1b-dependent mechanism in AS patients supporting the auto-inflammatory nature of the disease and possibly representing a future therapeutic target in AS.

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FRI0153 ROLE OF ROR GAMMA T INHIBITION IN THE IL-23 MINICIRCLE MODEL AND SPA PATIENT TISSUE CULTURES

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Background: Retinoic acid receptor related Orphan Receptor gamma t (RORγt) is a nuclear hormone receptor expressed in a subset of pathogenic T cells and innate lymphoid cells. RORγt regulates the transcription of key pro inflammatory cytokines such as IL-17 and IL-22 in response to multiple activation signals including cytokines and T cell receptor engagement. Antagonism of RORγt is hypothesised to block transcription of these pathogenic cytokines resulting in reduced tissue inflammation and aberrant joint remodelling.

Spondyloarthropathy (SpA) is characterised by a peripheral oligoarthritis and enthesitis. A key feature of SpA is the imbalance between bone resorption and formation leading to aberrant bone formation and ankylosis. The contribution of the IL-23/IL-17 axis to the pathogenesis of SpA is supported by several lines of evidence. However, the specific role of RORγt in regulating the cellular and molecular pathways contributing to enthesal and synovial inflammation remains incompletely understood.

Objectives: The goal of this study was to determine the role of RORγt antagonism in both an IL-23 minicircle *in vivo* model and *ex vivo* tissue culture model.

Methods: Model 1: Mice were administered an IL-23 minicircle via hydrodynamic injection to induce systemic IL-23 expression on day 1. Starting on day 2, mice were dosed p.o. for 28 days. Mice were monitored daily for signs of arthritis. Upon sacrifice tissue was collected for mRNA biomarker analysis and histologic assessment.

Model 2: Patients undergoing total hip replacement were recruited into 2 groups: SpA (either psoriatic arthritis or ankylosing spondylitis) or OA (osteoarthritis). Enthesal and synovial tissues were collected and cultured ±RORγt inhibitor and cytokine stimulation (hTNFα/hIL23) for 24 and 48 hours and then analysed for gene expression.

Results: Model 1: Overexpression of IL-23 induced SpA like phenotype including enthesitis, synovitis and aberrant bone formation. RORγt inhibition resulted in significant reduction of inflammation and arthritic score, histologic parameters of bone remodelling, and tissue biomarkers associated with the IL-23 axis (IL17A, IL17F, IL22).

Model 2: Both enthesal and synovial cultures from SpA patients expressed increased Th17 axis genes relative to OA after cultures. RORγt inhibition reduced the expression of these Th17 axis genes (IL17A, IL17F, IL22) as well as reducing tissue remodelling related genes (FN1, MMP1/3, BMP5), in alignment with the results seen in model 1.

Conclusions: IL-23 induced Th17 axis gene expression induced a SpA-like phenotype in mice, including arthritis and aberrant bone formation, that was reversed upon RORγt inhibition. Similarly, SpA patient explants showed increased expression of Th17 axis cytokines and tissue remodelling related genes that were decreased with RORγt inhibition. Together, these complementary approaches support the hypothesis that RORγt treatment could block inflammation as well the underlying pathologies associated with SpA.

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FRI0154

ADDED VALUE OF BIOMARKERS COMPARED TO ROUTINE CLINICAL PARAMETERS FOR THE PREDICTION OF RADIOGRAPHIC SPINAL PROGRESSION IN AXIAL SPONDYLOARTHRITIS

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Background: Structural damage in the spine determines the functional status and spinal mobility in axial spondyloarthritis (axSpA). Already present syndesmophytes, elevated C-reactive protein, cigarette smoking, and to a lesser extent male sex are routine clinical parameters predicting radiographic spinal progression. In the last years, several biomarkers with a predictive value for radiographic spinal progression were identified. It is, however, not known, if biomarkers have a meaningful added value over clinical parameters in prediction of radiographic spinal progression in axSpA.

Objectives: The objective of the study was to examine whether adding biomarkers to the routine clinical parameters would improve prediction of radiographic spinal progression in axSpA.

Methods: Altogether 117 patients with ankylosing spondylitis who completed a 2 year clinical and radiographic follow-up in the ENRADAS trial were included. Radiographic spinal progression was defined as a worsening of the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) by ≥ 2 points after 2 years. A clinical prediction model for radiographic spinal progression was constructed out of already present syndesmophytes, elevated CRP, cigarette smoking, and male sex. Serum biomarkers measured at baseline included: matrix metalloproteinase-3, vascular endothelial growth factor (VEGF), calprotectin, leptin, high molecular weight adiponectin (HMW-APN), osteoprotegerin, sclerostin, N-terminal telopeptide, procollagen type II N-terminal propeptide, and serum amyloid A.

Results: Repeated cross-validation analyses revealed the following biomarker combination with added predictive value for radiographic progression compared to the clinical model (syndesmophytes, smoking, elevated CRP, and sex): Leptin + HMW-APN + VEGF. A combination of these biomarkers resulted in an Area Under the Curve (AUC) of $AUC_{\text{Biomarkers}} = 0.731$ (95%CI 0.614–0.848), thus numerically superior to the clinical model ($AUC_{\text{Clinical}} = 0.665$ (95%CI 0.553–0.776)). A combination of both models resulted in improvement of the predictive value reflected by the $AUC_{\text{Clinical+Biomarkers}} = 0.768$ (95%CI 0.666–0.871); though this improvement was not statistically significant compared to the clinical model in the permutation test ($p = 0.051$). However, when only considering the part of receiver operating characteristic (ROC) curves with a specificity of $\geq 75\%$, the improvement becomes statistically significant (partial $AUC_{\text{Clinical+Biomarkers}} = 0.119$ versus partial $AUC_{\text{Clinical}} = 0.053$; $p = 0.010$).

Abstract FRI0154 – Figure 1. ROC curve analyses of biomarker and clinical model alone versus the combined model for the prediction of radiographic spinal progression (mSASSS worsening ≥ 2 after 2 years) in ankylosing spondylitis. Area under the curves (AUC) and respective 95% confidence intervals (CI) shown. *Leptin + HMW-APN + VEGF.