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Association between the initiation of anti-TNF therapy and the risk of herpes zoster

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Abstract

Importance—Herpes zoster (HZ) reactivation disproportionately affects patients with rheumatoid arthritis (RA). It is unclear whether anti-tumor necrosis factor (anti-TNF) therapy elevates HZ risk, and whether monoclonal antibodies carry greater risk than etanercept.

Objectives—To ascertain whether initiation of anti-TNF therapy compared with non-biologic comparators is associated with increased HZ risk

Design, Setting, and Patients—We identified new users of anti-TNF therapy among cohorts of rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis-psoriatic arthritis-ankylosing spondylitis (PsO-PsA-AS) patients during 1998–2007 within a large US multi-institutional collaboration combining data from Kaiser Permanente Northern California, Pharmaceutical Assistance Contract for the Elderly, Tennessee Medicaid, and national Medicaid/Medicare programs. We compared HZ incidence between new anti-TNF users and patients initiating non-biologic disease modifying drugs (DMARDs) within each inflammatory disease cohort (last participant follow-up Dec 31, 2007). Within these cohorts, we used Cox regression models to compare propensity-score adjusted HZ incidence between new anti-TNF and non-biologic DMARD users while controlling for baseline corticosteroid use.

Main Outcome Measure—Incidence of herpes zoster cases occurring after initiation of new anti- TNF or non-biologic DMARD therapy

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Results—Among 32,208 new users of anti-TNF therapy, we identified 310 HZ cases. Crude incidence rates among anti-TNF users for RA, IBD, and PsO-PsA-AS were 12.1/1000 pt-yrs, (95% CI 10.7–13.6), 11.3/1000 (95% CI 7.7–16.7), and 4.4/1000 (95% CI 2.8–7.0) respectively. Baseline use of corticosteroids of > 10mg/day was associated with elevated risk [adjusted HR 2.13 (1.64, 2.75) compared with no baseline use. For RA patients, 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 three anti-TNF therapies studied.

Conclusions and Relevance—Among patients with RA and other select inflammatory diseases, those who initiated anti-TNF therapies were not at higher risk for HZ compared to patients who initiated non-biologic treatment regimens.

Keywords

shingles; zoster; herpes; biologic therapy; tumor necrosis factor-alpha; rheumatoid arthritis; adverse events; psoriasis

Background

The reactivation of varicella zoster virus (herpes zoster [HZ] or “shingles”) is of substantial public health concern. Its predilection for the elderly and the immunosuppressed make it an important cause of morbidity, causing pain, depression, and long-term disability in the form of post-herpetic neuralgia. Further, the ability of HZ to cause disseminated complications and death in immunosuppressed individuals is well-documented.[1–3] In the United States, HZ incidence rates rise with age and range between 4 and 11/1,000 patient-years in patients age 50 and 80 respectively, with rates highest in women.[4] For patients with rheumatoid arthritis (RA), the risk of HZ is elevated an additional 2–3 fold.[5,6] Importantly, the contribution of widely-used biologic immunosuppressive therapy to this increased risk is not well-understood. These therapies, including anti-tumor necrosis factor–alpha (anti-TNF) antagonists, are commonly used in 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 tuberculosis, a clear mechanism for TNF antagonism to cause HZ has not been elucidated; and importantly, observational studies assessing this question have employed 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 SABER (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 four major US databases to describe rates of HZ in various inflammatory diseases in which we specifically evaluated whether initiation (i.e. new use) of anti-TNF therapy increases HZ risk, and whether the monoclonal antibodies infliximab and adalimumab carry greater HZ risk than etanercept.

