Title: Comparative persistence on methotrexate and TNF inhibitors in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

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Abstract

Objective: The role of methotrexate for the treatment of spondyloarthritis remains uncertain. Aims were to compare methotrexate and tumor necrosis factor inhibitor (TNFi) persistence in spondyloarthritis vs. RA and to determine whether concomitant conventional synthetic DMARD (csDMARD) use is associated with improved TNFi persistence in spondyloarthritis.

Methods: This retrospective cohort study using Optum's de-identified Clinformatics® Data Mart Database 2000-2014 identified patients with RA, psoriatic arthritis (PsA), and ankylosing spondylitis (SpA) without prior biologic use initiating methotrexate or a TNFi for the first time. Cox proportional hazards models compared time to medication discontinuation over the next two years between patients with RA, PsA, or AS, adjusting for potential confounders. In similar analyses stratified by disease, Cox models were used to assess whether concomitant use of csDMARDs was associated with TNFi persistence.

Results: We identified 31,527 methotrexate initiators (26,708 RA, 2,939 PsA, 1,880 AS) and 34,651 TNFi initiators (24,134 RA, 6,705 PsA, 3,812 AS). Methotrexate was discontinued sooner in patients with PsA [aHR 1.10 (1.04-1.16)] and AS [aHR 1.23 (1.16-1.31)] vs. RA, while TNFi were discontinued at similar rates in RA and AS and discontinued later in PsA [aHR 0.93 (0.89-0.97)]. Concomitant use of methotrexate (compared to no csDMARD) was associated with lower rates of TNFi discontinuation in RA [aHR 0.85 (0.80-0.89)], PsA [aHR 0.81 (0.74-0.89)], and AS [aHR 0.79 (0.67-0.93].

Conclusion: Methotrexate discontinuation occurs sooner in patients with PsA and AS vs. RA. Concomitant use of methotrexate with a TNFi, however, is associated with improved TNFi persistence in all three diseases.

Introduction

Methotrexate is the backbone of therapy for the treatment of rheumatoid arthritis (RA), but the role of methotrexate in the treatment of spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS) remains unclear. Methotrexate is an effective drug in RA; approximately 30% of patients with RA are able to achieve remission with initial therapy with methotrexate alone (1–3). Studies in PsA and AS are much more limited and have not documented clear benefit in these conditions. Whether the lack of evidence reflects a lack of efficacy of methotrexate in spondyloarthritis, heterogeneity of these diseases, or the lack of adequately powered trials is uncertain. The recent SEAM-PsA trial comparing methotrexate to etanercept in PsA found that a higher proportion of patients had improvements in disease activity with MTX monotherapy than previous studies had reported, but there was no placebo group comparison (4).

Consequently, the role of methotrexate and other csDMARDs in the treatment of peripheral spondyloarthropathies is controversial (biologics being preferred for axial disease). Recommendations from the European League Against Rheumatism (EULAR) recommend methotrexate as first line therapy for PsA (5), but recent guidelines from the American College of Rheumatology (ACR), influenced by the limited data for methotrexate and large studies of biologics, recommend a TNFi as first-line therapy, particularly in patients with more severe disease (6).

One potential benefit of methotrexate across all three conditions, however, is that combination treatment with a TNFi may prolong or enhance the effectiveness of

the TNFi. There is evidence that methotrexate use can help to prevent the formation of anti-drug antibodies in RA (7), but studies in PsA and AS have been mixed (8–12). Trials, including the recent SEAM-PsA trial have generally not demonstrated improved efficacy of combining csDMARD treatment with a TNFi (4,8,9,13). Because of the shorter duration of trials, however, they are limited in their ability to assess the impacts of csDMARDs on longer-term TNFi persistence (as opposed to initial efficacy). Some observational studies, on the other hand, have suggested an association between methotrexate use and TNFi persistence in PsA, even though biologics are the focus of these studies (14–16). Whether to initiate or continue methotrexate or other csDMARDS to influence the persistence of TNFi is an important and common clinical question.

Few studies have examined differences in persistence of methotrexate and TNFi across RA, PsA, and AS in a real-world setting. Furthermore, few studies have assessed how methotrexate and other csDMARDs impact persistence on a TNFi across these diseases. The objectives of this study were to compare rates of methotrexate and TNFi discontinuation across diseases and to evaluate whether concomitant use of different csDMARDs was associated with TNFi persistence. We hypothesized that patients with PsA and AS would demonstrate reduced persistence of methotrexate but similar persistence of TNFi (reflecting reduced efficacy of methotrexate in PsA and AS) and that use of csDMARDs with a TNFi would be associated with greater TNFi persistence in RA.

