Supplementary File to Risk of Diabetes Mellitus Associated With Disease-Modifying Antirheumatic Drugs and Statins In Rheumatoid Arthritis

Supplementary Methods and Tables

Determination of the treatment exposures and multivariable Cox regression model fits

Initially, the association of each DMARD individually with DM risk compared to its non-use was evaluated both in univariate and multivariate models. In these analyses, current MTX users had a lower risk of DM compared to MTX non-users. All models also showed a protective signal with HCQ and ABA without any significant risk change with TNFi or other biologics. Thereafter, considering the methodology used by Solomon et al. (*JAMA* 2011), we initially defined three different mutually exclusive DMARD variables in which references were "No DMARDS" or "Any non-MTX, non-TNFi, non-HCQ DMARDS" or "Any non-MTX, non-TNFi, non-ABA DMARDS", respectively. As an example, one of the DMARD variables was: 1. No DMARD (reference), 2. Any HCQ irrespective of concomitant DMARDs, 3. MTX monotherapy, 4. Any TNFi, 5. Any ABA, and 6. All others. When the reference was chosen as "No DMARDs", we observed a decreased DM risk with MTX. Alternatively, when the reference was set as "Any non-MTX, non-TNFi, non-HCQ DMARDS" or "Any non-MTX, non-TNFi, non-ABA DMARDS" or even "Biologic DMARDs either with or without MTX", we did not see any risk reduction with MTX. Consistently, HCQ and ABA were associated with a decreased DM risk regardless of the reference group. Considering the heterogeneity and inclusion of less-efficacious treatment alternatives of the above-mentioned reference groups, as a well-established homogenous treatment, "MTX monotherapy" was assigned as the reference. Based on the observed associations in the initial univariate and multivariate analysis, the DMARD variable was simplified as 1.MTX monotherapy (reference), 2. Any HCQ, 3. Any ABA, 4. Any other

biologic (non-ABA) or nonbiologic DMARDs in combination with MTX, 5. All others. Given that HCQ is often used in combination with other DMARDs, HCQ was assessed in the model separately. This provided a better model fit (described below) than being in the hierarchical DMARD group and there were no significant interaction effects.

Several Cox proportional hazard models were created to examine the association between medication exposure and incident DM. All the above-mentioned hierarchical DMARD variables, other treatment variables, sociodemographic and clinical variables were tested in the candidate models. The goodness of model fit was assessed with Akaike information criterion (AIC) which offers a relative estimate of the information lost when a given model is used. The model which included age, sex, ethnicity, income and employment status, rheumatic disease comorbidity index, hypertension, RA duration (log-transformed), HAQ, smoking status, and BMI (categorized according to WHO classification), 3-year calendar periods and the above hierarchical DMARD variable with separate HCQ, GC, statin and NSAID variables had by far the lowest AIC value.

Marginal Structural Models

As a strategy to reduce confounding bias, the restriction of only using a new-users design was adopted, i.e., selecting patients who were initiating HCQ in comparison with those who were initiating MTX. The control group was chosen to be comparable with the prevalent-user analysis. With this analysis, we wanted to be in the purest setting, as close as possible to an RCT as we could to mitigate issues that are a consequence of confounding by indication (Ray 2003; Schneeweiss 2007). Marginal structural models (MSM) offer a particularly useful tool that allows for the adjustment of time-varying confounders that are themselves affected by prior treatment (Robin et al. 2000). We estimated the MSM model using the inverse-probability-of-treatment weight (IPTW) estimator, which attempts to control for confounding

through assigning each patient a weight. The weight is proportional to the inverse probability of receiving observed treatment given the time-varying confounders and previous treatment history. The weights are then used to create a pseudo-population, in which patients-receiving treatment and those not receiving treatment are balanced over the time-varying confounders, but the relationship between treatment and outcome is not altered. This method is also useful when loss of follow-up occurs and allows accounting for differential loss to follow-up, using the censoring weighting distribution. We used stabilized weight as the final product of the IPTW and the inverse probability of censoring weights (IPCW). The IPCW were further corrected for the induced selection bias due to artificial censoring, in this case, the noncompliance with the treatment. As the intention to treat assumption was too unrealistic due to high discontinuation rate of HCQ-using patients, an on-treatment analysis was preferred instead, correcting for artificial censoring (Howe 2011). Patients who stopped taking HCQ were censored at the last observation they were on the drug.