Methods

Data sources and cohort formation

We utilized data from four 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 (TennCare, 1998–2005); 3) The New Jersey’s Pharmaceutical Assistance to the Aged and Disabled, and the Pennsylvania’s Pharmaceutical Assistance Contract for the Elderly (PAAD/PACE,

1998–2006); and, 4) Kaiser Permanente Northern California (KPNC, 1998–2007). We used validated algorithms to identify patients of interest including rheumatoid arthritis (RA), psoriatic arthritis (PsA), Psoriasis (PsO), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD).[10] Patients were eligible for inclusion if they had a baseline period of 365 days with continuous enrollment in the respective database preceding the first DMARD prescription fill. Patients with diagnoses for ≥2 autoimmune diseases, or history of HZ prior to first DMARD prescription fill were excluded. Among potential cohort members, we identified new users of study DMARDs, defined as having filled a prescription for a study DMARD after 365 baseline days without prescriptions filled for the specific study medication or others in the same group. We defined the date of this first DMARD fill (T_0) as the patient's "index date." Study DMARDs were classified in two groups: anti-TNF therapy (including infliximab, adalimumab and etanercept [note: etanercept was not included for IBD given its non-use in that disease]) and alternate non-biologic 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 6-mercaptopurine, whereas for PsO-PsA-AS the comparison was initiation of non-biologic DMARDs (including methotrexate, hydroxychloroquine, sulfasalazine and leflunomide). Follow-up continued through the earliest of the following dates: death, loss of enrollment, development of HZ, switch to another DMARD regimen or the 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 one exposure group. The end of follow-up was Dec 31, 2007. A detailed description of SABER methods has been reported elsewhere.[10,11]

HZ case-finding and rate calculations

For primary analysis, we defined HZ cases as the presence of either an inpatient or outpatient International Classification of Diseases, 9th Revision (ICD-9) code for HZ (053.xx) plus use of an anti-viral medication (acyclovir or valacyclovir) within ± 30 days of the code. For secondary analyses, we defined HZ cases using only the ICD-9 code and did not require anti-viral usage. Outpatient and hospital discharge code diagnoses have previously been validated and shown to have high sensitivity and positive predictive values (PPV ≥ 85%) for identification of new cases of HZ disease.[12,13] We calculated crude HZ rates by underlying inflammatory disease group, as well as within TNF-antagonist and non-biologic DMARD comparator groups.

Covariates and propensity score calculations

Baseline covariates were measured during the 365 day baseline-line period prior to index date (T_0) and included demographics: age, gender, race, residence (urban/rural), nursing home/community dwelling, area income, calendar year; generic markers of co-morbidities: number of hospitalizations, outpatient and emergency room visits, 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, use of DMARDs; and, other potential risk factors for HZ including history of cancer or diabetes. Within each inflammatory disease cohort, these covariates were included within propensity score (PS) calculations to estimate the probability a patient would receive a non-biologic DMARD regimen. Thus, a PS value summarizing covariate information for each new treatment episode was created and used to control for confounding factors between anti-TNF and non-biologic DMARD users. This score was calculated within each individual database and was grouped into quintiles and non-overlapping 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/no). For all baseline corticosteroid users, we calculated a mean daily dose of prednisone equivalents in the 6 months prior to index date: 0 --<5mg/day (low dose), 5--<10mg/day (medium dose) and ≥10 mg/day (high dose).[10,11,15,16]

Evaluation of HZ risk with anti-TNF therapy

Within each inflammatory disease group, we used Cox-proportional hazard regression models to assess the association between exposure groups and HZ diagnosis.[10,11] Covariates that potentially could confound this association were controlled for using the PS score. Since patients could contribute ≥1 episode of new use (with an updated set of covariates), we used the Huber-White "sandwich" 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, PS quintile, and the indicator for baseline glucocorticoid use. We also conducted head-to-head analysis of etanercept versus infliximab, and adalimumab versus infliximab in which similar cohort selection criteria and censoring rules were applied. All statistical tests were 2-sided, and $P \leq 0.05$ was considered to indicate statistical significance. All analyses were done in SAS. This study was approved by the institutional review boards of all SABER participating institutions.

