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Risks of Herpes Zoster in Patients with Rheumatoid Arthritis According to Biologic Disease Modifying Therapy

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Abstract

Objective—To evaluate whether the risks of herpes zoster (HZ) differed by biologics with different mechanisms of actions (MOAs) in older rheumatoid arthritis (RA) patients.

Methods—Using Medicare data from 2006–2011, among RA patients with prior biologic use and no history of cancer or other auto-immune diseases, this retrospective cohort study identified new treatment episodes of abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. Follow up started on the new biologic initiation and ended at the earliest date of: first HZ, a 30 day gap in current exposure, death, diagnosis of other auto-immune disease or cancer, loss of coverage or Dec 31, 2011. We calculated proportion of RA patients vaccinated for HZ in each calendar year prior to biologic initiation and HZ incidence rate (IR) for each biologic. We compared HZ risks among therapies using Cox regression adjusted for potential confounders.

Results—Of 29,129 new biologic treatment episodes, 28.7% used abatacept, 15.9% adalimumab, 14.8 % rituximab, 12.4% infliximab, 12.2% etanercept, 6.1% tocilizumab, 5.8% certolizumab and 4.4% golimumab. Proportion of RA patients vaccinated for HZ prior to biologic initiation ranged from 0.4% in 2007 to 4.1% in 2011. We identified 423 HZ diagnoses with the highest HZ IR for certolizumab (2.45/100 PYs) and the lowest for golimumab (1.61/100 PYs). Neither the crude

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incidence rate nor the adjusted hazard ratio differed significantly among biologics. Glucocorticoid use had a significant association with HZ.

Conclusion—Among older patients with RA, the HZ risk was similar across biologics, including those with different MOAs.

Keywords

Herpes zoster; rheumatoid arthritis; biologics; vaccination

Introduction

Herpes zoster (HZ), commonly known as shingles, is a viral disease characterized by a painful vesicular dermatomal rash caused by reactivation of latent varicella-zoster virus in cranial-nerve or dorsal-root ganglia (1, 2). More than one million HZ cases occur in the United States (U.S.) every year despite the availability of a vaccine. HZ may result in post-herpetic neuralgia and is associated with an estimated annual medical care cost of $1.1 billion (3, 4). More than 90% of HZ occurs in patients with compromised immune systems or taking immunosuppressive drugs, such as biologic therapies used for rheumatoid arthritis (RA) (3, 5).

Given that no head-to-head safety studies have directly compared the risk of HZ across biologics with different mechanisms of action (MOAs), we hypothesized that the risk for HZ would be related to the extent that the biologics' MOA affects T-cell function (2, 6). Secondarily, we were interested in examining the contribution of age, race and ethnicity to the risk for HZ in RA patients, along with the proportion of RA patients vaccinated before they initiated a new biologic.

Methods

Study Design and Data Sources

We conducted a retrospective cohort study using Medicare claims data from 2006–2011 for 100% of beneficiaries with RA. Medicare data included medical claims containing information on diagnoses, procedures, hospitalizations, physician visits and prescriptions. CMS and the Institutional Review Board of the University of Alabama at Birmingham approved the study.

Eligible Population

The study cohort consisted of RA patients who started a new course of adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab or tocilizumab during 2006–2011. The initiation date was defined as the 'index date,' and the 12 months before the index date was defined as the 'baseline' period. Based on previously validated algorithms with high positive predictive values (PPV) (7–9), we identified RA patients using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for RA (714.x) on two separate rheumatologist visits before the index date, with at least one visit occurring during baseline. We also required that a patient initiating a new biologic had a history of prior biologic use (assessed using all prior data), but had not

used that specific new biologic in the baseline period. The requirement for prior treatment with a different biologic agent was implemented because some biologics are not typically used as first-line therapies, and patients with more refractory RA, having failed multiple biologics, might have different risks for HZ. As a consequence, our study design was intended to yield a more homogeneous group of RA patients.

