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The Risk of Cardiovascular Disease in Patients with Rheumatoid Arthritis Treated with Conventional DMARDs: a Clinic Based Case Control Study

Conflict of interest: nothing to declare.
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Abstract

Purpose. This study examines possible associations between cardiovascular disease and the utilization of conventional disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA.
Materials and methods. Using a case-control study design, 246 patients with RA (82 with CVD and 164 without CVD) were studied. Data on RA, CVD, and DMARDs therapy were assessed from the verified medical history data. The dataset was categorized according to the use of DMARD: methotrexate (MTX) or sulfasalazine (SSZ). Odds ratios (ORs) for cardiovascular disease, adjusted for age, sex, smoking, and duration of RA, for each DMARD group. Patients who never used MTX or SSZ were used as a reference group.
Results. MTX treatment showed an association with a significant reduction in CVD risk: "MTX only", OR 0.18 (95% CI 0.09–0.74); "MTX and SSZ ever", OR 0.22 (95% CI 0.12–0.53). After additional correction, the risk reductions with the treatment remained significant for rheumatoid factor presence. While adjusting for diabetes hypertension, and high blood cholesterol level, only "MTX or SSZ" group showed a significant reduction in CVD risk. Rheumatoid factor significantly increased CVD risk, with ORs of 2.47 (95% CI 1.21 to 5.88). MTX and SSZ with the latter to lesser extent were associated with a significantly reduced risk of CVD than patients with RA who never used either of the drugs or combinations.
Conclusion. 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.
Keywords: rheumatoid arthritis, cardiovascular disease, risk, disease-modifying anti-rheumatic drugs, case-control, methotrexate

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Риск сердечно-сосудистых заболеваний у пациентов с ревматоидным артритом при лечении с применением традиционных БМАРП: исследование «случай – контроль»

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Резюме

Цель. В данном исследовании изучаются возможные ассоциации между сердечно-сосудистыми заболеваниями (ССЗ) и применением обычных болезнь-модифицирующих противоревматических препаратов (БМАРП) у пациентов с РА.
Материалы и методы. С использованием дизайна исследования «случай – контроль» было изучено 246 пациентов с РА (82 – с ССЗ, 164 – без ССЗ). Данные о РА, ССЗ и терапии БМАРП были получены из проверенной истории болезни. Данные были распределены по категориям в зависимости от использования БМАРП – метотрексата (МТ) или сульфасалазина (СС). Отношение шансов (ОШ) для сердечно-сосудистых заболеваний с поправкой на возраст, пол, курение и длительность РА для каждой группы БМАРП. Пациенты, которые никогда не использовали МТ или СС, были использованы в качестве контрольной группы.
Результаты. Лечение МТ показало ассоциацию со значительным снижением риска ССЗ: «только МТ» – ОШ 0,18 (95% ДИ 0,09–0,74); «МТ и СС» – ОШ 0,22 (95% ДИ 0,12–0,53). После дополнительной коррекции снижение риска при лечении оставалось значительным при наличии ревматоидного фактора. При поправке на диабет, гипертонию и высокий уровень холестерина в крови только в группе «МТ или СС» наблюдалось значительное снижение риска ССЗ. Ревматоидный фактор значительно повышал риск ССЗ, ОШ составило 2,47 (95% ДИ от 1,21 до 5,88). Применение МТ и СС, причем последнего в меньшей степени, было связано со значительным снижением риска ССЗ по сравнению с пациентами с РА, которые никогда не использовали ни один из этих препаратов или их комбинации.
Заключение. Это исследование предполагает, что применение БМАРП, в частности МТ, приводит к мощному подавлению воспаления суставов, а также может снизить вероятность развития атеросклероза и связанных с ним ССЗ.
Ключевые слова: ревматоидный артрит, сердечно-сосудистые заболевания, риск, болезнь-модифицирующие антиревматические препараты, случай – контроль, метотрексат

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 significantly increased risk of 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. 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 [6]. 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 [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 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) [12–14]. 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 the 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 the 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 investigating the relationship between DMARDs and CVD. Although, these studies showed conflicting evidence between CVD morbidity and mortality in patients treated with methotrexate (MTX) [18–22].

PURPOSE OF THE STUDY

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 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 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 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

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 MTX group has not showed a statistically significant difference.

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, additionally adjusted for hypertension, diabetes and 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 all three DMARD groups. This third model quantified the ORs for having positive

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)

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% CI)	Ref.	0.18 (0.09–0.74)	0.39 (0.19–1.12)	0.22 (0.12–0.53)
Model 2 OR (95% CI)	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)

■ DISCUSSION

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 is, 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 the development of CVD. Information on mechanisms under DMARD usage which potentially could influence the risk for CVD is scarce. It is proved that MTX can cause a folic acid deficiency increasing blood homocysteine levels eventually leading to the elevated risk of CVD [19–21]. 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 the 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 the 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 to 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 were 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 shown a lower risk for cardiovascular morbidity when compared with RA patients who were never treated with sulfasalazine or methotrexate. We hypothesize that patients treated with MTX, and those with SSZ to a lesser extent may be associated with less severe atherosclerotic inflammation which results in a decreased risk of CVD.

