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Abstract:

Background: Glucocorticoids are recommended for short-term use in rheumatoid arthritis (RA), but many patients remain on long-term therapy. We evaluated the variability in glucocorticoid prescribing across rheumatologists to inform interventions to limit long-term glucocorticoid use to the lowest dose necessary.

Methods: Two cohorts were created using Medicare data 2006-2015. Using cohort 1 (RA patients on DMARDs), we calculated each rheumatologist's "provider preference" for glucocorticoids (frequency of use compared to other providers), using ratio of observed to expected number of patients receiving glucocorticoids to account for case-mix. In cohort 2 (RA patients on stable DMARD therapy) we evaluated whether provider preference for glucocorticoids could independently predict use of ≥5mg/day of glucocorticoids 6-9 months after DMARD initiation.

Results: Using Cohort 1 (1,272,644 yearly observations, 385,597 patients) we calculated provider preference among 6,875 rheumatologists (28,936 yearly observations). Provider preference was highly variable, with physicians at the lowest and upper quartiles using glucocorticoids 33% less often (25th percentile) to 31% more often (75th percentile) than expected. In Cohort 2 (155,539 patients on stable DMARD therapy), provider preference was

strongly associated with glucocorticoid use ≥5mg/day at 6-9 months, with predicted probability of use 22% (95% CI 21.7-22.7) vs. 11% (10.2-10.9) for a patient seeing a provider in the highest versus lowest quintile of preference.

Conclusion: Glucocorticoid prescribing for RA varies greatly among rheumatologists; provider preference is one of the strongest predictors of a patient's long-term glucocorticoid use. These results raise quality of care concerns and highlight the need for stronger evidence to guide RA treatment.

Significance and Innovations

- Glucocorticoid prescribing for patients with rheumatoid arthritis varied widely among rheumatologists, even when considering differences in case mix.
- Patients who saw a rheumatologist who was a high glucocorticoid prescriber were substantially more likely to receive long-term glucocorticoids.
- Compared to other patient factors, provider preference for glucocorticoids was one of the strongest predictors of long-term glucocorticoid use.

Introduction

Glucocorticoids remain a common therapy for the treatment of patients with rheumatoid arthritis (RA). Several studies have demonstrated that the addition of low dose glucocorticoids to disease modifying anti-rheumatic drug (DMARD) therapy can improve patient outcomes, (1–3) but glucocorticoids also carry risks, including infections, weight gain, diabetes, cardiovascular disease, and osteoporosis, especially at higher doses. (4,5)

Although a number of observational studies suggest greater risk of infection even at glucocorticoid doses of 5mg per day (6–11), the role of long-term, low-dose glucocorticoids in the treatment of RA remains controversial. Current guidelines from the American College of

Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend short-term use of glucocorticoids, preferably for <3 months, in patients starting or changing DMARD therapy. (12,13) In contrast, German guidelines recommend starting at "low to moderately high" doses (e.g. 10-20mg/day) along with methotrexate, tapering to the lowest possible dose, targeting doses ≤7.5mg/day within 3 months. (14)

As many as 30-60% of patients with RA remain on long-term glucocorticoids. (15–18) A number of patient-specific factors may lead to long-term glucocorticoid use, including refractory disease activity, worsening symptoms with glucocorticoid tapering, or inability or reluctance to take biologic therapies to control disease. Physician factors, however, may also play a role, and some physicians may be less aggressive in trying to taper therapy. Given continued controversy in the underlying risks of low-dose glucocorticoids, physicians may vary in their prescribing patterns and their tolerance of long-term glucocorticoid use in RA.

Given the uncertainty and controversy surrounding the safety and optimal role for low-dose glucocorticoids in RA, we hypothesized that there would be substantial variability in glucocorticoid prescribing patterns between providers. Identifying areas of high variability in practice highlights the need for stronger evidence to guide physicians and also suggests potential targets for quality improvement. In addition, variability among providers may create a "natural experiment" – allowing use of epidemiologic tools such as instrumental variable analysis to study glucocorticoid safety. (19) In this study, our goals were to 1) examine variability in glucocorticoid prescribing among rheumatologists by developing a measure of "provider preference" for glucocorticoids, 2) identify provider factors associated with higher versus lower provider preference, and 3) test to what degree our measure of provider preference for use of glucocorticoids can predict a subsequent patient's long-term glucocorticoid use, beyond the 3-6 months of glucocorticoid 'bridge therapy' commonly used to allow slower acting DMARDs to exert their full effect.

Methods

This retrospective cohort study was conducted using Medicare claims data 2006-2015. Medicare is a public health plan covering more than 90% of U.S. adults age ≥65. Younger individuals with disabilities (e.g. RA) may also be covered. (20) We created two separate

cohorts of patients. First, we created a large cohort of patients with RA who were new or prevalent DMARD users (Cohort 1) to develop our measure of provider preference for glucocorticoids, based on how frequently a provider's patients were treated with glucocorticoids relative to other providers. Then we created a smaller cohort of patients with RA on stable DMARD therapy ≥9 months (Cohort 2) to test to what degree provider preference for glucocorticoids could predict long-term glucocorticoid use independent of patient factors.

