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The association between cardiovascular disease and conventional DMARDs in patients with rheumatoid arthritis

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***Abstract*---**This study investigates potential links between cardiovascular disease and the use of traditional disease-modifying anti-rheumatic medications (DMARDs) in RA patients. 246 individuals with RA (82 with CVD and 164 without CVD) were investigated using a case-control strategy. Methotrexate (MTX) and sulfasalazine were used to classify the dataset (SSZ). "MTX alone", OR 0.18 (95% CI 0.09-0.74); "MTX with SSZ ever", OR 0.22 (95% CI 0.12-0.53). After further rectification, the treatment's risk reductions for the existence of rheumatoid factor remained considerable. Only the "MTX or SSZ" group had a substantial decrease in CVD risk after controlling for diabetes, hypertension, and high blood cholesterol levels. Rheumatoid factor substantially elevated the risk of cardiovascular disease, with odds ratios of 2.47 (95% confidence interval: 1.21 to 5.80). MTX and

SSZ, the latter to a lesser degree, were related with a considerably lower risk of cardiovascular disease (CVD) compared to individuals with RA who had never taken either medication or combination. This research indicates that the use of DMARDs, namely MTX, resulted in a strong decrease of joint inflammation. It may help prevent the development of atherosclerosis and other cardiovascular diseases.

***Keywords*---**rheumatoid arthritis, cardiovascular disease, risk, DMARDs, case-control, methotrexate.

Introduction

In patients with rheumatoid arthritis (RA) cardiovascular diseases (CVDs) are considered to be the leading cause of death. When compared to the general population those with RA have a significantly increased risk of cardiovascular morbidity as well as mortality (Jamnitski et al., 2011; Pappas et al., 2018; Sarmiento-Monroy et al., 2012). There is a lack of evidence for a concise explanation for the elevated cardiovascular risk, however, several causes have been hypothesized. The first and the most reliable is an elevation in the prevalence of established cardiovascular risk factors, such as diabetes, hypertension and high blood cholesterol level. Second, is the possibility of undertreatment of cardiovascular comorbidity (Wasko et al., 2011). And lastly, there is evidence that RA as a disease may be responsible for increased cardiovascular morbidity and mortality, either because of a reduction in functional capacity or as a result of different inflammatory processes. A recent and growing amount of evidence suggests that atherosclerosis has inflammatory characteristics of disease (Crowson et al., 2013; England et al., 2018). In addition, inflammation can lead to fatty streaks deterioration making plaques unstable and leading to ruptures (Libby, 2008). On top of that, it may act as a complement activation or lead to facilitation of lipid profile deteriorations (Cavagna et al., 2012), with importance all aspects in the pathogenesis of atherosclerosis. One of the tangled parts of the link between RA and cardiovascular risk is the utilization of disease-modifying anti-rheumatic drugs. Patients with persistent disease activity require treatment with disease-modifying anti-rheumatic drugs (DMARDs) (Aletaha & Smolen, 2018 Naranjo et al., 2008; Westlake et al., 2010). Over the past few decades, significant progress has been made in modern approaches to the treatment of this systemic disease. One of these new approaches is the almost universal use of combinations of DMARDs to treat individual patients. Several years ago, DMARDs were quite rarely used in combination, while today, a great majority of rheumatologists use them to treat an increasing percentage of patients with RA (Naranjo et al., 2008). Recent studies showed that DMARDs can potentially modify the risk of cardiovascular diseases either by an effect on the process of atherosclerosis directly or indirectly by influencing the factors of cardiovascular risk (Roubille et al., 2015). However, there are limited reports investigating the relationship between DMARDs and CVD. Although, these studies showed conflicting evidence between CVD morbidity and mortality in patients treated with methotrexate (MTX) (Roubille et al., 2015; Shea et al., 2014). The present study examines the associations between cardiovascular diseases and the utilization of conventional DMARDs.

