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FRI0042

DISCREPANCIES BETWEEN RAPID3 AND DAS28 IN RHEUMATOID ARTHRITIS PATIENTS IN REMISSION OR LOW DISEASE ACTIVITY RECEIVING TNF INHIBITORS: WHAT IS THE ROLE OF THE INFLAMMATION BIOMARKERS?

J. Inciarte-Mundo¹, R. Morlà¹, B. Frade-Sosa¹, J. Ramírez¹, R. Castellanos-Moreira¹, V. Ruiz¹, J. D. D. Cañete¹, J. Gomez Puerta¹, R. Sanmartí¹. ¹Hospital Clínic de Barcelona, Rheumatology Department, Barcelona, Spain

Background: Patients and Rheumatologist often differ in their perception of RA disease activity. Remission or low disease activity should be the treatment target in RA, patients should be included in treatment decisions.

Objectives: To identify factors influencing patient's self-reported disease activity by RAPID3 test.

Methods: 47 RA patients in remission or low disease activity by DAS28ESR (DAS28ESR ≤ 3.2) receiving TNFi (etanercept, adalimumab and infliximab) stratified their disease activity by RAPID3, then two patients' groups were defined: *target group* (RAPID3 with remission 0-3 or low disease activity 3.1-6), *non-target group* (RAPID3 with moderate 6.1-12 or high disease activity >12). Demographic data, disease duration, autoantibody status, radiological data, concomitant csDMARD therapy was collected. Laboratory measurements included CRP, ESR, calprotectin serum levels, TNFi trough serum levels, and antidrug antibodies (enzyme-linked immunosorbent assay (ELISA) test kit (Calprolab™ Calpro AS, Oslo, Norway, and Promonitor®, Progenika SA, Spain, respectively) according to the manufacturers' protocol. Pearson's correlations coefficients were used to identify variables correlating with RAPID3 score. Mixed-effects analyses of covariance (ANCOVAs) models were used to identify factors influencing RAPID3 score.

Results: Patients in "target group" have shown a significant lower TJC, pain by VAS 0-10mm, and calprotectin serum levels, but higher TNFi serum trough levels in comparison to "non-target group". When patients were classified according to RAPID3 categories, patients in "remission" have shown lower calprotectin serum levels than those classified as in "high disease activity" (0.94 (4.88-0.14) vs. 4.57 (7.97-1.25), $p=0.001$, respectively). Accordingly, when classified according to pain by VAS 0-10mm, patients with low levels of pain had lower calprotectin serum levels vs. those with severe pain (1.43 (6.33-10.14) vs. 5.16 (8.80-1.25), $p=0.009$, respectively). When distributed according to PGA (1=very good, 2=good, 3=regular, 4=bad, 5=very bad) patients in "very good" group had lower mean of calprotectin serum levels than those in "very bad" group (0.94 (4.88-0.14) vs. 4.57 (7.97-1.25), $p=0.001$, respectively). PGA and Pain VAS have shown a strong correlation with RAPID3 (R^2 0.978, and 0.834, $p=0.001$, respectively), while calprotectin and TNFi serum trough levels showed a moderate correlation (R^2 0.311, and 0.372, $p=0.005$, respectively). The multivariate adjusted analysis showed a significant association between Pain and RAPID3 ($p<0.001$) according to the different covariates (age, gender, anti-CCP positivity, time in remission, SJC, TJC, DAS28ESR). In addition, calprotectin and TNFi trough serum levels were associated with RAPID3 ($p<0.005$). Backward selection of variables did not substantially modify the association between RAPID3 and pain, calprotectin and TNFi trough serum levels.

Conclusion: 61.7% of RA patients undergoing TNFi classified as in remission or low disease activity by DAS28ESR, self-reported their disease activity as moderate or high by RAPID3. The most significant factor influencing patient's perception of disease activity is pain (pain VAS and TJC). However, inflammation markers (calprotectin, TNFi serum trough levels) remain statistically significant after fully adjustment by different confounders. Thus, therapies improving these three domains will have a larger impact in patient's perception of disease activity.

