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Defining an Optimal Adherence Threshold for Patients Taking Subcutaneous Anti-TNFs for Inflammatory Bowel Diseases

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Abstract

OBJECTIVES—In patients with inflammatory bowel disease (IBD) using biological therapy, non-adherence leads to anti-drug antibody formation and reduced effectiveness. Little is known about the optimal level of adherence in IBD patients on biologic therapy. We aimed to identify the association between adherence and disease flare and determine an optimal level of adherence.

METHODS—We analyzed claims data for IBD patients prescribed adalimumab (ADA) and certolizumab (CZP) from the Truven Health MarketScan Commercial Claims and Encounters database from 2009 to 2013. Adherence was calculated using the medication possession ratio (MPR) from initiation until flare occurrence. A disease flare was defined as any hospitalization or new steroid prescription >90-days after drug initiation. The optimal MPR was determined using log-rank testing. The association between the optimal MPR and flare was assessed using multivariable Cox-Proportional hazards ratio.

RESULTS—There were 6,048 patients who were prescribed ADA ($n=5,325$) or CZP ($n=723$) for IBD. The average age was 41 years (± 15) and 54% were female. The optimal MPR identified was

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CONFLICT OF INTEREST

Potential competing interest: None.

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0.86 for ADA and 0.87 for CZP; 24% of the patients were below this level. Adjusting for age, gender, and concomitant medications at initiation, patients who were adherent above these levels had a 25% lower risk of flare for ADA (HR: 0.75, 95%CI: 0.67–0.83, $P<0.01$) and 41% lower risk for CZP (HR: 0.59, 95%CI: 0.46–0.76, $P<0.01$).

CONCLUSIONS—Patients who delay refills >2 days on average every 2 weeks of their subcutaneous biologics have significantly increased risk of flare. Further studies to improve adherence among those patients who consistently delay medication use are necessary.

INTRODUCTION

Approximately 1.5 million American have been diagnosed with inflammatory bowel disease (IBD), a chronic relapsing and remitting disorder of the gastrointestinal tract (1). For patients with moderate to severe disease, anti-tumor necrosis factors (anti-TNFs) such as certolizumab and adalimumab are more effective than oral immunosuppression for disease control (2–6). However, while these medications are initially effective in more than 50% of patients, $\sim 1/3$ of patients lose response over time (7). One of the principal reasons for loss of response is the development of antibodies that bind the drug itself. These anti-biologic antibodies reduce efficacy in two ways, by increasing clearance and/or by preventing the drug from binding TNF. Once antibodies develop against the drug, further dose escalation is often not effective (8). Switching to another anti-TNF can regain control of the disease (9), but there are limited options and the likelihood of response decreases with each drug change (10). Notably, intermittent use (i.e., non-adherence) of these drugs has been identified as a significant predictor of the development of antibodies (11). Yet, to date, little is known about the threshold of adherence necessary to avoid flares associated with steroid use and hospitalizations. Historically, possession of medication for $>80\%$ of the intended time of use has been considered acceptable adherence (12,13) and used as a target in adherence studies. However, due to the risk of auto-antibody formation, this may not apply to anti-TNFs. We hypothesized that a higher adherence threshold is necessary for these medications due to threat of antibody formation with intermittent use and that lower adherence is associated with increased risk of disease flares.

To address this gap in knowledge, we measured the adherence rates to subcutaneously delivered biologics from 2009 to 2013 among enrollees with IBD in a large health insurance claims database. We aimed to identify an optimal adherence threshold for these medications to prevent important clinical outcomes like steroid use and new hospitalizations based on medication possession ratio, determine the effect of non-adherence below this threshold on these outcomes using survival analysis, and identify other predictors of poor outcomes including concomitant medication use and costs of medications.

METHODS

Data source

We studied the medication refill patterns of patients identified to have IBD from the Truven Health MarketScan Commercial Claims and Encounters database from 2009 to 2013. This large administrative database is derived from data from insurance coverage of enrollees who

are covered by large employers in the United States. The database covers inpatient and outpatient visits in addition to pharmacy claims data on ~50 million people.

