Association Between Disease-Modifying Antirheumatic Drugs and Diabetes Risk in Patients With Rheumatoid Arthritis and Psoriasis

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Context Rheumatoid arthritis (RA) and psoriasis have been linked with insulin resistance and diabetes mellitus (DM). Prior investigations suggest that systemic immunosuppressive drugs may improve insulin resistance and reduce the risk of DM.

Objective To compare the risk of newly recorded DM among participants diagnosed with RA or psoriasis based on use of a variety of disease-modifying antirheumatic drugs (DMARDs).

Design, Setting, and Participants A retrospective cohort study among 121 280 patients with a diagnosis of either RA or psoriasis on at least 2 visits. The analyses were conducted in the context of 2 large health insurance programs, 1 in Canada and 1 in the United States, using administrative data. The mean follow-up was 5.8 months and began with the first prescription for a DMARD after study eligibility was met. Drug regimens were categorized into 4 mutually exclusive groups: (1) tumor necrosis factor (TNF) inhibitors with or without other DMARDs; (2) methotrexate without TNF inhibitors or hydroxychloroquine; (3) hydroxychloroquine without TNF inhibitors or methotrexate; or (4) other nonbiologic DMARDs without TNF inhibitors, methotrexate, or hydroxychloroquine (reference exposure).

Main Outcome Measure Newly recorded DM as evidenced by a new diagnosis of DM with use of a DM-specific medication.

Results The study cohort consisted of 13 905 participants with 22 493 treatment episodes starting 1 of the categories of DMARD regimens between January 1996 and June 2008. New diabetes cases and respective incidence rates per 1000 person-years were: other nonbiologic DMARDs (55 cases among 3993 treatment episodes; rate, 50.2; 95% confidence interval [CI], 47.3-53.2); TNF inhibitors (80 cases among 4623 treatment episodes; rate, 19.7; 95% CI, 19.1-20.3); methotrexate (82 cases among 8195 treatment episodes; rate, 23.8; 95% CI, 23.0-24.6); and hydroxychloroquine (50 cases among 5682 treatment episodes; rate, 22.2; 95% CI, 21.3-23.1). The multivariate adjusted hazard ratios for DM were 0.62 (95% CI, 0.42-0.91) for TNF inhibitors, 0.77 (95% CI, 0.53-1.13) for methotrexate, and 0.54 (95% CI, 0.36-0.80) for hydroxychloroquine compared with other nonbiologic DMARDS.

Conclusion Among patients with RA or psoriasis, the adjusted risk of DM was lower for individuals starting a TNF inhibitor or hydroxychloroquine compared with initiation of other nonbiologic DMARDs.

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INDIVIDUALS WITH SYSTEMIC INFLAMmatory conditions experience higher rates of cardiovascular disease.[1-3] Although part of this excess risk relates to the direct effects of inflammation on the development of atherosclerosis,[4,5] an increase in cardiovascular risk factors also plays a role.[6-8] Moreover, inflammation likely accelerates development of several cardiovascular risk factors such as diabetes mellitus (DM).[9,10] Inflammation may cause insulin resistance and DM through several mechanisms. Tumor necrosis factor α (TNF-α) and interleukin (IL) 6 appear to block the function of insulin at the receptor level; as well, C-reactive protein and plasminogen activator inhibitor–1 are negatively associated with insulin sensitivity.[11-14]

Two common systemic inflammatory conditions, rheumatoid arthritis (RA) and psoriasis, predispose patients to insulin resistance and may place patients at risk for DM.[15-17] The treatment of psoriasis and RA includes disease-modifying antirheumatic drugs (DMARDs) such as TNF inhibitors, which are directed against the inflammatory response. The relationship between these conditions and DM suggests that systemic immunosuppression may also reduce the risk for DM. This hypothesis is supported

See also p 2573 and Patient Page.

