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ORIGINAL RESEARCH

Disease-modifying anti-rheumatic drugs associated with different diabetes risks in patients with rheumatoid arthritis

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ABSTRACT

Objectives Patients with rheumatoid arthritis are prone to developing diabetes, which may lead to various sequelae and even cardiovascular diseases, the most common cause of death in such patients. Previous research has shown that some rheumatoid arthritis treatments may help prevent the development of diabetes. This study aimed to investigate whether patients using disease-modifying anti-rheumatic drugs (DMARDs) may have different levels of risk for diabetes and to analyse other risk factors for diabetes.

Methods This cohort study used data from the Chang Gung Research Database. 5530 adults with rheumatoid arthritis but without diabetes were eligible for the analysis. The endpoint of this study was new-onset diabetes, defined as an HbA1c value ≥7% during follow-up. The entire follow-up period was divided into monthly subunits. These 1-month units were then divided into methotrexate (MTX) monotherapy, any biological DMARDs (bDMARDs), MTX combination, other conventional DMARDs (cDMARDs) and non-DMARDs.

Results A total of 546 participants (9.87%) developed diabetes between 2001 and 2018. The risk of diabetes was significantly lower in the bDMARD periods (HR 0.51; 95% CI 0.32 to 0.83), MTX combination periods (HR 0.50; 95% CI 0.32 to 0.78) and other cDMARD periods (HR 0.56; 95% CI 0.37 to 0.84) than in the MTX monotherapy periods. Individual drug analysis showed that hydroxychloroquine (HR 0.52; 95% CI 0.42 to 0.65) reduced the risk of diabetes. Tumour necrosis factor-α inhibitors (HR 0.69; 95% CI 0.46 to 1.03) tended to be protective.

Conclusion Patients with rheumatoid arthritis may have different levels of risk of diabetes depending on the treatment options.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis are more likely than the general population to develop diabetes, further increasing the risk of cardiovascular disease.

WHAT THIS STUDY ADDS

⇒ Patients with rheumatoid arthritis have lower risk of diabetes with combination therapy or biologics compared with methotrexate monotherapy.

HOW MIGHT THIS STUDY AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Individually, hydroxychloroquine has significant protective effect on the development of diabetes in patients with rheumatoid arthritis, and tumour necrosis factor-α inhibitor also tends to be protective.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that mainly affects joints. In addition, it is a debilitating disease that affects the ability to manage activities of daily living and self-care and further leads to limited function and movement and even permanent disability. RA is associated with a shortened lifespan, most of which is associated with a nearly twofold increased risk of cardiovascular events compared with diabetes mellitus (DM).[1 2] If a patient has both RA and DM, the risk of cardiovascular events may increase approximately threefold.[3]

Clinically, patients with RA develop DM more frequently than the general population because RA may increase insulin resistance, causing them to produce more fat.[4] In addition, glucocorticoids are often used to control RA, which may increase the risk of DM.[5] On the contrary, RA often leads to poor patient activity and increases the incidence of DM. Since there are reports of the associations between RA and DM and coexistence increases the risk of cardiovascular disease, preventing the development of RA-associated DM should be an important topic.

Currently, several approaches may be beneficial for preventing DM development in patients with RA. In patients with RA, one of the greatest risk factors for developing DM is obesity, which is consistent with that in the general population. In addition to body weight, RA disease activity is another factor that should be controlled. Besides the overall disease activity, studies have mentioned

whether individual immunosuppressants have additional effects in preventing DM. For example, abatacept was mentioned in a previous US cohort study,[6] and another study found that tumour necrosis factor (TNF)-α inhibitors may have protective effects.[7] However, there are still some studies that do not show the above-mentioned protective effect of biologics.[8 9]

Therefore, these studies appear to have inconsistent results regarding which biologics are protective. It is uncertain whether other biologics or conventional disease-modifying anti-rheumatic drugs (bDMARDs or cDMARDs, respectively) would produce similar protective effects. We hypothesised that more effective DMARDs might protect patients with RA from developing DM. Therefore, we designed a large cohort study to understand the risk of DM in patients with RA taking different immunological drugs.

