Results: Mean disease duration was 11.8 ± 10.5 years for cancer and 12.8 ± 10.8 years for RMDs since diagnosis. 1.4% received cancer treatment (6.4% of malignancy group), 69.3% csDMARDs, 42.3% b/tsDMARDs and 46.4% glucocorticoids at the time of sample collection.

Most metabolites tested were significantly lower in the malignancy groups versus associated controls: Concentrations of amino acids V and L were significantly reduced in all malignancy samples. Additionally, T, D, N, Q, E, A, I were altered in RA, SpA and PsA, changes in G were seen in RA, PsA and SLE and P was altered in RA and PsA only. Furthermore, lower concentrations of short chain fatty acids and tricarboxylic acid cycle intermediates were present in the malignancy groups. In no case was a metabolite concentration significantly higher in the malignancy group than in the associated control. When comparing the metabolome within the four malignancy groups, only the concentrations of creatine, threonine and isoleucine were found higher in RA patients with malignancy.

Conclusion: Significant differences between the metabolomic fingerprints of RMD patients with and without malignancies could be observed. These changes might be characteristic for cancer burden, as in most cases the underlying RMD was not relevant when comparing the concentrations between the malignancy groups. Our results may promote understanding of the interrelationships of both disease entities as well as prove useful as biomarkers for diagnostic and therapeutic purposes.

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POS0473

AUTOIMMUNITY AGAINST COLLAGEN IN RHEUMATOID ARTHRITIS (RA): SERUM LEVELS OF IgG AGAINST DENATURED TYPE II COLLAGEN SIGNIFICANTLY ELEVATED IN RA

P. Drobinski¹, E. Aighobahi², A. C. Bay-Jensen³, M. Karsdal³. ¹University of Copenhagen/Nordic Bioscience, Department of Biomedical Sciences, Copenhagen, Denmark; ²Technical University of Denmark, Department of Biotechnology and Biomedicine, Copenhagen, Denmark; ³Nordic Bioscience, ImmunoScience, Herlev, Denmark

Background: The presence of autoantibodies in Rheumatoid Arthritis (RA) is a hallmark of the disease and one of main criteria for diagnosis and clinical classification. Identification of anti-citrullinated protein antibodies (ACPA) and RF-Factors in circulation of RA patients remains the most characteristic and established criteria for diagnosis. However, due to diagnostic limitation of these biomarkers, only approximately 70% of patients with RA can be identified. As a consequence, there is a lack of diagnostic biomarkers for large number of patients. Diagnosis of these patients relies mainly on assessment of their clinical symptoms such as swollen and tender joints. This problem leaves a need for diagnostic improvement and development of more sensitive biomarkers.

Objectives: In this study, we aimed to develop a sensitive biomarker assay capable to identify and quantify presence of autoantibodies against denatured type II collagen in circulation of patients with RA.

Methods: The presence and levels of autoantibodies was measured in serum samples from 50 patients with moderate to severe RA who had inadequate response to Methotrexate (average age 51.2, 86% of female, 78% of white race patients). Control cohort involved serum from 42 healthy age matched patients (average age 48.6, 50% of female, 60% of white race patients). Denaturation of the type II collagen was performed by heat treatment for 15 min at 72 °C. Improvement of assay sensitivity was investigated by measurements of autoimmunity levels against denatured and native type II collagen. Assay specificity was assessed by comparison of presence of autoantibodies against type II collagen versus albumin (non-sense control). The normality of data distribution was checked with Shapiro-Wilk test, significance between cohorts with Mann-Whitney nonparametric test and correlations with Spearman's correlation coefficient (rho).