To estimate the weights, a pooled logistic regression for the probability of receiving HCQ at a given time (t) using following time-varying covariates measured at baseline and time t: HAQ disability, comorbidity index (excluding DM and hypertension), current GC use (yes/no), statin use (yes/no), number of prior DMARDs (0, 1, 2, 3+), current use of biologics (yes/no), smoking status (never, past, current), being employed (yes/no), total income (<25; 25-45; 45-75, > 75 103 USD), BMI in categories (as described in the before) and follow-up time using a 3-knot spline. The model also included the following baseline variables: age in categories (<50, 50-60, 60-70, >70 years), sex, ethnic origin, disease duration (in categories: 0-3, 3-10, >10 years), history of hypertension, prior use of NSAIDs and year of entry in categories (as described before).

Similar weights were computed for censoring to adjust for potential selection bias due to loss of follow-up or induced selection bias due to non-compliance of HCQ. The product of

weights, treatment, and censoring, were used to estimate the weighted Cox model through a weighted pooled logistic model. This model included baseline covariates and the time-dependent HCQ (similar to what has been modeled by Choi 2002).

Several assumptions are made when fitting MSM. The first is that there are no unmeasured confounders. This is the reason why we include as many predictors as possible for both exposure and outcome. Secondly, and as a consequence of including as many variables as possible the bias of non-positivity may be introduced, the condition that both exposed and non-exposed at every level of the confounders are different from 0. We checked the presence of violations of this assumption by looking at the proportion of initiation of HCQ/MTX at the several levels of the confounders. Continuous variables were transformed into categorical, and the use of parametric models smoothers were strategies applied to control for non-positivity. We also assumed that the MSM for the effect of HCQ or MTX initiators on the incidence of DM is correctly specified, as well as the models for initiation of treatment and censoring are correctly specified. Based on the above-mentioned approaches, we found that the HR (95%) for incident DM in HCQ-initiators compared to MTX-initiators was 0.82 (0.30-2.30), P= 0.73.

References

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Table S1. Baseline (at the time of first entry to drug category) characteristics of the study population by DMARD use*

	Any HCQ, N=4,521	MTX monotherapy, N=5,280	Any Abatacept, N=839	Other DMARDs with MTX, N=5,452	Other or no DMARD, N=8,824
Age, years	57.3 (12.8)	60.4 (12.8)	60.0 (13.4)	57.0 (12.7)	57.4 (13.6)
Female,%	83.2	79.8	88.7	81.9	80.6
Non-Hispanic Caucasians, %	92.8	93.4	93.4	93.6	92.8
Education, years	13.8 (2.3)	13.6 (2.3)	14.3 (2.2)	13.8 (2.3)	13.8 (2.4)
BMI, kg/m^2	27.9 (6.6)	27.6 (6.1)	28.3 (6.5)	28.1 (6.7)	27.8 (6.6)
BMI in categories, %					
<18.5 kg/m^2	1.9	2.1	2.1	1.7	2.4
18.5-24.9 kg/m^2	35.9	35.3	32.4	34.6	35.7
25.0-29.9 kg/m^2	31.8	34.1	30.6	31.5	31.5
30.0-39.9 kg/m^2	24.9	23.9	30.3	26.1	25.3
≥40 kg/m^2	5.4	4.4	4.5	6.1	5.1
Ever-smoked, %	41.9	42.6	44.1	43.0	42.9
RA duration, years	13.1 (11.8)	14.1 (12.4)	14.1 (11.9)	13.9 (11.7)	14.5 (12.4)
HAQ (0-3)	1.0 (0.7)	1.0 (0.7)	1.2 (0.7)	1.1 (0.7)	1.1 (0.7)
Patient activity scale (0-10)	3.5 (2.2)	3.4 (2.2)	4.2 (2.0)	3.6 (2.1)	3.7 (2.3)
Rheumatic disease comorbidity Index (0-9)	1.5 (1.4)	1.4 (1.4)	1.9 (1.6)	1.5 (1.4)	1.7 (1.5)
CV event-ever, %	18.9	23.1	28.4	19.9	22.5

Prior use of HCQ, %	100	50.9	64.5	54.9	52.3
Prior use of MTX, %	67.6	100	92.0	100	55.3
Prior use of any TNFi, %	21.7	12.2	63.0	68.9	29.7
Prior use of any nonTNFi biologics, %	6.2	4.6	100	7.6	7.0
Prior use of GC, %	57.6	57.3	84.9	67.4	53.9
Prior use of statins, %	15.8	17.5	22.4	17.1	16.6

*****Values are presented as mean±SD, unless indicated otherwise.*

BMI=Body mass index; HAQ=Health assessment questionnaire; CV=Cardiovascular; HCQ=Hydroxychloroquine; MTX=Methotrexate; TFNi=Tumor necrosis factor-α inhibitor; GCS=Glucocorticoids.

