**Persistence to methotrexate treatment in early RA has a familial component**

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***Objectives:*** To assess whether persistence to treatment with methotrexate in early RA is correlated within first-degree relatives with rheumatoid arthritis (RA), and to estimate the potential heritability of such persistence.

***Methods:*** Individuals diagnosed with RA 1999-2019 and starting methotrexate in monotherapy were identified through the Swedish Rheumatology Quality Register, which has an estimated coverage of ≥ 85% of the RA patients in Sweden. We then identified all first-degree relatives of these patients via linkage to the Swedish Multi-Generation Register, and thus also those concordant for RA and treatment with methotrexate. Persistence to methotrexate in monotherapy at 1 and 3 years after treatment start was defined as remaining on treatment with no prescriptions of other disease modifying anti-rheumatic drugs at days 365 and 1096, respectively. We assessed associations of family history through relative risks (RR) with 95% confidence intervals (CI) estimated through log-binomial regression with robust standard errors accounting for dependencies within the data. Assuming a liability threshold model and no shared environment, estimates of the narrow-sense heritability were produced using tetrachoric correlations. To further assess the familiality of persistence to methotrexate over time we performed an exploratory analysis estimating the familial aggregation of European League Against Rheumatism (EULAR) response at 3 and 6 months. Additionally, to mimic what would be possible to assess in a clinical setting, we assessed the familial aggregation within a sub-cohort where only the patient that started their treatment after their first-degree relative were considered. We also performed a sensitivity analysis within a cohort diagnosed 2006-2018 where methotrexate treatment persistence was validated against the Prescribed Drug Register and incident RA-status against the National Patient Register.

***Results:*** Within our study cohort (N = 354 with RA and a first-degree relative with RA), 252 (72%) were female and the average age at start of methotrexate was 57 years (IQR: 22); 231 (67%) and 175 (50%) individuals were persistent at one and three years respectively. Familial persistence was not associated with persistence at one year (RR = 1.02, 95% CI 0.87-1.20) though an association was found for three years (RR = 1.41, 95% CI 1.14-1.74). Heritability was estimated to 0.08 and 0.58 for persistence at one and three years, respectively, though standard errors were large. No significant associations were found with family history and EULAR response at 3 and 6 months, nor within the clinical setting cohort. Results remained stable across sensitivity analyses.

***Conclusions:*** Our results indicate that persistence to methotrexate in monotherapy aggregates within families of early RA patients and that the magnitude of this aggregation increases over time.