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OP0267 A GENOME-WIDE INVESTIGATION OF PERSISTENCE TO TREATMENT WITH METHOTREXATE IN SWEDISH EARLY RHEUMATOID ARTHRITIS PATIENTS

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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's biobank, diagnosed with early RA and 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, neither for persistence at one nor at three years. The SNP-based heritability was estimated to 0.35 (95%CI 0.04-0.65) for persistence at one year and 0.09 (95%CI 0.00-0.37) for persistence at three years. Analyses stratified by sero-status provided results comparable to the main analysis with similar proportions of persistent patients and no SNP reaching genome-wide significance for any of the subgroups. Point estimates of heritability for persistence in the seropositive group at one year (h^2 = 0.08, 95%CI 0.00-0.51) was lower than for seropositive persistence at three years (h^2 = 0.19, 95%CI 0.00-0.62) 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 from common genetic variants on persistence to MTX is minor, and of a polygenic nature.

REFERENCES:

[1] Saevarsdottir, S., et al., Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis, 2011. **70**(3): p. 469-75.

[2] Ling, S., J. Bluett, and A. Barton, *Prediction of response to methotrexate in rheumatoid arthritis.* Expert Rev Clin Immunol, 2018. **14**(5): p. 419-429.

[3] Szostak, B., et al., *Using pharmacogenetics to predict methotrexate response in rheumatoid arthritis patients.* Expert Opin Drug Metab Toxicol, 2020. **16**(7): p. 617-626.

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OP0268 COMPARISON OF MAJOR CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS IN SAFETY REPORTS BETWEEN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH JAK INHIBITORS VERSUS ANTI-TNF: RESULTS FROM VIGIBASE

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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 (1.6%) in JAK-inhibitor treated patients and 3240 (1.4%) in anti-TNF treated patients were MACEs

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while 341 (0.9%) in JAK-inhibitors and 571 (0.2%) in anti-TNF treated patients were VTE. Disproportionality analyses identified an increased risk of reporting VTE events in JAK-inhibitors compared to anti-TNF (DVT: ROR = 3.99 [95%CI: 3.15-5.04], PE: ROR = 3.47 [2.90-4.13], Figure 1). This risk was not modified after stratification by age or sex. No increased ROR for MACE was found.

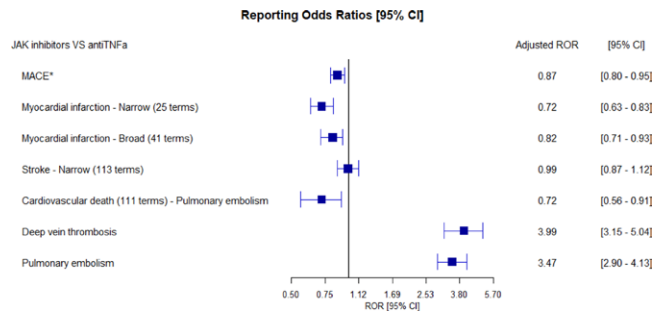

Figure 1.

Conclusion: Based on real-world data, the analysis did not identify an increase of declaration of MACEs with JAK-inhibitor compared to anti-TNF whereas we could observe more than three times declarations of VTE in Vigibase with JAK-inhibitors compared to anti-TNF.

REFERENCES:

[1] Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022;386(4):316-26.

[2] Khosrow-Khavar F, Kim SC, Lee H, Lee SB, Desai RJ. Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. Ann Rheum Dis. 2022.

[3] FDA. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. https://wwwfdagov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death. 2021.

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OP0269 BIOMARKERS TO PREDICT RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING TOFACITINIB OR TUMOUR NECROSIS FACTOR INHIBITORS

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Background: In the ORAL Surveillance study of patients (pts) aged ≥50 yrs with moderate to severe rheumatoid arthritis (RA) and ≥1 additional cardiovascular risk factor (NCT02092467), the incidence of pulmonary embolism was higher with tofacitinib than with tumour necrosis factor inhibitors (TNFi).1

Objectives: To explore whether biomarkers explained the associations of tofacitinib vs TNFi with venous thromboembolism (VTE) in ORAL Surveillance.

Methods: ORAL Surveillance was a prospective, open-label, event-driven, non-inferiority, post-authorisation safety study. Pts were randomised 1:1:1 to receive tofacitinib 5 or 10 mg twice daily or a TNFi (adalimumab 40 mg every 2 weeks or etanercept 50 mg once weekly). For this exploratory post hoc analysis, 294 soluble, proteomic, genetic and antibody biomarkers were assessed (of which 79 have a known role in inflammation, coagulation, vascular biology and/or Janus kinase signalling). Biomarkers were quantified in serum collected at baseline (BL) and Month (M)12 in VTE cases and 4:1 matched controls. D-dimer was analysed with a larger control group (all eligible pts without VTE) and final adjudicated data from BL, M12 and study end.