Methods

Study Setting

We conducted a retrospective cohort study using Optum's de-identified Clinformatics® Data Mart Database 2000-2014. OptumInsight is a de-identified United States administrative claims database from a nationally representative private health care insurer, with socio-demographic, inpatient, outpatient, and prescription claims available for over 60 million unique members.

We identified adults ≥ 18 years old with RA, PsA, or AS based on two ICD-9 diagnosis codes on separate days at any time prior to the index date and DMARD use (17–19). We used a hierarchical categorization approach for patients meeting criteria for multiple diseases based on the specificity of these codes (PsA > AS > RA) to create mutually exclusive groups, similar to previous studies (20). Results were similar if patients meeting criteria for multiple diseases were included within each of these diseases categories (non-mutually exclusive groups, not shown).

Patients were indexed at the time they received a first ever MTX prescription or a first ever TNFi prescription or infusion (study design in Supplemental Figure 1). We excluded patients with prior biologic use. We required at least 6 months of preceding data (baseline) to ensure that patients were new initiators of their therapy, and we required at least 90 days of available data after medication initiation. We excluded patients with a diagnosis code for systemic lupus erythematosus in the past year or missing demographic data.

Exposures

We first treated disease (RA vs. PsA vs. AS) as the exposure of interest, comparing rates of methotrexate or TNFi discontinuation. In subsequent analyses, the exposure of interest was the use of concomitant methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide, defined as a prescription fill 0-90 days after the first TNFi prescription fill or infusion. In this analysis, exposure was compared no use of any of the above csDMARDs.

Outcomes

The outcome of interest was the time to medication discontinuation within two years of starting methotrexate or a TNFi. We selected two years as the cut off based on the distribution of time to therapy discontinuation and the distribution of time in the cohort. Courses of therapy were identified by using days supply for prescriptions and set intervals for procedure codes (e.g. 56 days for infliximab and golimumab infusions, 30 days for certolizumab procedure codes), truncating for early prescriptions or infusions. The presence of a 90-day gap between the end of one prescription/infusion and the start of a new prescription/infusion was defined as a medication discontinuation (the end of a medication course). We also assessed rates of early discontinuation within 90 days of initiation and delayed discontinuation after 90 days of use. For example, a fill of a single 90-day prescription would be counted as early discontinuation.

Covariates

We evaluated a number of covariates that we hypothesized would be associated with medication persistence, including age, sex, calendar year, other treatments in the 90 days prior to medication initiation (opioids, non-steroidal anti-inflammatory drugs, glucocorticoids, csDMARDs), and comorbidities based on diagnosis codes in the past year including diabetes, cancer, chronic kidney disease, asthma or chronic obstructive pulmonary disease (COPD), congestive heart failure, coronary artery disease, cerebrovascular disease, liver disease, obesity, depression, anxiety, bipolar disorder, chronic pain, peptic ulcer disease, inflammatory bowel disease, as well as the Charlson score with RA codes removed (21). We also evaluated the number of hospitalizations, emergency department visits, and outpatient visits as a count of events, and included presence of inpatient or outpatient psychiatry visits in the past year. Analyses of TNFi persistence also included type of TNFi as a covariate.

Statistical Analysis

Median time to methotrexate discontinuation or TNFi discontinuation in patients with RA, PsA, or AS was evaluated using Kaplan-Meier methods. Cox proportional hazards models were used to compare time to either methotrexate or TNFi discontinuation over the next two years between patients with RA, PsA, or AS, adjusting for potential confounders. Patients were censored at the soonest of 1) end of health plan enrollment, 2) end of follow up (December 31st 2014) or 3) two years after the start of the medication course. Survivor functions were plotted at the mean of all covariates in the models. Delayed discontinuation was assessed in identical Cox proportional

hazards models among patients with at least 90 days of methotrexate or TNFi treatment. Early discontinuation within 90 days was assessed using similar logistic regression models for this binary outcome.