Materials and Methods

Data from a total of 246 RA patients registered between 2008-2019 were included in the present study. The sample of patients was randomly derived from the patient database in 1st Clinic of Samarkand State Medical Institute. Criteria for the inclusion in the study were the age 19-80 years, RA meeting the criteria presented by the American College of Rheumatology (ACR), duration of illness over 6 months and active illness, with a minimum of 3 of the following 4 characteristics: speed erythrocyte sedimentation rate (ESR)> 28 mm / h, duration of morning stiffness ≥45 minutes, ≥4 painful joints, and ≥2 swollen joints. In this case-control study, to investigate the risk factors for cardiovascular morbidity, we divided patients with RA into two groups: with any cardiovascular events (82 patients with RA) and without any CVD events (164 patients with RA). Cardiovascular diseases in patients were evaluated based on endpoint follow-up data from the official medical history of the patients. Cardiovascular disease was defined as any verified event of coronary, cerebral or peripheral arterial disease. Assessed risk factors for CVD included age, sex, hypertension, diabetes, smoking and hypercholesterolemia.

Statistical analyses

For comparisons between different DMARD groups in cases (RA patients with CVD) and controls (RA patients without CVD), we utilized Students' t-tests for continuous variables (age, disease duration, hypertension) and Pearson's Chi-square tests for dichotomous/binary variables (gender, smoking, drug doses). We categorized the data into groups in accordance with the use of DMARDs (sulfasalazine or Methotrexate), either given as monotherapy or in combinations of the drugs. The eventual study group consisted of patients with no prior use of these DMARDs. Logistic regression modelling was applied to calculate the odds ratios (ORs) with 95% confidence intervals (95% CIs) of CVD for the given DMARD groups. The first regression model adjusted for gender, age, smoking status and disease duration. In the second regression model to the existing variables in the first model, we additionally adjusted for hypertension, hypercholesterolemia and diabetes. Lastly, in the third model, data were adjusted for the presence or absence of a positive rheumatoid factor test. This allowed us to measure the ORs for cardiovascular diseases associated with the above-mentioned variables. All the models were also used to investigate whether there was any dose-response relationship in the possible associations between the conventional DMARDs and risk of cardiovascular morbidity. We considered a p-value of 0.05 or smaller as statically significant, and all tests were performed using the R studio 3.6.2.

Results and Discussions

Table 1 presents the baseline characteristics of the case and control groups in our research population. The patients in the main group (cases) were considerably older than those in the control group ($p<0.001$). In addition, their duration of RA was longer ($p<0.001$) and they were more likely to have a positive rheumatoid factor test ($p=0.05$). The use of DMARDs also varied between patients and controls. The number of patients who had never taken DMARDs or MTX or SSZ

was similarly larger among cases than among controls (p<0.001 for each). The cases were also more likely to have hypertension and elevated blood cholesterol (p<0.001 and p=0.01 respectively).

DMARD subgroups

Table 2 lists the fundamental features and factors of the study population and traditional DMARDs. Patients who had just MTX had substantially shorter RA duration (p<0.001), a larger proportion of diabetics (p<0.001), and a higher incidence of hypertension (p = 0.02). Those who got just SSZ did not demonstrate any meaningful relationships. Likewise, there was no statistically significant difference between the SSZ and MTX groups.

Table 1. Characteristics of case and control groups

	Cases (n=82)	Controls (n=164)	p-value
Demographics			
Mean age, years (SD)	63 (10)	49 (11)	<0.001
Sex (female)	69	132	0.16
RA characteristics			
Disease duration, years *(median, IQ range)*	11.6 (7-15)	6.4 (4-10)	<0.001
RF positive patients (%)	82	133	0.05
DMARD naive patients (%)	15	7	<0.001
never SSZ or MTX (%)	12	6	<0.001
SSZ ever (%)	72	106	0.04
MTX ever (%)	42	88	<0.001
Prednisone ever (%)	36	54	0.52
CVD characteristics			
Smoking (%)	71	70	0.91
Hypertension (%)	52	21	<0.001
Diabetes mellitus (%)	9	6	0.19
Hypercholesterolemia (%)	32	4	<0.01
IQ range- interquartile-range, SD- standard deviation			

Table 2. RA and CVD related variables per conventional DMARD groups (with p values)