We further excluded patients who had a physician diagnosis of cancer or other auto-immune diseases (i.e. psoriatic arthritis, psoriasis, ankylosing spondylitis, or inflammatory bowel disease) during baseline. To avoid classifying prevalent HZ during baseline as incident after the start of follow-up, patients who used antiviral medication (famvir, acyclovir, valacylclovir) during the 3 months before the index date or had a diagnosis code of HZ (053.x) at any time before the index date (not just the 12 month baseline) were not included in the main analysis. Additionally, all patients were required to have continuous “full coverage” by Medicare in baseline and throughout follow up. Full coverage was defined as Medicare fee-for-service (Part A and Part B Medicare coverage, and not enrolled in Medicare Advantage) and Part D coverage. Follow up ended at the earliest date of first HZ, a 30 day gap in current biologic exposure, switch to another biologic, death, a physician diagnosis of cancer or other auto-immune disease (defined above), loss of Medicare coverage or end of study (Dec 31, 2011). Patients could contribute multiple treatment episodes for different biologics, but only one treatment episode for each specific biologic. Patients who had at least one diagnosis code of HZ (053.x) at any time prior to the index date during 2006–2011 were considered having a history of HZ. We conducted a secondary analysis among these patients to examine the rate of HZ recurrence.

Exposures

Exposure was characterized “as treated” (i.e. current exposure). Based upon the days of supply for prescriptions in pharmacy records, we assigned days of exposure for each injected biologic (e.g. etanercept, adalimumab, certolizumab, golimumab, subcutaneous abatacept). For infused biologics (e.g. infliximab, abatacept, rituximab and tocilizumab) identified using Healthcare Common Procedures Coding System (HCPCS) J–codes, we assigned exposure as 30 days for abatacept and tocilizumab, 56 days for infliximab and 180 days for rituximab based on recommended dosing frequency. Patients were considered exposed for 30 days after the end of days’ supply or usual dosing interval to capture the attributable events (10).

Outcome

The outcome of interest was the first event of HZ during follow-up. We identified HZ using an ICD 9 inpatient diagnosis code alone (053.x) or an outpatient diagnosis code plus a claim for an antiviral medication within 30 days of the code. Inpatient and outpatient diagnoses alone have previously been validated with high sensitivity and PPVs (>=85%) for identification of new cases of HZ (11–13). We applied the additional requirement for antiviral drug use to further improve the PPVs and better distinguish the incident and prevalent HZ.

Potential predictors of HZ

We examined predictors of HZ among treatment episodes where patients had no history of HZ. In addition to biologic exposure, potential predictors measured during the 12-month baseline included age, gender, race/ethnicity (defined by Research Triangle Institution),(14) Medicaid eligibility, disability status, methotrexate use, glucocorticoid use (categorized as none, ≤ 7.5mg/day, >7.5 mg/day of prednisone or equivalent), comorbid medical conditions, concurrent medications, health behaviors and health services utilizations. Potential predictors measured using all data prior to patients' index date included most recent biologic use, number of biologics used and vaccination for HZ (identified using national drug codes from pharmacy claims and HCPCS codes from medical claims) (15).

Statistical analysis

Analyses were stratified by patients' HZ history. The primary analysis included patients without documented prior HZ. We compared baseline characteristics between patients who developed HZ during follow-up and those who did not. We calculated the incidence rate of HZ for each biologic and compared rates using Cox regression adjusting for potential confounders. Additionally, we descriptively evaluated the proportion of RA patients who were vaccinated before their biologic initiation, by calendar year.

To evaluate whether our main findings were robust to different assumptions, several subgroup analyses were performed. We conducted three separate analyses according to patients' age category at biologic initiation: < 65, 65–75 and > 75 years. We also stratified analyses based on patients' glucocorticoid use during baseline. We further performed two subgroup analyses, one limited to treatment episodes where patients were not vaccinated before their biologic initiation and the other limited to episodes where patients switched biologics only once prior to patients' index date.

