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SAT0050

PREDICTION OF RESPONSE TO CERTOLIZUMAB PEGOL TREATMENT BY FUNCTIONAL MRI OF THE BRAIN: AN INTERNATIONAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL (PRECEPRA)

J. Rech¹, K. Tascilar¹, H. Schenker¹, M. Sergeeva², M. Selvakumar², L. Konerth², J. Prade², S. Strobelt², M. Hagen¹, V. Schönau¹, L. Valor¹, A. Hueber³, D. Simon¹, A. Kleyer¹, F. Behrens⁴, J. A. P. Da Silva⁵, C. Baerwald⁶, S. Finzel⁷, R. Voll⁷, E. Feist^{8,9}, A. Doerfler¹⁰, N. Damjanov¹¹, A. Hess², G. Schett¹. ¹Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany; ²Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Institute for Experimental Pharmacology, Erlangen, Germany; ³Sozialstiftung Bamberg, Section Rheumatology, Bamberg, Germany; ⁴Goethe University Frankfurt, Rheumatology and Fraunhofer TMP, Frankfurt am Main, Germany; ⁵Hospitals da Universidade (SRHUC), Department Reumatologia, Coimbra, Portugal; ⁶Universität Leipzig, Medizinische Klinik III - Bereich Rheumatologie, Leipzig, Germany; ⁷Universitätsklinikum Freiburg, Klinik für Rheumatologie und Klinische Immunologie, Freiburg, Germany; ⁸Klinik für Rheumatologie der Helios Fachklinik, Vogelsang-Gommern, Germany; ⁹Charité - Universitätsmedizin Berlin, Dpt. of Rheumatology and Clinical Immunology, Berlin, Germany; ¹⁰Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Abteilung für Neuroradiologie, Erlangen, Germany; ¹¹Belgrade University School of Medicine, Institute of Rheumatology, Belgrade, Serbia

Background: Personalization of RA treatment is not optimal due to lack of predictors. We previously demonstrated in RA patients that central nervous system (CNS) pain response to tender joint compression, measured by using functional MRI (fMRI) of the brain rapidly wanes after 24 hours of anti-TNF administration and that a higher pre-treatment BOLD signal volume seems to predict clinical response to treatment with certolizumab-pegol (CZP)^{1,2}. We therefore hypothesized that the CNS pain response upon compression of a painful joint could predict subsequent anti-TNF treatment response.

Objectives: To compare disease activity after 12-weeks of CZP treatment to that of placebo in DMARD-refractory RA patients based on pre-treatment baseline CNS pain response measured using BOLD fMRI.

Methods: Adult RA patients fulfilling the 2010 ACR/EULAR classification criteria with a DAS28>3.2 under stable DMARD treatment for at least 3 months were eligible. Patients underwent fMRI scanning of the brain at screening for stratification by CNS pain response. Whole brain BOLD-signal-voxel-count of 700 units classifying between low and high, and were randomized to CZP or placebo (2:1). The primary outcome was low disease activity (LDA, DAS28 ≤3.2) after 12 weeks of treatment.

Results: 156 RA patients, inadequate responders to csDMARD, signed the informed consent. 139 patients (46/47, 46/49 and 42/43) (99 females, 71%) with moderate-high disease activity (mean (SD) DAS-28: 4.83 (1.03)) could be included respectively and completed the 12-week study treatment. Geometric mean (SD) numbers of baseline BOLD signal positive voxels were 559 (10), 81 (12) and 2498 (3) in the 3 arms respectively. The mean DAS28 (SD) scores after 12 weeks of study treatment were Placebo: 3.89 (1.29), CZP-L: 3.42 (1.06) and CZP-H: 3.06 (1.04). LDA was achieved in 12/47 patients (25.5 %) in placebo, 22/49 (44.9%) in the CZP-L, and 25/43, (58.1%) in the CZP-H arm. The linear effect term for the ordinal study group variable supported a linear trend of increasing CZP treatment effect with increasing baseline CNS pain response. RR (95% CI) for achieving LDA with each unit increase in treatment category over placebo was 1.79 (1.24 to 2.74, p=0.003).

Conclusion: A higher pre-treatment brain activity in response to pain measured with fMRI predicts the chance of achieving low disease activity with CZP treatment.

References:

- [1] Hess, A. et al. PNAS (2011)
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-1 Baseline characteristics of the study population overall and by study groups.

