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DOES SILDENAFIL IMPROVE ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS? – A PILOT CLINICAL TRIAL

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Background: Rheumatoid arthritis (RA) is independently associated with an increased risk of cardiovascular disease (CVD). One of the early stages of atherosclerosis is endothelial dysfunction, which is increased in RA. Using drugs to target endothelial dysfunction is a promising novel strategy for CVD prevention in RA. Sildenafil has been shown to improve endothelial function in diabetics, who have similar increased CVD risk. Our hypothesis was that sildenafil use may be a novel primary CVD prevention strategy in RA.

Objectives: To determine if sildenafil use in RA patients improves endothelial dysfunction (as measured by brachial artery flow-mediated dilation [FMD] and peripheral arterial tone [PAT]), as well as serum inflammatory and atherosclerosis biomarkers.

Methods: This NIH-funded study was a phase II, randomized double-blind placebo-controlled crossover efficacy trial of 25 RA patients, with no known history of CVD, but at least one traditional CVD risk factor. Patients were randomized 1:1 to receive either sildenafil or placebo for 3 months, then after a 2-week washout, crossed over to each respective group for an additional 3 months. Vascular studies (FMD and PAT) and serum atherosclerosis biomarkers (e-Selectin, ICAM-1, VCAM-1) were performed at baseline, 3 months pre- and post-washout, and 6 months. Adverse events were collected. Given the cross-over design, analyses included a random effects model for within-subject comparisons of sildenafil versus placebo periods, adjusting for the baseline (FMD or EndoPAT) within that period and a term for treatment order. All tests were 2-sided with $\alpha=0.05$.

Results: A total of 233 subjects were assessed for eligibility, with 25 subjects being randomized after written informed consent. A total of 13 subjects were randomized to placebo first, and 12 to sildenafil first. Baseline characteristics were similar between those randomized to Placebo vs. Sildenafil first. Mean age was 62.0±10.9 years; 84% were female; and 92% were white. A total of 6 adverse events experienced in 3 subjects occurred. The primary endpoint (increase in %FMD in Sildenafil period vs. Placebo period) was not significant ($p=0.19$). However, note the study was powered at 80% to detect an effect size of 0.37 for change in %FMD or biomarker with a sample size of 60, not 25. However, sildenafil use was associated with a significant increase (improvement) by 0.200 units of PAT ratio ($p=0.003$) compared with placebo, adjusted by treatment order and baseline PAT ratio (within the given treatment period). Exploratory linear mixed models comparing e-Selectin, ICAM-1, and VCAM-1 between Sildenafil vs. Placebo periods, adjusted for treatment order and the baseline biomarker level, did not show any significant differences except for ICAM-1 (55.3 units higher in Sildenafil vs. Placebo periods, $p=0.011$).

Conclusion: In this pilot trial of 25 RA subjects, sildenafil use was associated with a significant increase (improvement) in endothelial function as measured by PAT. However, there was no significant difference in FMD. The study is limited due to the small sample size, which was impacted by slow recruitment as well as the COVID-19 pandemic. Future larger studies are required to assess whether other PDE5 inhibitors may improve endothelial dysfunction in RA and other autoimmune disease patients at high risk of CVD.

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A NEW QUESTIONNAIRE AND SCORE (MISA) FOR ASSESSING METHOTREXATE INTOLERANCE IN RHEUMATOID ARTHRITIS

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Background: Methotrexate (MTX) intolerance refers to unpleasant symptoms that accompany use of MTX and may lead to its discontinuation. However, it lacks a validated score in RA patients; with the only option being to use the MISS score which was validated for use in children and not adults.

Objectives: To develop and validate a questionnaire and score (s) for measuring MTX intolerance and its severity in rheumatoid arthritis.

Methods: A 10-item questionnaire called 'Methotrexate Intolerance and Severity assessment in Adults' (MISA) was validated in 105 RA patients. A score was calculated by adding the scores of first 7 questions (0 to 3 based on severity on symptoms), to last 3 questions (0 or 1); it ranged from 0 to 24 (MISA score) and was assessed for correctly classifying MTX intolerance (compared to an interview) by ROC analysis. Its area-under-curve (AUC) was compared with 'Methotrexate Intolerance Severity Score' (MISS), developed for children. Subsequently, it was administered to 414 RA patients to assess the prevalence and associations of MTX intolerance. In addition, the MISA cross-products score, that was calculated by adding the cross-products (severity (1 to 3) x duration per week (0.5 to 7 days)) of symptoms, was compared to MISA and MISS for assessing severity of intolerance.

Results: In the initial phase, 105 RA patients on MTX≥6 months were included, a majority were female (87%), mean age was 51 (13.4) years and methotrexate dose was 18.8±6 mg/week. Thirty-five (33%) were found to be intolerant to MTX based on interview. MISA score had a good predictive ability (AUC of 0.904), to correctly classify MTX intolerance, and was better than MISS score (AUC of 0.823) (Figure 1A). The optimal cut-off for MISA was ≥1, with a sensitivity and specificity of 91.4% and 84.3%. Using the MISA score (≥1), 38.4% of 414 RA patients were found to have MTX intolerance: with nausea, lethargy and irritability being common symptoms. (Figure 1B, C) On multivariable analysis, age (OR 0.972) and BMI (OR 1.061) were significant predictors of MTX intolerance. (Table 1) On assessing for severity of intolerance, MISA cross product score performed the best, with an area-under-curve of 0.899 (95% CI 0.831-0.966), being higher than AUC for MISS and MISA score which were 0.847 (95% CI 0.768-0.927) and 0.837 (95% CI 0.754-0.920).

Conclusion: MISA is the first validated questionnaire for assessing methotrexate intolerance in rheumatoid arthritis, with the MISA score having a good accuracy (at cut-off ≥1), to detect MTX intolerance. Methotrexate intolerance was present in more than one-third of RA patients, with nausea, lethargy and irritability being most common.

Table 1. Baseline characteristics of 414 RA patients.

Variable	All (n=414)	Tolerant (n=255)	Intolerant (n=159)	p-value tol. vs intoler.	P-value multivariable model
Females, n (%)	370 (89)	231 (91)	139 (87)	0.31	
Age, yrs, mean (SD)	50 (12.5)	51.2 (12.6)	48.2 (12.2)	0.016*	0.008**
Duration of RA, yrs, mean (SD)	10.0 (7.0)	10.8 (7.4)	9.6 (6.3)	0.168	
BMI, Kg/m ² , mean (SD)	24.0 (4.9)	23.6 (4.9)	24.6 (4.7)	0.107	0.03*
RF positive ^b , n (%)	300 (73)	191 (82)	109 (78)	0.29	
CD4I, mean (±SD)	14.0 (11.8)	14 (12.1)	14.1 (11.4)	0.69	
Dose of MTX, mg/wk, mean (SD)	18.6 (5.6)	18.6 (5.5)	18.7 (5.8)	0.83	
Injectable MTX, n (%)	47 (11)	25 (10)	22 (14)	0.21	
Use of FA, n (%)	395 (95)	241 (95)	154 (97)	0.27	
Use of other DMARD, n (%)	272 (66)	160 (62)	112 (70)	0.11	
HCQ n (%)	209 (51)	123 (48)	86 (54)	0.25	
Prednisolone n (%)	156 (38)	87 (34)	69 (43)	0.058	0.21
Using antiemetics, n (%)	12 (3)	1 (0.5)	11 (7)	<0.001	

^a Available for 262 patients ^b Available for 372 patients