Table S2. Baseline characteristics of the study population by statin use during the followup*

	Statin never exposed, N=9,609	Statin ever exposed, N=4,060	*P* value
Age, years	57.6 (14.1)	63.2 (10.3)	<0.001
Female,%	83.6	72.4	<0.001
Non-Hispanic Caucasians, %	93.0	94.3	0.006
Education, years	13.8 (2.3)	13.6 (2.3)	<0.001
BMI, kg/m^2	27.6 (6.6)	28.5 (6.0)	<0.001
BMI in categories, %			<0.001
<18.5 kg/m^2	2.5	1.1	2.4
18.5-24.9 kg/m^2	38.1	28.6	35.7
25.0-29.9 kg/m^2	30.4	36.6	31.5
30.0-39.9 kg/m^2	23.7	29.1	25.3
≥40 kg/m^2	5.3	4.5	5.1
Ever-smoked, %	38.7	56.8	<0.001
RA duration, years	14.2 (12.3)	14.9 (12.6)	0.001
HAQ (0-3)	1.1 (0.7)	1.0 (0.7)	<0.001
Patient activity scale (0-10)	3.6 (2.2)	3.5 (2.2)	0.024
Rheumatic disease comorbidity Index (0-9)	1.4 (1.4)	1.8 (1.5)	<0.001
CV event-ever, %	13.7	29.7	<0.001
Prior use of HCQ, %	52.4	45.2	<0.001
Prior use of MTX, %	71.9	69.4	0.004

Prior use of any TNFi, %	27.8	25.1	0.001
Prior use of any nonTNFi biologics, %	6.6	4.8	<0.001
Abatacept, %	3.7	3.1	0.051
Prior use of GC, %	55.2	54.5	0.438

**Values are presented as mean±SD, unless indicated otherwise.*

BMI=Body mass index; HAQ=Health assessment questionnaire; CV=Cardiovascular; HCQ=Hydroxychloroquine; MTX=Methotrexate; TFNi=Tumor necrosis factor-α inhibitor; GC=Glucocorticoids.

Table S3. Association of demographic and disease-related features with incident diabetes in rheumatoid arthritis*

Variables	Adjusted Hazard Ratio (95% CI)	*P* value
Age baseline	0.99 (0.98-1.00)	0.083
Male sex	1.05 (0.89-1.24)	0.606
Disease duration	0.99 (0.99-1.00)	0.634
Employed	0.95 (0.81-1.13)	0.594
Total Household Income ($10K)	0.99 (0.99-0.99)	0.006
Non-Hispanic Caucasian	0.76 (0.61-0.95)	0.014
Smoking status		
Never (referent)	1.00	-
Former	1.02 (0.89-1.17)	0.647
Current	0.91 (0.71-1.16)	0.449
Hypertension-ever	1.00 (0.88-1.14)	0.950
Rheumatic Disease Comorbidity Index	1.44 (1.14-1.49)	<0.001
BMI by WHO categories		
<18.5 kg/m2	0.32 (0.14-0.80)	0.014
18.5-24.9 kg/m^2 (referent)	1.00	-
25-29.9 kg/m^2	1.32 (1.10-1.58)	0.002
30-39.9 kg/m^2	2.37 (1.99-2.83)	<0.001
≥40 kg/m^2	3.64 (2.87-4.61)	<0.001

HAQ	0.99 (0.91-1.10)	0.974
NSAID usage	0.91 (0.79-1.94)	0.164
Year of entry		
2000-2003 (referent)	1.00	-
2004-2007	0.91 (0.76-1.10)	0.309
2008-2011	1.04 (0.86-1.26)	0.697
2012-2015	1.16 (0.81-1.67)	0.427

***** *Multivariable model includes categoric DMARD group, hydroxychloroquine, glucocorticoids and statins as shown in the Table 3 of the manuscript.*

CI=Confidence interval; BMI=Body mass index; WHO=World Health Organization; HAQ=Health assessment questionnaire; NSAID=Nonsteroidal anti-inflammatory drug.