To assess the impact of concomitant csDMARDs on TNFi persistence, we evaluated patients with at least 90 days of TNFi treatment to allow a 90-day window after TNFi initiation to measure prescriptions for concomitant csDMARDs. In this population, we evaluated time to TNFi discontinuation within two years using Cox models. Here analyses were stratified by disease (RA, PsA, and AS) with separate models for each of the csDMARDs, comparing rates of TNFi discontinuation in patients receiving each csDMARD to rates of TNFi discontinuation in patients receiving no concomitant csDMARD. The same covariates were used in all models. To avoid overfitting these models, we selected covariates from a Cox model of delayed TNFi discontinuation including patients with RA, PsA, and AS, using step-wise backward deletion of covariates with $p > 0.1$, forcing age, sex, calendar year, type of TNFi, and glucocorticoid use into the models. We assessed interactions between disease and concomitant csDMARD use in models including patients with all three diseases as a three level variable. To assess heterogeneity in effect by type of TNFi, we also assessed interactions between type of TNFi and concomitant csDMARD. We performed additional sensitivity analyses in cases where interactions were observed.

All analyses were conducted using STATA version 15.0 (StataCorp, College Station, TX). As this study utilized a de-identified dataset, the study was deemed exempt by the University of Pennsylvania Institutional Review Board.

Results

Basic demographics

Among 44,897 patients with RA, PsA, and AS initiating methotrexate and 60,763 initiating a first TNFi, 31,527 methotrexate initiators (26,708 RA, 2,939 PsA, 1,880 AS) and 34,651 TNFi initiators (24,134 RA, 6,705 PsA, 3,812 AS) met all inclusion and exclusion criteria (Figure 1). The most common TNFi were etanercept (16,405) and adalimumab (9,592), followed by infliximab (6,734), golimumab (1,031) and certolizumab (880). Patients with RA were more frequently treated with csDMARDs and glucocorticoids. Opioid use, depression, and chronic pain were frequent in all patient groups, with the highest rates in patients with AS (Table 1). Median available follow-up time was 2.0 years (IQR 1.0-3.9) in the methotrexate cohort and 2.0 years (IQR 1.0-3.9) in the TNFi cohort.

Methotrexate and TNFi discontinuation rates in RA, PsA, and AS

Patients remained on methotrexate a median of 1.07 years, with 7,581 (24.0%) of patients discontinuing treatment within 90 days and 1 and 2-year drug survival rates of 51.4% and 36.6%, respectively. Methotrexate was discontinued sooner in patients with PsA [aHR 1.10 (1.04-1.16)] and AS [aHR 1.23 (1.16-1.31)] vs. RA (Table 2, Figure 2). There were greater rates of both early and delayed methotrexate discontinuation in patients with PsA and especially AS (Table 3).

Overall, patients remained on TNFi a median of 1.31 years, with 6,065 (17.5%) patients discontinuing treatment within 90 days. One and 2-year drug survival rates were 56.1% and 40.5%, respectively. TNFi discontinuation occurred slightly later in PsA [aHR 0.93 (0.89-0.97)] when compared with RA. Patients with AS had similar rates of discontinuation rates compared to RA [aHR 1.00 (0.97-1.05)] and (Table 2, Figure 2). Similar results were observed for early and delayed discontinuation (Table 3).

Concomitant csDMARD use and rates of TNFi discontinuation

Among patients who continued a TNFi for at least 90 days, 12,874/19,903 (64.7%) patients with RA, 2,307/5,604 (41.2%) of patients with PsA, and 888/3,079 (28.8%) of patients with AS received a concomitant csDMARD in the 90 days after TNFi initiation, most commonly methotrexate.

Concomitant use of methotrexate (compared to no csDMARD) was associated with lower rates of TNFi discontinuation in RA [aHR 0.85 (0.80-0.89)], PsA [aHR 0.81 (0.74-0.89)], and AS [aHR 0.79 (0.67-0.93] (Figure 3). Sulfasalazine was associated with lower rates of TNFi discontinuation in RA and PsA but not AS. Hydroxychloroquine was associated with significantly lower rates of TNFi discontinuation only in RA. Leflunomide was not associated with lower rates of TNFi discontinuation in RA, PsA, or AS (Figure 3).

There was a significant interaction between type of TNFi and csDMARD use only for methotrexate ($p < 0.01$), with evidence of a stronger association between methotrexate use and infliximab discontinuation compared to other TNFi: aHR 0.73 (0.65-0.81) in RA, aHR 0.77 (0.60-0.97) in PsA, and aHR 0.70 (0.49-1.00) in AS among

infliximab treated patients. We repeated analyses evaluating concomitant csDMARD use in patients treated with non-infliximab TNFi and found similar results (Supplemental Figure 2).