METHODS

Data sources

We designed a retrospective cohort study using the Chang Gung Research Database (CGRD), which includes both inpatient and outpatient data. CGRD is a de-identified database extracted from the original medical records of the Chang Gung Memorial Hospital (CGMH). The CGMH provides the largest and most comprehensive medical services in Taiwan, including seven branches in Linkou, Taipei, Taoyuan, Keelung, Yunlin, Chiayi and Kaohsiung. The CGMH has 1050 beds, and at least 2.4 million people are hospitalised each year. CGMH records an average of 8.2 million outpatient visits annually. Therefore, the CGRD is a huge medical database that can serve as an accurate data source for medical research.[10 11]

Patient inclusion

We identified 5849 patients diagnosed with RA according to the International Classification of Diseases, Ninth Clinical Revision (ICD-9-CM) diagnostic code of 714 before 2016 or the Tenth Clinical Revision (ICD-10-CM) diagnostic code of M05–M06 after 2016 from the CGRD within a total time frame of 2001 and 2018. To confirm the diagnosis of RA, we excluded patients without certification for catastrophic illness. RA is categorised as a catastrophic illness under Taiwan's National Health Insurance (NHI) policy. After a specialist doctor diagnoses a patient with RA, he can apply for a catastrophic illness certificate for the patient. A complete application file and relevant information, including detailed medical history, laboratory data and imaging reports, should be submitted to the NHI administration. The application will be formally reviewed anonymously by another senior and experienced rheumatologist assigned by the NHI administration. If patients with RA pass the catastrophic illness certification review, no co-payment is required. We excluded 140 patients aged <20 years based on the Institutional Review Board rules. In addition, we excluded 179 patients with DM before RA diagnosis. A total of 5530 adult patients with RA without DM were eligible for the analysis (online supplemental figure 1).

Study design

The index date was defined as the day that RA was diagnosed. We then divided the entire follow-up period into many subunits in 1-month units (figure 1A). Information regarding the drugs of interest during each follow-up month was extracted and updated. A prescription for the drug of interest was defined as having been prescribed during the individual follow-up month. Because the data unit was 1 month, we did not restrict the number of fills, days or dose; in other words, no minimal exposure to the drug was required. The duration of a drug's effects on the development of DM after it has been discontinued is uncertain. We use three half-lives of a drug as the period after discontinuation to provide a rough estimate. We call this the 'washout period' here. DM episode occurring within the washout period after the last drug prescription will be considered drug related. Because the data unit being referred to is measured in months, if the washout period for a drug is less than 1 month, it has been decided to round up and set the washout period to 1 month. The drug washout period for all types of cDMARDs,[12] tofacitinib,[13] baricitinib[13] and etanercept,[14] was set as 1 month. If the washout period falls between 1 and 2 months, it has been decided to set it at the longer duration of 2 months. The drug washout period for abatacept,[15] adalimumab,[16] certolizumab,[17] golimumab[18] and tocilizumab[19] was set as 2 months. The drug washout period for rituximab[20] was set as 6 months. Because of the low prescription rate of bDMARDs, the complex pattern of drug usage at each follow-up month was simplified into the following five distinct combinations: MTX monotherapy, any use of bDMARDs (regardless of the use of methotrexate (MTX) or other cDMARDs), MTX combined with other cDMARDs, use of other cDMARDs and non-DMARDs (non-treatment with DMARDs).

Covariates and outcomes

Comorbidities were those that might be associated with RA treatments and DM risks, such as hypertension, hyperlipidaemia, gout, chronic kidney diseases, hepatitis B virus infection, hepatitis C virus infection, coronary heart diseases and stroke. Comorbidity was recorded at the time of RA diagnosis, and the status was updated during the follow-up period. The ICD diagnostic codes are provided in the online supplemental table S1. We extracted the medications used that might be associated with the risk of DM development, including steroids and statins. Similar to the use of DMARDs, information on steroids and statins was updated during the follow-up period. We also extracted laboratory data (white cell count, haemoglobin and 10 others) at the time of RA diagnosis. The study outcome was new-onset DM, defined as an HbA1c value ≥7% during follow-up. The patient was followed up from the