■ REFERENCES

1. Jamnitski A., Visman I.M., Peters M.J.L., Boers M., Dijkmans B.A.C., Nurmohamed M.T. (2011) Prevalence of cardiovascular diseases in psoriatic arthritis resembles that of rheumatoid arthritis. *Annals of the rheumatic diseases,* no 70 (5), pp. 875–876.
2. Panoulas V.F., Douglas K.M., Milionis H.J. (2007) Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology,* no 46 (9), pp. 1477–1482.
3. Van Halm V.P., Peters M.J.L., Voskuyl A.E., Boers M., Lems W.F., Visser M., Nurmohamed M.T. (2009) Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Annals of the rheumatic diseases,* no 68(9), pp. 1395–1400.
4. Pappas D.A., Nyberg F., Kremer J.M., Lampl K., Reed G.W., Horne L., Greenberg J.D. (2018) Prevalence of cardiovascular disease and major risk factors in patients with rheumatoid arthritis: a multinational cross-sectional study. *Clinical rheumatology,* no 37 (9), pp. 2331–2340.
5. Sarmiento-Monroy J.C., Amaya-Amaya J., Espinosa-Serna J.S., Herrera-Díaz C., Anaya J.M., Rojas-Villarraga A. (2012) Cardiovascular disease in rheumatoid arthritis: a systematic literature review in Latin America. *Arthritis*.
6. Wasko M.C., Kay J., Hsia E.C., Rahman M.U. (2011) Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: risk reduction in a chronic inflammatory disease. *Arthritis care & research,* no 63 (4), pp. 512–521.
7. Crowson C.S., Liao K.P., Davis III J.M., Solomon D.H., Matteson E.L., Knutson K.L., Gabriel S.E. (2013) Rheumatoid arthritis and cardiovascular disease. *American heart journal,* no 166 (4), pp. 622–628.
8. Maradit Kremers H., Nicola P.J., Crowson C.S., Ballman K.V., Gabriel S.E. (2005) Cardiovascular death in rheumatoid arthritis: a population based study. *Arthritis & Rheumatism,* no 52 (3), pp. 722–732.
9. England B.R., Thiele G.M., Anderson D.R., Mikuls T.R. (2018) Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *Bmj*, 361.

10. Libby P. (2008) Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *The American journal of medicine,* no 121 (10), pp. 21–31.
11. Cavagna L., Boffini N., Cagnotto G., Inverardi F., Grosso V., Caporali R. (2012) Atherosclerosis and rheumatoid arthritis: more than a simple association. *Mediators of inflammation*.
12. Swierkot J., Szechiński J. (2006) Methotrexate in rheumatoid arthritis. *Pharmacological reports,* no 58 (473), pp. 473–492.
13. Aletaha D., Smolen J.S. (2018) Diagnosis and management of rheumatoid arthritis: a review. *Jama,* no 320 (13), pp. 1360–1372.
14. Ziyadullaev S.K., Sultonov I.I., Dushanova G.A., Akbarovna K.S. (2021) The Effectiveness Of Pharmacotherapy For DMARDs With Ra Depending On The C3435t Polymorphism Of The Mdr1 Gene. *International Journal of Aquatic Science,* vol. 12, issue 3, pp. 2908–2916.
15. Mikuls T.R., O'Dell J. (2000) The changing face of rheumatoid arthritis therapy: results of serial surveys. *Arthritis Rheum,* no 43, pp. 464–5.
16. Westlake S.L., Colebatch A.N., Baird J., Kiely P., Quinn M., Choy E., Edwards C.J. (2010) The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology,* no 49 (2), pp. 295–307.
17. Naranjo A., Sokka T., Descalzo M.A., Calvo-Alén J., Hørslev-Petersen K., Luukkainen R.K., Pincus T. (2008) Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis research & therapy,* no 10(2), pp. 1–10.
18. Roubille C., Richer V., Starnino T., McCourt C., McFarlane A., Fleming P., Haraoui B. (2015) The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Annals of the rheumatic diseases,* no 74 (3), pp. 480–489.
19. Shea B., Swinden M.V., Ghogomu E.T., Ortiz Z., Katchamart W., Rader T., Tugwell P. (2014) Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *The Journal of rheumatology,* no 41 (6), pp. 1049–1060.
20. Weinblatt M.E., Fraser P. (1989) Elevated mean corpuscular volume as a predictor of hematologic toxicity due to methotrexate therapy. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* no 32 (12), pp. 1592–1596.
21. Shodikulova G.Z., Pulatov U.S., Ergashova M.M., Tairova Z.K., Atoev T.T. (2021) The Correlation among Osteoporosis, Calcium-Phosphore Metabolism and Clinical Symptoms of Main Disease in Patients with Rheumatoid Arthritis. *Annals of the Romanian Society for Cell Biology,* pp. 4185–4190.
22. Kireev V.V., Sultonov I.I. (2021) Genetic Engineered Preparations – An Innovative Approach in the Treatment of Rheumatoid Arthritis. *Annals of the Romanian Society for Cell Biology,* pp. 4114–4119.