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FRI0045

DISEASE ACTIVITY TRAJECTORIES FOR EARLY AND ESTABLISHED RHEUMATOID ARTHRITIS: DATA FROM THE OBRI REGISTRY

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Background: Description of disease activity status in patients with rheumatoid arthritis (RA) at fixed points in time modelled as continuous (e.g. number of swollen joints counts), dichotomous variable (e.g. remission or low disease status using composite measures) do not reflect the patient's disease course in chronic and relapsing RA.

Objectives: We proposed to describe the longitudinal disease activity trajectories for patients with early and established RA over two years' follow-up in routine clinical care.

Methods: RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) with available DAS28-ESR over two years of follow-up were included. Using a latent growth curve modelling (LCGM), subgroups of patients following distinct pattern of DAS28-ESR change over time were identified. Fit statistics and model selection was based on Bayesian information criterion (BIC).

Results: A total of 1273 patients were included, 454 (36%) with early RA and 819 (64%) with established RA. At baseline, patients with early RA were significantly younger (57.3 vs. 59.1 years) and with higher DAS28-ESR (4.6 vs. 4.3), and were less likely to have an erosion (25.0% vs. 59.7%), to be RF-positive (70.3% vs. 76.8%), and to use biologic DMARDs (7.0% vs. 29.2%).

In patients with early RA (Figure 1A), three subgroups of patients were identified by LCGM with a better fit (BIC: -3070.84). Almost 88% patients with moderate disease activity reached remission (group 1: 48.4%) or low disease status (group 2: 39.3%) after two years, while 12% of patients with high disease profile remained in a moderate state (group 3).

Figure 1. Observed and fitted trajectories from the latent growth curve analysis in patients with early and established RA.

In patients with established RA (Figure 1B), seven subgroup of patients were identified by LCGM with a better fit (BIC: -5378.13). After two years' follow-up, 37.5% of patients in remission or low disease state at baseline remained or reached to remission (group 1 and 2, respectively). Two groups of patients with high disease activity at baseline had an improvement after two years (17.3% reached remission and 9.3% reached moderate state; group 5 and 7, respectively). 16.5% of patients with high disease activity at baseline remained in high disease status after two years (group 4 and 6). 19.4% of patients with moderate activity at baseline remained in a moderate state after two years (group 3).

Conclusion: Disease course is different between early and established RA. While 70% of early RA patients with moderate or high disease profiles reached remission, only 17% of established patients with high disease activity achieved remission after two years of follow-up. These findings suggest the potential effects of receiving early treatment and health care. The impact of sociodemographic,

clinical and medication profile on disease course will be examined as future work for this study.

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FRI0046

PHARMACOGENOMICS-DRIVEN INDIVIDUALIZED PREDICTION OF TREATMENT RESPONSE TO METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A MACHINE LEARNING APPROACH

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Background: Methotrexate (MTX) is the most common anchor drug for rheumatoid arthritis (RA), but the risk of missing the opportunity for early effective treatment with alternative medications is substantial given the delayed onset of MTX action and 30-40% inadequate response rate. There is a compelling need to accurately predicting MTX response prior to treatment initiation, which allows for effectively identifying patients at RA onset who are likely to respond to MTX.

Objectives: To test the ability of machine learning approaches with clinical and genomic biomarkers to predict MTX response with replications in independent samples.

Methods: Age, sex, clinical, serological and genome-wide association study (GWAS) data on patients with early RA of European ancestry from 647 patients (336 recruited in United Kingdom [UK]; 307 recruited across Europe; 70% female; 72% rheumatoid factor [RF] positive; mean age 54 years; mean baseline Disease Activity Score with 28-joint count [DAS28] 5.65) of the PhARmacogenetics of Methotrexate in RA (PAMERA) consortium was used in this study. The genomics data comprised 160 genome-wide significant single nucleotide polymorphisms (SNPs) with $p < 1 \times 10^{-5}$ associated with risk of RA and MTX metabolism. DAS28 score was available at baseline and 3-month follow-up visit. Response to MTX monotherapy at the dose of ≥ 15 mg/week was defined as good or moderate by the EULAR response criteria at 3 months' follow up visit. Supervised machine-learning methods were trained with 5-repeats and 10-fold cross-validation using data from PAMERA's 336 UK patients. Class imbalance (higher % of MTX responders) in training was accounted by using simulated minority oversampling technique. Prediction performance was validated in PAMERA's 307 European patients (not used in training).

Results: Age, sex, RF positivity and baseline DAS28 data predicted MTX response with 58% accuracy of UK and European patients ($p = 0.7$). However, supervised machine-learning methods that combined demographics, RF positivity, baseline DAS28 and genomic SNPs predicted EULAR response at 3 months with area under the receiver operating curve (AUC) of 0.83 ($p = 0.051$) in UK patients, and achieved prediction accuracies (fraction of correctly predicted outcomes) of 76.2% ($p = 0.054$) in the European patients, with sensitivity of 72% and specificity of 77%. The addition of genomic data improved the predictive accuracies of MTX response by 19% and achieved cross-site replication. Baseline DAS28 scores and following SNPs rs12446816, rs13385025, rs113798271, and rs2372536 were among the top predictors of MTX response.

Conclusion: Pharmacogenomic biomarkers combined with DAS28 scores predicted MTX response in patients with early RA more reliably than using demographics and DAS28 scores alone. Using pharmacogenomics biomarkers for identification of MTX responders at early stages of RA may help to guide effective RA treatment choices, including timely escalation of RA therapies. Further studies on personalized prediction of response to MTX and other anti-rheumatic treatments are warranted to optimize control of RA disease and improve outcomes in patients with RA.

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