Cohort

Individuals were defined as having IBD based on the presence of a single inpatient encounter or two outpatient claims on different days with an ICD-9CM code of Crohn's (555.x) or ulcerative colitis (556.x). Patients were excluded if they did not have at least 12 months of continuous coverage with pharmacy benefits. When patients had multiple periods of coverage, only the most recent coverage period was examined to ensure that relevant outcomes were captured. The diagnosis of Crohn's or ulcerative colitis was assigned if all the ICD9-CM codes were concordant with that diagnosis. In instances which this threshold was not met, the patient was given a diagnosis based on the majority of the most recent nine ICD-9 codes. The same rule applies to patients with less than nine ICD-9 codes; however, patients with equal number of ICD-9 codes were labeled as having indeterminate colitis (14). CZP users with an ulcerative colitis diagnosis were excluded from the study as CZP is not approved for ulcerative colitis.

Pharmaceutical claims were analyzed for dispenses of both adalimumab and certolizumab. Errant claims identified as those indicating that a quantity of zero or less was dispensed were excluded from analysis. Claims data that indicated that unusual quantities of medication were dispensed was also deleted. For adalimumab, we expected to find no more than six syringes dispensed in 14 days during induction (ratio of 2.33 days/injection) and no less than two syringes dispensed in 30 days for maintenance (ratio of 15 days/injection). For certolizumab, we expected to find no more than two kits dispensed in 14 days during induction (ratio of 7 days/kit) and no less than one kit dispensed for a 30-day period during maintenance (ratio of 30 days/kit). Analysis of each medication was limited to those patients who were exposed to the first anti-TNF during the study time period. Concomitant medication use at the time of the first anti-TNF was defined by a concomitant medication course starting before the first anti-TNF date and ending after that date. Concomitant drug courses allow for a maximum 14 day gap between prescriptions of the same drug class.

A medication possession ratio (MPR) was used to assess anti-TNF adherence. The medication possession ratio is calculated as (sum of the days of medication supplied)/(the sum of the days in the total refill intervals) (15). For example, if a patient is dispensed a 28 day supply on 1 January and then another 28 day supply on 1 February, the MPR is calculated as 56/59 or 0.95. Courses were classified as the prescription of an individual anti-TNF with no greater than 120 days between doses administered. Only the first course for each medication was analyzed in order to limit the effect of repeated starts and stops on medication efficacy and outcomes. Courses with an MPR above the 99th percentile (MPR>1.4) were deleted as possible outliers. These were suspected to contain errant claims data. MPR was therefore capped at 1.4. An average payment per injection/kit was calculated for each course using the patient copay and deductible data from each claim. The optimal MPR cut points were then identified and patients classified into adherent vs. non-adherent groups accordingly. In order to determine if medication side effects were the reason behind medication non-adherence or discontinuation we compared medication related side effect

frequencies (pneumonia, psoriasis/rash, lupus, and infection) between the adherent and non-adherent cohort. The ICD-9CM codes used for these side effects are presented in Supplementary Data online. We also determined the percentage of patients who experienced anti-TNF escalation before discontinuation. To achieve this, we compared prescriptions at the beginning and end of the maintenance period and identified any increase in dosage.

Statistical analysis

The statistical analyses were performed using SAS 9.4 (Cary, NC). Continuous variables were analyzed with the Mann–Whitney *U* test. Categorical variables were analyzed with the χ^2 test. The relationship between MPR and adverse outcomes (hospitalization or first corticosteroid use) was examined using Cox proportional hazard models taking into consideration time-to-event. MPR was initially included as a continuous variable. Only events that occurred within 120 days of the last fill were counted since it was assumed that events that occurred later were unrelated to the use of these medications. In order to identify an optimal cutoff for MPR, the findcut macro was utilized (16) with selection of a cutoff based on Contal and O’Quigley Method (17). This method has been used in a number of studies to identify cutoffs in continuous variables in survival analysis (18,19). It involves calculating all the log-rank statistic for all possible splits and selecting the optimal cutpoint based on maximizing the log-rank statistic. This is the point which maximally separates patients above and below the point with regards to outcomes. A sensitivity analysis was also conducted to examine the change in multivariable hazard of an outcome by varying the cutoff. Hospitalization or corticosteroid initiation within 90-days of initiation were not counted as events. Short, individual courses (<14 days with no subsequent prescriptions) of steroids were also excluded as events. Patients who were not hospitalized or prescribed steroids were censored at the last day of their last prescription fill.