Results: Serum levels of autoantibodies against denatured type II collagen were significantly higher in RA patients than in healthy controls ($P < 0.0001$) (Figure 1). We observed nearly 4-fold difference between both cohorts. Denaturation of type II collagen showed high improvement of assay sensitivity and increased accessibility of collagen for binding of autoantibodies. Developed assay showed specificity for detection of type II collagen autoantibodies by displaying no levels of autoimmunity against other control proteins (albumin). The levels of serum autoantibodies correlated significantly ($P < 0.03$) with patient disease activity (DAS28) at baseline, displaying $\rho = 0.3$. Our assay showed good technical performance with acceptable inter- and intra- assay variations (18% and 5% respectively).

Figure 1. Differences in serum levels of autoantibodies against denatured type II collagen between healthy controls and patients with Rheumatoid Arthritis.

Conclusion: Present findings show that patients with RA carry upregulated levels of circulating autoantibodies directed against type II collagen. Heat-treatment of type II collagen increased exposure of immunogenic epitopes of collagen and enabled for more sensitive detection of autoantibodies directly in patient serum. Developed assay demonstrated potential for specific detection of autoantibodies and may provide additional diagnostic value in RA patients.

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POS0474

SUBSTANTIAL IMPACT OF AUTOANTIBODY ENRICHMENT ON OUTCOMES IN EARLY RHEUMATOID ARTHRITIS TREATED WITH ABATACEPT: DATA FROM A LARGE POOLED ANALYSIS OF 4 RCTS

K. Michaud^{1,2}, S. S. H. Park³, K. Lozenski⁴, J. Vaile⁵, V. Khaychuk⁶, J. Pope⁷, P. G. Conaghan^{8,9}. ¹University of Nebraska Medical Center, Internal Medicine Division of Rheumatology, Omaha, NE, United States of America; ²FORWARD, The National Data Bank for Rheumatic Diseases, Wichita, KS, United States of America; ³Bristol-Myers Squibb, US HEOR, Princeton, NJ, United States of America; ⁴Bristol-Myers Squibb, Medical Data Generation, Princeton, NJ, United States of America; ⁵Bristol-Myers Squibb, Worldwide Medical, Princeton, NJ, United States of America; ⁶Bristol-Myers Squibb, US Medical Immunology and Fibrosis, Princeton, NJ, United States of America; ⁷Western University, Schulich School of Medicine, Division of Rheumatology, London, Ontario, Canada; ⁸University of Leeds, Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom; ⁹Leeds Teaching Hospitals NHS Trust, NIHR Leeds Biomedical Research Centre, Leeds, United Kingdom

Background: Biomarkers are commonly used as prognostic tools in rheumatoid arthritis (RA) and have additional potential to guide treatment decisions. Previous clinical trials of abatacept (ABA) such as the Early AMPLE trial (eAMPLE) and real-world data suggest differential treatment effects of ABA based on the presence of biomarkers and disease stage.¹⁻⁴

Objectives: To supplement evidence of enhanced efficacy of ABA among patients with enriched autoantibody biomarkers and early disease stage by applying key inclusion criteria from the eAMPLE trial retrospectively to historic ABA RCTs.

Methods: Individual patient data (IPD) from four early-RA ABA trials (AGREE [NCT00122382], AMPLE [NCT00929864], AVERT [NCT01142726], AVERT-2 [NCT02504268]) were pooled. Patients were defined as enriched at baseline if they had: 1) RA disease duration ≤ 12 months, 2) DAS28-CRP ≥ 3.2 , 3) ≥ 3 times the upper limit of normal on an anti-cyclic citrullinated peptide (anti-CCP) test, and 4) were rheumatoid factor positive (RF+). Patients were grouped according to treatment status (ABA [monotherapy or with methotrexate (MTX)] or non-ABA [MTX or adalimumab (ADA) plus MTX]). Outcomes included DAS28-CRP mean

change from baseline to week 24, DAS28-CRP remission and ACR 20/50/70 at week 24. IPD mixed-effects meta-regressions were estimated with trial fixed effects, main effects and interaction of enrichment status and treatment type, trial-level random effects on the interaction, and baseline DAS28-CRP score for DAS28-CRP outcomes. These regressions were conducted in the full population and among ABA patients only. Sensitivity analyses defining enrichment using only criteria 3 and 4 were also conducted.