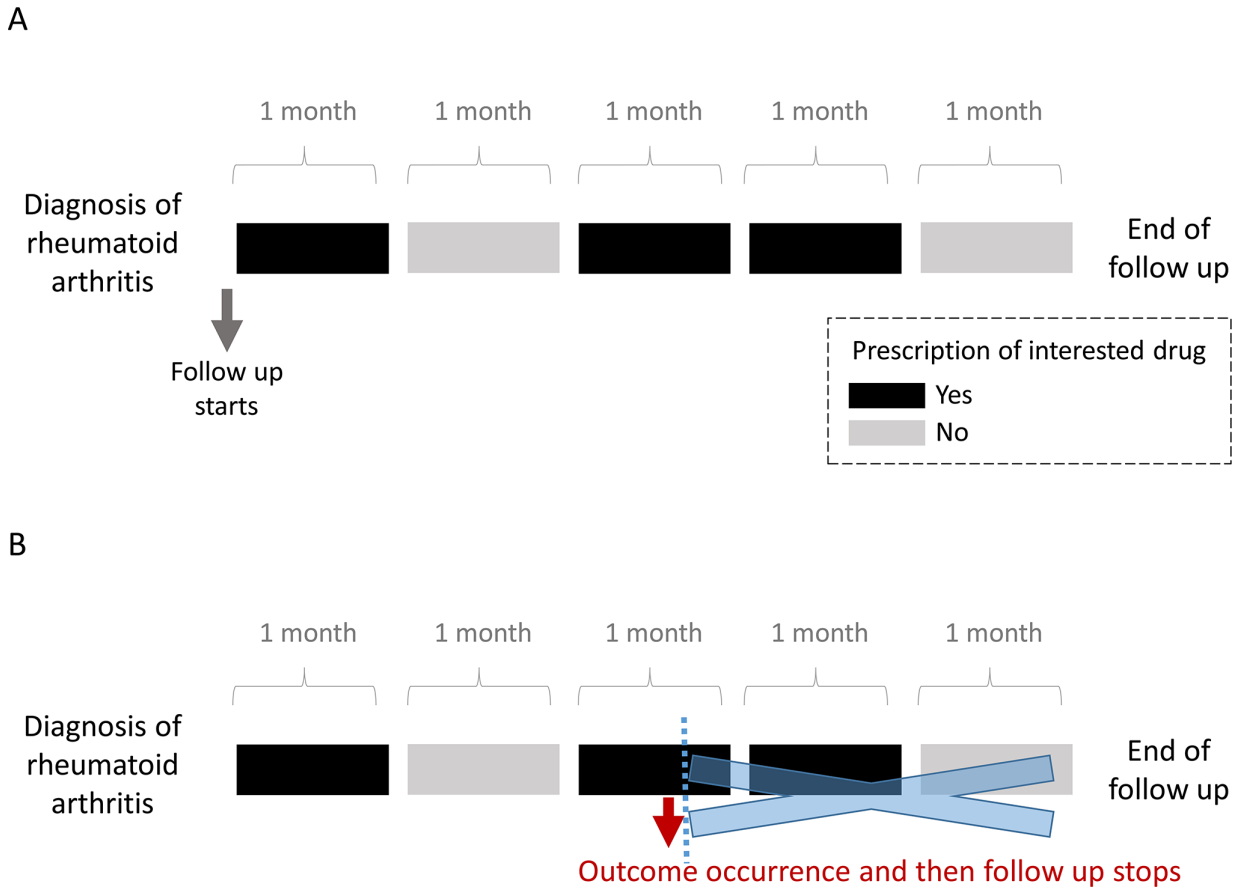

Figure 1 Illustration for the schema of the study design (A) and follow-up periods (B). Several biological drugs had a lag effect after prescription, including additional 1 month for abatacept, certolizumab, golimumab and tocilizumab, and additional 6 months for rituximab.

day of RA diagnosis to the day of DM diagnosis, last visit in the CGMH (including death) or until 31 December 2018 (figure 1B).

Statistical analysis

We compared the baseline characteristics at RA diagnosis (including demographics, comorbidities, laboratory data and medications) of patients with RA with and without future incident DM using an independent sample t-test for continuous variables or a X^2 test for categorical variables. The incidence of DM was determined using incidence density, which is the number of events per 1000 person-years (PYs). The risk of incident DM under different treatment combinations was compared pairwise using a time-dependent Cox proportional hazard model. The outcome dependency of the multiple follow-up months for one patient was considered using a robust SE. We adjusted for several known risk factors for DM in the multivariable Cox model, including age, sex, body mass index (BMI, grouping), smoking, alcohol consumption, all comorbidities (time dependent) and time-dependent use of statins and steroids. Statistical significance was defined as a two-sided p value of <0.05. All analyses were conducted using the SAS software (V.9.4; SAS Institute).