Cohort 1 (all RA cohort): Measuring provider preference for glucocorticoids

We created a measure of provider preference for glucocorticoids for each rheumatologist in the dataset based on the prevalence of glucocorticoid use for the provider's RA patients in each calendar year. To do this, we identified the patients with RA seen by the rheumatologist within each calendar year, measuring preference separately in each year to allow preference to change over time. In each calendar year, we identified patients with ≥2 diagnoses for RA (714.x) ≥7 days apart who either 1) filled a prescription or received an infusion of a biologic or targeted synthetic DMARD or 2) filled a prescription for methotrexate and received no biologics or targeted synthetic DMARDs during that year. Patients could be new users or prevalent users of their DMARD (i.e. had use in the previous calendar year). We excluded patients with diagnoses of psoriatic arthritis (PsA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), or systemic lupus erythematosus (SLE) during that calendar year and required that patients have ≥180 days of available follow up after the first filled prescription or infusion. Patient were considered glucocorticoid users if they received ≥30 day supply of glucocorticoids within 90 days of the first biologic/tsDMARD or methotrexate prescription of that year, based on filled prescriptions for oral prednisone, prednisolone, or methylprednisolone. Patients could contribute observations to each qualifying calendar year but had to meet the same inclusion/exclusion criteria described above each year.

For each patient, we identified the treating rheumatologist using the National Provider Index (NPI) number from the most recent rheumatology outpatient visit (Medicare provider type 66) prior to the first biologic/tsDMARD or methotrexate prescription of the year that included an RA diagnosis. We then defined each individual rheumatologist's preference for glucocorticoids for any year in which they treated at least 10 qualifying RA patients (to enable

stable preference estimates) in that year. Preference was re-calculated each year, which allowed a provider's preference to change over time. Provider preference was defined as the ratio of the observed number of patients with RA using glucocorticoids compared to the expected number, based on each physician's case mix. To obtain the expected number, we predicted each patient's probability of receiving glucocorticoids based on a predefined set of patient characteristics and then summed the predicted probabilities for the patients seen by each provider. Predicted probability of receiving glucocorticoids was calculated by including all patients in a logistic regression model with glucocorticoid use as the outcome and covariates including age; sex; race; calendar year; type of DMARD; receipt of a new biologic/tsDMARD, methotrexate, or other csDMARD in the preceding 3 months (capturing new versus prevalent use); Charlson comorbidity score and each individual component comorbidity from the preceding year (including COPD). The coefficients from this model were then used to calculate the predicted probability of glucocorticoid use for each patient based on this patient's characteristics. In this analysis we aimed to include a limited set of commonly available patient factors and did not include measures of healthcare utilization or use of other medications such as opioids which are likely also to vary substantially across providers.

Cohort 2 (stable DMARD RA cohort): Evaluating ability of provider preference to predict a patient's long-term glucocorticoid use

To determine to what degree provider preference could predict glucocorticoid use in a patient with RA on stable DMARD therapy, we identified a separate cohort of stable patients with RA. Included patients had ≥2 diagnoses of RA ≥7 days apart, initiated a biologic/tsDMARD or methotrexate without a biologic/tsDMARD and remained on their DMARD continuously for at least 9 months (no new biologic/tsDMARD initiation and no gaps in DMARD therapy >90 days). The date 6 months after the DMARD course initiation was the index date. All patients were required to have 6 months of preceding data before the DMARD course date – this 6 month period and the first 6 months of the DMARD course were the baseline period. We excluded patients with PsA, AS, IBD, SLE, malignancy, or HIV during the baseline period and also measured covariates during this window. The primary outcome of interest was an average glucocorticoid dose ≥5mg/day in the 3 months after the index date (6-9 months after DMARD

initiation) based on filled prescriptions for oral prednisone, prednisolone, and methylprednisolone (Figure 1). The treating rheumatologist was again identified based on the last outpatient visit with a rheumatologist including a diagnosis of RA before the index date. The provider preference for glucocorticoids for this rheumatologist was obtained from the larger cohort after subtracting out the contribution of the patient of interest to ensure patients were not contributing to their own provider preference measure. As a sensitivity analysis we also evaluated alternative outcomes – any glucocorticoid use at ≥10mg/day and glucocorticoid use at any dose.

We used multivariable logistic regression to determine whether provider preference for glucocorticoids (observed/expected ratio divided into quintiles) could predict use of ≥5mg/day of glucocorticoids 6-9 months after DMARD initiation, adjusting for a comprehensive set of covariates including age, race, sex, year, region, urban versus rural residence, skilled nursing facility residence, zip code-based median household income, number of previous biologics, type of DMARD use, use of NSAIDs, opioids, and antibiotics in the 90 days before the index date; comorbidities (Charlson score, diabetes, hypertension, chronic kidney disease, COPD, asthma, cerebrovascular disease, obesity, congestive heart failure, coronary artery disease, peptic ulcer disease, extra-articular RA, anemia, myocardial infarction, depression, chronic pain), number of outpatient visits, rheumatology visits, hospitalizations, hospitalized infections, and emergency department visits in the past year; use of durable medical equipment, and cancer screening. Analysis was clustered by patient to account for patients contributing observations in multiple years. Because some patients receiving methotrexate may not have been on "stable" DMARD therapy because of dose increases or addition of other csDMARDs, we also conducted a sensitivity analysis limited to patients on continuous biologic/tsDMARD therapy.