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FRI0043

JOINT SPACE NARROWING PRECEDES EROSIVE RADIOGRAPHIC DAMAGE IN PATIENTS WITH RHEUMATOID ARTHRITIS

A. Kerschbaumer¹, F. Alasti¹, G. Supp¹, J. S. Smolen¹, D. Aletaha¹. ¹Medical University of Vienna, Department of Medicine III, Division of Rheumatology, Vienna, Austria

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized through symmetric polyarthritis leading to joint destruction over time in many patients. Radiographic damage is an important outcome in RA clinical trials, most commonly assessed by conventional radiographs and quantified/ reported by the modified total Sharp van der Heijde Score (mTSS). The mTSS is assessing erosive (ERO) changes as well as joint space narrowing (JSN; reflecting cartilage wasting) in the small joints of the hands and feet. While erosions are the hallmarks of RA, loss of cartilage has been reported to be highly relevant for functional limitations in RA. The sequence of occurrence of these events is not completely understood.

Objectives: To investigate the time to radiographic progression and assess potential differences between time-to-JSN progression and time-to-ERO progression.

Methods: Radiographs of RA patients from a large prospective clinical routine cohort were scored using the mTSS by one experienced reader (G.S.) unaware of the aim of this project. Time-to-JSN and time-to-ERO was estimated using survival analyses utilizing the Kaplan-Meier estimator. In additional analyses, patients were stratified based on JSN and/or ERO damage at baseline. Further, potential predictors (demographics, csDMARD/bDMARD treatment/combotherapy) of time-to-ERO and time-to-JSN were evaluated using Cox-regression techniques. All statistical analyses were conducted using SAS v9.4 (Cary, New York, USA).

Results: We assessed 798 patients longitudinally for radiographic progression. JSN occurred significantly earlier than erosions ($p<0.001$, Figure 1). After stratification for baseline damage (Figure 2), these differences remained significant with a shorter time-to-JSN in patients without any baseline ERO or JSN ($n=44$, $p=0.008$), patients with JSN but no ERO at baseline ($n=200$, $p<0.001$), and patients with baseline ERO and JSN ($n=536$, $p<0.001$). Only in the small group of patients with isolated erosions (without JSN) at baseline there was no difference in time-to-progression of ERO vs. JSN ($n=18$, $p=0.241$). Overall, shorter time to progression of ERO was significantly predicted by positivity for rheumatoid factor or anti-citrullinated peptide antibodies (CCP; $p<0.003$), as well as by erosions at baseline ($p<0.001$) in Cox regression. In contrast, seropositivity for neither RF nor CCP was associated with shorter time to JSN progression ($p=0.226$); however, baseline concomitant JSN and ERO damage did show to be a significant predictor ($p<0.001$).

Figure 1. Time to joint space narrowing and time to erosive damage (n=798).

Figure 2. Time to JSN/ERO stratified by presence or absence of ERO/JSN at baseline.

Conclusion: We identified a significantly shorter time to progression of JSN compared to ERO in this longitudinal cohort of RA patients. JSN remains an important radiographic outcome, as it is strongly associated with impairment of physical function. This calls for a stronger focus on cartilage damage in RA, and a stronger consideration of JSN in routine evaluation of RA radiographs in clinical practice.

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FRI0044

ROBUST ANALYSES FOR RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS

R. B. M. Landewé¹, L. Sun², Y. F. Chen², D. Schlichting², D. Van der Heijde³.

¹Academic Medical Center University of Amsterdam and Atrium Medical Center, Department of Clinical Immunology & Rheumatology, Amsterdam, Netherlands; ²Eli Lilly and Company, Indianapolis, United States of America; ³Leiden University Medical Centre, Leiden, Netherlands

Background: Reducing structural damage is an important treatment goal for rheumatoid arthritis (RA). Demonstrating a clinically meaningful, statistically significant difference in radiographic progression (assessed by van der Heijde modified total Sharp score, mTSS) is a common objective in trials for RA treatments. Complete collection of radiographic data is challenging, especially in long term follow-up and pediatric studies. Therefore, scores for individual joints or entire patients are regularly missing. A frequently used analysis method for mTSS is the analysis of covariance model, in which missing data are imputed using linear extrapolation (ANCOVA+LE). However, other ways to deal with missing information have also been proposed.