Subgroup and sensitivity analyses

We performed a number of planned subgroup and sensitivity analyses. Within the RA cohort, where the majority of HZ cases occurred, we compared crude and adjusted HZ incidence rates between exposure groups by database and within a number of pre-specified groups including those with diabetes mellitus, chronic pulmonary obstructive disease (COPD), 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 time-varying fashion beginning 90 days prior to and thereafter index date until censor or study end. Lastly, we conducted a sub-group analysis within RA restricted only to anti-TNF and non-biologic DMARD patients who had used methotrexate in the baseline period.[10] No differences in HR were observed in this subgroup analyses and for simplicity, the data are not shown herein

Results

We identified 407,319 potentially eligible IMID patients in the respective study databases, of which 170,788 (42%) patients were excluded due to having more than one auto-immune disease or auto-immune diseases other than RA, IBD, Pso-PsA, or AS. We identified 35,235, 7,332 and 12,905 RA, IBD and Pso-PsA-AS patients respectively who were either new-users of anti-TNF therapy or a comparator non-biologic DMARD (Table 1). Overall, 20% of patients were aged ≥ 65 years (25%, 7% and 14% for RA, IB and Pso-PsA-AS, respectively). Within each disease group, baseline demographic and covariates were relatively similar between anti-TNF initiators and non-biologic DMARD users (Table 1)

Overall, across all disease indications, there were 310 and 160 HZ cases among anti-TNF and non-biologic DMARD users, and crude HZ incidence rates per 1000 patient-years of exposure were similar between exposure groups (Table 2). Crude HZ incidence rates were highest for RA and lowest for the PsO-PsA-AS cohort, and within each disease indication, crude incidence was similar between medication exposure groups (Table 2). After adjustment for PS quintiles and baseline corticosteroid use, no significant difference in HZ

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 ≥ 10mg) were associated with a significantly increased risk for HZ (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 hazard ratios as our primary analysis (supplementary table 6). Within the RA cohort, where most cases occurred, we obtained descriptive data regarding HZ cases that occurred in anti-TNF users. Cases in this group (n=266) occurred in patients of median age 60 (range, 20-90 years), at a median of 294 days (2-2,425 days) after drug start. Among patients who developed HZ while using anti-TNF (n=266), 16 (6.0%) required hospitalization, while 5 (5.5%) of those who developed HZ while using non-biologic DMARDs (n=90) were hospitalized.

Subgroup and sensitivity analyses

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

We explored potential interactions between drug exposure and underlying chronic disease and age. While absolute HZ rates varied according to various co-morbidities and age, within each strata (e.g. diabetes versus no diabetes), the adjusted HZ incidence associated with anti-TNF therapy was not significantly elevated in any subgroup and no interactions were noted between sub-groups (Table 3).

We evaluated drug-specific risk within RA where the majority of cases occurred, allowing for such analysis. Within the RA cohort, crude incidence rates were highest among those starting infliximab (13.6/1,000 patient-years, and lowest for those starting adalimumab (10.0/1,000 patient-years); however, there was no significant difference between rates after adjustment for baseline steroid usage and PS quintile (Table 4). Further, a higher proportion of infliximab-users used concomitant methotrexate at baseline and after index-date as compared to those using etanercept or adalimumab (Table 5).

Comment

Within SABER, a multi-institutional research initiative within the United States, we performed a large cohort study examining HZ rates within inflammatory disease groups. Our results suggest that patients initiating anti-TNF drugs are at similar risk for HZ as patients who initiate non-biologic medications, and that HZ risk is similar among different anti-TNF compounds. Within RA, HZ risk is associated with increasing age, female sex, and overall health status and higher dose corticosteroid use.

Our study adds substantially to several other large population-based studies that have evaluated the relative risks of HZ with anti-TNF and non-biologic DMARD therapy in RA