Discussion

This large study using de-identified administrative claims data is one of the first to demonstrate reduced persistence of methotrexate in patients with PsA and AS compared to patients with RA. In contrast, rates of TNFi discontinuation were similar across the groups. Additionally, we evaluated associations between csDMARD use and TNFi discontinuation, and found that the concurrent use of methotrexate was similarly associated with lower discontinuation rates for TNFi in RA, PsA, and AS.

Methotrexate discontinuation was more common in PsA and AS compared to RA, with greater rates of both early discontinuation (which might be expected to reflect differences in side effects or toxicity, such as hepatotoxicity) and delayed discontinuation (presumably more affected by treatment efficacy). The similar rates of TNFi discontinuation in RA, PsA, and AS suggest that the methotrexate results are not due to greater rates of discontinuation of all medications in SpA. Although the magnitude of difference at a population level was modest, it should be noted that many fewer patients with SpA initiated methotrexate compared to the number initiating a TNFi. SpA patients receiving methotrexate are a select group of patients that the treating physician may consider to be the most likely to respond to methotrexate; given that neither EULAR nor ACR guidelines recommend methotrexate for patients with

purely axial disease (5,6,22), these patients likely have more peripheral predominant disease. Thus, in our study, the persistence of methotrexate in PsA and AS may in fact be inflated due to this channeling.

The suggestion that methotrexate may be less effective in the treatment of SpA vs. RA is supported by a randomized trial of 221 patients with PsA did not show a significant difference in ACR20, DAS28, or joint counts with methotrexate compared to placebo, although the dose given was generally low with the mean dose <15 mg weekly (23). The more recent SEAM-PsA trial comparing methotrexate to etanercept or combination therapy found that half of treatment naïve patients with PsA initiating methotrexate achieved an ACR20 response, but there was no placebo comparison and these patients rarely achieved a more "deep" response defined by fulfillment of the minimal disease activity criteria (4). A previous, smaller observational study from the Norweigan NOR-DMARD registry 2000-2006 comparing MTX use in RA vs. PsA found that patients with PsA had smaller improvements in some disease activity measures and in patient reported outcomes, although 2 year persistence of MTX was similar in RA and PsA (24). Differences in practice patterns or the smaller number of alternative treatment options available during the time of this study might explain why MTX persistence differed from our results.

Overall, rates of both MTX and TNFi discontinuation were relatively high in this study compared to previously published data, with median TNFi persistence of 1.31 years in TNFi treated patients and a 1-year retention rate of only 56%. Previous registry studies have shown 1-year retention rates of approximately 70-80% (14,16,25). One of

these studies also showed substantially longer TNFi persistence in spondyloarthritis vs. RA, unlike in our study (14). These differences might be explained by different study populations (registry studies vs. a general population study), outcome measurements (patient-report vs. prescription data), and differences over time and by country or insurance plan; as more treatment options for spondyloarthritis have become available, rates of discontinuation would be expected to rise with patients and physicians less willing to accept suboptimal outcomes. Indeed, as in other studies (26), in our study discontinuation occurred sooner in later calendar years for all diseases (data not shown).

Concomitant use of methotrexate in patients initiating a TNFi was associated with lower rates of TNFi discontinuation in patients with RA, PsA, and AS, suggesting that methotrexates may help prolong the efficacy of TNFi in both RA and spondyloarthritis. While the effect size was largest in patients receiving infliximab, the association remained in patients treated with other TNFi. Secondary analyses of clinical trials have not found evidence of greater TNFi efficacy in patients with PsA receiving concomitant methotrexate (8,13,27), and the recent SEAM-PsA trial showed no benefit of etanercept with methotrexate over etanercept alone (4). Previous observational studies, however, have suggested an association between methotrexate use and longer TNFi persistence (14–16). Discrepancies in these results could be related to inadequate power or shorter duration of clinical trials, differences between clinical trial protocols and real-world treatment, or to confounding in observational studies, with methotrexate treated patients perhaps having different health behaviors (healthy

adherer effect) or better medication tolerability. Interestingly, in our study we found that the magnitude of the effect of methotrexate on TNFi discontinuation in PsA and AS was very similar to the magnitude of effect in RA. Given that the efficacy of methotrexate use with a TNFi has been well established in RA (7), similar results in PsA and AS may suggest a similar biologic effect in these diseases. Methotrexate has been associated with lower rates of anti-drug antibodies in patients with SpA in some studies as in patients with RA (9–12).