Results: 2,087 patients [1,328 (64%) enriched, 759 (36%) non-enriched] were included (AGREE 492 [24%], AMPLE 509 [24%], AVERT 339 [16%], AVERT-2 747 [36%]). Disease duration, RF+, and anti-CCP values differed as expected between the two groups, while DAS28-CRP was high regardless of enrichment status (Table 1). Among ABA-treated patients, outcomes were more favorable for enriched patients compared to non-enriched patients across all outcomes, either statistically or directionally (Figure 1, ABA treatment arm only analysis). The differences in outcomes between enriched vs. non-enriched patients were larger for ABA than for comparators across all outcomes with the exception of ACR 50, where the difference was directionally consistent (Figure 1, ABA vs. comparator analysis). The relative odds of improved efficacy of ABA vs. comparators ranged from 37% to 87% for remission and ACR responses. The results were consistent in the sensitivity analysis using only anti-CCP and RF seropositivity to define enrichment.

Table 1. Baseline characteristics

	All patients		Non-enriched patients		Enriched patients	
	Abatacept		Comparators		Abatacept	
	N = 2,087	N = 385	N = 374	N = 784	N = 544	
Demographics						
Age (years)	49.3 ± 12.9	49.4 ± 12.6	50.6 ± 12.9	48.6 ± 12.5	49.2 ± 13.5	
Female	79.3%	81.3%	83.4%	77.2%	77.9%	
Disease characteristics						
Disease duration (months)	8.5 ± 12.5	19.9 ± 15.9	18.3 ± 15.1	2.4 ± 2.8	2.4 ± 2.9	
RF Positive	91.0%	74.2%	76.1%	100%	100%	
Anti-CCP Positive	81.8%	52.2%	47.3%	100%	100%	
DAS28-CRP Score	5.71 ± 1.13	5.72 ± 1.19	5.66 ± 1.20	5.68 ± 1.09	5.76 ± 1.08	

Comparators included MTX and MTX+ADA.

Figure 1. Analysis results

Conclusion: This post-hoc study corroborates previous evidence of improved outcomes among ABA-treated, seropositive early RA patients by applying eAMPLE inclusion criteria retrospectively to ABA RCTs. The findings support a differential treatment effect for costimulation blockade using ABA among enriched and double antibody positive early RA patients, suggesting a potential for patient-tailored RA treatment approaches.

REFERENCES:

- [1] Buckner J, et al. *Arthritis Rheumatol.* 2019; 71 (suppl 10).
- [2] Huizinga T, et al. *Annals of the Rheumatic Diseases* 2015;74:234-235.
- [3] Harold L, et al. *Rheumatol Ther.* 2019 Jun;6(2):217-230.
- [4] Sokolove J, et al. *Ann Rheum Dis* 2016 Apr;75:709-714.

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POS0475 INTEGRATIVE CLINICAL, MOLECULAR AND COMPUTATIONAL ANALYSES ALLOW THE IDENTIFICATION OF DISTINCTIVE PHENOTYPES OF RHEUMATOID ARTHRITIS PATIENTS RELATED TO THE CLINICAL INVOLVEMENT AND THE RESPONSE TO TNF INHIBITORS