Secondary analysis of biologic episodes having history of HZ prior to index date

We calculated the incidence rate of recurrent HZ infection among biologic episodes with a history of HZ and assessed the median time from the most recent HZ before the index date to the recurrence date. Data were too sparse to evaluate the incidence rate of recurrent HZ infection for specific biologics. Therefore, we pooled all exposure episodes together.

RESULTS

Treatment episodes without history of HZ

We identified 29,129 biologic treatment episodes meeting eligibility criteria and 423 incident HZ events during follow-up. Of biologic exposure episodes, 28.8% entailed use of abatacept, 15.4% adalimumab, 14.8 % rituximab, 12.4% infliximab, 12.2% etanercept, 6.1% tocilizumab, 5.8% certolizumab and 4.4% golimumab. Baseline characteristics by occurrence of HZ are presented in Table 1. Mean age was 64 years for episodes without incident HZ during follow-up and 67 years for episodes with HZ. Overall, treatment episodes were similar between those with and without HZ, except that episodes where HZ occurred were more likely to have a history of glucocorticoid use during baseline and less likely to have Medicaid eligibility or be disabled.

The crude incidence rate of HZ among Medicare RA patients taking biologics was 1.97 per 100 person years (PYs) overall, with the highest rate observed for certolizumab (2.45/100 PYs) and the lowest for golimumab (1.61/100 PYs) (Table 2). After adjustment for potential confounders, the adjusted hazard rate for each type of biologic was not significantly different from abatacept (referent). Patients on higher dose glucocorticoids (hazard ratio (HR): 2.35, 95% CI: 1.81–3.04) or lower dose glucocorticoids (HR: 1.55, 95% CI: 1.25–1.94) during baseline had significantly higher rate of HZ compared to those not using glucocorticoids. Compared to Caucasians, African Americans (HR: 0.59, 95% CI: 0.38–0.91) were less likely to have HZ whereas Asians (HR: 1.20, 95% CI: 0.63–2.25) and Hispanics (HR: 0.79, 95% CI: 0.56–1.11) had similar risk of HZ. Compared to patients without HZ vaccination before the index date, patients who were vaccinated before the index date had a lower rate of HZ (HR: 0.79, 95% CI: 0.39–1.61). The incidence rate of HZ was comparable across different calendar years (1.72–2.07/100 PYs). The proportion of RA patients vaccinated for HZ before biologic initiation was very low, ranging from a low of 0.4% in 2007 to a high of 4.1% in 2011. All subgroup and sensitivity analyses described in the methods found results consistent with those of the primary analysis (not shown).

Recurrent HZ among those with a history of HZ

Among 1,766 treatment episodes with a history of HZ during baseline, we identified 40 recurrent HZ infections, yielding an incidence rate of 3.35 (2.46 – 4.56) per 100 person-years. The median time to the recurrence after the most recent HZ before index date was 25 months. Drug-specific associations with recurrent HZ were not evaluated due to limited sample size.

DISCUSSION

In this large cohort of mostly older RA patients, the incidence rate of HZ among patients initiating new biologic treatments ranged from 1.6–2.5 /100 person-years. Using multivariable-adjusted Cox regression, we did not find significant differences in the rate of HZ among anti-TNF agents and biologics with other MOAs. These findings were consistent in all subgroup analyses. We also found that even through 2011, the proportion of RA patients vaccinated for HZ was low before a new biologic initiation.