patients, but it is notable that our methodology differed in important ways than these other studies. First, our study is the largest RA cohort in which HZ risk has been evaluated. Our cohort, over 35,000 individuals, is 7-10 times larger than the other two major cohort studies addressing this question.[18,19] Second, our study is one of the few to evaluate this question using a "new user" design in which only new users of TNF antagonists were compared to patients initiating new non-biologic 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 (i.e. survivor bias).[18] Further, 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 HZ has been conflicting. In a nested case-control study, Smitten et al found HZ risk to be slightly elevated in RA patients using biologic DMARDs (OR 1.54) or traditional DMARDs (OR 1.37) compared to no DMARD therapy.[5] A large cohort study conducted within the German RABBIT registry reported outcomes in over 5,000 patients documenting 86 HZ episodes for crude incidence rates of 11.1, 8.9, and 5.6 per 1,000 patients-years for monoclonal antibody, etanercept, and conventional DMARDs respectively, while in multivariate analysis, HZ risk was significantly higher in patients using monoclonal antibodies (infliximab and adalimumab were evaluated together) compared to non-biologic DMARDs.[19] No increased risk was observed for those using etanercept. In stark contrast, a large cohort study among 20,000 RA patients within the US Veteran's Affairs health system documented significant protective associations for etanercept (HR 0.62) and adalimumab (HR 0.53), and a non significant risk elevation for infliximab (HR 1.32).[18] Overall, these two large cohort studies described similar, although slightly lower, rates of HZ in TNF-antagonist using patients with RA (approximately 10/1,000 person-years) as found within our study; however, HZ rates in comparator groups were very different across these studies. As compared to the RABBIT study, HZ rates among our RA patients are nearly double in the non-biologic 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 PS score stratification) but the use of concomitant corticosteroids at baseline in both non-biologic and biologic treated patients (77–86% respectively) in their study was higher than in ours (57–60%), 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 T_0 (DMARD initiation) could have contributed to differences in findings between the two studies. Further, our study population contained a large number of Medicare and Medicaid recipients who might have had higher baseline HZ risk due to co-morbidities 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. Females are known to be at higher HZ risk (a phenomenon not well-understood), and this difference in underlying cohorts likely explains the lower HZ rates observed in the VA cohort compared to ours. Similar to these prior studies, however, we have identified corticosteroid use as risk for HZ. This has been clearly shown in a number of cohort studies addressing this question where collectively, higher dose corticosteroid increases HZ risk 1.5–2 fold.[9]

In our study, with the exception of IBD, crude incidence rates of HZ were observed to be numerically, but not significantly, lower among anti-TNF users. After adjustment for co-morbidities and steroid usage, HZ hazard ratios within each disease cohort remained 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 HZ and anti-TNF therapy start were recapitulated within our secondary analysis that used only the presence of HZ codes (i.e.

without evidence of anti-viral therapy) to define HZ. Interestingly, with this presumably more sensitive (and less specific) case definition, our HZ rates were approximately 20–30% higher in all disease groups and not different between exposure groups. Lastly, we evaluated potential differences in disease rates between exposure groups according to various co-morbidities, between our four database sites, and within steroid users and non-users. In no subgroup did TNF antagonists start significantly increase the risk of HZ.

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

A live-attenuated vaccine to prevent HZ (*Zostavax®,* Merck, Whitehouse station, New Jersey) is approved for use in patients aged ≥50 years in the United States.[4,21] The high HZ rates observed within our study support the widespread vaccination of all RA patients 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 HZ while on anti-TNF therapy are no more likely to be hospitalized than HZ cases using non-biologic DMARDs. Other data suggest that a small number of RA patients have been vaccinated with zostavax 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, within RA, our cohort study effectively compared patients initiating anti-TNF therapies (either with or without background non-biologic DMARD use) with those starting a new non-biologic DMARD after exposure to methotrexate (ie methotrexate “failures”). 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 non-biologic DMARD groups (table 5). We did assess changes in corticosteroid use in time-varying fashion after the index date within our model however, and controlling for this factor produced no difference in our hazard ratios between treatment groups. .

In summary, we have conducted the largest study to date examining the risk of HZ in patients using biologic therapy. Among patients with RA and other select inflammatory diseases, those who initiated anti-TNF therapies were not at higher risk for HZ compared to patients who initiated non-biologic treatment regimens. Further, we detected no significant difference in HZ risk between etanercept and the monoclonal antibodies infliximab and adalimumab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of DMARD new users by immune-mediated imflammatory disease cohort.

