SAT0115

FLARING OF RHEUMATOID ARTHRITIS DUE TO TAPERING OF DMARDS: HOW DOES IT AFFECT PATIENTS' WELL-BEING? A STUDY ON PATIENT REPORTED OUTCOMES

Elise van Mulligen¹, Angelique Weel^{1,2}, Martijn Kuijper², Johanna Hazes¹, Annette van der Helm - van Mil^{1,3}, Pascal de Jong¹. ¹Erasmus MC, Rheumatology, Rotterdam, Netherlands; ²Maasstad Hospital, Rheumatology, Rotterdam, Netherlands; ³Leiden University Medical Center (LUMC), Rheumatology, Leiden, Netherlands

Background: Previous studies have shown that it is possible to taper DMARDs in RA patients with an inactive disease, but this is accompanied with a higher chance of disease flares. Current recommendations advise to taper DMARDs from a clinical viewpoint. However, data on the feasibility of tapering DMARDs from a patient's perspective are sparse.

Objectives: To determine the impact of flare after DMARD-tapering on patients quantifying the changes in patient relevant domains e.g. functional ability, fatigue, quality of life, and worker productivity, and to explore the duration of the effect.

Methods: Data were used from all 113 patients that flared after tapering DMARDs in the TARA study, a multicenter randomised controlled trial in which patients in sustained remission (DAS<2.4&SJC<1) tapered either their csDMARDs or TNF-inhibitor per protocol. For the current analysis, we compared the following secondary outcomes before and after flare over time; DAS44, functional ability (HAQ-DI), fatigue (BRAF-MDQ), quality of life (EQ-5D and SF36), anxiety and depression (HADS), morning stiffness, VAS general health, and worker productivity. Follow-up started three months before flare, at the moment of flare, and every 3 months thereafter. These were compared to baseline values, calculated by taking the average of 12, 9 and 6 months before flare. We used Linear Mixed Models (LMMs) with a random intercept and an autoregressive covariance matrix to determine an overall effect of flare. We adjusted for multiple testing with a Bonferroni correction. For determining the duration of the effect of a flare, we tested if the separate time points differed from the baseline with the same model. For the worker productivity we used descriptive statistics.

Results: In total, 113 patients experienced a flare. Patients who had a flare had a less stable course of the outcomes over time, compared with patients without flare (Figure 1A-G). When comparing all time points to baseline, statistical significant differences were found for DAS44 ($p<0.0001$), VAS general health ($p<0.0001$), morning stiffness ($p<0.0001$), HAQ-DI ($p=0.0002$), EQ-5D ($p<0.0001$), BRAF-MDQ ($p=0.04$), and the SF36 physical component scale ($p=0.0004$) (Figure 1A-H). The duration of these effects was more than 12 months for the DAS44, morning stiffness, and VAS general health. For the HAQ-DI, EQ5D, BRAF-MDQ, and SF36 PCS the duration of the effect of a flare was 6 months (Figure 1H). The effect sizes, expressed as differences with baseline, are indicated in Figure 1H and were rather small for most outcomes. The number of patients with payed work and unemployment were not affected by flare. The amount of sick leave increased from 1 to 1.3 days per month in the 6 months after flare and productivity decreased 1 point on a 0-10 scale in the 3 months after flare.

Conclusion: Having a flare does affect patient reported outcomes. It affects DAS44, VAS general health, morning stiffness, functional ability, quality of life, and fatigue. This effect lasted for more than 6 months. Although we only found minor differences with baseline on group level, on the individual patient level this can still be of great importance.

Figure 1: Patient-reported outcomes (DAS44, VAS general health, morning stiffness, HAQ-DI, EQ-5D, BRAF-MDQ, SF36 PCS) over time (months) for patients with and without a flare. The graphs show that outcomes generally worsen after a flare and remain significantly different from baseline for up to 12 months. A table below the graphs provides the mean difference and 95% confidence interval for each outcome at various time points.

Disclosure of Interests: Elise van Mulligen: None declared, Angelique Weel: None declared, Martijn Kuijper: None declared, Johanna Hazes: None declared, Annette van der Helm - van Mil Grant/research support from: The research leading to these results has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Starting grant, agreement No 714312) and from the Dutch Arthritis Foundation.