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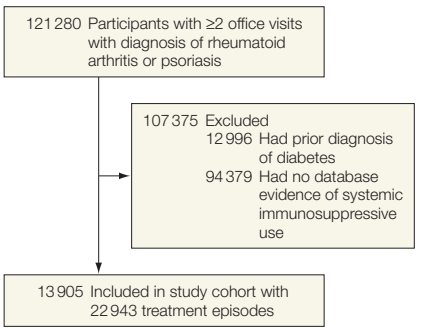
Figure 1. Study Cohort



by evidence from interventional and epidemiological studies. Several longitudinal investigations have found that TNF inhibitors improve insulin resistance.[18,19] One small randomized controlled trial found that the IL-1 receptor antagonist anakinra significantly reduced glycated hemoglobin levels in patients with type 2 DM.[20] Furthermore, a large observational study in a cohort of patients with RA found that the use of hydroxychloroquine, a US Food and Drug Administration (FDA)–approved DMARD for the treatment of RA, was associated with a reduced risk of incident DM.[21]

We examined the relationship between DMARD medications and the risk of newly diagnosed DM among participants with RA or psoriasis. The analyses were conducted in the context of 2 large health insurance programs, 1 in Canada and 1 in the United States, using administrative data. We hypothesized that the use of a TNF inhibitor and hydroxychloroquine would be associated with a reduced relative risk (RR) of DM compared with other nonbiologic systemic immunosuppressive drugs.

METHODS

Study Design

We conducted a cohort analysis of the risk of newly recorded or incident DM among participants with RA or psoriasis. Participants were enrolled in a population-based database from the British Columbia provincial health care system or a commercial US health plan that insures mainly working adults and a small Medicare population.

After the diagnosis of RA or psoriasis, identification of incident DM in unique participants occurred following a change in DMARD therapy. The RR of DM was estimated for TNF inhibitors, methotrexate, and hydroxychloroquine compared with other DMARDs in Cox proportional hazards regression. The study protocol was approved by the Partners Healthcare institutional review board and patient consent requirements were waived.

Study Cohort

Potentially eligible participants (N=121 280) were older than 18 years and diagnosed with RA or psoriasis, based on at least 2 visits separated by at least 7 days coded with the appropriate diagnoses from *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM* 714.x, 696.0, or 696.1). Continuous enrollment in the health plan for 12 months prior to the second diagnosis was required. From this group, all participants with a diagnosis of DM (*ICD-9-CM* 250.x) in the 12 months before their second qualifying diagnosis were excluded. Participants entered the study cohort at the first change in DMARD regimen after the presence of RA or psoriasis was established; thus, all individuals in the study cohort were required to have had 2 diagnoses and at least 1 filled prescription for a DMARD before the start of follow-up. Algorithms to define diseases in large diagnosis and treatment databases that require both a diagnosis and treatment have been found to have a positive predictive value of 81% for RA[22] and are the standard for psoriasis diagnosis in such databases.[23] Study duration was from January 1996 through June 2008. Participants were observed until they experienced an outcome, died, disenrolled from the health plan, or follow-up ended.

Diabetes Mellitus End Point

The outcome of interest was a newly recorded diagnosis (incident) of DM and the use of medications specific for DM. We did not have data on the fasting blood glucose level or glycated hemoglobin in the study database. The primary definition of DM required at least 1 diagnosis of DM (*ICD-9-CM* 250.x) combined with a new prescription for a DM-specific medication (all insulin preparations as well as oral agents such as rosiglitazone, pioglitazone, troglitazone, acetohexamide, chlorpropamide, tolbutamide, tolazamide, glipizide, gliclazide, glibenclamide, glyburide, glimepiride, gliquadone, acarbose, miglitol, repaglinide, sitagliptin, exenatide, and metformin). The date of the first prescription was considered the incident date of DM. Similar definitions have been used in prior studies and found to have positive predictive values greater than 90%.[24,25]

New Use of DMARDs

We defined 4 mutually exclusive groups of DMARDs: TNF inhibitors, methotrexate, hydroxychloroquine and other nonbiologic DMARDs (ie, sulfasalazine, leflunomide, cyclosporine, azathioprine, cylclophosphamide, mycophenolate mofetil, 6-thioguanine, acitretin, D-penicillamine, gold, auranofin, myochrysine, and solganol; see eTable 1 [available at http://www.jama.com] for the individual frequencies of the nonbiologic DMARDs included in this group). The TNF inhibitor group included adalimumab, etanercept, or infliximab and any other nonbiologic DMARDs. The methotrexate group included oral or injectable methotrexate. Participants in the methotrexate group could not simultaneously use a TNF inhibitor or hydroxychloroquine; however, they could use other nonbiologic DMARDs. The hydroxychloroquine group could not simultaneously use a TNF inhibitor or methotrexate but could use other nonbiologic DMARDs. The other nonbiologic DMARD group could not simultaneously use a TNF inhibitor, methotrexate, hydroxychloroquine, or another biologic systemic immunosuppressive drug. This group was chosen as the comparator group. Participants who used methotrexate and hydroxychloroquine simultaneously were excluded.