RESULTS

From 2009 to 2013, 22,285 Individuals with IBD were prescribed an anti-TNF. Of these patients, 55% were female, average age was 41.7 years ($\pm$ 14.9) and 80.6% had Crohn’s disease. Of these individuals, 90.7% received one anti-TNF type during the study period, 9.1% received two anti-TNF types and just 0.2% were prescribed three anti-TNFs.

Adalimumab

During the study period, 17,988 patients were prescribed adalimumab. After applying exclusion criteria, 6,937 were prescribed adalimumab as their only anti-TNF, and 5,325 were given at least 3 months supply without other errant fill data. The primary outcome of hospitalization or new steroid prescription was met in 1,725 (32.4%), and 14.8% were on steroids at initiation of adalimumab (Table 1). Only 15.2% of the cohort were on an immunomodulator at the time of anti-TNF initiation while 10.6% were using narcotics.

The mean cumulative MPR for adalimumab was 0.94 ($\pm$ 0.13). In bivariate analyses, the cumulative MPR was significantly associated with either hospitalization or a new steroid prescription. Using the Contal–O’Quigley method to examine the cumulative MPR, a cutoff of 0.86 created the greatest difference in outcomes between non-adherent and adherent

patients (HR 0.71, 95%CI: 0.64–0.79, $P<0.01$). Using this cutoff, 20.5%, were classified as non-adherent. The time to outcome was statistically significant between adherent patients with an MPR of at least 0.86 and those below 0.86 (Figure 1a). A small but statistically significant difference in median copay was found ($P=0.04$) between patients who were adherent (\$43.4, IQR: 25.0–90.0) and those who were not adherent (\$40.0, IQR: 23.1–79.4).

Multivariable analysis of the effect of adherence using a cumulative MPR threshold of 0.86 found that adherent patients were less likely to be hospitalized or to be given a new steroid prescription (HR 0.75, 95%CI: 0.67–0.83, $P<0.001$), after adjusting for age, gender, and concomitant medication use at initiation of anti-TNF. Narcotic use at anti-TNF initiation was associated with future hospitalization or steroid prescription (HR 1.57, 95%CI: 1.37–1.81, $P<0.001$).

No difference in infection and medication related side effects was found between adherent and non-adherent patients during the period of anti-TNF use (Table 2). In addition, non-adherent patients did not experience higher proportion of escalation compared with adherent patients (16.6 vs. 14.2%).

The sensitivity analysis of varying cutpoints of MPRs in a multivariable model is presented in Table 3. The beneficial effects of increased adherence continue with MPRs up to 0.97 at which point there does not appear to be a significant improvement in outcomes above and below this cutoff (plateau point).

Certolizumab

There were 4,241 individuals prescribed certolizumab during the study period. Of these, 1,221 were prescribed the drug as the only anti-TNF with at least 6 months of coverage prior to drug initiation and at least 6 months of coverage after initiation. After removing patients with errant data, multiple courses of the drug, and less than three fills, there were 723 patients remaining in the cohort. Among these patients, 269 (37.2%) had a hospitalization or new steroid prescription more than 90 days after first starting the medication, and 9.7% were on steroids at the time of anti-TNF initiation.

The average cumulative MPR was 0.87 (± 0.14), with 14.7% of the cohort with an MPR of 1.0 or higher. Selecting an MPR of 0.87 as the cutoff was identified as having the greatest difference between adherent and non-adherent groups based on the Contal and O'Quigley method. Using this as the adherence threshold, 43.7% of the cohort was non-adherent. There was a significant difference in time to hospitalization or new steroid prescription based on this adherence threshold (Figure 1b). The median copayment was similar ($P=0.32$) between those with an MPR >0.87 (\$50.0, IQR: 31.3–98.3) and those below this threshold (\$50.0, IQR: 35.0–100.0).

In bivariate analyses, the hazard ratio of hospitalization or new steroid prescription was 0.54 (95%CI: 0.42–0.69, $P<0.01$) for patients with an MPR above 0.87 compared to those below (Table 4). Narcotic users were more likely to have an outcome after starting an anti-TNF (HR: 2.01, 95%CI: 1.49–2.71, $P<0.01$). Multivariable analysis found that adherence above a cumulative MPR >0.87 remained protective (HR 0.59, 95%CI: 0.46–0.76, $P<0.001$) for these

outcomes after adjusting for age, gender, and concomitant medications at initiation (Table 5). In the multivariable model, narcotic use remained associated with an increased risk of hospitalization or new steroid use.