The funding source had no role in the design and conduct of the study., Pascal de Jong: None declared

DOI: 10.1136/annrheumdis-2019-eular.4550

SAT0116

DYNAMIC PREDICTION OF FLARES IN RHEUMATOID ARTHRITIS USING JOINT MODELLING AND MACHINE LEARNING: SIMULATION OF CLINICAL IMPACT WHEN USED AS DECISION AID IN A DISEASE ACTIVITY GUIDED DOSE REDUCTION STRATEGY

Paco Welsing¹, Alfons den Broeder², Janneke Tekstra¹, Marlies van der Goes¹, Floris Lafeber¹, Johannes W. G. Jacobs¹, Oj Medina³, Asmir Vodencarevic⁴, Marcus Zimmermann-Rittereiser⁴, Saskia Haitjema^{3,5}, Jacob M. van Laar¹. ¹University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, ²Department of Rheumatology and Clinical Immunology, Utrecht, Netherlands; ³St. Maartenskliniek, Nijmegen, The Netherlands, ⁴Department of Rheumatology, Ubbbergen, Netherlands; ⁵University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, ⁶Applied Data Analytics in Medicine programme, Utrecht, Netherlands; ⁷Digital Services, Siemens Healthcare GmbH, Erlangen, Germany, ⁸Erlangen, Germany; ⁹University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, ¹⁰Laboratory of Clinical Chemistry and Haematology, Utrecht, Netherlands

Background: Most rheumatoid arthritis (RA) patients on a (biological) DMARD achieve and maintain remission or low disease activity. Then, tapering the drug is safe and cost-effective¹, but with increased risk of short lived flares and joint damage progression. We developed so-called dynamic prediction models, using joint-modelling (JM) and machine learning (ML) respectively to predict an individual patients' risk of flaring. These models can make short-term (e.g. 3 month) predictions repeatedly at every clinic visit, based on routine care data, i.e. the longitudinal course of the patients' disease activity and medication, demographic and disease characteristics.²

Objectives: To externally validate the JM and ML model and evaluate the clinical impact on flare occurrence and bDMARD use, when using predictions as decision aid for tapering bDMARDs in a protocolised disease activity guided tapering strategy.

Methods: For external validation, an RCT comparing protocolised dose reduction (stepwise increase injection interval, until flare or discontinuation, n=121) with usual care (n=59) was used.¹

Both models were applied to the trial data and AUC-ROC and calibration were assessed. To simulate our dose-reduction strategy, first, we defined optimal cut-offs for predictions using Youden's index as well as a cut-off at higher/lower predicted risks. Thereafter we applied them to the dose reduction arm of the trial. Assumptions were that 1) no further tapering was performed when the cut-off was reached without any flares occurring over time in the simulation and 2) when in the trial a flare occurred for which the bDMARD dose was increased to a value higher than when tapering was stopped in simulation, this flare occurred and the higher dose was used in simulation as well.

Results: AUC-ROC's in external validation were, as expected, somewhat lower than in the development cohort: 0.76 (95%CI 0.71–0.85) and 0.73 (0.72–0.74) versus 0.78/0.79 for JM/ML respectively, but still satisfactory. Calibration was better for ML, resulting in different cut-offs for the models. Results show that about 40% and 50% of flares can be prevented respectively and that the majority (66% and 76%) of the dose reduction can be maintained using the optimal cut-offs in our prediction aided dose reduction strategy over 18 months. Table 1 shows the proportion of full dose used, mean number of flares per patient, and percentage of patients experiencing a flare for several cut-offs as well as in the disease activity guided dose reduction strategy (in bold). As context values are also shown for usual care (trial control arm; in italic).

Strategy	Prop. full bDMARD dose (95%CI)	Mean # flares (95%CI)	% pat. flaring (95%CI)*
Usual care arm	0.89 (0.85-0.93)	0.34 (0.22-0.46)	25 (18-33)
Tapering arm	0.50 (0.45-0.55)	1.42 (1.24-1.61)	80 (73-87)
Simulation tapering JM (optimal)	0.62 (0.58-0.66)	0.81 (0.62-1.00)	49 (40-58)
Simulation tapering JM (< risk score)	0.68 (0.64-0.72)	0.66 (0.48-0.84)	39 (30-48)
Simulation tapering ML** (optimal)	0.67 (0.64-0.70)	0.67 (0.49-0.85)	41 (32-50)
Simulation tapering ML** (> risk score)	0.57 (0.53-0.61)	1.12 (0.92-1.31)	64 (55-73)

* Flare based on van der Maas et al. Ann Rheum Dis. 2013;72:1800-5. **fitted without variable selection; <> cut-off at lower/higher flare risk than optimal cut-off; higher/lower cut-off for JM/ML did not lead to meaningful reductions in flares / savings in bDMARD use

Conclusion: Both models proved to be externally valid. Using them to aid decisions on biological dose reduction has the potential to reduce the occurrence of flares significantly while largely retaining the reduction in dose as obtained by a disease activity guided dose reduction strategy.