Study follow-up began with entry into 1 of these 4 exposure groups. Because the timing of the potential association between DMARDs and DM prevention is not clear, our primary analysis permitted participants to enter the study cohort more than once and considered them to be in a given exposure group during the period of an active prescription plus a 30-day extension if a participant stopped filling a given medication. These assumptions were tested in sensitivity analyses. First, we restricted participants to enter the cohort only once. Second, we carried the first DMARD exposure forward for a fixed period of 180 days (first exposure carried forward); this second analysis mirrors an intention-to-treat analysis.

Statistical Analysis

We compared the baseline characteristics across the 4 exposure groups. Newly recorded DM was identified during follow-up and person-years calculated from the start of follow-up until DM onset or censoring. The incidence rate and 95% confidence interval (CI) for DM were estimated for each exposure group. Time-to-event curves for diabetes were constructed for each of the exposure groups. The hazard ratio (HR) of DM was estimated in a series of Cox proportional hazard models with increasing adjustment: model 1 was only adjusted for diagnosis (RA or psoriasis) and data source; model 2 was also adjusted for age and sex; and model 3 was also adjusted for Charlson Score,[26] number of rheumatology and dermatology visits, number of other physician visits, number of different medications, number of hospital visits, prior TNF inhibitor use, prior methotrexate use, prior hydroxychloroquine use, prior nonbiologic systemic immunosuppressive drug use, prior oral and topical glucocorticoid use, and year of cohort entry. These covariates were defined using data from the 12 months prior to the start of study follow-up. No information was available on body mass index or family history of diabetes. We tested the proportional hazards assumption for each exposure of interest.[27]

Sensitivity analyses included the variations on exposure definition as noted previously. Other sensitivity analyses included (1) limiting follow-up to the first 90 days; (2) only including DM that occurred 90 days or more after the start of follow-up; (3) focusing only on individuals with prior oral or topical glucocorticoid use; and (4) focusing only on individuals without prior oral or topical glucocorticoid use. Sensitivity analyses were preplanned with the intent of testing whether the main findings were robust to different assumptions.

All statistical analyses were carried out using SAS statistical software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

We found 121 280 potentially eligible participants with at least 2 visits for RA or psoriasis (FIGURE 1). From this group, we excluded individuals with a prior diagnosis of DM (n=12 996) and persons without evidence in the database of use of a systemic immunosuppressive drug (n=94 379). Our final study cohort consisted of 13 905 participants with 22 493 new treatment episodes.

Baseline characteristics of the 4 exposure groups are shown in TABLE 1. The groups were similar with respect to age, sex, underlying systemic immunologic condition, number of different medications used, use of topical glucocorticoids, and visits to rheumatologists and dermatologists. They differed with respect to number of co-