Variables	Rheumatoid Arthritis N (%)		Inflammatory Bowel Disease N (%)		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis N (%)	
	Anti-TNF (n=24,384)	Non-biologic DMARD (n=11,828)	Anti-TNF (n=3,850)	Non-biologic DMARD (n=6,867)	Anti-TNF (n=5,090)	Non-biologic DMARD (n=7,047)
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)
Female	20955 (85.9)	10205 (86.3)	2559 (66.5)	4330 (63.1)	2854 (56.1)	4331(61.4)
Race						
White	15244 (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	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 during baseline	6995 (28.7)	3305 (27.9)	2133 (55.4)	3387 (49.3)	1042 (20.5)	1613 (22.9)
Charlson-Deyo Comorbidity score[1], mean (SD)	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 (urban/rural)	5773 (23.7)	2835 (24.0)	1030 (26.8)	1491 (21.7)	1180 (23.2)	1651 (23.4)
area income ($)	40025.40 (16905.28)	40869.18 (18126.73)	41814.94 (16988.80)	45408.74 (19972.94)	43025.17 (18606.87)	43879.51 (19909.48)
outpatient and emergency room visits	24364 (99.9)	11813 (99.9)	3844 (99.8)	6837 (99.6)	5087 (99.9)	7047 (100.0)
Mean glucocorticoid use, prednisone equivalents						
None	9732 (39.9)	5079 (42.9)	1714 (44.5)	2773 (40.4)	4038 (79.3)	5461 (77.5)
(0<5 mg)	7552 (31.0)	3650 (30.9)	609 (15.8)	973 (14.2)	700 (13.8)	1162 (16.5)
(5–10 mg)	4604 (18.9)	2045 (17.3)	594 (15.4)	1167 (17.0)	196 (3.9)	153 (2.2)
(>10 mg)	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)
Comorbidites						
COPD	3241 (13.3)	1584 (13.4)	311 (8.1)	484 (7.0)	502 (9.9)	870 (12.3)
Cerebrovascular	947 (3.9)	419 (3.5)	82 (2.1)	118 (1.7)	116 (2.3)	248 (3.5)
Disease						
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	16627 (68.2)	7234 (61.1)	2775 (72.1)	4419 (64.4)	3178 (62.4)	4075 (57.8)
Medication initiated[y]						

Variables	Rheumatoid Arthritis N (%)		Inflammatory Bowel Disease N (%)		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis N (%)	
	Anti-TNF (n=24,384)	Non-biologic DMARD (n=11,828)	Anti-TNF (n=3,850)	Non-biologic DMARD (n=6,867)	Anti-TNF (n=5,090)	Non-biologic DMARD (n=7,047)
Adalimumab	5888 (24.1)	-	118 (3.1)	-	294 (5.8)	-
Etanercept	10283 (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)		-

[y]Medication initiation data were collected for specific treatments in each inflammatory disease; blank cells reflect an absence of data Other race include Hispanics, Asian/Pacific islander, Native American, unknown

Table 2

Crude incidence and adjusted hazard of herpes zoster among new users of anti-TNF therapy or non-biologic DMARDs.