Objectives: To evaluate robust analysis methods for mTSS data.

Methods: Simulated data were used to compare a random coefficient model (RC) without imputation, ANCOVA+LE and ANCOVA with last observation carry forward imputation (LOCF).

A log-normal distribution was used to generate baseline patient level data to simulate a 2-arm clinical trial using baseline mTSS and rate of change in mTSS from recently completed trials. Changes in mTSS (12, 28 and 44 week time-points) were generated under linear, concave quadratic (fast progression then slow progression), and convex quadratic (slow progression then fast progression) assumptions, with the proportion of change forced to be 0 (a proportion of simulated patients do not have progression). A monotone missing pattern was assumed to generate a data set with missing data (the 'observed' dataset).

ANCOVA analyses were performed using baseline and treatment as predictors. The RC model was applied using baseline, treatment, time, and time-by-treatment interactions as fixed effect and time as a random effect. Bias (difference between average of simulation sample mean and true value, the smaller the better), root mean square error (RMSE, a measure of variation among simulation samples, the smaller the better), power and type I error rate were compared between methods.

Results: The random coefficient model provided better or at least similar results in bias, RMSE, power and type I error rate as ANCOVA+LE under evaluated scenarios (Table 1).

Progression assumption	Simulation parameters (Number of simulations = 500; common sample size=300, baseline mTSS=-11.7)	Model	Bias	Power	RMSE
Linear	$p_{pbo} = 0.6, r_{pbo} = 0.065$ $p_{trt} = 0.68, r_{pbo} = 0.046$ $\Delta_{wk44} = -0.49$	ANCOVA + Full	0.002	0.924	0.140
		ANCOVA + LE	0.003	0.866	0.155
		ANCOVA+LOCF	0.154	0.844	0.190
		RC + FULL	0.001	0.92	0.139
		RC + OBS	-0.002	0.872	0.156
Concave	$p_{pbo} = 0.6, r_{pbo} = -0.0009, q_{pbo} = 0.11$ $p_{trt} = 0.68, r_{pbo} = -0.0011, q_{trt} = 0.093$ $\Delta_{wk44} = -0.611$	ANCOVA + Full	0.002	0.982	0.141
		ANCOVA + LE	-0.002	0.926	0.180
		ANCOVA+LOCF	0.188	0.94	0.222
		RC + FULL	0.002	0.978	0.141
		RC + OBS	-0.005	0.924	0.174
Convex	$p_{pbo} = 0.6, r_{pbo} = 0.0037, q_{pbo} = -0.09$ $p_{trt} = 0.68, r_{pbo} = 0.003, q_{trt} = -0.1$ $\Delta_{wk44} = -0.83$	ANCOVA + Full	0.003	1	0.139
		ANCOVA + LE	0.343	0.948	0.368
		ANCOVA+LOCF	0.391	0.974	0.405
		RC + FULL	-0.004	1	0.140
		RC + OBS	0.199	0.988	0.249

Abbreviations: FULL = complete dataset with no missing values trt = active treatment, OBS = the 'observed' dataset, pbo = placebo, p = proportion of patients with no progression, r = linear progression rate (mTSS units per week), q = quadratic term coefficient. Δ = active treatment progression - placebo r

Conclusion: RC is a robust analysis method for mTSS. We recommend its use in primary analyses, especially for long-term extension and pediatric studies with a higher likelihood of missing data. This method can also provide reference for time points when no data are collected via estimated slope. ANCOVA+LE can be used for sensitivity analysis.

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