Associations between other csDMARD use and TNFi discontinuation rates were more variable across diseases. Sulfasalazine use was associated with lower rates of TNFi discontinuation in RA and PsA with a magnitude similar to the effect of concomitant methotrexate use, suggesting that sulfasalazine might also be effective in promoting TNFi persistence in these diseases. The utility of sulfasalazine in TNFi treated patients has not been well studied. One previous small study of 117 patients with AS found that sulfasalazine use was associated with lower rates of switching to a second anti-TNFi in patients with pure axial involvement (28). We were not able to replicate these findings in AS although we were not able to differentiate patients with pure axial involvement from those with peripheral involvement.

Real-world observational studies have inherent limitations. We were unable to determine reasons for medication discontinuation. While discontinuations, especially after the first 3 months, likely are frequently due to inadequate efficacy, discontinuation because of side effects, patient choice, or tapering off of therapy because of disease control are also possible. Patient and provider expectations of efficacy, influenced by

trials and promotion of biologics, may also influence persistence. Disease severity and phenotypes also cannot be captured in this data; patients with PsA and AS who are treated with methotrexate monotherapy might be expected to have more peripheral predominant and RA-like disease. We expect this bias would favor of overestimating the benefit of methotrexate monotherapy, however, as these would be the patients most likely to respond to treatment. We did not have laboratory data or drug-antibody levels, and so cannot know whether associations between csDMARD use and TNFi discontinuation rates are mediated by prevention of anti-drug antibodies, synergistic effects with the TNFi on disease control, or confounding factors. Medication courses were based on prescription fill data, and it is possible that some patients may fill prescriptions even after stopping their medication. Finally, we did not statistically compare time on TNFi versus time on MTX due to potential unmeasured confounding by indication.

Strengths of this study include its size, allowing evaluation of multiple different csDMARDs and the ability to adjust for potential confounding factors. Additionally, this data source provides real-world data about current discontinuation rates of methotrexate and TNFi, without limiting evaluation to a population of patients willing to enroll in a registry.

In conclusion, in this large claims data analysis, patients with PsA and AS were more likely to discontinue methotrexate compared to patients with RA. Rates of TNFi discontinuation, however, were similar in RA, PsA, and AS. In patients treated with a

TNFi, use of methotrexate was associated with lower rates of TNFi discontinuation in RA, PsA, and AS.

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Figure legends

Figure 1: Cohort identification flow diagram.
RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, TNFi = tumor necrosis factor inhibitor, SLE = systemic lupus erythematosus

Figure 2: Time to methotrexate or TNFi discontinuation in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).
Survivor function from Cox regression models at the means of all covariates: age, sex, year, prescriptions for opioids, NSAIDs, methotrexate (TNF analyses only), sulfasalazine, hydroxychloroquine, leflunomide use in the past 3 months, diabetes, cancer, chronic kidney disease, asthma/chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, cerebrovascular disease, liver disease, obesity, depression, anxiety, bipolar disorder, chronic pain, peptic ulcer disease, Charlson score, hospitalizations in the past year, ED visits in the past year, number of outpatient visits, psychiatry visits. TNFi models also adjusted for which TNFi patients received

Figure 3: Association between conventional DMARD use and TNFi discontinuation in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).
Adjusted hazard ratios (aHR) from separate Cox models created for each medication, stratified by disease (RA, PsA, or AS). Models also included age, sex, year, type of TNFi, glucocorticoid use, NSAIDs, depression, bipolar disorder, chronic pain, Charlson score, inflammatory bowel disease, asthma/chronic obstructive pulmonary disease, liver disease, hospitalizations past year. Interactions to assess differences in csDMARD effects across diseases from models with all three diseases combined: disease*methotrexate $p = 0.62$, disease*sulfasalazine $p = 0.03$, disease*hydroxychloroquine $p < 0.01$, disease*leflunomide $p = 0.77$.