Non-adherent patients did not experience increased medication related side effects or infections during the period of anti-TNF use compared with adherent patients (Table 2). Similarly, no increased escalation proportion was found in non-adherent patients compared with those who were adherent (6.0 vs. 7.6%).

The sensitivity analysis of varying cutpoints of adherence for certolizumab found that increasing adherence up to an MPR of 0.95 was beneficial (plateau point). Patients with an MPR of 0.95 or greater did not have a reduction in adverse outcomes compared to those below this threshold.

DISCUSSION

Using the classic MPR benchmark for adherence of 0.8, the patients in our cohort taking anti-TNFs would be considered adherent, with only 13.5% of patients taking adalimumab and 25.6% of those taking certolizumab falling below this level. In this study of an administrative database, we found that an MPR of 0.87 or higher is associated with a significantly lower risk of hospitalization or new steroid prescription for those initiating certolizumab and an MPR of 0.86 or higher for those starting adalimumab. These adherence measures equate to missing only 4 days of medication in a 28 day cycle. These findings confirm our hypothesis that adherence targets for these medications should be set higher than traditional medications and establish the relationship between non-adherence and disease flares.

Our study is unique in that it is the largest study of adherence to biologics among IBD patients specifically and examined the effects of non-adherence on downstream consequences such as hospitalizations and steroid use. Another analysis of adalimumab use for all indications found an average MPR of 0.84 (20), lower than the average MPR we found here for adalimumab for IBD alone: 0.94. A small percentage of the patients in the comparison study had Medicare or Medicaid, both of which have been associated with lower adherence than private insurance (21). It is also possible that patients who take adalimumab for IBD may be more adherent than patients who take this drug for other indications. We found no meaningful relationship between patient costs and adherence for the two drugs studied. Consistent with our findings, Goldman *et al.* found no association between patient costs and adherence for specialty drugs in autoimmune conditions; they speculate that cost is not an issue once patients are placed on biologics because these patients' other costs are so high and deductible reached rapidly (22). Other studies, however, have revealed a relationship between patient costs and patient adherence in other disease states (23–25).

The adherence results for the two biologics are notably different with lower adherence among patients taking certolizumab compared to adalimumab. The dosing of certolizumab is less frequent than adalimumab which may influence the benefit of developing routines on adherence. Adalimumab is available as an injector pen while certolizumab is not; this may

influence patients' adherence either through differences in pain with administration or ease of administration. There also maybe differences in the copay assistance programs which led to differences in adherence between ADA and CZP. It is also notable that while the MPR cutoff identified for these two drugs was similar, the association between non-adherence and rate of hospitalization or steroid use was stronger for those taking certolizumab. We speculate that drug levels have to be higher in patients with certolizumab and that those who are non-adherent have more inflammation and consequently, worse clinical outcomes (26).

Our analysis identified an MPR cutoff that created the greatest difference in outcomes above and below the cutoff. A number of studies across a range of disease states have arbitrarily set the adherence threshold at 0.8 in defining adherence (13,27). Others have identified that adherence above this level is beneficial in reducing hospitalizations or achieving clinical targets (28–31). We have identified a cutoff for adherence based on one method of selecting thresholds, in order to maximize the difference in outcomes between adherent and non-adherent patients. We also examined increasing MPR thresholds and found that MPRs up to 0.95–0.97 lead to improved outcomes. At MPRs over this plateau point, there did not appear to be difference in outcomes compared to those patients who did not meet this cutoff. An adherence level of 0.87 corresponds to missed or delayed dosing by only 4 days per month on average. This may be particularly problematic for these medications as they are given relatively infrequently, every 2 or 4 weeks, and in many instances have to be obtained from a specialty pharmacy by mail. Prior authorizations, annual renewals, delays in filling prescriptions, and holidays frequently lead to delayed or missed doses. Our findings suggest that these medications, like antiretrovirals for HIV (32) and antivirals for hepatitis C (31), require exceptionally high levels of adherence. Interventions to help IBD patients achieve and maintain these high levels of adherence are essential to the long-term success of, and deriving the most value from these expensive medications.