	Overall	Study group		
		Certolizumab-Hq	Certolizumab-Lc	Placebo
	139	43	49	47
mean (SD)	54.3 (11.8)	54.3 (10.8)	56.5 (12.2)	52.1 (12.0)
Female	99 (71.2)	34 (79.1)	35 (71.4)	30 (63.8)
Male	40 (28.8)	9 (20.9)	14 (28.6)	17 (36.2)
Age, years				
Mean(SD)	6.2 (8.1)	6.0 (8.3)	6.4 (8.6)	6.2 (7.6)
Median(IQR)	2.0 (1.0-8.1)	2.0 (1.0-9.0)	3.0 (1.0-8.0)	3.0 (1.0-8.0)
CRP				
Negative	34 (24.5)	15 (34.9)	9 (18.4)	10 (21.3)
Positive	105 (75.5)	28 (65.1)	40 (81.6)	37 (78.7)
ESR				
Negative	39 (28.1)	12 (27.9)	13 (26.5)	14 (29.8)
Positive	100 (71.9)	31 (72.1)	36 (73.5)	33 (70.2)
ESR (28), mean (SD)	10.2 (6.5)	9.3 (6.4)	11.3 (6.7)	9.9 (6.2)
ESR (28), mean (SD)	7.9 (5.3)	7.0 (4.4)	8.7 (6.3)	8.0 (4.8)
Visual analogue scale VAS, mm, mean (SD)	50.0 (20.0)	57.2 (19.9)	59.1 (17.8)	57.6 (22.5)
Global VAS, mm, mean (SD)	49.6 (18.7)	46.0 (20.2)	49.5 (19.2)	53.1 (16.2)
mm, mean (SD)	55.2 (19.3)	53.5 (18.0)	57.1 (17.0)	54.9 (22.7)
CRP, mean (SD)	25.8 (19.9)	23.7 (18.0)	25.2 (17.1)	28.2 (23.2)
CRP, mean (SD)	8.7 (13.0)	6.8 (12.7)	7.9 (8.7)	11.2 (16.5)
ESR/h, mean (SD)	4.8 (1.0)	4.7 (1.0)	5.0 (1.1)	4.9 (1.0)

SD, standard deviation; IQR, interquartile range; ACPA, anti-citrullinated peptide antibodies; RF, Rheumatoid factor; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; DAS-28, disease activity score 28 joints.

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SAT0051

REMISSION IN RHEUMATOID ARTHRITIS PATIENTS: A CLUSTER ANALYSIS TO IDENTIFY AND CHARACTERIZE SUBPOPULATIONS OF PATIENTS

A. Madrid García¹, D. Freitas Nuñez², J. Font³, I. Hernandez³, L. León², J. I. Colomer², I. González-Álvarez⁴, B. Fernandez³, J. A. Jover³, L. Abasolo², L. Rodríguez Rodríguez². ¹Fundación para la Investigación Biomedica - HCSC, Madrid, Spain; ²Fundación para la Investigación Biomedica - HCSC, Rheumatology, Madrid, Spain; ³Hospital Clínico San Carlos, Rheumatology, Madrid, Spain; ⁴Hospital Universitario La Princesa, Madrid, Spain

Background: Disease Activity Score (DAS) is a continuous measure of Rheumatoid Arthritis (RA) activity, used in clinical practice for monitoring disease progression and for documenting treatment response. According to EULAR, the clinical desired target is to achieve a remission state (or failing that, low disease activity). However, the population of RA patients in this state could be heterogeneous.

Objectives: To characterize the level of heterogeneity of RA patients in remission by identifying clusters based on the DAS28 components; and to describe inter and intra-class cluster demographic and clinical characteristics

Methods: Patients from Hospital Clínico San Carlos cohort, stored in a departmental electronic health record from January 1st, 2000 to December 30th, 2018, diagnose with RA according ACR 1986/ 2010 criteria were eligible for this study. Only observations with a DAS28 Erythrocyte Sedimentation Rate (ESR) value < 2.6 value were considered. ESR, patient's Global Health (GH), and tender and swollen joints were used for calculating the clusters. Different aggregation levels for joints were studied as well as the input variable types. Isolated joints, joints grouped by the type of affection (swollen or tender) or anatomic location or laterality aggregation levels were considered. Variables expressed as present or absent (i.e. dichotomous), continuous (count of joints) and categorical (type of joints) were also studied. Gower's distance, used for dealing with variables of different type, was employed to calculate the distance matrix. The number of suitable clusters was chosen from two to seven clusters based on the width value of a Silhouette analyses. Finally, Partitioning Around Medoids (PAM) was used as the clustering algorithm. Differences among clusters regarding demographic and clinical characteristics were analyzed using t-student chi2 test.