RESULTS

Patient characteristics

In total, 5530 adult patients with RA were included in this study. During the mean follow-up period of 9.2 years (SD=5.6 years), 546 subjects (9.9%) developed DM, with an incidence of 11.6 events per 1000 PYs (95% CI 10.6 to 12.6). The baseline characteristics of patients with RA with and without future incident DM were compared (table 1). Compared with patients without DM, those with future incident DM were older; had higher BMI values; had a higher prevalence of hypertension, gout and hepatitis C virus infection; were more likely to be prescribed statins; and had higher white cell counts, lower estimated glomerular filtration rate, higher C reactive protein levels and more rheumatoid factor positivity (p<0.05).

Use of DMARDs and DM risk

Pairwise comparisons of different RA treatment patterns are summarised in table 2. The results showed that the risk of DM was significantly lower in the bDMARD periods (HR 0.51; 95% CI 0.32 to 0.83), MTX combination periods (HR 0.50; 95% CI 0.32 to 0.78) and other cDMARD periods (HR 0.56; 95% CI 0.37 to 0.84) than in MTX monotherapy periods. On the contrary, the risk of DM was significantly higher in the non-DMARD periods

Table 1 Baseline characteristics of patients with rheumatoid arthritis (RA) according to future incident diabetes or not

Variable	Valid no	Total (n=5530)	Incident diabetes		P value
			No (n=4984)	Yes (n=546)	
Demographics					
Age, years	5530	55.7±13.8	55.4±14.1	58.6±10.7	<0.001
Female, %	5530	4393 (79.4)	3966 (79.6)	427 (78.2)	0.468
Body mass index, kg/m^2	4672	23.8±4.8	23.6±4.7	25.5±4.9	<0.001
Weight status	4672				<0.001
<18.5 kg/m^2		408 (8.7)	389 (9.3)	19 (3.9)	
18.5–25 kg/m^2		2706 (57.9)	2476 (59.1)	230 (47.4)	
25–30 kg/m^2		1181 (25.3)	1011 (24.1)	170 (35.1)	
≥30 kg/m^2		377 (8.1)	311 (7.4)	66 (13.6)	
Substance use					
Smoking	5530	484 (8.8)	440 (8.8)	44 (8.1)	0.578
Alcohol drinking	5530	245 (4.4)	219 (4.4)	26 (4.8)	0.742
Comorbidity					
Hypertension	5530	817 (14.8)	702 (14.1)	115 (21.1)	<0.001
Hyperlipidaemia	5530	154 (2.8)	132 (2.6)	22 (4.0)	0.073
Gout	5530	249 (4.5)	213 (4.3)	36 (6.6)	0.017
Chronic kidney disease*	5530	533 (9.6)	471 (9.5)	62 (11.4)	0.169
Hepatitis B virus infection	5530	304 (5.5)	280 (5.6)	24 (4.4)	0.239
Hepatitis C virus infection	5530	437 (7.9)	375 (7.5)	62 (11.4)	0.002
Coronary heart disease	5530	208 (3.8)	187 (3.8)	21 (3.8)	1.000
Stroke	5530	82 (1.5)	75 (1.5)	7 (1.3)	0.719
Medication at diagnosis of RA					
Steroids	5530	1851 (46.7)	1679 (46.3)	172 (50.6)	0.131
Statins	5530	71 (1.8)	60 (1.7)	11 (3.2)	0.036
Laboratory data at diagnosis of RA					
White cell count, ×10^9/L	3834	8.0±3.3	7.9±3.3	8.8±3.0	<0.001
Haemoglobin, g/L	3854	118±18	118±18	120±18	0.078
Platelet, ×10^9/L	3829	270 (213, 337)	269 (212, 337)	276 (223, 349)	0.239
Creatinine, mg/dL	3778	0.79 (0.63, 0.92)	0.78(0.62, 0.91)	0.80 (0.70, 1.00)	0.626
eGFR, mL/min/1.73 m^2	3778	92.2±35.5	92.9±36.0	84.0±28.3	<0.001
ALT, U/L	2819	21 (17, 28)	21 (17, 28)	21 (16, 27)	0.940
AST, U/L	3133	17 (12, 26)	17 (12, 26)	19 (14, 27)	0.687
ESR, mm/hour	3337	34 (17, 62)	34 (16, 62)	35 (18, 65)	0.311
CRP, mg/L	2393	13 (4, 44)	13 (3, 42)	18 (4, 75)	<0.001
RF	4064	2683 (66.0)	2390 (65.5)	293 (70.6)	0.038
Anti-CCP antibody	705	383 (54.3)	335 (54.5)	48 (53.3)	0.910
RF or anti-CCP antibody	4153	2786 (67.1)	2476 (66.6)	310 (71.4)	0.046