Our findings are consistent with several published studies examining risks associated with different anti-TNFs (13), (16). One study that combined data from 4 major US databases reported that among patients with RA and other inflammatory diseases, the HZ risk was similar among different anti-TNFs (13). Similarly, using a cohort with 5 years of follow-up, another study showed that infliximab, adalimumab and etanercept had comparable HZ risks and did not significantly increase HZ risk in comparison with non biologic disease-modifying anti-rheumatic drugs (DMARDs) (16). In contrast, data from the German biologics register RABBIT suggested that adalimumab and infliximab may be associated with increased risk of HZ infection compared to etanercept (2). In the British Society for Rheumatology Biologics register (BSRBR), Galloway et al. reported a significantly increased risk of HZ infection in an anti-TNF treated cohort compared to non-biologic DMARDs with the HR being lowest for adalimumab (HR: 1.5, 95% CI 1.1–2.0) and highest

for infliximab (HR 2.2; 95% CI 1.4–3.4) (2, 6). These conflicting results could reflect differences of age, concomitant steroid use and dose, and statistical power. Our study was consistent with the above studies in finding an increased risk of HZ associated with increasing doses of glucocorticoids.

A live attenuated vaccine to prevent HZ is approved for use in patients aged 50 years or older in the U.S. (13). In 2010, 14.4% of adults in the U.S. aged ≥ 60 years reported receiving HZ vaccination(17) and 4% among older patients (≥ 60) with selected immune-mediated diseases (15). Our findings of infrequent HZ vaccination among RA patients initiating new biologics are consistent with prior reports and indicate a compelling need for vaccination for RA patients. However, this may present practical challenges for patients to follow guidance to discontinue all biologics, allow for a washout, vaccinate, wait 4 additional weeks, and then initiate a new biologic (18). We found that patients who were vaccinated before the index date were less likely to be diagnosed with HZ compared to patients without vaccination. Vaccination was uncommon in this cohort of RA patients, and thus statistical power to find benefit associated with vaccination was quite limited. However, these results are compatible with the 39% relative risk reduction for HZ observed in a previous report of a larger cohort of patients with a more diverse group of autoimmune and inflammatory diseases (15).

We examined differences in the rate of HZ according to race and ethnicity. Some prior reports have suggested that the rates of HZ are greater in Asia, particularly Japan (19). We did not find significantly higher rates in Asians in our study. Our study found that the hazard rate for HZ was 40% lower rate of HZ among African Americans than among Caucasians. This result, although statistically significant, has not been reported previously. Possible explanations include differences in the detection and diagnosis of HZ compared to patients of other racial/ethnic groups, or residual confounding (e.g. disease severity, patterns of steroid use)

Our study has several limitations. Residual confounding for our main exposure was possible due to lack of detailed information on disease severity and life style factors. Given that patients switching to a non-TNF MOA often have been shown to have somewhat greater RA-related disease severity and comorbidity burden, residual confounding would likely yield higher HZ rates for users of non-TNF biologics. Additionally, no medical records were available to confirm HZ infection. However, HZ is typically a clinical diagnosis, and our diagnostic criterion of an outpatient HZ diagnosis accompanied by anti-viral drug use presumably conferred greater specificity to identify HZ infections compared to algorithms without using anti-viral medications, and the claims-based algorithms used have been shown to have good positive predictive values. Moreover, we would expect that misclassification of HZ was unlikely to be differential by drug exposure. We could have underestimated the occurrence of HZ vaccination if individuals paid for their vaccination without using their insurance coverage. However, because all of these individuals had full coverage and the cost of the vaccine is appreciable (approximately $180–200 for a single dose, not including administration costs), vaccination administered outside of the context of insurance is unlikely (20). Finally, this study was not designed to estimate the efficacy of vaccination,

and the number of vaccinated patients in this sample was very small, so our exploratory result of the benefit of vaccination should be interpreted cautiously.

In conclusion, among patients with RA, the rate of HZ was similar among biologics, including those with non-TNF MOAs. Moreover, we found that most RA patients were not vaccinated, even through 2011, suggesting a need for greater awareness among rheumatologists to provide this important preventive health service.

