A GENOME WIDE INVESTIGATION OF PERSISTENCE TO TREATMENT WITH METHOTREXATE IN SWEDISH EARLY RHEUMATOID ARTHRITIS PATIENTS

A. Öberg Sysojev1, S. Saevarsdottir1,2, L. M. Diaz-Gallo3, L. Alfredsson4, L. Klareskog5, SRQ Biobank Group5, T. Frisell1, L. Padyukov3, J. Askling1,6, H. Westerling7 on behalf of Swedish Rheumatology Quality Register Biobank Group. 1Karolinska Institute, Clinical Epidemiology Division, Department of Medicine Solna, Stockholm, Sweden; 2University of Iceland, Faculty of Medicine, School of Health Sciences, Reykjavik, Iceland; 3Karolinska Institute, Division of Rheumatology, Department of Medicine Solna, Stockholm, Sweden; 4Karolinska Institute, Division of Environmental Medicine, Stockholm, Sweden; 5Karolinska Institute, Department of Medicine, Solna, Stockholm, Sweden; 6Department of Rheumatology, Theme Infection and Inflammation, Stockholm, Sweden

Background: Despite being the anchor drug for treating rheumatoid arthritis (RA), methotrexate (MTX) provides a good response only in some of the treated patients [1]. If MTX treatment outcome has a substantial genetic component, genetic variants could provide useful predictors for identification of patients likely to respond and remain on treatment. So far, studies have focused mainly on primary response, and attempts to explain the inter-patient variability through genetic variants have been inconclusive or underpowered [2,3].

Objectives: We aimed to investigate whether there are genetic variants associated with persistence to treatment with MTX (at one and three years) in early RA, and to estimate any underlying heritability.

Methods: We conducted a genome-wide association study (GWAS) on persistence to treatment with MTX in DMARD-monotherapy. We included participants from the Epidemiological Investigation of RA (EIRA) study and the Swedish Rheumatology Quality Register Biobank Group. 75% of the participants were treated with MTX as their first ever DMARD. Persistence to MTX was defined as remaining on treatment at one and three years, respectively, with no additional DMARDs added during that period. Estimation of SNP-based heritability was done using restricted maximum likelihood. We performed the analyses for all RA, and two disease subsets: those positive for either ACPA or rheumatoid factor, and those negative for both.

Results: After quality control, 3403 of an initial 3609 early RA patients of European ancestry and above five million SNPs remained for the primary analysis. Among these, 65% were persistent at one year, and 44% were persistent at three years. In secondary analysis we excluded 218 patients due to missing sero-status. Of the remaining, 72% were seropositive. No SNP reached genome-wide significance for persistence at one year (OR = 1.02, 95% CI 0.98-1.06). No SNP reached genome-wide significance for persistence at three years. Analyses stratified by sex showed no association. No SNP reached genome-wide significance for persistence in the seropositive group at one year (OR = 0.98, 95% CI 0.90-1.07) and three years (OR = 0.98, 95% CI 0.90-1.06) while point estimates for the seronegative heritability were zero for both persistence outcomes.

Conclusion: Despite being the largest GWAS on an MTX treatment outcome to date, no genome-wide significant associations were detected. The low heritability observed along with the lack of strong independent associations, may indicate that genetic influence is not from common genetic variants on persistence to MTX is minor, and of a polygenic nature.

REFERENCES:

Acknowledgements: The authors would like to thank the participants of the EIRA study and the SRQ biobank as well as deCODE genetics for making this study possible.

Disclosure of Interests: Anton Öberg Sysojev: None declared, Saedis Saevarsdottir Employee of: Part-time employee of deCODE genetics Inc., Lina M. Diaz-Gallo: None declared, Lars Alfredsson: None declared, Lars Klareskog: None declared, - SRQ Biobank Group: None declared, Thomas Frisell: None declared, Leonid Padyukov: None declared, Johan Asling: None declared, Pfizer, Axell Finckh: Speakers bureau: AF reports honoraria and consultancies from Pfizer, Abbvie, BMS, Eli Lilly, Galapagos, Samsung Bioepis, and Sanofi., Helga Westerling: None declared, Pfizer INC, AbbVie, Galapagos, Eli Lilly


OP2067

OP2068

COMPARISON OF MAJOR CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS IN SAFETY REPORTS BETWEEN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH JAK INHIBITORS VERSUS ANTI-TNF: RESULTS FROM VIGIBASE

F. Montastruc1, C. Flumian2, Y. Degboe3, A. Constantin4, A. Ruyssen-Witrand2. 1Toulouse University Hospital, Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Centre d’Investigation Clinique 1436, Team PEPPS « Pharmacologie En Population cohortes et biobanqueS », Toulouse, France; 2Toulouse University Hospital, Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology,Toulouse, France; 3Toulouse University Hospital, Rheumatology Center, Inserm UMR Infinity. Paul Sabatier University, Toulouse, France; 4Toulouse University Hospital, Rheumatology Department, Centre d’Investigation Clinique 1436, Team PEPPS « Pharmacologie En Population cohortes et biobanqueS », Toulouse University Hospital, Toulouse, France

Background: Recently, awareness has raised regarding JAK inhibitor safety in rheumatoid arthritis (RA), in particular with tofacitinib. Indeed, in a trial involving more than 4,000 patients (ORAL Surveillance), a numerically higher number of major cardiovascular events (MACEs) in patients treated with tofacitinib compared to anti-TNF (1), and a higher risk of venous thromboembolic events (VTE) in patients treated with tofacitinib 10mg twice a day compared to patients treated with tofacitinib 5mg twice a day or anti-TNF was observed. This increased risk of MACEs was also suspected in another study performed on American Health databases (2). Recently, the FDA extended warnings and use’s recommendations to other JAK-inhibitor drugs (3).

Objectives: To corroborate these safety warnings, we compared the reporting MACES and VTEs with JAK inhibitors versus anti-TNF alpha drugs from the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database (VigiBase).

Methods: We selected reports in Vigibase of patients aged between 18 and 75 years, between 01/01/2011 and 12/31/2020, with JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib) or anti-TNF (etanercept, adalimumab, infliximab, certolizumab pegol, golimumab) with a diagnosis of RA. In these reports we selected MACES including myocardial infarction, strokes and cardiovascular deaths and VTE including deep venous thromboses (DVT) and pulmonary embolisms (PE). Characteristics of reports including age of patients, country of declaration, drug involved, co-reported drugs, and type of event were described. The reporting risk was investigated using disproportionality analyses and expressed as Reporting Odds Ratios (ROR) with 95% Confidence Interval (95%CI). A sensibility analysis was performed stratifying by age category (≥ 65 years, ≥ 50 years), and by sex.

Results: Of the 11,455,891 reports in patients aged between 18 and 75 years in the period of interest, 39,097 of reports were for a JAK-inhibitor in RA (mean age 60.6 years, SD:16.3) and 231,860 of reports were for an anti-TNF in RA (mean age: 57.2 years, SD: 13.0). Most of the reports came from USA and Canada (respectively 77.4% and 12.5% for JAK-inhibitor and 86.4% and 2.6% for anti-TNF). Among the reports, 611 (1.5%) in JAK-inhibitor treated patients and 3240 (1.4%) in anti-TNF treated patients were MACES.