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RHEUMATOID ARTHRITIS TREATED WITH DMARDS AND CARDIOVASCULAR DISEASE RISK

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ABOUT ARTICLE

Key words: RA, CVD, risk, DMARD, case-control, methotrexate

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Abstract: Rheumatoid arthritis (RA) is a disease characterized by joint inflammation and an increased risk of cardiovascular diseases (CVDs). This study examines possible associations between cardiovascular disease and the utilisation of conventional disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA. MTX and SSZ with the latter to lesser extent were associated with a significant reduced risk of CVD than patients with RA who never used either of the drugs or combinations. This study suggests that the use of DMARD, in particular the use of MTX, results in potent suppression of joint inflammation. It also can reduce the development of atherosclerosis and associated CVDs.

KO‘ARP BILAN DAVOLALANGAN REVMATOID ARTRIT VA YURAK-QON TOMIR KASALLIKLARI XAVFI

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MAQOLA HAQIDA

Kalit so‘zlar: RA, QTK, xavf, KO‘ARP, metotreksat.

Annotatsiya: Revmatoid artrit (RA) bo‘g‘imlarning yallig‘lanishi va yurak-qon tomir kasalliklari (QTK) xavfi ortishi bilan tavsiflangan kasallikdir. Ushbu tadqiqot yurak-qon tomir kasalliklari va RA bilan og‘rigan bemorlarda an'anaviy kasalliklarni o‘zgartiruvchi revmatik dorilarni (KO‘ARP) qo‘llash o‘rtasidagi mavjud bog‘liqlikni o‘rganadi. MTX va SSZ hech qachon dori yoki kombinatsiyani ishlatmagan RA bilan og‘rigan bemorlarga qaraganda QTK xavfining sezilarli darajada pasayishi bilan bog‘liq edi. Ushbu tadqiqot shuni ko‘rsatadiki, KO‘ARP dan foydalanish, xususan, MTX dan foydalanish qo‘shma yallig‘lanishni kuchli bostirishga olib keladi. Bundan tashqari, ateroskleroz va unga bog‘liq bo‘lgan yurak-qon tomir kasalliklarining rivojlanishini kamaytirishi mumkin.

РИСК СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ ПРИ ТЕРАПИИ РЕВМАТОИДНОГО АРТРИТА С БМАРП

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О СТАТЬЕ

Ключевые слова: РА, ССЗ, риск, БМАРП, случай-контроль, метотрексат

Аннотация: Ревматоидный артрит (РА) - заболевание, характеризующееся воспалением суставов и повышенным риском сердечно-сосудистых заболеваний (ССЗ). В данном исследовании изучаются возможные ассоциации между сердечно-сосудистыми заболеваниями и применением обычных болезнь-модифицирующих противоревматических препаратов (БМАРП) у пациентов с РА. MTX и SSZ, причем последний в меньшей степени, были связаны со значительным снижением риска CVD по сравнению с пациентами с РА, которые никогда не использовали ни один из препаратов или их комбинаций. Это исследование предполагает, что применение БМАРП, в частности MTX, приводит к мощному подавлению воспаления суставов. Это также может уменьшить развитие атеросклероза и связанных с ним ССЗ.

INTRODUCTION

Cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is considered to be the leading cause of death. Compared to the general population people with RA have a significant increased risk of a cardiovascular morbidity as well as mortality [1-5]. There is a lack of evidence for a concise explanation for the elevated cardiovascular risk, however several causes have been hypothesized. 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, the possibility of undertreatment of cardiovascular comorbidity [6]. And lastly, there is an evidence that RA as a disease may possibly be responsible for an increased cardiovascular morbidity and mortality, either because of a reduction in functional capacity or as a result of different inflammatory processes. Recent and growing amount of evidence suggests that atherosclerosis has an inflammatory characteristics of disease [7-9]. In addition, inflammation can lead to fatty streaks deterioration making plaques unstable and leading to ruptures [10]. On top of that it may act as a complement activation or lead to facilitation of lipid profile deteriorations [11], with importance all aspects in the pathogenesis of atherosclerosis. One of the tangled part 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) [12-14]. Over the past few decades, clearly 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 great majority of rheumatologists use them to treat an increasing percentage of patients with RA [15]. Recent studies showed that DMARDs can potentially modify risk of cardiovascular diseases either by an effect on the process of atherosclerosis directly or indirectly by influencing the factors of cardiovascular risk [16, 17]. However, there are limited reports investigated the relationship between DMARDs and CVD. Although, these studies showed conflicting evidence between CVD morbidity and mortality in patients treated with methotrexate (MTX) [18]. Therefore, the present study examines the associations between cardiovascular diseases and the utilization of conventional DMARDs.