Table 1. Baseline Characteristics of Study Cohorts, by DMARD Use

	No. (%)[a]			
	Other Nonbiologic DMARDs	Hydroxychloroquine	Methotrexate	TNF Inhibitors
Treatment episodes	3993	5682	8195	4623
Women	2906 (72.8)	4439 (78.1)	5994 (73.1)	3295 (71.3)
Age, mean (SD), y	53.7 (13.2)	54.2 (13.3)	53.5 (13.2)	50.8 (11.8)
Rheumatoid arthritis	3713 (93.0)	5535 (97.4)	7614 (92.9)	4478 (96.9)
Psoriasis or psoriatic arthritis	280 (7.0)	147 (2.6)	581 (7.1)	145 (3.1)
No. of different medications, mean (SD)	8.6 (5.2)	8.6 (5.0)	8.0 (4.6)	8.5 (4.8)
No. of physician visits, mean (SD)	9.0 (7.8)	8.5 (7.1)	8.5 (7.8)	7.7 (6.1)
Comorbidity index, mean (SD)	1.4 (1.2)	1.3 (1.0)	1.2 (1.0)	1.4 (1.2)
Oral glucocorticoids	1848 (46.3)	2603 (45.8)	3611 (44.1)	2495 (54.0)
Topical glucocorticoids	207 (5.2)	244 (4.3)	361 (4.4)	215 (4.7)
Acute care hospital stay, any	409 (10.2)	527 (9.3)	589 (7.2)	339 (7.3)
Dermatologist visit, any	444 (11.1)	523 (9.2)	921 (11.2)	483 (10.5)
Rheumatologist visit, any	2454 (61.5)	3504 (61.7)	4977 (60.7)	3041 (65.8)
Prior use of TNF inhibitors	287 (7.2)	176 (3.1)	979 (12.0)	
Prior use of methotrexate	1870 (46.8)	3585 (63.1)		833 (18.0)
Prior use of hydroxychloroquine	1264 (31.7)		3930 (48.0)	467 (10.1)
Prior use of other nonbiologic DMARDs		788 (13.9)	1436 (17.5)	759 (16.4)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.
[a]Values are presented as No. (%) unless otherwise indicated.

morbidities, physician visits, and use of oral glucocorticoids was more common among TNF inhibitor users. The Canadian and US cohorts were very similar in most respects (eTable 2).

We found 267 newly diagnosed cases of DM (55 among nonbiologic DMARD users; 80 among TNF inhibitor users, 82 among methotrexate users, and 50 among hydroxychloroquine users) over a mean follow-up of 5.8 months (SD, 8.8). The incidence rates for DM were highest for individuals who switched to other nonbiologic DMARDs and lowest for TNF inhibitor users (TABLE 2). The unadjusted time-to-event curve for diabetes for each of the 4 DMARD exposure groups show substantial differences between other nonbiologic DMARDs and each of the 3 other exposure groups (FIGURE 2).

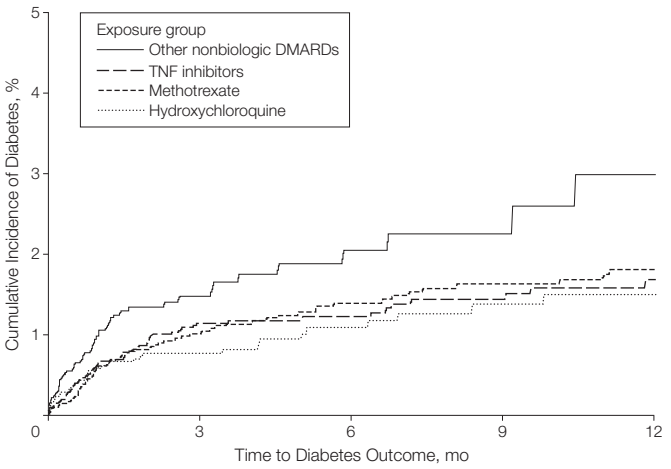
TABLE 3 contains the HRs for each of the 3 models. The fully adjusted models suggest a reduced relative risk of DM for TNF inhibitor and hydroxychloroquine compared with other nonbiologic DMARDs. These results were similar in the 2 separate cohorts from Canada and the United States (eTable 3), and we found no significant violation of the proportional hazards assumption for any exposure variable (each P value $>.25$). The sensitivity analyses (FIGURE 3) suggest that the primary findings are robust. Initiation of methotrexate was not associated with a statistically significant reduction in DM risk in any of the analyses. The risk of DM was reduced among TNF inhibitor and hydroxychloroquine users in the period beyond 90 days after the start of exposure. Among participants exposed to oral or topical glucocorticoids, there was also a meaningful reduction in DM risk for the TNF inhibitor and hydroxychloroquine initiators. Two sensitivity analyses that carried the first exposure forward for 180 or 365 days found very similar results.