Provider characteristics associated with greater glucocorticoid prescribing

Provider characteristics (sex, practice type, employment, years in practice, United States medical school graduate, region, years in practice), were identified using the 2017 American Medical Association Physician Masterfile. (21) We used a multivariable GEE model with an exchangeable correlation structure to evaluate associations between provider characteristics and likelihood of having a higher provider preference for glucocorticoid use. We defined

"higher" provider preference first as a observed/expected preference >1 (observed number of RA patients receiving glucocorticoids greater than expected number based on case mix). We then alternatively defined a higher glucocorticoid prescriber as observed/expected preference for glucocorticoids >80th percentile (top quintile) vs. ≤80th percentile

Results:

Identifying provider preference for glucocorticoids (Cohort 1 – all RA cohort)

We identified 385,597 patients contributing to 1,272,644 yearly observations – 56.3% receiving a biologic/tsDMARD and 43.7% receiving methotrexate without a biologic/tsDMARD during a given year. Of these, 1,204,836 (94.7%) observations were associated with a rheumatologist who saw at least 10 qualifying patients during that calendar year. In total, 6,875 unique providers saw at least 10 qualifying patients with RA (median 32, IQR 18-54) and contributed 28,936 yearly observations.

Figure 2 shows the distribution of provider preference for glucocorticoids, with observed/expected measures of glucocorticoid use >1 indicating more use than expected based on patient characteristics in that rheumatologists' practice, and observed/expected <1 indicated less use than expected. Provider preference was highly variable, with interquartile range 0.67 (33% lower prescribing than expected) to 1.31 (31% greater prescribing than expected). The median observed proportion of a rheumatologist's patients receiving glucocorticoids was 24.3% [IQR 16.7% to 33.3%]. While variability among physicians seeing a small number of patients (i.e. <20) may be expected due to imprecision in measurement, variability remained high even among rheumatologists seeing a large number of patients (Figure 2). The correlation between provider preference for glucocorticoid use within each rheumatologists practice was relatively strong from year to year (e.g. r = 0.66 for consecutive years).

Provider preference and other predictors of glucocorticoid use in patients on stable DMARD therapy (Cohort 2 – stable DMARD RA cohort)

We identified 197,352 treatment episodes among 149,857 unique patients with RA who received stable DMARD therapy for at least 9 months. For 155,539 of these treatment episodes (among 120,660 patients) there was an identifiable rheumatologist who had seen ≥10 RA

patients during that year in the larger dataset. Glucocorticoids were received 6-9 months after DMARD course initiation in 45.3% of patients (median dose of 4.2mg/day), with 16.4% of patients receiving ≥5mg/day and 3.4% receiving ≥10mg/day. Select patient characteristics are shown in Table 1, comparing patients receiving ≥5mg/day versus <5mg/day of glucocorticoids.

Patients seeing rheumatologists with a higher provider preference for glucocorticoids were more likely to receive ≥5mg/day glucocorticoids, independent of other patient characteristics (OR 2.51, 95% CI 2.39-2.63 for highest quintile of preference vs. lowest quintile) (full model in Supplemental Table 1). Predicted probabilities of glucocorticoid use generated from this model are shown in Figure 3, with a more than two-fold difference in predicted use of ≥5mg/day ranging from 10.6% to 22.2% for patients seen by physicians in the lowest vs. highest quintile of provider. Results were similar in a sensitivity analyses restricted to patients on stable biologic/tsDMARD use (Supplemental Figure 1, Supplemental Table 2). Other factors associated with continued use of ≥5mg/day glucocorticoid use included male sex, greater number of previous biologics, opioid use, recent antibiotic use, COPD, extra-articular RA, more frequent outpatient visits, previous hospitalized infection, previous ED visits, and absence of diabetes, hypertension, chronic kidney disease, or coronary artery disease. Glucocorticoid use was slightly less common in later years. Provider preference was also associated with receiving ≥10mg/day of prednisone [OR 1.80 (1.63-1.98) for highest quintile of preference vs. lowest quintile] and any dose of glucocorticoids [OR 3.14 (3.03-3.26) for highest quintile of preference vs. lowest quintile] (Supplemental Table 1). Older patients were more likely to receive any dose of glucocorticoid but less likely to receive higher glucocorticoid doses.

Physician characteristics associated with glucocorticoid prescribing

Using the 2016 AMA Masterfile data, we were able to identify physician characteristics for 4019 providers contributing 24,124 (83.4%) provider-years. Characteristics of physicians are shown in Table 2. In a multivariable model, physicians who were female, part of a solo practice (vs. a group practice), in practice ≥10 years, and who saw a greater number of RA patients were less likely to be high glucocorticoid prescribers (observed/expected prescribing >1) (Table 3). Associations were similar when evaluating predictors of being in top 20th percentile of

observed/expected glucocorticoid prescribing except that solo practice was no longer associated with prescribing preference (Table 3).

Discussion

In this large national cohort study, we created a measure of provider preference for using glucocorticoids for RA management that adjusted for the case mix of each rheumatologist's practice. We found substantial variability in the prescribing of glucocorticoids among rheumatologists. Among a cohort of patients with RA on stable DMARD therapy, provider preference for glucocorticoids was one of the strongest predictors of continued glucocorticoid use at doses ≥5mg/day and also predicted higher dose use ≥10mg/day. In other words, seeing a provider who frequently treats other patients with RA with glucocorticoids makes it much more likely that a patient will receive long-term glucocorticoids, independent of all other measured patient and disease-related characteristics.