Continued

Table 1 Continued

Variable	Valid no	Total (n=5530)	Incident diabetes		
			No (n=4984)	Yes (n=546)	P value
Demographics					

Data were presented as frequency (percentage), mean±SD or median (first quartile, third quartile).
*eGFR <60 mL/min/1.73 m^2.
ALT, alanine aminotransferase; anti-CCP, anti-cyclic citrullinated peptide; AST, aspartate aminotransferase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

than in the bDMARD periods (HR 2.01; 95% CI 1.38 to 2.94), MTX combination periods (HR 2.07; 95% CI 1.50 to 2.84) and other cDMARD periods (HR 1.86; 95% CI 1.43 to 2.42). The results of these pairwise comparisons are shown in online supplemental figure 2.

The PYs of bDMARDs accounted for only 8.7% of all PYs (table 2). If further classified, TNF-α inhibitors (3181.6 PYs) accounted for 6.9% of all PYs. Other bDMARDs (865.4 PYs) accounted for 1.9% of all PYs.

Associated factors of future incident DM

In addition to drugs, other possible factors for DM development in patients with RA were further investigated, including age, sex, BMI, smoking, alcohol consumption, hypertension, hyperlipidaemia, gout, chronic kidney disease, chronic hepatitis B and C virus infections, coronary artery diseases and stroke. The results showed that advanced age (HR 1.02; 95% CI 1.01 to 1.03), male sex (HR 1.33; 95% CI 1.04 to 1.70), higher BMI, hypertension (HR 1.89; 95% CI 1.55 to 2.31), hyperlipidaemia (HR 2.09; 95% CI 1.42 to 3.06) and hepatitis C virus infection (HR 1.35; 95% CI 1.02 to 1.79) were associated with a higher risk of DM development. In the individual medication analysis, hydroxychloroquine (HCQ) (HR 0.52; 95% CI 0.42 to 0.65) and sulfasalazine (SSZ) (HR 0.69; 95% CI 0.54 to 0.87) were associated with a decreased risk of DM, whereas TNF-α inhibitors (HR 0.69; 95% CI 0.46 to 1.03) tended to be protective. Other bDMARDs (HR 0.78; 95% CI 0.39 to 1.53) were not associated with a reduced risk of DM. By contrast, the time-dependent use of steroids (HR 2.18; 95% CI 1.74 to 2.72) correlated with an increased risk of DM (table 3). The association between the use of each drug and the risk of DM is shown in online supplemental figure 3.

DISCUSSION

RA increases the risk of DM events.[4] Our study further showed that patients with RA who receive different treatments have different levels of DM risks. Patients receiving bDMARD or cDMARD combination therapy will have fewer DM events than those taking MTX monotherapy. HCQ, SSZ and TNF-α inhibitors appear to offer greater potential protection. Since cardiovascular events are the main cause of morbidity in RA, early selection of appropriate drugs to avoid DM development, such as bDMARDs or combination therapy with cDMARDs, should be considered.

Several factors have been proposed to explain the increased incidence of DM in patients with RA. One of the key risks is the higher disease activity in RA.[21] Systemic inflammatory processes triggered by RA may lead to insulin resistance and DM. Several cytokines/chemokines, including interleukin (IL)-1 and IL-6, are associated with an increased incidence of DM. Therefore, the aggressive control of disease activity to reduce the levels of these cytokines may be suitable for the prevention of DM. This may explain why, in the present study, more effective treatments, including bDMARDs or a combination of cDMARDs, were more effective than MTX alone, which was possibly related to better control of disease activity.