The limitations to our study are related to the shortcomings of using an administrative database. We cannot account for valid reasons for skipping or missing medications such as bacterial infections or injection reactions. Patients may be instructed to skip medication doses during lower respiratory tract infections or other infections. The downstream effect of skipping these doses however is still notable in that it leads to higher risk of hospitalization or steroid use for IBD. However, we noticed no increase in infections and medication related side effects between the adherent and non-adherent groups. Our analysis cannot adjust for other important factors including smoking or disease severity which are known to influence the effectiveness of these medications. The use of an administrative database limits our assessment of adherence to an indirect measure like MPR which may not truly account for patient adherence. Additionally, errant data were excluded in the MPR calculation which may limit generalizability. Anti-TNFs, however, are unlikely to be obtained and then not used in a repeated fashion due to their cost. Our study encompasses the time period just before and after the landmark study showing dual therapy to be superior to monotherapy (2) and only a small percentage of biologic users were on an immunomodulator at the time of initiation. Dual therapy is known to reduce the risk of anti-drug antibodies and prolong drug use. It is possible that future studies may show differences in outcomes among adherent patients to biologics if taking (and adherent) to immunomodulators. Finally, our estimates of adherence to anti-TNFs may not reflect the true estimates of adherence nationally since the

data source includes only patients with commercial insurance only and does not sample those with Medicare or Medicaid or no insurance coverage.

In conclusion, we have identified an association between adherence to subcutaneous biologics and hospitalizations and steroid use. We show that adherence levels should be maximized for these medications, ideally above an MPR of 0.87, with a plateau point of 0.95–0.97, to prevent poor outcomes. The adherence threshold of 0.87 allows for less than 4 days of missed medication per 28 day period. Future work on the most effective interventions targeted to high-risk patients taking these medications who fall below this level of adherence is necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Anti-TNFs are very effective for inflammatory bowel disease (IBD) but many patients lose response over time.
- ✓ Patients with IBD are often non-adherent to medications.
- ✓ Intermittent use of anti-TNFs can lead to the development of auto-antibodies which can reduce efficacy and lead to loss of response.

WHAT IS NEW HERE

- ✓ Patients taking adalimumab possessed the medication 94% of the time of intended use on average while patients taking certolizumab possessed the medication an average of 87% of the time of intended use.
- ✓ Patients who possessed their medications less than 86–87% of the time of intended use were more likely to be hospitalized or be treated with corticosteroids.
- ✓ More than 20% of patients treated with these drugs fell below this threshold.

Figure 1.

Kaplan–Meier curve demonstrates increased risk of hospitalization or new corticosteroid use among patients initiating adalimumab (**a**) and certolizumab (**b**). A full color version of this figure is available at the *American Journal of Gastroenterology* journal online.

Table 1

Characteristics of subcutaneously injected anti-TNFs for inflammatory bowel disease

	Adalimumab (n=5,325)	Certolizumab (n=723)
Age ($\pm$ s.d.)	41.3(15.4)	41.1 (13.8)
Male (%)	2459 (46.2)	305 (42.2)
Crohn's disease (%)	4,108 (77.2)	719 (99.4)
Steroid user at anti-TNF start (%)	786 (14.8)	70 (9.7)
Narcotic user at anti-TNF start (%)	563 (10.6)	114 (15.8)
Immunomodulator user at anti-TNF start (%)	807 (15.2)	117 (16.2)
Cumulative MPR ($\pm$ s.d.)	0.94 (0.13)	0.87 (0.14)
Hospitalization or new steroid prescription >90 after anti-TNF start	1725 (32.4)	269 (37.2)

MPR, medication possession ratio; TNF, tumor necrosis factor.