Our finding that glucocorticoid prescribing varies widely between rheumatologists is supported by several previous studies, each with different approaches. Wallace et al. described significant variability in both glucocorticoid and DMARD prescribing during the first year after RA diagnosis. (18) Black et al examined general practitioners in the UK and defined provider preference based on the average proportion of time a physician's patient received glucocorticoids. (22) Criswell et al. examined a longitudinal panel of RA patients and also found significant variability in GC prescribing among the 63 included rheumatologists which persisted after adjusting for patient factors. (23) Two aspects of our approach represent an important advance over these prior studies. First, we allowed provider preference to differ from year to year, recognizing that practice patterns can change over time. Secondly, recognizing that case mix may vary between rheumatologists, we created a measure of provider preference that accounts for differences in the demographics and comorbidities of a physician's RA patient panel. Even after accounting for variation over time and differences in case mix, we observed a wide range of glucocorticoid prescribing patterns across thousands of providers that likely included the majority of practicing rheumatologists in the U.S. Although our data was restricted to 2006-2015, reductions in glucocorticoid use over this time frame were small, and results are expected to be similar after 2015.

An additional unique feature of our study is the evaluation of how our provider preference measure can predict long-term glucocorticoid use in a separate cohort of patients with RA on stable DMARD therapy, excluding patients with more refractory disease who continued to undergo changes in their RA treatment regimen. Despite the fact that many current RA treatment guidelines recommend only short-term use of glucocorticoids as bridging therapy, (12,13) nearly 1 in 6 patients continued to receive ≥5mg/day of glucocorticoids 6-9 months after starting MTX or a new biologic or tsDMARD. The predictive ability of our measure of provider preference remained robust even after adjusting for patient factors previously shown to predict glucocorticoid use. (22,24,25) Notably, our measure of provider preference was one of the factors most strongly associated with long-term glucocorticoid use. Interestingly, while provider preference was associated with higher dose glucocorticoids ≥10mg/day, we found even stronger associations with long-term low-dose use, an area of substantial controversy.

Rheumatologists who were male, in practice for less than 10 years, and who saw a smaller number of RA patients were more likely to be high glucocorticoid prescribers. While it is interesting that physicians with more clinical experience, both in terms of years and RA patients seen, tended to be lower prescribers, these associations were modest in magnitude. It is also possible that the types of patients without RA seen by a rheumatologist influence glucocorticoid prescribing for patients with RA, although examining broader practice patterns was beyond the scope of this study.

Identifying high variability in glucocorticoid prescribing has important implications. Areas of high practice variability can identify potential targets for quality improvement and highlight the need for stronger evidence to guide practice. In the absence of clear evidence on who should continue to receive low-dose glucocorticoids beyond 6 months after starting a new DMARD or biologic, we cannot say definitively whether our results reflect over-use of glucocorticoids by some providers, under-use by some providers, or both. It is notable, however, that provider preference was also strongly associated with continued glucocorticoid use ≥10mg/day, which is known to carry higher risks and is part of established quality metrics. (26) Additionally, our finding that a patient's likelihood of receiving glucocorticoids is highly

dependent on the provider they see creates a "natural experiment" – provider preference may be a potential instrumental variable for future pharmacoepidemiologic studies of glucocorticoid safety that have the potential to better address unmeasured confounding. (19,27)

Several limitations are important to note. Some of the measured variability in provider preference may be the result of variability in the severity or refractoriness of the provider's patient panel, which we could not directly measure in these data. We could not directly measure disease activity, which is known to strongly predict glucocorticoid use, but our measure of provider preference was adjusted for expected use based on variables available in administrative data. Additionally, provider preference strongly predicted glucocorticoid use even after adjustment for measures of healthcare utilization, use of durable medical equipment, opioid use, current biologic use, and number of previous biologics. Misclassification of glucocorticoid use is possible – some patients may have filled a prescription only for short-term use for flares, may have filled a prescription and not taken it, may have received intramuscular glucocorticoids (not captured in this study), or may have received glucocorticoids for other indications (e.g. COPD, acute bronchitis) or from a non-rheumatologist provider. While these factors could increase prescribing variability, they would be hypothesized to reduce the degree to which provider preference could predict glucocorticoid use. We only had information about a provider's Medicare patients, who might be more likely to receive glucocorticoids, and it is uncertain whether provider behavior would be similar in the treatment of younger, healthier patients with other insurance coverage. The impact on provider preference on glucocorticoid use in younger patients with RA may also differ. Additionally, we recognize that rheumatologists are increasingly reliant on working with advanced practice providers (i.e. physician assistants and nurse practitioners) and these individuals may be the prescribers of glucocorticoids in some cases. While our study included a large number of rheumatologists in the United States, behavior could be different among providers seeing only a small number of patients with RA (these physicians were excluded) or among physicians in other countries. Finally, we measured actual glucocorticoid prescription fills, and it is possible that rheumatologists unsuccessfully attempted to taper glucocorticoid therapy. Unlike a registry or some electronic medical record data systems, administrative claims data is not able

to capture the intent to change RA treatments, but only records whether treatment changes were actually made.