Table 2. Incidence Rates of Diabetes Mellitus by DMARD Use

	Other Nonbiologic DMARDs[a]	Hydroxychloroquine	Methotrexate	TNF Inhibitors
Diabetes mellitus, new cases[b]	55	50	82	80
Total person-years	1097	2254	3453	4062
Incidence rate (95% confidence interval)[c]	50.2 (47.3-53.2)	22.2 (21.3-23.1)	23.8 (23.0-24.6)	19.7 (19.1-20.3)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.
[a] Other nonbiologic DMARDs include sulfasalazine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, 6-thioguanine, acitretin, D-penicillamine, gold, auranofin, myochrysine, and solganol. However, we did not find all of these in the database. See eTable 1 for the frequencies of the drugs included in this category.
[b] Event refers to new-onset diabetes mellitus.
[c] Incidence rates are per 1000 person-years.

Figure 2. Time to Event for Diabetes Among 4 Exposure Groups



Nonbiologic DMARDs					
No. at risk	3993	1232	561	310	196
No. events	0	45	50	51	53
Hydroxychloroquine					
No. at risk	5682	2055	1215	865	633
No. events	0	34	39	42	43
Methotrexate					
No. at risk	8195	3338	1994	1383	977
No. events	0	66	68	72	75
TNF inhibitors					
No. at risk	4623	3331	2412	1832	1413
No. events	0	44	55	60	63

The unadjusted log-rank P values compared with nonbiologic disease-modifying antirheumatic drugs (DMARDs) are: tumor necrosis factor (TNF) inhibitors, $P=.05$; hydroxychloroquine, $P=.001$; and methotrexate, $P=.001$.

COMMENT

Cardiovascular disease represents a major source of morbidity and mortality for populations with RA and psoriasis. The inflammation underlying these conditions contributes to atherosclerosis directly and indirectly through its effects on traditional cardiovascular risk factors such as DM.[1-3] Several small trials have found improvements in glucose and insulin metabolism among users of different systemic immunosuppressive agents and 1 epidemiologic study found that hydroxychloroquine reduced the incidence of DM.[18-21] We examined the risk of DM associated with a variety of DMARDs used for RA and psoriasis. The incidence rate of DM was meaningfully reduced in users of TNF inhibitors and hydroxychloroquine, compared with other nonbiologic DMARDs. There was a suggestion of a reduced risk with methotrexate but this was estimated less precisely and not statistically significant. These findings held up across a variety of sensitivity analyses.

Several prior studies have examined insulin metabolism among patients with RA initiating a TNF inhibitor. A short-term longitudinal study assessed insulin metabolism immediately before infliximab infusions and 120 minutes after.[18] This study noted improved insulin sensitivity and reduced insulin resistance after the infusion. A longer longitudinal study examined insulin resistance over the 14 weeks of infliximab infusions and found steady improvement between weeks 0, 6, and 14.[28] In addition to these studies suggesting improved insulin metabolism with TNF inhibitors, 1 study calculated the relative risk of new-onset DM among a large RA cohort based on exposure to hydroxychloroquine.[21] The incidence rate of DM was lower in hydroxychloroquine users, with an adjusted relative risk of 0.62 (95% CI, 0.42-0.92). Two randomized controlled trials of hydroxychloroquine among patients with poorly controlled type 2 DM have found significant improvements in glycated hemoglobin.[29,30] Finally, anakinra, an IL-1 receptor antagonist, was found to reduce glycated hemoglobin in type 2 DM compared with placebo.[20]

Taken in the context of prior research, the current study supports the potential role for systemic immunosuppression in prevention and control of DM. If future studies show this convincingly, systemic immunosuppression in such situations would be predicated on a favorable benefit-risk ratio. The balance of risks and benefits would likely differ across clinical scenarios. For example, among individuals without DM or a systemic rheumatic disease, use of a potent immunosuppressive may carry more risk than benefit. However, if an individual also has a systemic rheumatic disease for which a DMARD may be indicated, the ratio may shift toward benefit over risk. In an individual with diagnosed DM, who may be at an elevated risk of infection, use of immunosuppressive drugs may present unacceptable risk. Furthermore, the risk-benefit calculation likely changes depending on the specific immunosuppressive agent.