This finding, and its cost-effectiveness, should be validated in a clinical study.

REFERENCES

- [1] Kievit W., et al.. *Ann Rheum Dis* 2016; 75:1939-1944
- [2] Vodencarevic A., et al.. *DATA* 2018; 187-192

Disclosure of Interests: Paco Welsing: None declared, Alfons den Broeder: None declared, Janneke Tekstra: None declared, Marlies van der Goes: None declared, Floris Lafeber Shareholder of: ArthroSave, Grant/research support from: FOREUM; Dutch Arthritis Society, Johannes W. G. Jacobs Grant/research support from: Roche, Consultant for: Roche, OJ Medina: None declared, Asmir Vodencarevic Shareholder of: Owning shares of Siemens Healthcare GmbH as its employee. Siemens Healthcare GmbH is a medical technology company (NOT a pharmaceutical company)., Employee of: An employee of Siemens Healthcare GmbH. Siemens Healthcare GmbH is a medical technology company (NOT a pharmaceutical company)., Marcus Zimmermann-Rittereiser Shareholder of: Owning shares of Siemens Healthcare GmbH as its employee. Siemens Healthcare GmbH is a medical technology company (NOT a pharmaceutical company)., Employee of: An employee of Siemens Healthcare GmbH. Siemens Healthcare GmbH is a medical technology company (NOT a pharmaceutical company)., Saskia Haitjema: None declared, Jacob M. van Laar Grant/research support from: Genentech, Consultant for: F. Hoffmann-La Roche

DOI: 10.1136/annrheumdis-2019-eular.2881

SAT0117 THE IMPACT OF DIFFERENT CRITERIA SETS ON EARLY REMISSION AND IDENTIFYING ITS PREDICTORS IN RHEUMATOID ARTHRITIS: RESULTS FROM AN OBSERVATIONAL COHORT (2009–2018)

Wenhui Xie, Xiaoying Sun, Zhuoli Zhang. *Peking University First Hospital, Department of Rheumatology and Clinical Immunology, Beijing, China*

Background: Currently, with increased awareness of early diagnosis and intervention and the identified association of early remission with a better clinical outcome in patients with rheumatoid arthritis (RA), shorter time to remission appears to be a more attractive goal. There are several studies reported the prevalence of early remission, no study so far has demonstrated the issue in Chinese population. Moreover, further investigative studies need to be performed due to limited and conflicting predictors of early remission in previous studies.

Objectives: To assess rates of early remission and investigate the concordance across different remission definitions, and to identify predictors of early remission in Chinese patients with RA.

Methods: For this study, clinical records were retrospectively reviewed for RA patients at rheumatologic clinic in Peking University First Hospital from 2009 to 2018. Disease activity and remission were determined according to DAS28-ESR, CDAI, SDAI, and Boolean criteria. Early remission was defined as time to remission ≤ 6 months. A secondary definition evaluated early remission as ≤ 3 months. Logistic-regression analyses were performed to identify determinants of early remission.

Results: 869 consecutive patients contributing 8,640 clinic visits were studied. Early remission rates were respectively 42.0% (DAS28-ESR), 25.0% (CDAI), 29.4% (SDAI), and 26.1% (Boolean). Notably, patients achieving remission within 6 months more frequently attained sustained remission by contrast to those not achieving early remission (68.7-75.1% vs. 31.2-33.1%, $P < 0.0001$). Further logistic-regression analyses revealed male (OR=1.42-1.74, $p < 0.05$), early RA (OR=1.64-2.22, $p < 0.05$), as well as initial hydroxychloroquine treatment (OR=1.41-1.81, $p < 0.05$) were independently associated higher probability of early remission, as demonstrated by nearly all definitions, while a higher baseline disease activity (DAS28-ESR, CDAI, and SDAI) lowered the possibility of early remission in corresponding remission indices. However, the significant associations of treatment-naïve, serological features with early remission were not confirmed.