In conclusion, there is large variability among rheumatologists in the prescribing of glucocorticoids for patients with RA, highlighting the need for stronger evidence to guide treatment decisions. Rheumatologists who are younger or see fewer RA patients are more likely to use glucocorticoids. A physician's preference for glucocorticoids is one of the strongest predictors that a patient will receive long-term glucocorticoids.

References

1. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329–339.

2. Svensson B, Boonen A, Albertsson K, Heijde D van der, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: A two-year randomized trial. *Arthritis Rheum* 2005;52:3360–3370.

3. Buttgereit F, Mehta D, Kirwan J, Szechinski J, Boers M, Alten RE, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis* 2013;72:204–210.

4. Mahajan T, O'Dell JR. It is the Best of Treatments, It is the Worst of Treatments: The Continuing Love-Hate Relationship With Glucocorticoids in Rheumatoid Arthritis. *Arthritis Care Res* 2017;69:1131–1133.

5. Strehl C, Bijlsma JWJ, Wit M de, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *Ann Rheum Dis* 2016;75:952–957.

6. Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL, et al. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011;306:2331–2339.

7. Dixon WG, Abrahamowicz M, Beauchamp M-E, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–1133.

8. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:785–791.

9. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol* 2008;35:387–393.

10. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;54:628–634.

11. Weaver A, Troum O, Hooper M, Koenig AS, Chaudhari S, Feng J, et al. Rheumatoid arthritis disease activity and disability affect the risk of serious infection events in RADIUS 1. *J Rheumatol* 2013;40:1275–1281.

12. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol Hoboken NJ* 2016;68:1–26.

13. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–977.

14. Albrecht K, Krüger K, Wollenhaupt J, Alten R, Backhaus M, Baerwald C, et al. German guidelines for the sequential medical treatment of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. *Rheumatol Int* 2014;34:1–9.

15. Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. *J Rheumatol* 2007;34:696–705.

16. Makol A, Davis JM, Crowson CS, Therneau TM, Gabriel SE, Matteson EL. Time trends in glucocorticoid use in rheumatoid arthritis: results from a population-based inception cohort, 1980-1994 versus 1995-2007. *Arthritis Care Res* 2014;66:1482–1488.

17. Thiele K, Buttgereit F, Huscher D, Zink A, German Collaborative Arthritis Centres. Current use of glucocorticoids in patients with rheumatoid arthritis in Germany. *Arthritis Rheum* 2005;53:740–747.

18. Wallace BI, Lin P, Kamdar N, Noureldin M, Hayward R, Fox DA, et al. Patterns of glucocorticoid prescribing and provider-level variation in a commercially insured incident rheumatoid arthritis population: A retrospective cohort study. *Semin Arthritis Rheum* 2019.

19. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiol Camb Mass* 2006;17:268–275.

20. Medicare C for, Baltimore MS 7500 SB, Usa M. SummaryMedicareMedicaid. 2015. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareProgramRatesStats/SummaryMedicareMedicaid.html. Accessed May 1, 2015.

21. AMA Physician Masterfile | American Medical Association. Available at: https://www.ama-assn.org/practice-management/masterfile/ama-physician-masterfile. Accessed January 6, 2020.

22. Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG. Half of U.K. patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study. *Arthritis Res Ther* 2015;17:375.

23. Criswell LA, Redfearn WJ. Variation among rheumatologists in the use of prednisone and second-line agents for the treatment of rheumatoid arthritis. *Arthritis Rheum* 1994;37:476–480.

24. Black RJ, Lester S, Buchbinder R, Barrett C, Lassere M, March L, et al. Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. *Arthritis Res Ther* 2017;19:253.

25. George MD, Sauer BC, Teng C-C, Cannon GW, England BR, Kerr GS, et al. Biologic and Glucocorticoid Use after Methotrexate Initiation in Patients with Rheumatoid Arthritis. *J Rheumatol* 2019;46:343–350.

26. Centers for Medicare and Medicaid Services Quality Payment Program. MIPS Quality ID #180: Rheumatoid Arthritis (RA): Glucocorticoid Management. Available at: https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2019_Measure_180_MIPSCQM.pdf. Accessed January 20, 2020.

27. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19:537–554.

Figure 1: Study Design.

In Cohort 1 (all RA cohort), provider preference for glucocorticoids for each rheumatologist was determined by evaluating all qualifying patients with RA seen by a rheumatologist in a given year and dividing the observed number of the rheumatologist's patients who received glucocorticoids by the expected number of patients receiving glucocorticoids based on patient characteristics. In Cohort 2 (stable DMARD RA cohort) we evaluated patients with RA with at least 9 months of continuous treatment with methotrexate or a biologic/tsDMARD and 6 months of preceding data before DMARD course initiation to determine whether the treating rheumatologist's provider preference for glucocorticoids was independently associated with glucocorticoid use in the 3 months after the index date (6-9 months after starting the DMARD course).