Study groups		Entire group	Never MTX or SSZ	Only MTX	Only SSZ	MTX and SSZ
n (%)		246 (100)	32 (13)	45 (18)	37 (9)	131 (53)
RA factors (p-value)	Disease duration	9	14 (0.21)	8 (<0.001)	11 (0.20)	12 (0.13)
	RF (%)	87	58 (0.44)	81 (0.09)	73 (0.15)	71 (0.18)
CVD factors (p-value)	Hypertension (%)	36	21 (0.61)	32 (0.02)	29 (0.38)	26 (0.57)
	Diabetes	7	9 (0.21)	18	4 (0.56)	9 (0.30)

	(%)			(<0.001)		
	Cholesterolemia (%)	21	9 (0.28)	12 (0.52)	16 (0.24)	3 (0.61)

The first model, which took into account age, gender, smoking status, and the length of RA illness, found that those patients who got just MTX or the combination of the two medicines had statistically significant decreases in their risk for cardiovascular disease. However, the second model, which added accounted for hypertension, diabetes, and hypercholesterolemia, revealed that the only people with a significantly reduced risk of cardiovascular disease were those who had taken MTX and SSZ in combination. It is interesting to note that the previous model that was adjusted for the rheumatoid factor revealed a substantial decrease in the risk of CVD for all three DMARD groups. This third model provides the odds ratios for a positive rheumatoid factor test (OR 2.47, 95%, CI 1.21 - 5.88), indicating an increased risk of cardiovascular disease among relevant RA patients. We investigated the use of prednisone in the first model as an extra analysis. The results revealed that there was no significant connection between the use of corticosteroids and cardiovascular disease (OR 0.81; 95% CI 0.39-2.49).

Table 3. Results of logistic regression models

Study groups	Never MTX and SSZ	Only MTX ever	Only SSZ ever	MTX and SSZ ever
Model 1 OR (95% Cl)	Ref.	0.18 (0.09-0.74)	0.39 (0.19-1.12)	0.22 (0.12-0.53)
Model 2 OR (95% Cl)	Ref.	0.47 (0.21-3.48)	0.31 (0.16-1.69)	0.24 (0.19-0.81)
Model 3 OR (95% CI)	Ref.	0.11 (0.14-0.67)	0.37 (0.18-0.89)	0.16 (0.10-0.56)

This research demonstrates that the usage of DMARDs reduces the risk of cardiovascular disease. Moreover, it reveals that the rheumatoid factor raises the risk of CVD in people with RA. Previous research focused mostly on MTX, making it less helpful regarding other conventional DMARDs, such as SSZ. This research examined the function of not only various CVD-related components but also RA-specific variables in the development of CVD, which is an advantage. Less is known about the processes behind DMARD use that may impact the risk of CVD. It has been shown that MTX may result in folic acid shortage, leading to an increase in blood homocysteine levels and an increased risk of cardiovascular disease (Roubille et al., 2015; Shea et al., 2014). On the other hand, several studies have found a decreased prevalence of cardiovascular illnesses in RA patients on MTX, which is consistent with the findings of the present research. The findings of this research indicate that the use of other standard DMARDs, notably sulfasalazine, is also related with a reduced risk of cardiovascular disease, confirming the idea that inflammation reduction is crucial for decreasing the risk of cardiovascular disease. In addition, our findings indicates that the association between inflammation and the risk of cardiovascular disease is confirmed by the discovery that the presence of rheumatoid factor is related with cardiovascular disease. These findings highlight the need of proactive, aggressive

therapy for RA, since it not only improves patient mobility but also may avoid comorbidities such as cardiovascular disease. The limitations of this research should also be highlighted. First, the data were extracted from a database of patient records, some of which may have been lost or compromised. To eliminate further bias, data were gathered by two independent observers.

Conclusion

Compared to RA patients who were never treated with sulfasalazine or methotrexate, MTX-treated individuals with rheumatoid arthritis had a decreased risk for cardiovascular morbidity. We believe that individuals treated with MTX, and to a lesser degree those with SSZ, may be linked with less severe atherosclerotic inflammation, resulting in a lower risk of CVD.

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