References

1. Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013; 369(3):255–63. [PubMed: 23863052]
2. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009; 301(7):737–44. [PubMed: 19224750]
3. Yawn BP, Itzler RF, Wollan PC, Pellissier JM, Sy LS, Saddier P. Health care utilization and cost burden of herpes zoster in a community population. Mayo Clin Proc. 2009; 84(9):787–94. [PubMed: 19720776]
4. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007; 82(11):1341–9. [PubMed: 17976353]
5. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002; 347(5):340–6. [PubMed: 12151472]
6. Galloway JB, Mercer LK, Moseley A, Dixon WG, Ustianowski AP, Helbert M, et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2013; 72(2):229–34. [PubMed: 22532633]
7. Kim SY, Servi A, Polinski JM, Mogun H, Weinblatt ME, Katz JN, et al. Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther. 2011; 13(1):R32. [PubMed: 21345216]
8. Maclean C, Park GS, traina SB, Liu H, Hahn BH, Paulus HE, et al. Positive Predictive Value (PPV) of an administrative data-based algorithm for the identification of patients with RA. Arthritis & Rheumatism. 2001; 44(S9):S106.
9. Singh JA, Holmgren AR, Noorbaloochi S. Accuracy of Veterans Administration databases for a diagnosis of rheumatoid arthritis. Arthritis Rheum. 2004; 51(6):952–7. [PubMed: 15593102]
10. Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA. 2011; 306(21):2331–9. [PubMed: 22056398]
11. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med. 1995; 155(15):1605–9. [PubMed: 7618983]
12. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997–2002. Epidemiol Infect. 2005; 133(2):245–53. [PubMed: 15816149]
13. Winthrop KL, Baddley JW, Chen L, Liu L, Grijalva CG, Delzell E, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. JAMA. 2013; 309(9): 887–95. [PubMed: 23462785]
14. Eicheldinger C, Bonito A. More accurate racial and ethnic codes for Medicare administrative data. Health Care Financ Rev. 2008; 29(3):27–42. [PubMed: 18567241]
15. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012; 308(1):43–9. [PubMed: 22760290]
16. Dewedar AM, Shalaby MA, Al-Homaid S, Mahfouz AM, Shams OA, Fathy A. Lack of adverse effect of anti-tumor necrosis factor-alpha biologics in treatment of rheumatoid arthritis: 5 years follow-up. Int J Rheum Dis. 2012; 15(3):330–5. [PubMed: 22709496]

17. Centers for Disease Control and Prevention (CDC). [assess on Apr 19th, 2014] Adulat Vaccination Coverage - United States. 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a2.htm

18. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012; 64(5):625–39. [PubMed: 22473917]

19. Toyama N, Shiraki K. Society of the Miyazaki Prefecture D. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. J Med Virol. 2009; 81(12):2053–8. [PubMed: 19856466]

20. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med. 2013; 10(4):e1001420. [PubMed: 23585738]

Significance and Innovations

- The absolute rates of herpes zoster among older RA patients enrolled in Medicare and taking biologics were between 1.61 and 2.45 per 100 person years
- Among patients with RA, the rate and adjusted hazard ratios of herpes zoster was similar among biologics, including those with non-TNF mechanisms of action
- Even through the end of 2011, most RA patients were not vaccinated against HZ. The need for vaccination remains compelling

Table 1

Baseline characteristics by occurrence of herpes zoster (HZ) among Medicare Rheumatoid Arthritis Patients during follow-up, 2007–2011