Figure 2: Variability in provider preference for glucocorticoids

Variability in provider preference was assessed among rheumatologists seeing at least 10 RA patients in a given calendar year. An observed/expected measure > 1 represents greater glucocorticoid prescribing than expected based on patient characteristics while a measure < 1 represents lower prescribing (e.g. 1.4 = 40% more glucocorticoid prescribing than expected based on patient characteristics). Box plots are shown with median, interquartile range (box), and range excluding outliers (whiskers) for providers seeing 10-20, 20-40, 40-60, or >60 qualifying patients. Horizontal lines indicate the values of provider preference separating the 5 quintiles of provider preference.

Figure 3: Impact of provider preference on glucocorticoid use in patients on stable DMARD therapy.

Predicted probability of a patient receiving ≥5mg/day glucocorticoids in the 6-9 months after start of a stable DMARD course, generated from a logistic regression model (Supplemental Table 1) based on the provider preference of the patient's rheumatologist and adjusted for patient demographics, DMARD type, other medication use, comorbidities, and healthcare utilization measures. 95% confidence intervals shown in parentheses, all $p < 0.01$ between groups.

Table 1: Select characteristics of patients with rheumatoid arthritis on stable DMARD therapy

	None to <5mg/day glucocorticoids 6-9 months after DMARD course initiation N = 85,011	≥5mg/day glucocorticoids 6-9 months after DMARD course initiation N = 70,528	Standardized mean difference*
Age	69.0 +/- 11.4	67.8 +/- 11.8	**-0.106**

Female	105,660 (81.2%)	19,540 (76.6%)	**-0.113**
White	61,859 (47.6%)	51,702 (202.8%)	0.038
Methotrexate without biologic/tsDMARD	64,992 (50.0%)	11,955 (46.9%)	-0.062
TNF inhibitor	41,507 (31.9%)	7,871 (30.9%)	-0.023
Abatacept	12,696 (9.8%)	2,727 (10.7%)	0.031
Rituximab	5,897 (4.5%)	1,648 (6.5%)	0.085
Tocilizumab	3,766 (2.9%)	997 (3.9%)	0.056
Tofacitinib	1,186 (0.9%)	297 (1.2%)	0.025
Glucocorticoid dose			
None	85,011 (65.4%)	(0.0%)	N/A
<5mg	45,033 (34.6%)	(0.0%)	N/A
5 to <10mg	(0.0%)	20,173 (79.1%)	N/A
≥10mg	(0.0%)	5,322 (20.9%)	N/A
Prior biologics			
None	85,326 (65.6%)	14,223 (55.8%)	**-0.202**
1	30,960 (23.8%)	7,150 (28.0%)	0.097
2	9,782 (7.5%)	2,714 (10.6%)	**0.109**
≥3	3,976 (3.1%)	1,408 (5.5%)	**0.122**
NSAIDs	33,336 (25.6%)	6,185 (24.3%)	-0.032
Opioids	57,097 (43.9%)	15,231 (59.7%)	**0.321**
Charlson score	2.3 +/- 2.6	2.7 +/- 2.8	**0.166**
Diabetes	27,819 (21.4%)	5,834 (22.9%)	0.036
Hypertension	75,086 (57.7%)	15,369 (60.3%)	0.052
Chronic kidney disease	9,971 (7.7%)	2,437 (9.6%)	0.067
COPD	14,769 (11.4%)	4,486 (17.6%)	**0.178**
Asthma	9,716 (7.5%)	2,554 (10.0%)	0.09
Obesity	12,437 (9.6%)	2,910 (11.4%)	0.06
Coronary artery disease	25,413 (19.5%)	5,615 (22.0%)	0.061

Anemia	29,091 (22.4%)	6,997 (27.4%)	0.118
Extra-articular RA	3,331 (2.6%)	1,084 (4.3%)	0.093
Hospitalized infection past year	11,097 (8.5%)	3,844 (15.1%)	**0.204**
Hospitalization past year	28,820 (22.2%)	8,146 (32.0%)	**0.222**

Mean +/- standard deviation or N (%) shown. *Standardized mean difference is shown with absolute values >0.1 considered potentially meaningful differences between groups. NSAIDs = non-steroidal anti-inflammatory drugs; COPD = chronic obstructive pulmonary disease

Table 2: Characteristics of included rheumatologists based on the 2016 American Medical Association Survey

	Rheumatologists N = 4019
Female	1480 (36.8%)
Type of Practice	
Office	3056 (76.0%)
Hospital Staff	340 (8.5%)
Other	623 (15.5%)
Employment	
Group Practice	2315 (57.6%)
Solo Practice	791 (19.7%)
Medical school	84 (2.1%)
Local Government	281 (7.0%)
Federal Government	481 (12.0%)
US graduate	2746 (68.3%)
Region	
Northeast	903 (22.5%)
Midwest	881 (21.9%)
South	1451 (36.1%)
West	784 (19.5%)

Years in practice*	
< 10 years	17.8%
10-29 years	52.6%
>=30 years	30.3%
Number of qualifying RA patients treated*	
< 20	27.0%
20-40	32.8%
40-60	18.2%
≥60	22.0%