Table 1: Patient characteristics

	MTX initiators			TNF initiators		
	RA	PsA	AS	RA	PsA	AS
	N = 26708	N = 2939	N = 1880	N = 24134	N = 6705	N = 3812
Age	56.8 (14.2)	52.3 (13.1)	53.9 (14.30)	52.7 (13.1)	48.9 (12.2)	45.9 (12.9)
Female	19921 (74.6%)	1575 (53.6%)	1285 (68.4%)	18240 (75.6%)	3388 (50.5%)	1825 (47.9%)
Previous csDMARD	10459 (39.2%)	744 (25.3%)	687 (36.5%)	20160 (83.5%)	4498 (67.1%)	1839 (48.2%)
Treatments past 90 days						
Methotrexate	N/A	N/A	N/A	12799 (53.0%)	2768 (41.3%)	766 (20.1%)
Sulfasalazine	1716 (6.4%)	357 (12.1%)	238 (12.7%)	1739 (7.2%)	451 (6.7%)	470 (12.3%)
Hydroxychloroquine	5996 (22.5%)	125 (4.3%)	244 (13.0%)	4319 (17.9%)	206 (3.1%)	204 (5.4%)
Leflunomide	744 (2.8%)	44 (1.5%)	21 (1.1%)	2686 (11.1%)	274 (4.1%)	106 (2.8%)
Glucocorticoids	11423 (42.8%)	641 (21.8%)	663 (35.3%)	11020 (45.7%)	1535 (22.9%)	1065 (27.9%)
NSAIDs	8679 (32.5%)	988 (33.6%)	655 (34.8%)	7064 (29.3%)	2022 (30.2%)	1365 (35.8%)
Opiates	7917 (29.6%)	657 (22.4%)	817 (43.5%)	7390 (30.6%)	1611 (24.0%)	1435 (37.6%)
Comorbidities						
Diabetes	3867 (14.5%)	412 (14.0%)	280 (14.9%)	2896 (12.0%)	852 (12.7%)	324 (8.5%)
Cancer	1438 (5.4%)	137 (4.7%)	90 (4.8%)	835 (3.5%)	188 (2.8%)	98 (2.6%)
Kidney disease	1780 (6.7%)	139 (4.7%)	141 (7.5%)	1171 (4.9%)	275 (4.1%)	179 (4.7%)
COPD/asthma	4184 (15.7%)	299 (10.2%)	334 (17.8%)	3396 (14.1%)	619 (9.2%)	457 (12.0%)
CHF	1263 (4.7%)	81 (2.8%)	92 (4.9%)	723 (3.0%)	123 (1.8%)	81 (2.1%)
CAD	2951 (11.0%)	249 (8.5%)	206 (11.0%)	1926 (8.0%)	431 (6.4%)	224 (5.9%)
CVD	969 (3.6%)	55 (1.9%)	89 (4.7%)	601 (2.5%)	95 (1.4%)	73 (1.9%)
Liver disease	854 (3.2%)	110 (3.7%)	126 (6.7%)	978 (4.1%)	380 (5.7%)	186 (4.9%)
Obesity	1813 (6.8%)	222 (7.6%)	162 (8.6%)	1502 (6.2%)	523 (7.8%)	255 (6.7%)
Depression	3460 (13.0%)	357 (12.1%)	416 (22.1%)	3145 (13.0%)	845 (12.6%)	616 (16.2%)
Anxiety	2216 (8.3%)	242 (8.2%)	257 (13.7%)	1824 (7.6%)	584 (8.7%)	399 (10.5%)

Bipolar disorder	181 (0.7%)	19 (0.6%)	34 (1.8%)	131 (0.5%)	62 (0.9%)	38 (1.0%)
Chronic pain	5795 (21.7%)	447 (15.2%)	698 (37.1%)	4576 (19.0%)	1082 (16.1%)	1025 (26.9%)
Peptic ulcer disease	465 (1.7%)	38 (1.3%)	43 (2.3%)	437 (1.8%)	76 (1.1%)	77 (2.0%)
IBD	290 (1.1%)	21 (0.7%)	71 (3.8%)	630 (2.6%)	78 (1.2%)	427 (11.2%)
Charlson score	1 [0-3]	0 [0-2]	1 [0-3]	0 [0-2]	0 [0-2]	0 [0-2]
Hospitalizations						
None	22046 (82.5%)	2564 (87.2%)	1472 (78.3%)	20350 (84.3%)	5866 (87.5%)	3185 (83.6%)
1	3255 (12.2%)	276 (9.4%)	283 (15.1%)	2741 (11.4%)	652 (9.7%)	437 (11.5%)
> 1	1407 (5.3%)	99 (3.4%)	125 (6.6%)	1043 (4.3%)	187 (2.8%)	190 (5.0%)
Psychiatric visits	1160 (4.3%)	151 (5.1%)	157 (8.4%)	1073 (4.4%)	336 (5.0%)	270 (7.1%)

Mean (SD), N (%),and median [IQR] shown. RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, NSAIDs = non-steroidal anti-inflammatory drugs, COPD = chornic obstructive pulmonary disease, CHF = congestive heart, CAD = coronary artery disease, CVD = cerebrovascular disease, IBD = inflammatory bowel disease

