Figure. ESSDAI Change from Baseline over Time up to Week 24 Reveals a Statistically Significant Dose Response Relationship

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Meniscus : an innocent bystander in osteoarthritis?.

OP0303

CORTICOSTEROID INJECTION IN KNEE OSTEOARTHRITIS IS ASSOCIATED WITH REDUCTION IN MENISCAL THICKNESS AND JOINT SPACE WIDTH WITH NO EFFECT ON CARTILAGE THICKNESS: A CASE CONTROL STUDY

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Background: Intra-articular corticosteroid injections (IACI) are commonly used for the treatment of symptomatic knee osteoarthritis (OA) and therapeutic guidelines have recommended their use. However, their safety regarding the evolution of structural changes remains unknown.

Objectives: This study explored the effects of IACI on the evolution of knee OA structural changes assessed by magnetic resonance imaging (MRI).

Methods: Participants were selected from the Osteoarthritis Initiative database. In this nested case-control design study, participants who received one treatment with IACI and had MRI exams available at the yearly follow-up visits before (pre-treatment), during (treatment), and after (post-treatment) were defined as "cases". Each case was matched with one control for age, gender, body mass index (BMI), height, joint space width (JSW), cartilage volume, bone marrow lesion (BML), meniscal extrusion, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain at baseline. Ninety-three (93) participants fulfilling the inclusion criteria were selected and matched to controls ($n=93$). The study structural variables were MRI (cartilage volume, meniscal thickness, bone marrow lesion (BML), bone curvature), X-rays (JSW), and symptoms (WOMAC pain), assessed at the yearly consecutive visits and changes measured within the follow-up periods.

Results: At baseline, the control and treatment groups were balanced. In the pre-treatment period, the cartilage volume loss in the medial compartment was significantly greater in the IACI ($p=0.006$) compared to the control group, with a numerical trend ($p=0.071$) in the lateral compartment. In the treatment period, the cartilage loss was not different between groups, with the exception

of a significantly greater loss in the lateral compartment in the IACI group ($p=0.041$). In the post-treatment period there was no difference in the cartilage loss between the groups in both compartments. For the meniscal thickness loss in the pre-treatment period, no difference was found between groups; however, there was a significantly greater loss ($p=0.007$) during the treatment period in the IACI. In the post-treatment period, the loss of the medial meniscus was similar in both groups. For the lateral meniscus, there was no significant difference at any time between the two groups. The loss in JSW in the pre- and post-treatment periods was not different between groups, but was significantly greater ($p=0.011$) in the IACI group in the treatment period. The changes in the BML sizes over time were small and similar between groups. For the bone curvature, IACI group showed a smaller change compared to the control ($p=0.037$) at the treatment period. The WOMAC pain changes in both groups were small and unlikely to be clinically relevant.

Conclusion: This study provides evidence that in knee OA, IACI were not associated with the occurrence of any deleterious effect on knee structures post-treatment, including cartilage volume and loss. The increase in the rate loss of medial meniscal thickness, which was associated with a loss of JSW, was a transient phenomenon and its clinical relevance unknown at that time.

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SpA: Innovative techniques in spondyloarthritis research – Is there light at the end of the tunnel for our patients?

OP0304

METABOLOMICS PROFILING OF HUMAN SERUM FOR DISCOVERING BIOMARKERS TO DIAGNOSE PSORIATIC ARTHRITIS AND ANKYLOSING SPONDYLITIS WITH HIGH SPECIFICITY

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Background: High-specificity biomarkers that can differentiate PsA and AS patients from healthy people, as well as RA patients, would be extremely helpful for early diagnosis and treatment of these two diseases. Based on the hypothesis that each disease state may cause specific changes to the metabolome, metabolomics is becoming a powerful tool for biomarker discovery. In this work, we applied a high-performance chemical isotope labeling (CIL) LC-MS platform to search for biomarker candidates of PsA and AS in human serum samples.

Objectives: We aimed to identify metabolite biomarkers with high specificity for PsA and AS.

Methods: Serum samples were collected from 331 subjects, including 100 healthy controls, 48 PsA patients, 52 AS patients and 131 RA patients. The average age of each group was: 52.6 (control), 50.7 (PsA), 51.8 (AS) and 53.1 (RA) years. After pre-treatment, each sample was incubated with ¹²C-dansyl chloride, which can label the amine/phenol-containing metabolites. The reference sample for relative quantification was prepared by mixing all individual samples and then labeled by ¹³C-dansyl chloride. With this normalization, the individual samples and the reference sample were mixed at an equal amount. Finally, we used an LC-QTOF-MS platform to analyze the mixtures and measure the ¹²C/¹³C peak pairs.