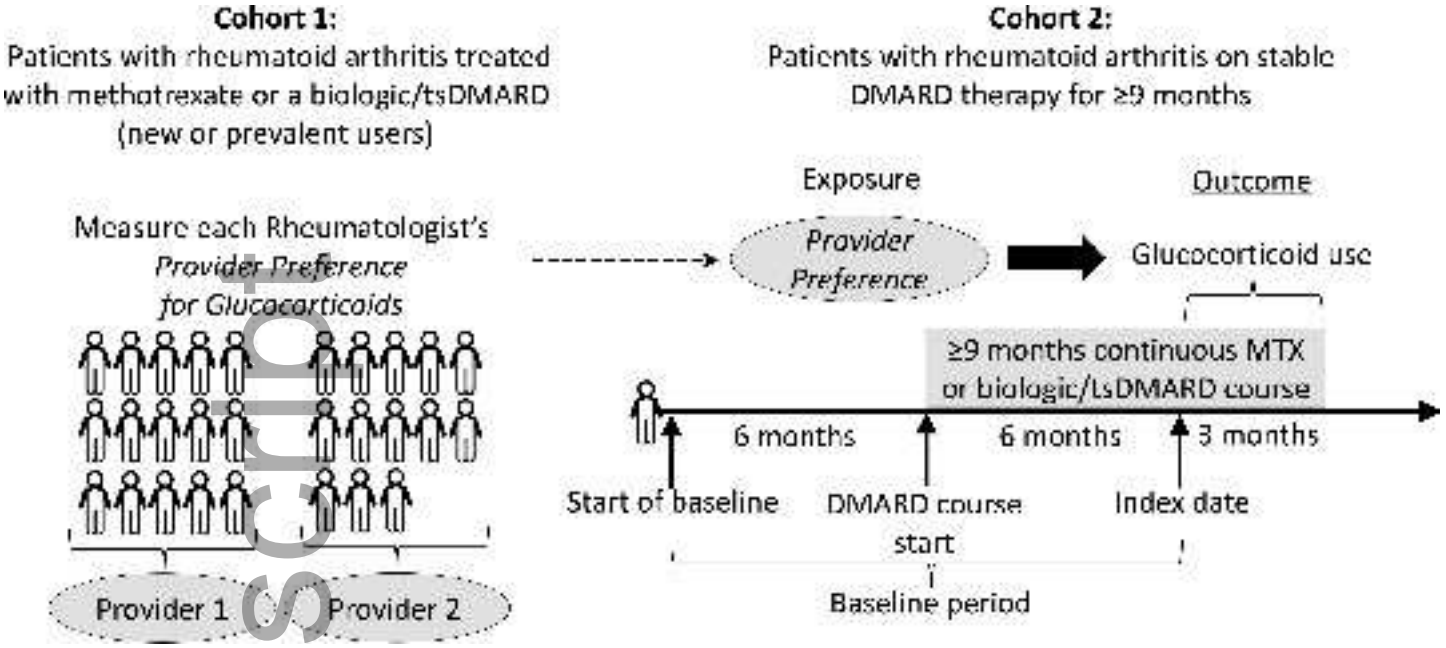
* Years in practice and number of qualifying Medicare patients could vary within a provider in different years. Percentages shown are the proportion of provider-year observations (n = 24,124) with these characteristics

Table 3: Physician characteristics associated with higher versus lower glucocorticoid prescribing

	Obs/Exp > 1 OR (95% CI)	Top quintile (>80th percentile) of Obs/Exp OR (95% CI)
Female physician	**0.81 (0.73-0.90)**	**0.73 (0.64-0.82)**
Practice type		

Office	Reference	Reference
Hospital staff	1.05 (0.77-1.42)	0.93 (0.66-1.32)
Other	**1.19 (1.02-1.38)**	1.16 (0.97-1.39)
Employment		
Group practice	Reference	Reference
Solo practice	**0.83 (0.74-0.94)**	0.99 (0.85-1.15)
Medical school	1.28 (0.90-1.83)	1.11 (0.74-1.64)
Local Government	0.95 (0.70-1.29)	1.10 (0.77-1.56)
Federal Government	1.03 (0.66-1.60)	0.92 (0.54-1.56)
Other	1.00 (0.84-1.19)	1.08 (0.88-1.32)
Years in practice		
<10	Reference	Reference
10-30	**0.81 (0.74-0.88)**	**0.80 (0.73-0.89)**
≥30	**0.88 (0.78-0.99)**	**0.84 (0.73-0.96)**
US graduate	0.92 (0.83-1.02)	1.00 (0.88-1.13)
Region		
Northeast	Reference	Reference
Midwest	1.09 (0.94-1.25)	1.14 (0.96-1.35)
South	1.11 (0.97-1.26)	**1.20 (1.03-1.39)**
West	0.89 (0.77-1.03)	0.92 (0.77-1.10)
Number of qualifying Medicare patients with RA seen in year		
10-20	Reference	Reference
20-40	**0.85 (0.79-0.90)**	**0.71 (0.66-0.77)**
40-60	**0.80 (0.73-0.87)**	**0.52 (0.47-0.58)**
≥60	**0.78 (0.71-0.85)**	**0.44 (0.39-0.49)**
Year	1.00 (0.99-1.01)	**1.01 (1.00-1.03)**

Results from two separate multivariable logistic regression models, first evaluating physician associations with observed/expected glucocorticoid prescribing > 1 (observed prescribing greater than expected based on patient characteristics) and then physician characteristics associated with being in the top 20th percentile of glucocorticoid prescribing preference based on the observed/expected measure. Bolded measures are statistically significant with $p < 0.05$. Obs/Exp = observed glucocorticoid prescribing divided by expected glucocorticoid prescribing