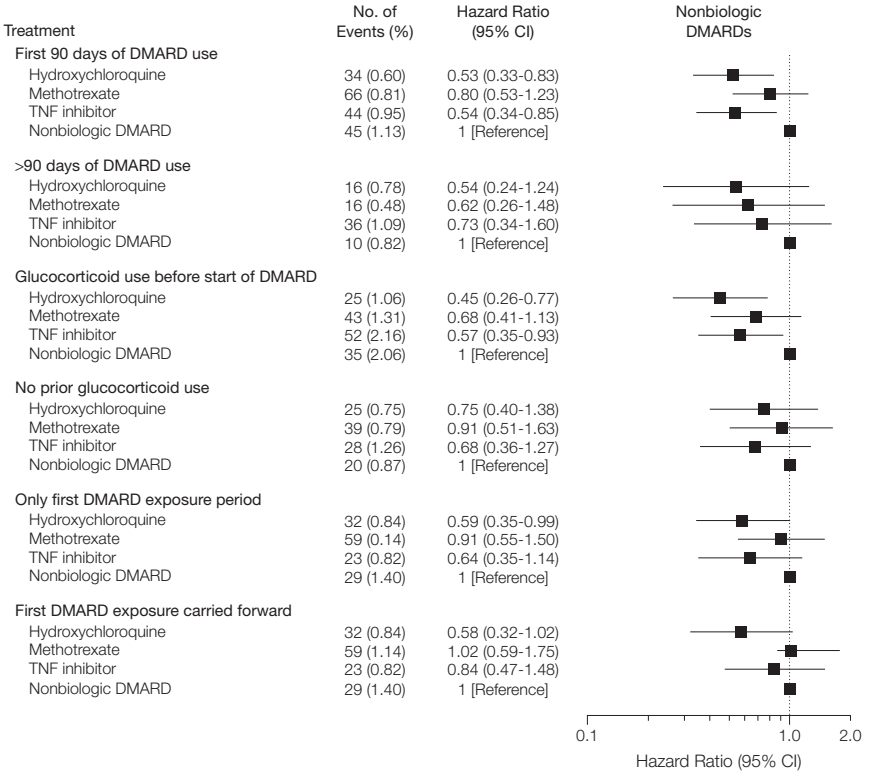
Immunosuppression may underlie the potential beneficial role of certain DMARDs in DM prevention; however, hydroxychloroquine and the closely related antimalarial chloroquine may also have direct effects on pancreatic islet cells. In the streptozocin-treated type 1 diabetic rat model, chloroquine led to higher levels of insulin with concomitant drops in blood glucose.[31] As well, in other models of type 2 diabetes, hydroxychloroquine reduced cytosolic insulin metabolism.[32] These

Table 3. Adjusted Cox Proportional Hazards for Risk of Diabetes Mellitus in Rheumatoid Arthritis and Psoriasis

	Other Nonbiologic DMARDs[a]	Hazard Ratio (95% Confidence Interval)		
		Hydroxychloroquine	Methotrexate	TNF Inhibitors
Model 1[b]	1 [Reference]	0.58 (0.39-0.85)	0.63 (0.45-0.88)	0.72 (0.50-1.03)
Model 2[c]	1 [Reference]	0.58 (0.39-0.85)	0.62 (0.44-0.87)	0.76 (0.53-1.09)
Model 3[d]	1 [Reference]	0.54 (0.36-0.80)	0.77 (0.53-1.13)	0.62 (0.42-0.91)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.
[a] Other nonbiologic DMARDs include sulfasalazine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, 6-thioguanine, acitretin, D-penicillamine, gold, auranofin, myochrysine, and solganol. However, we did not find all of these in the database. See eTable 1 for the frequencies of the drugs included in this category.
[b] Model 1 was adjusted for diagnosis (rheumatoid arthritis or psoriasis) and data source.
[c] Model 2 was adjusted as model 1 plus age and sex.
[d] Model 3 was adjusted as model 2 plus Charlson score, dermatologist visits, number of different medications, number of hospital visits, number of physician visits, prior hydroxychloroquine use, prior methotrexate use, prior nonbiologic systemic immunosuppressive drugs, prior oral glucocorticoids, and year of cohort entry.

