depleted mice (4), prompting us to hypothesize that inter-individual differences in the human gut microbiome could impact drug bioavailability and thus clinical efficacy.

Objectives: To determine differences in the microbiome of drug-naïve, new onset RA (NORA) patients that could predict response to MTX therapy.

Methods: We performed 16S rRNA gene and shotgun metagenomic sequencing on the baseline gut microbiomes of 27 drug-naïve, NORA patients.

Results: Our analysis revealed significant associations between the abundance of gut bacterial taxa and genes including gene families related with purine and methotrexate metabolism. Machine learning techniques were applied to this metagenomic data, resulting in a robust predictive model based on bacterial gene abundance that accurately predicted response to MTX therapy in an independent group of patients. Finally, MTX available levels remaining after *ex vivo* incubation with distal gut samples from pre-treatment RA patients significantly correlated with the magnitude of future clinical response, suggesting a direct effect of the gut microbiome on MTX bioavailability and response to therapy.

Conclusion: Together, these results provide the first step towards predicting response to oral MTX in NORA patients and support the utility of the gut microbiome as a prognostic tool and perhaps even as a target for manipulation in the treatment of rheumatic and autoimmune disease.

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OP0120

BASELINE CELLULAR AND MOLECULAR CHARACTERISTICS OF SYNOVIAL TISSUE AND RELATION WITH TNFI RESPONSE. RESULTS FROM THE PATHOBIOLOGY OF THE EARLY ARTHRITIS COHORT (PEAC)

Gloria Lliso Ribera¹, Frances Humby¹, Alessandra Nerviani¹, Myles Lewis¹, Stephen Kelly², Michele Bombardieri¹, Katriona Goldmann¹, Rebecca Hands¹, Chris Buckley³, Peter C. Taylor⁴, Iain B McInnes⁵, Costantino Pitzalis¹. ¹William Harvey Research Institute, Experimental Medicine and Rheumatology, London, United Kingdom; ²Barts Health. Mile End Hospital, Rheumatology, London, United Kingdom; ³Division of Immunity and Infection, The University of Birmingham, Birmingham, United Kingdom; ⁴Kennedy Institute of Rheumatology, University of Oxford Botnar Research Centre, Oxford, United Kingdom; ⁵Glasgow Biomedical Research Centre, University of Glasgow, Glasgow, United Kingdom

Background: Despite early intervention with disease modifying therapy a high percentage of patients (~30%) fail to respond and require escalation to advanced therapies such as TNFi, with no available biomarkers to predict response. Whether synovial signatures predicting subsequent response to TNFi therapy can be identified at disease onset remains an unanswered question although critical for long term prevention of disease progression and overall health economic impact.

Objectives: The aim of this study was to evaluate in a cohort of treatment naïve early RA patients, whether baseline synovial cellular and molecular signatures predict subsequent response or not to anti-TNF therapy.

Methods: A total of 186 consecutive DMARD naïve inflammatory arthritis patients (disease duration <1 year) recruited as part of the multicentre PEAC study at Barts Health NHS Trust were evaluated. After 12 months 35 patients commenced therapy with a TNFi (DAS28>5.1, failed 2 x cDMARDs as per UK NICE guidelines). EULAR response (DAS28 and DAS improvement from baseline) was calculated 12 months after TNFi was initiated. All patients underwent an US guided baseline synovial biopsy of a clinically active joint along with collection of clinical characteristics. Following H&E staining, sections underwent immunohistochemical staining and semi-quantitative scoring (0-4) to determine the degree of CD20+Bcells, CD3+T cells, CD68+ lining (l) and sublining (sl) macrophage and CD138+ plasma cell

infiltration. Sections were categorised into three pathotypes: (i) Fibroid: (CD68 SL<2 and or CD3, CD20, CD138<1), (ii) Myeloid: (CD68SL>2, CD20<1 and or CD3>1) and (iii) Lymphoid: (grade 2-3 CD20+ aggregates, CD20>2). Synovial gene expression was evaluated with Nanostring and RNA sequencing.

Results: 12 months after TNFi was initiated 17/35 (48%) patients responded to therapy (TNFi good EULAR response) and 18/35 (52%) had a moderate or non-response to TNFi. Baseline demographic or US characteristics did not differentiate between the 2 groups. Although we saw no significant differences between groups there was a trend for higher levels of B (CD20+) and T (CD3+) cells, sublining macrophages (CD68+) and plasma cells (CD138+) in the TNFi response group. The cohort was segregated by pathotype and each clinical parameter was compared from baseline to 12months. Interestingly, we observed a significant reduction of levels of CRP, VAS and DAS28 and number of tender and swollen joints in those patients with Lymphoid and Myeloid pathotype ($p<0.05$), but not in those with Fibroid pathotype (Figure 1). We also evaluated gene expression (using Nanostring and RNA-sequencing) and observed increased expression of genes related to macrophages, plasma cells and B/T regulatory cells expression/activation and/or stimulation at baseline in patients who responded to TNFi.

Conclusion: This study demonstrates first evidence of potential novel signatures/biomarkers of TNFi response in treatment naïve early RA. Clinical or US assessment cannot discriminate between responders to TNFi. Lymphoid and Myeloid pathotypes associated with significant falls in clinical outcome. Finally, molecular signatures including differential upregulation of T cells, B cells and macrophage associated genes are associated with good response to TNFi therapy.

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Figure 1. Clinical parameters progression from baseline to 12m post-TNFi according to pathotype