**Does persistence to methotrexate treatment in rheumatoid arthritis run in families?**

**Background**

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder primarily manifesting in the joints of the body. The progressive nature of the disease leads to joint deterioration and physical disability within the affected individual, though early and appropriate treatment can help reduce inflammation, mitigate deterioration of joints and improve general quality of life [Smolen]. Currently, the first-line treatment for newly diagnosed patients is methotrexate (MTX) in mono-therapy [EULAR, ACR]. However, this approach does not take the innate heterogeneity of RA into account and only about 30% exhibit a good response to treatment after 3 months [Saevarsdottir]. As rapid and efficient treatment is crucial to slow disease progression and prevent irreversible joint damage, early-stage identification of those who will not have a satisfactory response to MTX in monotherapy, and might be better off on other treatments, is of utmost importance.

The existence of a familial component behind RA has been well documented within the literature [Frisell 1, 2, 3]. However, evidence of a similar familial component within aspects of the clinical presentation of the disease, such as disease severity or treatment response, has so far been limited [Frisell 1, 4]. For persistence to MTX in monotherapy, a previous study found that family history of RA alone was unable to predict persistence to MTX in monotherapy, though the study did not take family history of treatment response into account [Frisell 4].

In this study we will investigate the familial aggregation of persistence to MTX in monotherapy both through estimates of familial risks and heritability of persistence. Additionally, we will assess family history of persistence as a predictor for persistence to MTX in monotherapy in the index patient. Evidence of familial aggregation would allow for early identification of patients more likely to respond well to MTX through assessment of their family history of treatment of the disease. Here, we will use data on first-degree relatives concordant for treatment with MTX in monotherapy, obtained from a Swedish nation-wide register-linkage.

**Methods**

*Materials*

We will use data from the Swedish Rheumatology Quality register (SRQ) (n = 52,910) linked to various national registries. Established in 1995, the SRQ is a nation-wide clinical quality register including individuals aged 16 and above that meet the 1987 American College of Rheumatology criteria for RA [ACR87]. Coverage is considered high, with estimates putting the register at above 85% coverage for all prevalent patients with RA in Sweden [SRQ]. The SRQ contains extensive baseline as well as longitudinal information including data on patient characteristics, disease activity as well as prescribed drug treatments. Identification of first-degree relatives will be done through linkage to the Multi-Generation Register, a Swedish national register containing information on parenthood for residents born after 1931 and registered as living in Sweden since 1961. Through such a linkage, siblings can be identified as individuals sharing biological parents. Register coverage is high, with close to perfect coverage for individuals born in Sweden after 1961 [MGR].

Our cohort will consist of first-degree relative pairs concordant for early-onset RA with MTX in monotherapy as their first prescribed treatment. Inclusion will be restricted to individuals born in 1932 or after and who were included into SRQ between 1999 and 2018. Early-onset RA will be defined as having symptom onset less than 12 months prior to inclusion, where RA will be identified as diagnosed by the treating rheumatologist per the ACR1987 or EULAR2010 criteria [ACR87, EULAR10]. Patients will be considered eligible if they had been treated with MTX as their first ever DMARD without any additional DMARDs within 30 days of the first prescription. This does not include patients treated with MTX in combination with glucocorticoids or nonsteroidal anti-inflammatory drugs. See Figure 1 for a visualization of the full data extraction. Persistence to MTX in monotherapy will be defined as a binary variable in two versions: persistence at one and three years respectively, where an individual is considered persistent if they are still being treated with MTX in monotherapy at 365 or 1096 days after their first prescription without prior treatment history with other DMARDs, as recorded in SRQ. Furthermore, we will perform an exploratory analysis of the association between persistence and EULAR response at 3 and 6 months within the first-degree relatives [EULAR Response 1, 2]. Relatives will be considered responders if they had achieved a good or moderate EULAR response at evaluation, where they otherwise, or if a treatment switch had occurred, will be considered non-responders

For our analysis of the predictive capabilities of a family history of MTX in monotherapy, we will filter the cohort into a set of index patients. These will be defined as all individuals with a first-degree relative starting MTX in monotherapy at least one or three years prior to the index patient (for assessment of persistence at one and there years respectively) with family history defined as a binary variable.

In the addition to the above described analyses, we will extract two secondary cohorts for replication and sensitivity purposes. In the first sensitivity cohort we will consider exclusively full-sibling pairs while in the second we will keep only individuals included into SRQ between 2006 and 2018, where both RA diagnosis and first-line treatment with MTX in monotherapy will be additionally validated against the National Patient Register and the Prescribed Drug Register.

*Statistical analysis*

Treatment persistence of subjects will be treated as outcome with persistence of the first-degree relative as exposure. Familial aggregation of persistence to treatment with MTX in monotherapy within early RA will be estimated using tetrachoric correlation. We will additionally fit a log-binomial regression model to estimate the familial risks of treatment persistence given the patients’ family history of MTX persistence. Logistic regression will be employed for the exploratory analysis as log-binomial regression suffers from convergence issues within the sub-cohorts. For the former model, a robust sandwich variance estimator will be employed to account for familial clustering, as each individual may have more than one first-degree relative. Covariates to adjust for include sex, age and year of diagnosis, where age will be binned into three categories for the log-binomial regression to avoid convergence issues. All statistical analysis will be carried out for both definitions of persistence. To assess sensitivity of our results, analysis will additionally be repeated within the two replication cohorts where we only considered the familial aggregation within full-siblings as well as individuals included into the SRQ between 2006-2018, where we also will use the Prescribed Drug Register to validate the treatment status.

