cohort compared with ours. Similar to these prior studies, however, we have identified corticosteroid use a risk factor for herpes zoster. This has been clearly shown in a number of cohort studies in which collectively, higher-dose corticosteroid increases herpes zoster risk 1.5- to 2-fold.[9]

In our study, with the exception of IBD, crude incidence rates of herpes zoster were observed to be lower among anti-TNF users, and after adjustment for comorbidities and steroid usage, herpes zoster HRs within each disease cohort remained at or below 1.0 for those starting anti-TNF therapy. When truncating our exposure to 3 or 6 months after drug start, we found no difference in risk associated with anti-TNF therapy similar to our primary analysis. The lack of association between herpes zoster and the start of anti-TNF therapy were recapitulated within our secondary analysis that used only the presence of herpes zoster codes (ie, without evidence of antiviral therapy) to define herpes zoster. With this presumably more sensitive (and less specific) case definition, our herpes zoster rates were approximately 20% to 30% higher in all disease groups and not different between exposure groups. We evaluated potential differences in disease rates between exposure groups according to various comorbidities, between our 4 database sites, and within steroid users and nonusers. In no subgroup did initiation of TNF antagonists significantly increase the risk of herpes zoster.

For patients who develop herpes zoster while taking anti-TNF therapy, it is unclear if such therapy increases the risk of disseminated complications. Although we did not directly assess this question, we observed that a very small percentage of patients with herpes zoster were hospitalized. In fact, within the RA cohort, in which most of our cases occurred, a similar proportion of herpes zoster cases within the anti-TNF group (6%) and DMARD group (5.5%) were hospitalized.

A live attenuated vaccine to prevent herpes zoster is approved for use in patients aged 50 years or older in the United States.[4,21] The high herpes zoster rates observed within our study support the widespread vaccination of all patients with RA in this age group. Currently vaccination during active use of anti-TNF therapy is contraindicated due to theoretical safety concerns of using a live vaccine during such therapy; however, it is unclear if such concerns are valid. Our data suggest that patients who develop herpes zoster while taking anti-TNF therapy are no more likely to be hospitalized than persons with herpes zoster using nonbiologic DMARDs. Other data suggest that a small number of patients with RA have been vaccinated while using anti-TNF therapy without dissemination of varicella or zoster occurrence.[22,23] Given these findings, the potential importance of this vaccine within the RA setting and the difficulty in vaccinating patients given the widespread use of anti-TNF therapy, we believe that a trial to evaluate the safety of this live virus vaccine among current anti-TNF users is warranted.

Our study was not without limitations. First, our RA cohort study effectively compared patients initiating anti-TNF therapies (either with or without background nonbiologic DMARD use) with those starting a new nonbiologic DMARD after exposure to methotrexate. After their inception date into the comparison cohorts, we did not assess differential use of methotrexate or other DMARD use between the groups within our model, although we did assess the proportion of patients using methotrexate within each exposure group at various time points after the index date, and these data do not suggest this as a potential confounder for our findings of a lack of differential risk between the TNF-antagonist and nonbiologic DMARD groups (Table 5). We did assess changes in corticosteroid use in a time-varying fashion after the index date within our model, and controlling for this factor produced no difference in our HRs between treatment groups.

In summary, among patients with RA and other select inflammatory diseases, those who initiated anti-TNF therapies were not at higher risk of herpes zoster compared with patients who initiated nonbiologic treatment regimens. Furthermore, we detected no significant difference in herpes zoster risk between etanercept and the monoclonal antibodies infliximab and adalimumab.

Author Contributions: Dr Patkar, who is independent of any commercial funder, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Winthrop, Chen, Liu, Grijalva, Delzell, Beukelman, Patkar, Herrinton, Solomon, Lewis, Curtis.
Acquisition of data: Grijalva, Saag, Herrinton, Curtis.
Analysis and interpretation of data: Winthrop, Baddley, Chen, Grijalva, Delzell, Beukelman, Patkar, Xie, Saag, Herrinton, Curtis.
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Study supervision: Winthrop, Patkar, Saag, Herrinton, Solomon.
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