Baseline Characteristics	Occurrence of herpes zoster (HZ) during follow-up		
	ALL	Yes	No
Total, n	29,129	423	28, 706
HZ vaccination*, %	2.29	< 2	2.29
Age, Years (SD)	64.4 (13.0)	67.4 (11.6)	64.4 (13.0)
Female, %	85.0	87.0	85.0
Medicaid eligible, %	44.8	36.4	44.9
Disabled, %	58.2	48.9	58.3
New biologic treatment occurring on the index date, %			
Adalimumab	15.4	10.9	15.5
Certolizumab	5.8	4.5	5.9
Etanercept	12.2	11.4	12.2
Golimumab	4.4	2.6	4.5
Infliximab	12.4	13.5	12.4
Abatacept	28.8	33.6	28.7
Rituximab	14.8	19.4	14.8
Tocilizumab	6.1	4.3	6.2
Number of biologics previously used*, %			
1	70.1	71.90	70.0
2	22.7	20.1	22.7
≥ 3	7.2	8.0	7.3
Comorbidities, %			
Diabetes	20.7	19.2	20.8
Chronic obstructive pulmonary disease	22.9	23.6	22.9
Heart failure	6.3	7.8	6.3
Renal disease	4.9	6.60	4.9
Any fracture	7.9	10.4	7.9
Hospitalized infections during baseline			
None	89.1	86.3	89.2
1–2 episodes	10.1	11.8	10.1
≥3 episodes	0.8	1.9	0.8
Medications, %			
Prednisone, mean mg/day			
None	39.9	30.3	40.0
≤7.5	44.5	49.4	44.5
>7.5	15.6	20.3	15.5

Baseline Characteristics	Occurrence of herpes zoster (HZ) during follow-up		
	ALL	Yes	No
Methotrexate	56.7	59.3	56.7
Non-steroidal anti-inflammatory drugs	39.1	37.6	39.1
Health behaviors and health services utilization, %			
Prostate specific antigen screening test (men only)	41.4	32.7	41.5
Mammography (women only)	37.2	40.5	37.1
All-cause hospitalization during baseline			
No hospitalization	72.0	69.5	72.0
1–2 hospitalizations	24.6	23.2	24.6
≥ 3 hospitalizations	3.4	7.3	3.4
Outpatient infection	46.0	48.7	46.0
Had long-term care stay during baseline	1.9	2.1	1.9

* assessed using all prior data, even beyond the 12 month baseline

Table 2

Events, absolute incidence rate and adjusted hazard ratio of herpes zoster infection by different types of biologics and other RA Medication

Biologic Exposures	Events	Person years (pys)	Absolute incidence rate per 100 pys (95% CI)	Adjusted hazard ratio* (95% CI)
Non-Anti TNF mechanism of action				
Abatacept	142	7614	1.87 (1.58–2.20)	1.00 (Ref)
Rituximab	82	3611	2.27 (1.83–2.82)	1.20 (0.88–1.63)
Tocilizumab	18	839	2.15 (1.35–3.40)	1.05 (0.60–1.84)
Anti-TNF mechanism of action				
Adalimumab	46	2638	1.74 (1.31–2.33)	1.04 (0.72–1.51)
Certolizumab	19	774	2.45 (1.57–3.85)	1.30 (0.77–2.23)
Etanercept	48	2229	2.15 (1.62–2.86)	1.26 (0.87–1.81)
Golimumab	11	683	1.61 (0.89–2.91)	0.91 (0.47–1.76)
Infliximab	57	3135	1.82 (1.40–2.36)	0.98 (0.69–1.39)
Other RA Medications				
Methotrexate				
No	172	8844	1.94 (1.67–2.26)	1.00 (Ref)
Yes	251	12678	1.98 (1.75–2.24)	1.07 (0.88–1.29)
Oral Glucocorticoids (prednisone-equivalent dose)				
None	128	8548	1.50 (1.26–1.78)	1.00 (Ref)
≤ 7.5mg/day	209	9841	2.12 (1.85–2.43)	1.55 (1.25–1.93)
> 7.5mg/day	86	3134	2.74 (2.22–3.39)	2.35 (1.81–3.04)

*Adjusted for age, gender, race, oral glucocorticoids use during baseline, methotrexate use during baseline, number of hospitalizations during baseline, previous biologic type, disabled status, number of hospitalizations during baseline, and zoster vaccination before new biologic treatment initiation. All other variables in table 1 were not significant in the full multivariate analyses, thus were not adjusted for in the final model.