Table 2

Comparison of side effects profile between adherent and non-adherent anti-TNF users

	Adherent	Non-adherent	P value
<i>Adalimumab</i>			
Pneumonia (%)	32 (0.8%)	12 (1.1%)	0.26
Lupus (%)	9 (0.2%)	1 (0.1%)	0.67
Psoriatic rash (%)	112 (2.7%)	32 (2.9)	0.60
Any infection (%)	1059 (97.1%)	4144 (97.2%)	0.86
<i>Certolizumab</i>			
Pneumonia (%)	5 (1.2%)	1 (0.3%)	0.24
Lupus (%)	1 (0.3%)	2 (0.6%)	0.83
Psoriasis/rash (%)	12 (3.0%)	1 (0.3%)	0.01
Any infection (%)	399 (98.0%)	305 (96.5%)	0.21

TNF, tumor necrosis factor.

Table 3

Sensitivity analysis of varying MPR cutoffs on the risk of hospitalization or new corticosteroid use controlling for medications and demographics

Adherence threshold (MPR)	HR	95% CI	P value
<i>Adalimumab</i>			
>0.75 (compared to <0.75)	0.62	0.54–0.71	<0.001
>0.80 (compared to <0.80)	0.71	0.63–0.81	<0.001
>0.85 (compared to <0.85)	0.74	0.66–0.83	<0.001
>0.90 (compared to <0.90)	0.82	0.74–0.91	<0.001
>0.93 (compared to <0.93)	0.87	0.79–0.96	0.004
>0.95 (compared to <0.95)	0.91	0.83–1.00	0.05
>0.97 (compared to <0.97)	0.95	0.86–1.05	0.29
<i>Certolizumab</i>			
>0.75 (compared to <0.75)	0.64	0.48–0.87	0.005
>0.80 (compared to <0.80)	0.73	0.55–0.97	0.03
>0.85 (compared to <0.85)	0.58	0.46–0.75	<0.001
>0.90 (compared to <0.90)	0.68	0.53–0.86	0.002
>0.93 (compared to <0.93)	0.75	0.58–0.97	0.03
>0.95 (compared to <0.95)	0.88	0.67–1.15	0.35
>0.97 (compared to <0.97)	1.07	0.80–1.43	0.63

MPR, medication possession ratio.

Table 4

Bivariate Cox-proportional hazards of hospitalization or new corticosteroid prescription

	HR	95% CI	P value
<i>Adalimumab</i>			
Cumulative MPR	0.40	0.28–0.59	<0.001
Female (versus Male)	1.06	0.96–1.16	0.26
Taking immunomodulators at anti-TNF start	0.98	0.86–1.11	0.72
Taking narcotics at anti-TNF start	1.61	1.40–1.85	<0.001
Adherent (MPR >0.86) vs. non-adherent	0.71	0.64–0.79	<0.001
<i>Certolizumab</i>			
Cumulative MPR	0.22	0.07–0.56	0.002
Female (versus Male)	1.26	0.99–1.62	0.06
Age	0.99	0.98–1.00	0.03
Taking steroids at anti-TNF Start	0.72	0.45–1.16	0.18
Taking immunomodulators at anti-TNF start	1.11	0.80–1.52	0.54
Taking narcotics at anti-TNF Start	2.01	1.49–2.71	<0.001
Adherent (MPR >0.87) vs. non-adherent	0.54	0.42–0.69	<0.001

Table 5

Multivariable predictors of new steroid prescription or hospitalization after anti-TNF initiation

	HR	95% CI	P value
<i>Adalimumab^a</i>			
Female (vs. male)	1.02	0.93–1.12	0.68
Adherent (MPR>0.86) vs. non-adherent	0.76	0.67–0.83	<0.001
On immunomodulators at anti-TNF start	0.99	0.87–1.13	0.88
On narcotics at anti-TNF start	1.57	1.37–1.81	<0.001
<i>Certolizumab</i>			
Female (vs. male)	1.24	0.97–1.58	0.09
Age	0.99	0.98–1.00	0.03
Adherent (MPR>0.87) vs. non-adherent	0.59	0.46–0.76	<0.001
Taking steroids at anti-TNF start	0.74	0.46–1.19	0.21
On immunomodulators at anti-TNF start	1.14	0.83–1.57	0.41
On narcotics at anti-TNF start	1.93	1.43–2.62	<0.001

MPR, medication possession ratio; TNF, tumor necrosis factor.

^a Age and the status of taking steroids at anti-TNF start were included as strata in the model as they violated the proportional hazard assumption. Age was categorized to <18, 18–34, 35–50, 51–65, 66–80, >80.