Methotrexate treatment lowers blood pressure over time in patients with rheumatoid arthritis

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Background

Treatment with methotrexate (MTX) has been shown to be associated with lower cardiovascular risk and lower blood pressure (BP) compared with other disease modifying anti-rheumatic drugs (DMARDs) in cross-sectional and epidemiological studies in patients with rheumatoid arthritis (RA) [1,2]. However, the evidence in longitudinal, randomized trials is lacking. We sought to address this issue by performing a randomized trial comparing the effect of MTX on BP against a control group on sulfasalazine

Aim

To perform a randomised blind trial to examine the effects of methotrexate therapy on blood pressure over time compared with the effect of sulfasalazine treatment in a cohort of patients with rheumatoid arthritis.

Methods

Adult treatment-naïve patients, recently diagnosed with RA according to the 2010 ACR/EULAR criteria, were randomized to clinically guided doses of subcutaneous MTX (Group 1, n=31, age 57±15 years, 65% females) or the DMARD sulfasalazine (SSZ, Group 2, n=31, age 54±17 years, 58% females). Clinic systolic (SBP, primary study endpoint), diastolic (DBP), and mean arterial pressure (MAP), and the augmentation index (AIx), (a marker of arterial wave reflection) were measured at baseline (before treatment), and after 1 and 6 months (ClinicalTrials.gov: NCT03254589).

Results

At baseline, the two groups were matched for age, gender, body mass index, and 28-joint disease activity score (p>0.05 for all comparisons). After 1 month of treatment, group 1 had a trend towards a significant reduction in SBP (mean difference -2.6±10.6 mmHg, p=0.09) and DBP (mean difference -1.8±6.7 mmHg, p = 0.053) and a significant reduction in MAP (mean difference -2.1±7.5 mmHg, p=0.049) compared to Group 2. After 6 months of treatment, group 1 had a significant reduction in SBP (mean difference -4.0±10.8 mmHg, p=0.038) and MAP (mean difference -4.3±17.9 mmHg, p=0.023) and a trend towards a significant reduction in DBP (mean difference -0.7±6.82 mmHg, p=0.053). There were no significant between-group differences in AIx over time

Table 1 Baseline clinical and demographic characteristics of the MTX (group 1) and the SSZ (group 2) groups.

Variable	Group 1	Group 2	*p* value
Age	57 ± 15	54 ± 17	ns
Gender (% of female)	65	58	ns
BMI (Kg/m²)	30 ± 6	31 ± 8	ns
Clinical peripheral SBP (mmHg)	126.7 ± 15.7	122.2 ± 19.0	ns
Clinical peripheral DBP (mmHg)	82.9 ± 9.5	80.7 ± 9.3	ns
Clinical peripheral PP (mmHg)	43.8 ± 14.1	41.4 ± 16.3	ns
Clinical peripheral HR (pulse/min)	70 ± 12	70 ± 10	ns
AI@75 (%)	23 ± 9	21 ± 13	ns
24h peripheral PWV (m/s)	8.4 ± 2.1	8.2 ± 2.1	ns
Patient global health VAS (mm)	50 ± 23	56 ± 23	ns
DAS28 - CRP	4.73 ± 1.20	5.00 ± 0. 83	ns
DAS28 - ESR	5.29 ± 1.44	5.31 ± 1.22	ns
CRP	4.0 ± 3.6	7.0 ± 7.4	ns
ESR	24 ± 17	24 ± 21	ns

Table 2 . Differences between MTX-group (group 1) and SSZ group (group 2) after 1 month and 6 months treatment.

	Differences (mean ± SD) between Group 1 and Group 2 after 1 month	*p* value	Differences (mean ± SD) between Group 1 and Group 2 after 6 months	*p* value
Clinical peripheral SBP (mmHg)	-2.6 ± 10.6	.09	-4.0 ± 10.8	.038*
Clinical peripheral DBP (mmHg)	-1.8 ± 6.7	.053	-0.7 ± 6.8	.053*
Clinical peripheral PP (mmHg)	-.8 ± 7.2	ns	-4.8 ± 11.3	ns
Clinical peripheral MAP (mmHg)	-2.1 ± 7.5	.049	-4.3 ± 17.9	.023*
AIx (%)	-1.1 ± 1.6	ns	-0.5 ± 1.6	ns

*Not corrected for ties

MTX, methotrexate; SSZ, sulfasalazine; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure.

Conclusion

The results of this study provide the first evidence that MTX treatment causes a significant reduction in SBP (primary endpoint) at 6 months in RA patients in intervention studies. The effects of MTX on BP are not mediated by changes in arterial wave reflections. Further research is warranted to identify the mechanisms involved in the MTX-induced BP lowering effects and whether such effects account for the protective effects of MTX against cardiovascular disease observed in RA.

References

Roubille C, Richer V, Starnino T, et al. 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. *Ann Rheum Dis* 2015; 74: 480-489. DOI: 10.1136/annrheumdis-2014-206624.

Xie F, Chen L, Yun H, et al. Benefits of Methotrexate Use on Cardiovascular Disease Risk Among Rheumatoid Arthritis Patients Initiating Biologic Disease-modifying Antirheumatic Drugs. *J Rheumatol* 2021; 48: 804-812. 20201015. DOI: 10.3899/jrheum.191326.

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