Table 2 Incidence of diabetes for the patients with rheumatoid arthritis according to use of cDMARDs and bDMARDs

Treatment exposure	Total person-year	Incidence (95% CI)†	Column vs row: aHR (95% CI)*			
			Any bDMARDs	MTX combination	Other cDMARDs	Non-DMARDs
MTX monotherapy	1536.6	19.5 (12.5 to 26.5)	0.51 (0.32 to 0.83)‡	0.50 (0.32 to 0.78)‡	0.56 (0.37 to 0.84)‡	1.03 (0.68 to 1.57)
Any bDMARDs	4047.0	9.1 (6.2 to 12.1)	–	0.98 (0.65 to 1.46)	1.08 (0.75 to 1.57)	2.01 (1.38 to 2.94)‡
MTX combination	6846.8	9.6 (7.3 to 12.0)	–	–	1.11 (0.82 to 1.50)	2.07 (1.50 to 2.84)‡
Other cDMARDs	11 037.8	12.2 (10.2 to 14.3)	–	–	–	1.86 (1.43 to 2.42)‡
Non-DMARDs	22 869.4	11.7 (10.3 to 13.1)	–	–	–	–

*Models were adjusted for age, sex, body mass index grouping (the patients with missing data were one of the groups), smoking, alcohol drinking, hypertension, hyperlipidaemia, gout, chronic kidney disease, hepatitis B virus infection, hepatitis C virus infection, coronary arterial disease, stroke, and time-dependent use of statins and steroids.
†Expressed as number of events per 1000 person-years.
‡P<0.05.
aHR, adjusted HR; bDMARDs, biological disease-modifying anti-rheumatic drugs; cDMARDs, conventional disease-modifying anti-rheumatic drugs; MTX, methotrexate.

Table 3 The associated factors of incident diabetes for the patients with rheumatoid arthritis (RA)

Predictor	Adjusted HR (95% CI)	P value
Age, per year	1.02 (1.01 to 1.03)	<0.001
Male	1.33 (1.04 to 1.70)	0.022
Body mass index at RA diagnosis, kg/m^2		
<18.5 kg/m^2	Reference	
18.5–25 kg/m^2	1.68 (1.05 to 2.69)	0.032
25–30 kg/m^2	2.38 (1.47 to 3.85)	<0.001
≥30 kg/m^2	3.30 (1.97 to 5.51)	<0.001
Missing	1.77 (1.04 to 2.99)	0.034
Smoking	0.93 (0.65 to 1.32)	0.669
Alcohol drinking	1.18 (0.77 to 1.79)	0.453
Comorbidity		
Hypertension	1.89 (1.55 to 2.31)	<0.001
Hyperlipidaemia	2.09 (1.42 to 3.06)	<0.001
Gout	1.03 (0.75 to 1.42)	0.837
Chronic kidney disease	1.06 (0.80 to 1.41)	0.676
Hepatitis B virus	0.89 (0.59 to 1.34)	0.578
Hepatitis C virus	1.35 (1.02 to 1.79)	0.036
Coronary artery disease	0.97 (0.75 to 1.26)	0.841
Stroke	0.72 (0.45 to 1.15)	0.167
Medication		
Methotrexate	0.88 (0.70 to 1.11)	0.287
Hydroxychloroquine	0.52 (0.42 to 0.65)	<0.001
Sulfasalazine	0.69 (0.54 to 0.87)	0.002
Leflunomide	0.79 (0.51 to 1.21)	0.284
TNF-α inhibitors*	0.69 (0.46 to 1.03)	0.067
Other bDMARDs†	0.78 (0.39 to 1.53)	0.467
Time-dependent use of steroid	2.18 (1.74 to 2.72)	<0.001
Time-dependent use of statin	0.96 (0.61 to 1.51)	0.844

*Etanercept, adalimumab, certolizumab and golimumab.
†Abatacept, tofacitinib, baricitinib, tocilizumab and rituximab.
bDMARDs, biological disease-modifying anti-rheumatic drugs; TNF, tumour necrosis factor.

In the present study, the follow-up in each of the non-DMARD periods showed that the patients were only on pain medication or glucocorticoids, but not DMARDs, during this time. We noted that these periods had a significantly increased risk of developing DM compared with the bDMARD or cDMARD combination therapy periods. In these periods, RA inflammation may be primarily controlled by glucocorticoids rather than standard immunotherapy. On the contrary, the DM-preventive effects of bDMARD or cDMARD combination therapy may be attributable to their glucocorticoid-sparing effects. In the current study, the prevalence of glucocorticoid use was 76.3% during the non-DMARD period but only 8.4% during the DMARD period. As presented in table 3, glucocorticoids have been shown to increase time-dependent DM risk. The long-term use of glucocorticoids stimulates gluconeogenesis in the liver, whereas in the skeletal muscle and adipose tissue, they reduce glucose uptake and utilisation by antagonising insulin response.[22] Additionally, it alters body composition, including the expansion of trunk adipose tissue depots, which then creates insulin resistance.[23] Therefore, long-term glucocorticoid use is not recommended in the American College of Rheumatology and European Alliance of Associations for Rheumatology guidelines.[24 25]