Results: We detected 1,149 peak pairs commonly existing in the serum samples. Using our dansyl-library of 700 dansyl-labeled standards and a prediction library, which contains the predicted retention times and mass values of 3,431 dansylated human metabolites, we identified 134 and 141 peak pairs, respectively. The relative concentrations are calculated from the intensity ratios of ¹²C/¹³C peak pairs. We first visualized the entire amine/phenol-submetabolome for all phenotypes using the partial least squares discriminant analysis (PLS-DA). We found that the most significant between-group separation was between healthy controls and all the patients. No significant sex or age effect was observed. Furthermore, among the three diseases, PsA and AS samples were closely clustering, while the RA group was well separated from them. Therefore, we chose a two-step diagnosis approach that first differentiates PsA patients from controls/RA patients and then filters out the AS patients wrongly classified as PsA in the first step. The same strategy was conducted for AS. Stipulating a fold change larger than 1.5 with the false discovery rate lower than 5%, we found 74 metabolites having significantly

higher or lower concentrations in the PsA group compared to the control or the RA group. We selected two of these significant metabolites to build a classification model based on the linear support vector machine (SVM) method, and the area-under-the-curve (AUC) value of the resulting receiver operating characteristic (ROC) curve was 0.929 (95% confidence interval: 0.899-0.956). Similarly, 37 metabolites could differentiate AS samples from RAs and controls. A proposed diagnostic panel containing four metabolites demonstrated an AUC value of 0.890 (0.843-0.934). For the last step, distinguishing between PsA and AS, there were 15 significantly increased metabolites and 9 lowered ones. The biomarker panel consisting of the top three metabolites also achieved good discriminatory power with AUC = 0.827 (0.717-0.919).

Conclusion: Isotope-labeling-LC-MS-based metabolomics has revealed biomarker candidates that can specifically differentiate PsA or AS patients from control populations.

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OP0305

RHO-GTPASE PATHWAYS MAY DIFFERENTIATE RESPONDER AND NON-RESPONDERS TO TUMOUR NECROSIS FACTOR INHIBITOR (TNFi) AND INTERLEUKIN-17A INHIBITOR (IL-17Ai) THERAPY IN PSORIATIC ARTHRITIS (PSA)

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Background: In PsA there is a pressing need to develop a coherent strategy for identifying initial and subsequent biologic responders. PsA patients present substantial heterogeneity in response to biologics, and molecular subtyping will help to identify the right patient for the right treatment.

Objectives: To identify transcript profiles (biomarkers) that will select TNFi and IL-17Ai responders in PsA using baseline CD4+ cells; and elucidate novel signaling pathways relevant to biologic disease modifying antirheumatic drug (bDMARD) response using a systems biology approach.

Methods: Consenting patients initiating TNFi agents (20 patients) or IL-17Ai agents (20 patients) with moderate-to-severe PsA were assessed with a comprehensive standardized protocol at baseline and at 3 months. Responder to bDMARDs was defined by Disease Activity Index for Psoriatic Arthritis (DAPSA) score of less than 14 (low disease activity). Global transcript profiling was performed on all patients prior to initiation of and 3 months post bDMARDs. We mapped RNA-seq reads to the hg19 reference genome using STAR and quantified transcripts with Cufflinks. The transcripts per million (TPM) values were log-transformed for statistical analyses

Results: The demographics of PsA patients for both treatment groups are presented (Table 1). Differentially expressed genes (DEGs) were identified using the limma tool for TNFi and IL-17Ai responders and non-responders (Figure 1) as well as DEGs that differentiated TNFi from IL-17Ai response and non-response. Integration of differential gene expression data with tissue-specific protein-protein interactions (IID version 2018-11) identified 117 and 132 DEGs between responders and non-responders to TNFi and IL-17Ai treatments, respectively. Comprehensive pathway enrichment analysis of these genes using pathDIP (v 4.1) revealed 576 (out of 5380) pathways enriched in 117 DEGs between responders and non-responders to TNFi, and 125 pathways enriched in 132 DEGs between responders and non-responders to IL-17Ai. Interestingly, while these two gene lists share only 17 genes, they have 79 enriched pathways in common suggesting potential effect of two different treatments on similar pathways but through different pathway members (Figure 2). Moreover, it suggests potential importance of the 17 shared genes in association with these pathways. Most of these pathways are related to innate and adaptive immune system, and to "osteoclast differentiation". Among 46 pathways specific to response to IL-17Ai, multiple Rho-GTPase-related pathways were identified. It has been shown that experimental inhibition of ROCK2, a target of Rho-GTPase family is effective in psoriatic disease through regulation of IL-17/23/10, but not IL-6 and TNFα.

Table 1. Demographics of psoriatic arthritis (PsA) patients.

	IL-17Ai	TNFi
Number of PsA patients	20	20
Gender (% female)	55%	75%
Mean Age (Years)	55.9 (9.5)	56.8 (7.9)
Mean Disease Duration (Years)	10.4 (6.9)	7.3 (7.9)
Mean DAPSA baseline	38.8 (17.5)	45.6 (28.9)
Responders (%) (DAPSA <14)	35%	65%
Biologic naïve (%)	40%	60%

Figure 1. PCA plots illustrating that DEGs of CD4+ cells can differentiate responders from non-responders when treated with: **A.** IL-17Ai; and **B.** TNFi.

Figure 2. Over-represented terms in significantly enriched pathways considering DEGs between: **A.** IL-17i responders and non-responders (125 pathways); **B.** TNFi responders and non-responders (576 pathways).

Conclusion: Integration of cell-specific transcriptomic data with protein networks represents a very promising strategy for identifying biologic responders and pathways involved in predicting response that may have identified the Rho-GTP pathway as a potential marker to guide the choice of biologic agents for individual patients.

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Newly identified cell subsets driving disease pathogenesis

OP0306

CD11C-SPECIFIC ABLATION OF SHP1 INDUCES AUTOIMMUNE SIALADENITIS SIMILAR TO SJÖGREN'S SYNDROME

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