Extraction of the study cohort from the previously mentioned registers will be done in SAS version 9.4, with the statistical analyses performed with R version 4.0.2.

**Preliminary results**

We found a total of 15,855 early RA patients prescribed MTX in monotherapy as their first treatment. Among these, we identified 310 individuals with a first-degree relative concordant for both early RA and treatment, taken here as the working study cohort. Only six of these had more than one first-degree relative. The majority of first-degree relatives were siblings, with siblings in ~43% of pairings, offspring in ~29% of pairings and otherwise a parent (~18% and ~11% mothers and fathers respectively). The distribution of individuals into categories of persistent and non-persistent, as well as further cohort characteristics, can be found in Table 1a below. The groups were generally comparable, both when comparing between persistent/non-persistent and between persistence at one and three years. The non-persistent individuals were generally more often women and started treatment at an earlier age. Early onset RA and being female are both risk factors for increased disease severity which could explain the slight imbalance observed here [Saevarsdottir, Katchamart]. Being seropositive is also a known characteristic associated with increased disease severity [Katchamart] though only negligible differences were here discerned between the two groups.

For the analysis of prediction we identified 138 and 102 index patients respectively, who had a first-degree relative starting treatment at least one or three years prior to treatment start within the index patient. Cohort characteristics of the index patients can be found in Table 1b below. Distributions are generally similar to those of the full cohort observed in Table 1a with slightly fewer seropositive cases (most likely a result of the majority of individuals with missing serostatus remaining among the index patients). One major distinguishing factor is the much later year of MTX treatment start; this is an expected result of using only individuals with first-degree relatives treated prior to their own treatment start as index patients.

**Author list**

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| TABLE 1A: COHORT CHARACTERISTICS | PERSISTENCE AT 1 YEAR | | PERSISTENCE AT 3 YEARS | |
|  | PERSISTENT | NOT PERSISTENT | PERSISTENT | NOT PERSISTENT |
| N (%) | 198 (65%) | 106 (35%) | 150 (49%) | 154 (51%) |
| Female (%) | 137 (69%) | 80 (75%) | 101 (67%) | 116 (75%) |
| SERO+ (%) | 142 (74%) | 75 (72%) | 105 (72%) | 112 (74%) |
| Mean age at MTX-start (SD) | 59 (15) | 54 (15) | 61 (14) | 54 (15) |
| Median year of subject MTX-start (Q1 – Q3) | 2011 (07 – 15) | 2011 (05 - 15) | 2012 (06 – 15) | 2011 (06 – 15) |
| Median number of first-degree relatives (Q1 – Q3) | 4 (3 – 5) | 4 (3 - 5) | 4 (2 – 5) | 4 (3 – 5) |

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| TABLE 1B:  INDEX PATIENT CHARACTERISTICS | PERSISTENCE AT 1 YEAR  (n = 138) | | PERSISTENCE AT 3 YEARS  (n = 102) | |
|  | PERSISTENT | NOT PERSISTENT | PERSISTENT | NOT PERSISTENT |
| N (%) | 92 (66%) | 46 (33%) | 44 (43%) | 58 (57%) |
| Female (%) | 64 (70%) | 33 (72%) | 30 (68%) | 43 (74%) |
| SERO+ (%) | 60 (67%) | 29 (66%) | 28 (67%) | 37 (66%) |
| Mean age at MTX-start (SD) | 60 (15) | 53 (15) | 62 (14) | 58 (54) |
| Median year of subject MTX-start (Q1 – Q3) | 2015 (11 – 16) | 2015 (11 – 17) | 2015 (13 – 17) | 2015 (11 – 17) |
| Median number of first-degree relatives (Q1 – Q3) | 4 (3 – 5) | 4 (3 – 4) | 4 (3 – 5) | 4 (3 – 5) |

**Figure 1:**

**N = 87,690**

Unique individuals

Excluded any **non-unique** (duplications)

START: **N =** **87,692** individuals

(SRQ\_basdata)

**N = 310**

Individuals with a first-degree relative concordant for early RA and mono-MTX as first treatment

**N = 15,855**

Ordinated mono-MTX as their first treatment

Excluded all individuals that were **not prescribed mono-MTX as their first treatment.**

Extracted all individuals that **had a first-degree relative** within the current data set.

Excluded all individuals **included** into SRQ **more than a year from their first RA visit**

**N = 20,444**

Included into SRQ less than a year prior to, or after first RA visit

Excluded all **non-early-onset RA** patients

**N = 20,663**

Early RA patients

**N = 50,796**

Included into SRQ between 1999 and 2018

Excluded all individuals **included** into SRQ **prior to 1999 and after 2018**

**N = 52,910**

RA patients

Excluded any **non-RA** patients