Results: 812 patients with 1,431 observations were analyzed in this study. The joint aggregation level which showed a highest Silhouette width value (0.708) was the anatomic one. In this aggregation level, five dichotomous variables (presence of tenderness and/or swelling in right and/or left shoulder, elbow, wrist, knee and hand (including both metacarpophalangeal and proximal interphalangeal joints) and two continuous variables (ESR and GH) were used. Two clusters were found: the cluster A) with 1,305 observations and 742 patients and the B) with 126 observations and 115 patients. Cluster b) had a statistically significant higher DAS28-ESR value (higher number of tender and swollen joints, and higher GH, but lower ESR), longer follow-up time (6.5 vs. 4.7 years), higher VAS-pain score (10 vs. 2), and higher HAQ score (0.25 vs. 0.12). In addition, the proportion of patients treated with oral corticosteroids (63% s. 50%) and biological therapy (29% vs. 12%) was higher.

Conclusion: We have identified two clinically distinct populations of RA patients in remission according to DAS28-ESR <2.6. Each subgroup could be associated with different outcomes during follow-up, such as radiographic progression or risk of relapse.

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SAT0052

THERAPEUTIC STRATEGIES IN DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: PRELIMINARY RESULTS OF A SYSTEMATIC LITERATURE REVIEW INFORMING THE 2020 EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS

N. M. T. Roodenrys¹, A. Hamar², M. Kedves³, G. Nagy⁴, J. M. Van Laar¹, D. Van der Heijde⁵, P. Welsing¹. ¹University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands; ²University of Debrecen, Department of Rheumatology, Debrecen, Hungary; ³Bács-Kiskun County Hospital, Department of Rheumatology, Kecskemét, Hungary; ⁴Semmelweis University, Department of Genetics, Cell- and Immunobiology & Department of Rheumatology, 3rd Department of Internal Medicine, Budapest, Hungary; ⁵Leiden University Medical Center, Department of Rheumatology, Leiden, Netherlands

Background: Rheumatoid arthritis (RA) patients treated according to European League Against Rheumatism (EULAR) recommendations failing ≥2 biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) with a different mode of action who still have complaints which may be suggestive of active disease may be defined as suffering from 'difficult-to-treat RA'. Management recommendations for RA focus predominantly on the earlier phases of the disease and specific recommendations for difficult-to-treat RA patients are currently lacking.¹

Objectives: To systematically summarise evidence in the literature on pharmacological and non-pharmacological therapeutic strategies for difficult-to-treat RA

patients, informing the 2020 EULAR recommendations for the management of difficult-to-treat RA.

Methods: A systematic literature review (SLR) was performed: PubMed, Embase and Cochrane databases were searched up to December 2019. Relevant papers were selected and appraised.

Results: Thirty articles were selected for therapeutic strategies in patients with limited DMARD options due to contraindications, 73 for patients in whom previous b/tsDMARDs were not effective ('true refractory RA'), and 51 for patients with predominantly non-inflammatory complaints. For patients with limited DMARD options, limited evidence was found on effective DMARD options for patients with concomitant obesity, and on safe DMARD options for patients with concomitant hepatitis B and C. In patients who failed ≥2 bDMARDs, tocilizumab, tofacitinib, baricitinib, upadacitinib and filgotinib were found to be more effective than placebo, but evidence was insufficient to prioritise. In patients who failed ≥1 bDMARD, there was a tendency of non-tumour necrosis factor inhibitor (TNFi) bDMARDs to be more effective than TNFi (Figure 1). Generally, b/tsDMARDs become less effective when patients failed more bDMARDs, this tendency was not clear for upadacitinib and filgotinib (Figure 2). In patients with predominantly non-inflammatory complaints (mainly function, pain and fatigue), exercise, education, psychological and self-management interventions were found to be of additional benefit.

Conclusion: This SLR underscores the scarcity of evidence on the optimal treatment of difficult-to-treat RA patients. As difficult-to-treat RA is a newly defined disease state, all evidence is to an extent indirect. Several b/tsDMARDs were found to be effective in patients who failed ≥2 bDMARDs and generally effectiveness decreased with a higher number of failed bDMARDs. Additionally, a beneficial effect of non-pharmacological interventions was found on non-inflammatory complaints.