Exposures	Events	Person-years exposure	¥ Crude incidence rate	+ Adj. HRs
) **Rheumatoid Arthritis**				
Non biologic DMARD	90	7,100	12.7(10.3, 15.6)	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)*				
None	124	11,671	10.6(8.9, 12.7)	Reference
0<5 mg/day	111	8,917	12.4(10.3, 15.0)	1.19 (0.92, 1.54)
5-<10 mg/day	61	5,609	10.9(8.5, 14.0)	0.99 (0.72, 1.35)
≥10 mg/day	60	2,922	20.5(15.9, 26.4)	1.87 (1.37, 2.57)
) **Inflammatory Bowel Disease**				
AZA/6MP	43	4,556	9.4 (7.0,12.7)	Reference
± New users of TNF antagonists	26	2,292	11.3 (7.7,16.7)	0.79 (0.41, 1.53)
) *Baseline glucocorticoid use (prednisone equivalents)*				
None	21	2,706	7.8(5.1, 11.9)	Reference
0<5 mg/day	7	846	8.3(3.9, 17.4)	0.93 (0.38, 2.31)
5-<10 mg/day	7	1,133	6.2(2.9, 13.0)	0.87 (0.37, 2.03)
≥10 mg/day	34	2,164	15.7(11.2, 22.0)	1.99 (1.12, 3.52)
) **Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis**				
Non biologic DMARD	27	3,931	6.9 (4.7,10.0)	Reference
New users of TNF antagonists	18	4,081	4.4 (2.8, 7.0)	0.63 (0.28, 1.43)
) *Baseline glucocorticoid use (prednisone equivalents)*				
None	28	6,262	4.5(3.1, 6.5)	Reference
0<5 mg/day	9	1,146	7.9(4.1, 15.1)	1.70 (0.77, 3.72)
5-<10 mg/day	5	354	14.1(5.9, 33.9)	3.33 (1.27, 8.72)
≥10 mg/day	3	250	12.0(3.9, 37.3)	3.32 (0.98, 11.16)
Across all disease indications				
Non biologic DMARD	160	15,586	10.3 (8.8, 12.0)	Reference

Exposures	Events	Person-years exposure	¥ Crude incidence rate	+ Adj. HRs
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)				
None	173	20,639	8.4(7.2, 9.7)	Reference
0<5 mg/day	127	10,909	11.6(9.8, 13.9)	1.37 (1.08, 1.72)
5-<10 mg/day	73	7,096	10.3(8.2, 12.9)	1.18 (0.89, 1.56)
≥10 mg/day	97	5,335	18.2(14.9, 22.2)	2.13 (1.64, 2.75)

γ Number of subjects for each exposure group are given in table 1

¥ Crude incidence rates per 1,000 patient years of exposure

+ Adjusted for PS quintile and mean daily prednisone dose in 6 months prior to index

± infliximab or adalimumab only

TNF=tumor necrosis factor; DMARD=disease-modifying anti rheumatic drug; AZA=azathioprine; 6MP=6 mercaptopurine

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Table 3

Crude incidence and adjusted hazard of herpes zoster in rheumatoid arthritis patients stratified by baseline demographics and medical comorbidities

Subgroup	Exposure	Events	Person- years exposure	Crude rate per 100 person-years (95% CI)	+ Adjusted HRs
Age <50	MTX failures (n=3,212)	13	1731	7.5(4.4, 12.9)	reference
	New users of TNF antagonists (n=7,014)	47	5903	8.0(6.0, 10.6)	1.39 (0.70, 2.77)
Age ≥ 50	MTX failures (n 8,942)	77	5369	14.3(11.5, 17.9)	reference
	New users of TNF antagonists (n=17,591)	219	16116	13.6(11.9, 15.5)	0.94 (0.70, 1.24))
Age <60	MTX failures (n=6,276)	35	3597	9.7(7.0, 13.6)	reference
	New users of TNF antagonists (n=13,102)	114	11546	9.9(8.2, 11.9)	1.09 (0.73, 1.63)
Age ≥ 60	MTX failures (n=5,878)	55	3503	15.7(12.1, 20.5)	reference
	New users of TNF antagonists (n=11,503)	152	10474	14.5(12.4, 17.0)	0.93 (0.66, 1.31)
No baseline history of COPD	MTX failures (n=10,539)	75	6164	12.2(9.7, 15.3)	reference
	New users of TNF antagonists (n=21,329)	224	19465	11.5(10.1, 13.1)	0.96 (0.72, 1.28)
Baseline history of COPD	MTX failures (n=1,615)	15	936	16.0(9.7, 26.6)	reference
	New users of TNF antagonists (n=3,276)	42	2554	16.4(12.2, 22.3)	1.21 (0.65, 2.27)
No baseline history of DM	MTX failures(n=9,846)	69	5907	11.7(9.2, 14.8)	reference
	New users of TNF antagonists (n=19,950)	214	18208	11.8(10.3, 13.4)	1.09 (0.81, 1.47)
Baseline history of DM	MTX failures (n=2.308)	21	1192	17.6(11.5, 27.0)	reference
	New users of TNF antagonists (n=4,655)	52	3812	13.6(10.4, 17.9)	0.74 (0.43, 1.27)
Female gender	MTX failures (n=10,476)	78	6047	12.9(10.3, 16.1)	reference
	New users of TNF antagonists (n=21,133)	237	18778	12.6(11.1, 14.3)	0.94 (0.72, 1.24)
Male gender	MTX failures (n=1,678)	12	1053	11.4(6.5, 20.1)	reference
	New users of TNF antagonists (n=3,272)	29	3241	8.9(6.2, 12.9)	1.46 (0.66, 3.23)
* No-steroid use in 90 days	MTX failures (n=6,066)	28	2511	11.1(7.7, 16.1)	reference
	New users of TNF antagonists (n=11,021)	74	7043	10.5(8.4, 13.2)	0.78 (0.52, 1.17)
* Steroid users	MTX failures (n=6,088)	62	4588	13.5(10.5, 17.3)	Reference