Table 2: Rates of MTX and TNFi persistence in patients with RA, PsA, and AS

	N	PY	Median persistence (years)	HR (95% CI)	aHR (95% CI)
MTX					
RA	26708	23773	1.13	Ref	Ref
PsA	2939	2477	0.94	1.12 (1.06-1.18)*	1.10 (1.04-1.16)*
AS	1880	1378	0.70	1.35 (1.28-1.44)*	1.23 (1.16-1.31)*
TNFi					
RA	24134	23062	1.28	Ref	Ref
PsA	6705	6570	1.53	0.91 (0.87-0.95)*	0.93 (0.89-0.97)*
AS	3812	3460	1.15	1.06 (1.01-1.11)*	1.00 (0.94-1.05)

Adjusted hazard ratio (aHR) from multivariable Cox models adjusted for age, sex, year, prescriptions for opioids, NSAIDs, methotrexate (TNF analyses only), sulfasalazine, hydroxychloroquine, leflunomide use in the past 3 months, diabetes, cancer, chronic kidney disease, asthma/chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, cerebrovascular disease, liver disease, obesity, depression, anxiety, bipolar disorder, chronic pain, peptic ulcer disease, Charlson score, hospitalizations in the past year, ED visits in the past year, number of outpatient visits, psychiatry visits. TNFi models also adjusted for which TNFi patients received. * $p < 0.05$. MTX = methotrexate, TNFi = tumor necrosis factor inhibitor, RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, PY = person-years

Table 3: Rates of early and delayed methotrexate and TNFi discontinuation in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

	Early Discontinuation				Delayed Discontinuation			
	N	Early DC, N (%)	OR	aOR	PY	Median persis-tence (years)	HR	aHR
MTX								
RA	26708	6270 (23.5%)	Ref	Ref	17993	1.88	Ref	Ref
PsA	2939	726 (24.7%)	1.07 (0.98-1.17)	1.06 (0.97-117)	1842	1.61	1.16 (1.09-1.23)*	1.13 (1.06-1.20)*
AS	1880	585 (31.1%)	1.47 (1.33-1.63)*	1.32 (1.20-1.48)*	990	1.35	1.29 (1.20-1.40)*	1.18 (1.09-1.27)*
TNFi								
RA	24134	4231 (17.5%)	Ref	Ref	17584	1.85	Ref	Ref
PsA	6705	1101 (16.4%)	0.92 (0.86-0.99)*	0.91 (0.84-0.98)*	5044	2.08	0.91 (0.88-0.95)*	0.95 (0.91-1.00)
AS	3812	733 (19.2%)	1.12 (1.02-1.22)*	1.04 (0.94-1.14)	2605	1.79	1.02 (0.97-1.08)	0.99 (0.93-1.06)

Adjusted odds ratio (aOR) and adjusted hazards ratio (aHR) from multivariable logistic or Cox regression models adjusted for age, sex, year, prescriptions for opioids, NSAIDs, methotrexate (TNF analyses only), sulfasalazine, hydroxychloroquine, leflunomide use in the past 3 months, diabetes, cancer, chronic kidney disease, asthma/COPD, congestive heart failure, coronary artery disease, cerebrovascular disease, liver disease, obesity, depression, anxiety, bipolar disorder, chronic pain, peptic ulcer disease, Charlson score, hospitalizations in the

past year, ED visits in the past year, number of outpatient visits, psychiatry visits. TNF inhibitor models also adjusted for which TNF inhibitor patients received. * $p < 0.05$. MTX = methotrexate, TNFi = tumor necrosis factor inhibitor, RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, PY = person-years, DC = discontinuation