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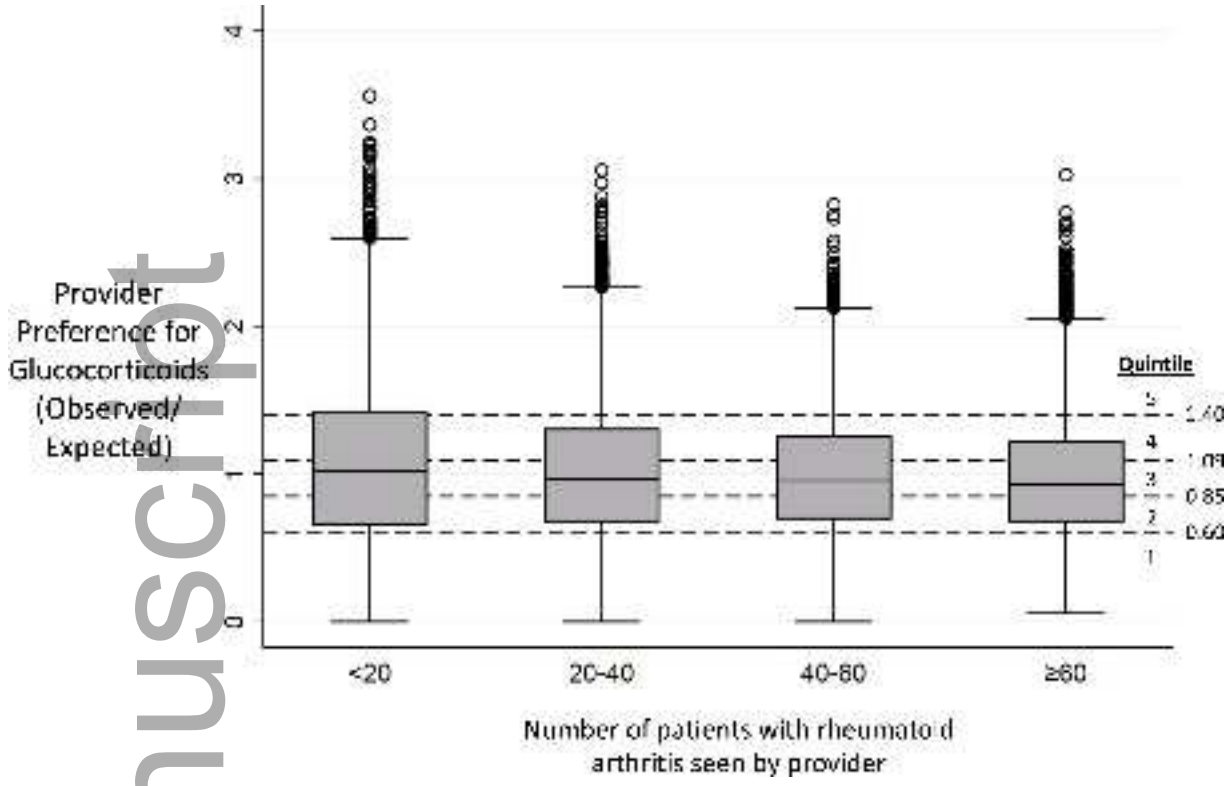

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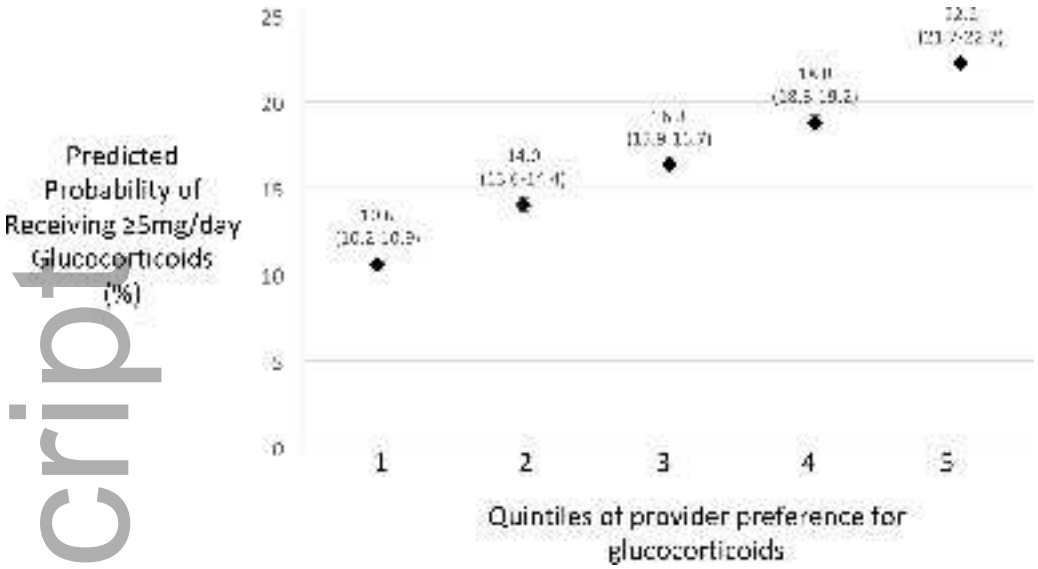

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