M. Luque-Tévar¹, C. Perez-Sanchez¹, N. Barroja Puerto¹, A. M. Patiño-Trives¹, I. Arias de la Rosa¹, M. D. C. Abalos-Aguilera¹, J. A. Marin-Sanz¹, D. Ruiz¹, R. Ortega Castro¹, C. López-Medina¹, F. U. Pilar¹, M. Romero-Gómez¹, C. Rodríguez-Escalera², J. J. Pérez Venegas³, D. Ruiz-Montesinos³, C. Domínguez³, C. M. Romero-Barco⁴, A. Fernandez-Nebro⁵, N. Mena-Vázquez⁵, J. L. Marengo⁶, J. Uceda⁶, M. D. Toledo-Coello⁷, M. Á. Aguirre-Zamorano¹, A. Escudero Contreras¹, E. Collantes Estevez¹, C. Lopez-Pedraza¹.
¹IMIBIC/Hospital Reina Sofía/Universidad de Córdoba (UCO), IMIBIC/Hospital Reina Sofía/Universidad de Córdoba (UCO), Córdoba, Spain; ²Hospital Universitario de Jaén, Hospital Universitario de Jaén, Jaén, Spain; ³Hospital Universitario Virgen Macarena, Hospital Universitario Virgen Macarena, Sevilla, Spain; ⁴Hospital Clínico Universitario, Hospital Clínico Universitario, Málaga, Spain; ⁵Hospital Regional Universitario de Málaga, Hospital Regional Universitario de Málaga, Málaga, Spain; ⁶Hospital Universitario Virgen de Valme, Hospital Universitario Virgen de Valme, Sevilla, Spain; ⁷Hospital Universitario de Jerez de la Frontera, Hospital Universitario de Jerez de la Frontera, Cadiz, Spain

Background: TNF inhibitors (TNFi) represent an extraordinary advance in the management of Rheumatoid Arthritis (RA). Despite their benefits, there is a percentage of patients (20–40%) that do not achieve clinical improvement. Therefore, it is necessary to search for new and easily accessible biomarkers predictive of therapeutic response that might guide precision medicine.

Objectives: 1. To explore changes in the molecular profile of RA patients following TNFi therapy in serum samples. 2. To search for new and reliable biomarkers predictive of TNFi response, based on clinical and molecular profiles of RA patients, by using machine learning algorithms.

Methods: In a prospective multicenter study, 79 RA patients undergoing TNFi and 29 healthy donors (HD) were enrolled. Twenty-two RA patients were further included as a validation cohort. Serum samples were obtained before and after 6 months of treatment, and therapeutic efficacy was evaluated. Patients' response was determined following EULAR response criteria. Serum inflammatory profile was analyzed by a multiplex immunoassay, along with oxidative and NETotic profiles, evaluated by commercial kits. A circulating miRNA array was also performed by next-generation sequencing. Clustering analysis was carried out to identify groups of patients with distinctive molecular signatures. Then, clinical and molecular changes induced by TNFi were delineated after 6 months of therapy. Finally, integrative clinical and molecular signatures as predictors of response were assessed at baseline by supervised machine learning methods, using regularized logistic regressions.

Results: Inflammatory, oxidative stress and NETosis-derived biomolecules were found altered in RA patients versus HD, closely interconnected and associated with several deregulated miRNAs. This altered molecular profile at baseline allowed the unsupervised division of three clusters of RA patients with distinctive clinical phenotypes, further linked to TNFi effectiveness. Cluster 1 included RA patients with low levels of pro-inflammatory cytokines, associated with a medium-low disease activity score and good clinical response. Clusters 2-3 comprised patients with high levels of pro-inflammatory cytokines, associated with a high disease activity and a non-response rate of 30%.

After 6 months of therapy the molecular profile found altered in RA patients was reversed in responder patients, who achieved a molecular phenotype similar to HDs. However, non-responder patients' molecular profile remained significantly deregulated, including alterations in inflammatory mediators (IL-6, L-8, TNF α , VEGF, IL-1RA, IL-5, IL-15, GM-CSF, G-CSF, FGFb), oxidative stress markers (LPO) and NETosis-derived products (Elastase), along with specific miRNAs (miR-199a-5p). These molecular changes further correlated with changes in disease activity score. Machine-learning algorithms identified clinical (Creatinine, IgM, Vitamin D, Swollen Joints, C4, Disease Duration and Triglycerides) and molecular (Nucleosomes, IL-10, miR-106a-5p, IL-13, IL-12p70, IL-15 and