Figure 3. Sensitivity Analyses



Hazard ratios with 95% confidence intervals (CIs) for the sensitivity analyses are fully adjusted. The reference group for all analyses is other nonbiologic disease-modifying antirheumatic drugs (DMARDs) (eTable 1 shows a listing of the frequencies of various agents in this category).

studies seem to show that the antimalarials slow insulin clearance, possibly through slowing the breakdown of the internalized insulin-receptor complex.

Although our results are intriguing in light of prior research, this study has limitations, mostly with respect to the study data sources. As an observational study without random assignment of treatments, it is difficult to infer causation between the treatments of interest and a reduced risk of DM. It is possible that patients receiving a TNF inhibitor or hydroxychloroquine were different from the reference group of other nonbiologic DMARD users in ways that went unmeasured, such as body mass index, exercise participation, family history, or disease severity.

We attempted to deal with unmeasured disease severity in 2 ways. First, we used an active comparator group of other nonbiologic DMARDs, but it is impossible to prove that this adequately controls for unmeasured confounding. Second, exposure periods were started with a change in treatment, thus restricting analyses to patients with active disease requiring new medications.[33] However, the measured variables in Table 1 suggest more similarities than differences across treatment groups. Moreover, since we are studying an effect not expected by prescribers (reduced diabetes risk), it is unlikely that unmeasured confounding is a major issue since confounding is generally considered mild in studies of unintended effects.[34]

The outcome of DM is likely misclassified in some participants, with both false positives and false negatives. To limit such misclassification, we required the use of a diabetes-specific medication such as insulin or a hypoglycemic. The accuracy of a diagnosis of DM with a diabetes-specific medication is more than 90%.[24,25] We cannot be certain that we have found new cases of DM since the study databases do not contain all information on prior diagnoses and treatments, although we excluded participants with a diagnosis of DM or use of medications specific for DM. Furthermore, we did not differentiate between type 1 vs type 2 DM in our analyses. However, 10% of our newly diagnosed diabetes cases used insulin-only regimens and 0.4% had a recent pregnancy. Moreover, the majority of new diabetic patients are likely to have type 2 DM due to the relatively older age of our cohort. There is likely some misclassification of RA and psoriasis but by requiring use of a DMARD, these diagnoses are relatively accurate.[22,23]

There are several strengths of this analysis. The use of pharmacy claims information to describe treatment history, while not perfect, is more accurate than the use of medical records or patient reports.[35] The study databases contain typical patients seen across a variety of settings. In fact, the data from Canada are population-based. Such databases comprise many thousands of patients, often allowing one to generalize from the findings of a specific study. Finally, the incident user design used in this study, in which exposure time begins with the start of a new systemic immunosuppressive, allows for a more valid comparison of treatments than mixing ongoing users with new users in the same analysis.[36]

In conclusion, we found that the use of a TNF inhibitor or hydroxychloroquine but not methotrexate was associated with a reduced risk of DM compared with other nonbiologic DMARDs among patients with 1 of 2 systemic inflammatory conditions, RA or psoriasis. The findings from this epidemiologic study should be considered hypothesis-generating. However, considering these results in light of prior findings regarding improved insulin and glucose metabolism and reduced DM risk with hydroxychloroquine and TNF inhibitors, there is evidence suggesting a possible role for DMARDs and immunosuppression in DM prevention. A randomized controlled trial testing the ability of these agents to prevent DM among participants with systemic inflammatory disorders should be considered.

Author Contributions: Dr Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Solomon, Schneeweiss.
Acquisition of data: Solomon.
Analysis and interpretation of data: Solomon, Massarotti, Garg, Liu, Canning, Schneeweiss.
Drafting of the manuscript: Solomon, Schneeweiss.
Critical revision of the manuscript for important intellectual content: Solomon, Massarotti, Garg, Liu, Canning, Schneeweiss.
Statistical analysis: Solomon, Liu, Canning, Schneeweiss.
Obtained funding: Solomon.
Administrative, technical, or material support: Solomon, Massarotti.
Study supervision: Solomon, Schneeweiss.
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Online-Only Material: eTable 1, eTable 2, and eTable 3 are available at http://www.jama.com.

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