Subgroup	Exposure	Events	Person- years exposure	Crude rate per 100 person-years (95% CI)	[+] Adjusted HRs
	New users of TNF antagonists (n=13,584)	192	14977	12.8(11.1, 14.8)	1.17 (0.83, 1.65)

[¥] Crude incidence rates per 1,000 patient years of exposure

[+] Adjusted for PS quintile and mean daily prednisone dose in 6 months prior to index

[*] Adjusted for PS quintile only. Steroid use (y/n) in 90 days before index date

Abbreviations: MTX, methotrexate; TNF, tumor necrosis factor-α; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

Table 4

Crude HZ incidence rates and adjusted hazard of HZ among RA patients stratified according to TNF-antagonist exposure.

Exposure	Infliximab (n=8,087)	Etanercept (n=10,138)	Adalimumab (n=6,711)
HZ cases	124	105	42
Person-years exposure	9,086	8,513	4,218
¥Crude incidence rate (95% CI)	13.6 (11.4–16.3)	12.3 (10.2, 14.9)	10.0 (7.4, 13.5)
***Adj. HR (95% CI)**	REF	1.09 (0.82, 1.45)	0.82 (0.55, 1.22)

¥Crude incidence rates per 1,000 patient years of exposure

*Adjusted for PS 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.

Disease Cohort	Exposure date	Concomitant methotrexate and prednisone use among new DMARD exposure groups							
		Infliximab		Adalimumab		Etanercept		Non-biologic DMARD	
RA		(n=8,212)		(n=5,889)		(n=10,283)		(n=11,828)	
		Pred (%)	MTX (%)	Pred (%)	MTX (%)	Pred (%)	MTX (%)	Pred (%)	MTX(%)
	Index	51.8	50.3	56.6	43.4	57.6	39.7	56.1	66.4
	Day 180	45.5	46.9	49.1	42.3	48.1	35.9	52.6	50.9
	Day 365	43.9	48.0	45.5	43.9	46.5	37.0	51.0	50.4
IBD		(n=3,808)		(n=121)		---------)γ		(n=7,267)	
	Index	52.3	2.5	60.3	14.1	N/A	N/A	67.9	0.5
	Day 180	33.9	4.3	55.9	2.9	N/A	N/A	41.5	0.4
	Day 365	29.9	7.1	44.4	11.1	N/A	N/A	35.9	0.2
		(n=541)		(n=302)		(n=4.361)		(n=8,068)	
AS/PsO/PsA	Index	37.7	42.0	38.1	31.8	46.4	19.8	51.9	76.8
	Day 180	28.9	42.0	26.5	32.5	33.5	11.7	39.2	78.4
	Day 365	26.7	38.1	27.4	29.0	31.8	13.4	39.9	74.0

RA, rheumatoid arthritis; IBD, inflammatory bowel disease; AS/PsO/PsA, ankylosing spondylitis, psoriasis, psoriatic arthritis; Pred, prednisone; MTX, methotrexate

γ etanercept is not used in IBD, so cell is blank