Of the various bDMARDs, which one is most effective in preventing the development of diabetes is not yet established because the results of previous studies were not consistent. In the US Corrona dataset, a significant reduction in the risk of DM was found in patients with RA treated with TNF-α inhibitors.[7] In the present study, a lower risk of DM was observed in patients receiving TNF-α inhibitors despite borderline significance (p=0.067). This finding underscores that the choice of RA treatment

may have a broad influence on the patients. However, the observed effects may be the result of bDMARDs modulating disease activity rather than the direct effect of TNF-α inhibitors. Regarding other biological agents, abatacept is often mentioned to be able to reduce the incidence of DM.[6] In addition to controlling inflammation, the direct effect of abatacept on glucose metabolism may play a key role in explaining the protective effect due to the reduction of insulin resistance and inhibition of T cell co-stimulation.[26] In another study, more pronounced reductions in HbA1c were seen in patients treated with tocilizumab rather than TNF inhibitors.[27] However, we observed that abatacept and tocilizumab did not reach statistical significance, which may be due to the small number of cases.

In this study, the use of HCQ and SSZ appeared to reduce the incidence of DM. Previous reports have shown that patients using HCQ have significantly lower blood sugar levels.[28] The hypothesised mechanism of its antidiabetic effect may be an increase in insulin sensitivity and adiponectin levels. Although SSZ was also found to reduce HbA1c, this may be due to a haemolysis-related HbA1c reduction, rather than a real reduction in glucose levels.[29] In the present study, we defined DM as HbA1c >7, so some patients treated with SSZ may not be judged as DM due to the above-mentioned effects. Therefore, we may mistakenly believe that SSZ has a protective effect, but in fact the protective effect may not exist.

Attention to DM prevention in patients with RA is important for improving cardiovascular outcomes and reducing early mortality. Therefore, in addition to the drug options mentioned in the present study, which may be helpful, several aspects need to be emphasised. Controlling disease activity in RA remains key, as other factors may also be affected by RA. Excessively static lifestyles, which may be associated with RA-induced pain, joint deformities or fatigue, should be avoided. Weight control may be easier if a patient can move freely. Body weight is also a risk factor for increased inflammatory activity.[30] In addition to body weight, people with rheumatoid disease should be screened for DM regularly and adopt a healthy lifestyle to reduce DM risk.

However, this study had some limitations. First, some data may be missing, such as patients with DM who had been stably controlled in other hospitals but were mistaken for having no DM because of normal HbA1c levels. Alternatively, patients were included in the periods not taking DMARDs, but were receiving medications in other hospitals. Treatment exposure (DMARD) and outcome (defined by HbA1c level) may be misclassified. These possibilities will affect the results of the study. Second, this is a database retrospective study and does not provide actual disease activity. However, disease activity may confound the effect of the drug and affect the results. For example, the partial protective effect of HCQ could also be explained by its frequent use in patients with low disease activity. Disease activity could not be adjusted for, leading to indication confounding, which may have biased the effect estimate. Therefore, it is necessary to conduct randomised controlled trials or prospective registration studies to verify the protective effect of these drugs on the occurrence of diabetes. Third, as the database used was only up to the end of 2018, the use of other mechanistic bDMARDs in CGMH is still low, except for TNF-α inhibitors. Therefore, we could not provide sufficient evidence for comparison with other studies.

In conclusion, bDMARDs and the combination of DMARDs are more likely to reduce the risk of DM in patients with RA than MTX alone. HCQ and TNF-α inhibitors may have additional protective effects, while bDMARDs with different mechanisms of action have shown no effect, possibly due to being underused. In addition, steroids have a dose-dependent risk in DM events; thus, long-term use should be avoided. Therefore, a judicious choice of treatment may help control the development of DM in patients with RA and may even reduce cardiovascular events in the future.

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Contributors Y-JS and H-MC wrote the article. T-MC and T-TC did the data mining. S-FY draw the figure. J-FC made the table. C-YL applied for the IRB. C-YH supervised the design and study and acted as guarantor.

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