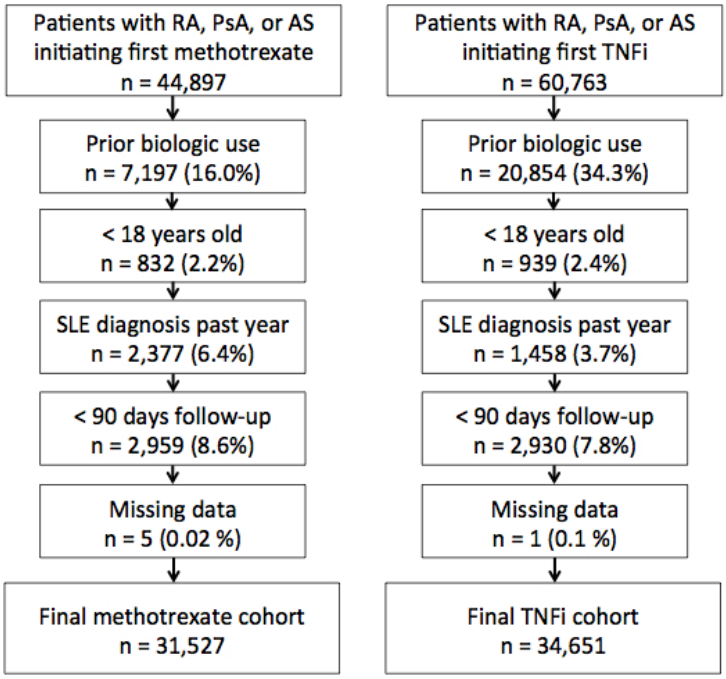

Figure 1. Cohort identification flow diagram.
RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, TNFi = tumor necrosis factor inhibitor, SLE = systemic lupus erythematosus

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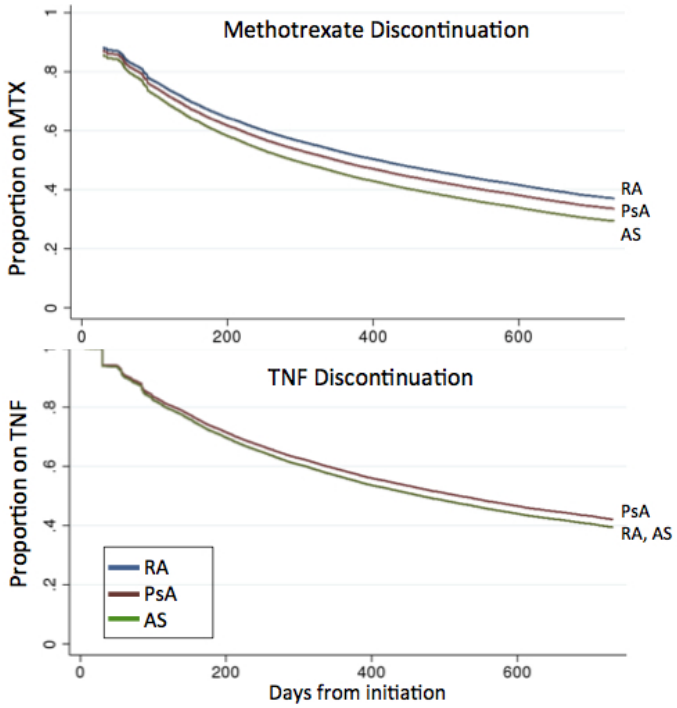

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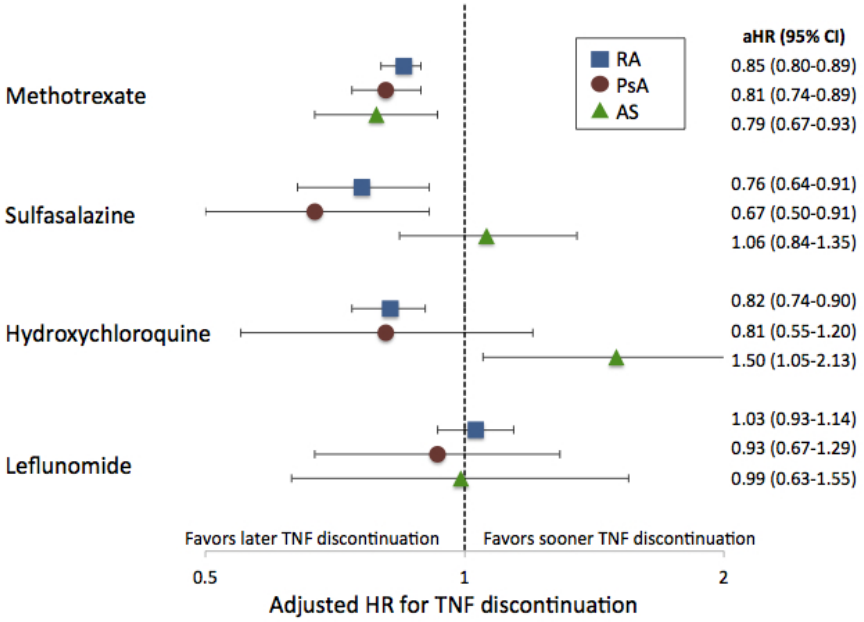

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