THE MAIN RESULTS AND FINDINGS

Data from a total of 246 RA patients registered between 2008-2019 were included in 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 suggested 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 was 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.

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 modeling 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 the 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 was adjusted for presence or absence of a positive rheumatoid factor test. This allowed us to measure the ORs for cardiovascular diseases associated with 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 a 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.

The baseline characteristics of the case and control groups in our study population are presented in Table 1. The patients in the main group (cases) were significantly older ($p<0.001$). Also, they had a longer duration of RA ($p<0.001$) and were more likely to have a positive rheumatoid factor test ($p=0.05$). DMARDs usage was also different between the cases and controls. The number of DMARD naive patients and those who never used MTX or SSZ was also higher among cases compared to controls ($p<0.001$, for each respectively). Lastly, the cases more frequently had hypertension and increased blood cholesterol levels ($p<0.001$ and $p=0.01$ respectively).

DMARD groups

Basic characteristics and different variables of the study population and the conventional DMARDs are given in Table 2. Patients who received only MTX had a significantly shorter RA duration ($p < 0.001$) and a higher percentage of diabetics ($p <0.001$) and hypertension ($p=0.02$).

While those who received only SSZ ever showed no significant associations. Similarly, the results for the 'SSZ and MXT group has not showed statistically significant difference.

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 (<0.001)	4 (0.56)	9 (0.30)
	Cholesterolemia (%)	21	9 (0.28)	12 (0.52)	16 (0.24)	3 (0.61)

The first model, adjusted for age, gender, smoking status and RA disease duration, revealed statistically significant reductions in risk for CVD for those who received only MTX or the combination of two drugs. However, the second model, additional adjusted for hypertension, diabetes and the hypercholesterolemia showed significant risk reductions for CVD only among

those who had received MTX and SSZ in combination. Interestingly, in the last model, corrected for rheumatoid factor showed significant CVD risk reduction for the all three DMARD groups. This third model quantified the ORs for having positive rheumatoid factor test (OR 2.47 (95% CI 1.21 to 5.88) showing an elevated CVD risk among respective RA patients. As an additional analysis we tested the use of prednisone to the initial model, which showed no significant association (OR 0.81 (95%CI 0.39-2.49) between corticosteroid use and CVD.

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 study demonstrates a protective role of the DMARDs use for the risk of cardiovascular diseases. Furthermore, it demonstrates that rheumatoid factor increases the risk for CVD among RA patients. Previous studies predominantly investigated MTX which therefore less informative about other traditional DMARDs, such as SSZ. As an advantage, this study explored the role of not only several CVD-related factors but also RA specific variables in development of CVD. Information on mechanisms under DMARD usage which potentially could influence the risk for CVD are scarce. It is proved that MTX can cause a folic acid deficiency increasing blood homocysteine levels eventually leading to the elevated risk of CVD [19, 20]. On the other hand, some studies reported a lower incidence of cardiovascular diseases in RA patients with MTX, which supports the results obtained in this study. The results of present study show that the use of other conventional DMARDs, particularly sulfasalazine, is also associated with a reduction in the risk of cardiovascular disease, supporting the hypothesis that the reduction in inflammation is important for reducing the risk of cardiovascular disease. Also, our evidence suggests the link between inflammation and the risk of cardiovascular disease is supported by the observation that rheumatoid factor positive is associated with cardiovascular disease. These results underscore the importance of proactive aggressive treatment for RA, as it will not only benefit patient mobility, but may also prevent co-morbidities such as cardiovascular disease. There are also some limitations in this study. First, the data was obtained from a database of patients, some of which

may be lost or corrupted. However, to avoid further bias, data was collected by two independent observers. Second, there may be a confounding bias affecting the estimate towards the null.

CONCLUSION

RA patients treated with MTX, have showed a lower risk for cardiovascular morbidity when compared with RA patients who never treated with sulfasalazine or methotrexate. We hypothesize that patients treated with MTX, and those with SSZ to lesser extent may be associated with less severe atherosclerotic inflammation which results in a decreased risk of CVD.

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