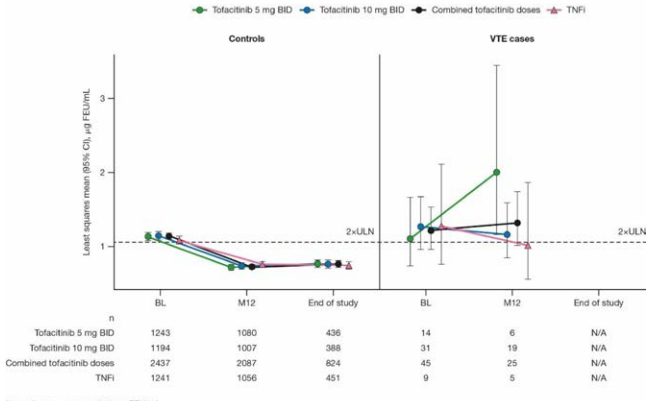
Results: Of the 4362 randomised and treated pts, D-dimer was quantified in 3732 pts (54 with VTE; 3678 without) and the remaining biomarkers were analysed in 285 pts (57 VTE cases; 228 matched controls). BL characteristics were generally similar in those with or without VTE and between treatment groups. At BL, D-dimer levels were ≥2×upper limit of normal for ~50% of controls and 67% of VTE cases. Mean D-dimer levels decreased from BL to M12 in controls across treatment groups (Figure 1). Key findings from the biomarker analyses are shown in the Table 1. No biomarker showed a clear mechanistic association with the increased risk of VTE for tofacitinib vs TNFi, or demonstrated adequate performance for prognostic use in pts with RA.

Table 1. Summary of results from biomarker analyses

Biomarker	Key results
Tier 1	
C-reactive protein	• No association with VTE in any treatment arm at BL or M12
D-dimer Thrombopoietin	• Higher M12 levels were prospectively associated with greater risk of subsequent VTE with tofacitinib 10 mg BID ○ For D-dimer, the same effect was observed with tofacitinib 5 mg BID • Treatment specificity of effects could not be established
Tier 2	
Factor VIII Thrombin–antithrombin complex Tissue factor pathway inhibitor Plasminogen activator inhibitor-1 Protein C Antithrombin Apolipoprotein C-III Leptin	• No clinically meaningful differences across treatment arms
Tiers 3 & 4	
Exploratory proteomic assays (276 markers from multiplex panels)	• Two biomarkers with no known relationship to VTE (angiogenin and TNFSF13B) showed significant associations with pulmonary embolism in the tofacitinib 10 mg BID arm ○ Treatment specificity of effects could not be established for either analyte
Genetic biomarkers	
Factor V Leiden R506Q, prothrombin G20210A and JAK2 V617F mutations	• Factor V Leiden and prothrombin risk alleles, individually or combined, were associated with increased incidence of VTE but did not explain excess events with tofacitinib • No VTE cases or matched controls had the JAK2 mutation
Antibody biomarkers	
ACA IgG and IgM, anti-β2GP1 IgG and IgM	• No statistical differences were observed between treatment arms or between VTE cases and matched controls

ACA, anticardiolipin antibody; β2GP1, beta-2-glycoprotein 1; IgG, immunoglobulin G; IgM, immunoglobulin M; JAK2, Janus kinase 2; TNFSF13B, tumour necrosis factor ligand superfamily member 13B

Fig. Least squares mean (95% CI) values of D-dimer by treatment arm in VTE cases and controls at BL, M12 and end of study



Normal assay range: <0.53 µg FEU/mL
VTE events included deep vein thrombosis and pulmonary embolism
Data collected after pts who were randomised to tofacitinib 10 mg BID had their dose reduced to 5 mg BID were included in the tofacitinib 10 mg BID group
The TNFi group received adalimumab 40 mg every 2 weeks (US, Puerto Rico and Canada) or etanercept 50 mg once weekly (rest of the world)
The end of study visit was conducted within 1 month of study completion, which was declared when the targeted number of major adverse cardiovascular events and malignancies (excluding non-melanoma skin cancer) had been met. The median duration of treatment was 44 months. To exclude the confounding effect of anticoagulant therapy, M12 samples were not analysed in pts with early VTE events (before M12) and end of study samples were not analysed in VTE cases
BID, twice daily; CI, confidence interval; FEU, fibrinogen equivalent units; N/A, not available; ULN, upper limit of normal

Conclusion: This post hoc exploratory analysis did not identify biomarkers at BL or M12 that explain the increased VTE risk for tofacitinib vs TNFi. Notably, ORAL Surveillance was neither designed nor powered to compare the risk of VTE across treatments or to identify biomarkers with a mechanistic relationship

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