Conclusion: Early remission was strongly associated with sustained remission, however infrequently achievable in real-life practice. Male, early RA, a low baseline disease activity, and initial hydroxychloroquine treatment were stable independent predictors of early remission.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2527

SAT0118 PRETREATMENT PREDICTION OF INDIVIDUAL OUTCOME OF RHEUMATOID ARTHRITIS PATIENTS TO INFLIXIMAB THERAPY USING SERUM BIOMARKERS AND CLINICAL DATA

Kazuyuki Yoshizaki¹, Kazuko Uno², Tsutomu Takeuchi³, Keisuke Izumi³, Mitsuhiro Iwahashi⁴, Hitoshi Fujimiya⁵. ¹Osaka University, Graduate School of Information Science and Technology, Osaka, Japan; ²Louis Pasteur Center for Medical Research, Kyoto, Japan; ³Keio University, Department of Rheumatology, School of Medicine, Tokyo, Japan; ⁴Higashi Hiroshima Memorial Hospital, Hiroshima, Japan; ⁵Dynacom Co., Ltd., Chiba, Japan

Background: Infliximab (IFX), is a most effective b-DMARD, and results in a 60% remission rate on average in rheumatoid arthritis (RA) patients. The remaining 40% of patients undergo other biologics treatments that follow a 'treat-to-target method' until they achieve remission. Predicting in advance that a patient cannot achieve clinical remission with IFX, would allow doctors to start such patients on treat-to-target treatments sooner. Unfortunately, no reliable method has yet been found to predict patient-response.

Objectives: We tried to establish a prediction method using the serum of individual patient with RA related biomarkers present in varying amounts before they underwent IFX.

Methods: This study uses an observational retrospective study with 85 patients. 22 clinical data were used as explanation variables, such as, disease duration, combination of c-DMARDs, DAS 28-ESR, and day 0 laboratory data. 84 biomarkers in patients' pretreatment serum were measured using Multi-Plex Human Cytokine Chemokine beads array. DAS-28-ESR after 24 weeks was used as an objective variable. Patients administered IFX with regular method were divided into two groups: complete remission (DAS 28-ESR <2.6) and non-remission (DAS 28-ESR ≥ 2.6) at 24 weeks. The log-transformed value of all parameters were used for the statistical analysis. We used the least absolute shrinkage and selection operator (Lasso) approach to select combination markers that were most predictive of remission. In the process of multi-marker prognostic model building, to avoid over fitting, leave-one-out cross validation (LOOCV) was used to evaluate the performance of the multi-marker model.

The receiver operating characteristic (ROC) analysis was used to evaluate the ability of the models to predict the 24-week outcome of patients. The area under the ROC curve is the product of the cross validation procedure.

Results: We selected a combination from 104 markers. 3 to 5 combinations were most predictive of remission with 1.405 Cohen's d and at 0.85 AUC, 0.826 PPV, 0.882 NPV, and 0.689 ACC. On the contrary, using 22 clinical parameters, AUC, PPV, NPV and ACC were 0.726, 0.713, 0.649 and 0.673, respectively.

Conclusion: Using the pre-treatment serum, we were able to predict with high accuracy patients who would achieve remission. Our method is stable and economical; therefore, it may be applicable as a way of identifying individual patients who are resistant to IFX therapy, so as to avoid treating them with IFX in the first place. The next step is to confirm these results in larger scale retrospective and prospective studies. The first highly accurate method identified for predicting remission and non-remission in individual RA patients who are targeted for IFX treatment.

REFERENCE

- [1] Uno K, Yoshizaki K, et al. Pretreatment Prediction of Individual Rheumatoid Arthritis Patients' Response to Anti-Cytokine Therapy Using Serum Cytokine/Chemokine/Soluble Receptor Biomarkers. *PLoS One*. 2015 Jul 15;10(7): e0132055.

Acknowledgement: Russel Pandra for helping abstract translation

Disclosure of Interests: Kazuyuki Yoshizaki: None declared, Kazuko Uno: None declared, Tsutomu Takeuchi Grant/research support from: Astellas Pharma Inc, Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., AbbVie GK, Asahikasei Pharma Corp., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Eisai Co., Ltd., AYUMI Pharmaceutical Corporation, Nipponkayaku Co. Ltd., Novartis Pharma K. K., Grant/research support from: AbbVie, Asahi Kasei, Astellas, AstraZeneca, AYUMI, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly Japan, Janssen, Mitsubishi Tanabe, Nippon Kayaku, Novartis, Pfizer Japan Inc, Taiho, Taisho Toyama, Takeda, Teijin, Grant/research support from: Astellas Pharma Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., AbbVie GK, Asahi Kasei Pharma Corp., Taisho Toyama