Results: Upregulated Lasp1 levels were found in synovial tissue and FLS of hTNFtg compared to wt mice. Assays showed that Arp2/3 is part of the adherens junction (AJ) machinery in FLS although Arp2/3 expression levels were not changed between the genotypes. *In vivo* evaluation of *lasp1*$^{-/-}$hTNFtg mice revealed a milder arthritis score, less cartilage degradation and reduced FLS attachment to articular cartilage compared to hTNFtg mice. *In vitro*, the loss of Lasp1 led to clear alterations in AJ arrangement indicated by altered β-catenin pattern. As expected, β-catenin expression was mainly located at adhesion sites between adjacent cells. In hTNFtg FLS, these structures were characterized by a zipper-like pattern. In contrast, these structures were disrupted in *lasp1*$^{-/-}$hTNFtg FLS. Interestingly, CK666 induced zipper-like structures in hTNFtg FLS comparable to the pattern found in *lasp1*$^{-/-}$hTNFtg cells. Furthermore, *lasp1*$^{-/-}$hTNFtg FLS showed decreased Src phosphorylation following PDGF stimulation in comparison to hTNFtg FLS.
Conclusion: Lasp1 represents an interesting target involved in RA-caused joint destruction, because its loss results in significantly reduced cartilage destruction and altered FLS contacts mediated by Arp2/3.
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POS0447 TREATMENT WITH UPADACITINIB IN RA PATIENTS FOR WHICH BIOLOGIC THERAPY FAILED

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Background: Upadacitinib is a JAK inhibitor recently approved for rheumatoid arthritis treatment with promising results in its studies for severe moderate RA for which conventional therapies failed.
Objectives: To study and describe the evolution of patients diagnosed with RA and treated with Upadacitinib who had inadequate response to biological therapy in association or not with DMARDs and GC for 6 months.
Methods: A population of 23 patients (19 of them female) with RA on treatment with Upadacitinib was analyzed over 6 months. Using patient-reported outcomes (PROs) to measure disease activity by visual analogue scale (VAS), the HAQ Disability Index (HAQ-DI), Disease Activity Score (DAS28), and morning stiffness duration. The age´s (average ± SD) = 53 ± 10 years and time of disease evolution (average ± SD) = 17.6 ± 23.3 years. Pretreatment HAQ (average ± SD) = 2.2 ± 0.5. All patients received previous biologic treatments and 61% (14 patients) combined therapy with DMARDs. Only 2 cases had no glucocorticoid treatment prior to treatment with Upadacitinib.
Results: In 3 months' time, most patients (81%, n = 21) treated with Upadacitinib were able to reduce GC dose, and this reduction was maintained 6 months from the beginning of the treatment. After 3 months of treatment, most patients experienced an enhancement in DAS28 (89%, n = 18), with an average improvement in DAS28 of (± SD) 1.87±1.09 units. Regarding the pain (VAS), 67% of the patients showed improvement after 3 months (n=18), reaching 71% after 6 months (n=17). Sixty-eight percent of treated patients showed a reduction in morning stiffness after 3 months (n = 19), and this improvement increased up to 84% of treated patients at 6 months (n = 19). Side effects were observed in five patients, consisting of dizziness and nausea. In no case were they a reason for the withdrawal of the drug. Treatment was withdrawn in three patients due to primary failure.
Conclusion: Treatment with Upadacitinib allows GS dose reduction, as well as an improvement in DAS28, VAS and morning stiffness at three months and six of treatment. These data are in line with the evidence published in Upadacitinib pivotal studies, meaning a good alternative in the treatment of patients with moderate or severe RA.
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POS0448 SYNOVIAL TRANSCRIPTOMIC PROFILES CORRELATE WITH DISEASE ACTIVITY IN EARLY UNTREATED RHEUMATOID ARTHRITIS

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Background: Synovitis is the common feature across all individuals with a diagnosis of rheumatoid arthritis (RA). Yet, cellular and transcriptomic alterations occuring in RA synovium are highly variable amongst patients. So far, most data on clinical-tissue correlations either rely on hypothesis-driven approaches or are potentially biased by heterogeneous clinical characteristics (e.g. disease duration or disease-modifying antirheumatic drugs).
Objectives: We used transcriptomic profiling of synovial tissue from early, untreated rheumatoid arthritis patients (ERA) to 1/ identify the genes with the most variable expression amongst patients and 2/ explore the ability of unbiased (data-driven) approaches to define clinically relevant ERA subgroups.
Methods: Synovial biopsies were harvested from clinically involved joints of ERA patients using needle arthroscopy or ultrasound-guided biopsy. Data on disease activity were collected at inclusion. For each sample, 350ng total RNA was sent for RNAsequencing using a standardized protocol (Macrogen Europe). After quality control (Fast QC) and genome alignement (HiSat2), normalized read counts were analyzed on Qlucore Omics Explorer. To focus on inter-sample heterogeneity, genes were filtered based on variance (σ/σ_{max}). Unbiased approaches (Principal Component Analysis, Unsupervised Clustering) were applied to define patients' clusters. Pathway enrichment analysis were performed on Metascape. CibersortX was used to extrapolate the immune cell subsets relative composition from gene expression data. All other statistical analyses were performed on GraphPad Prism v9.
Results: Total RNA was obtained from synovial biopsies from 74 patients. We first applied variance filtering to identify the genes whose expression showed the greatest variation between patients (n = 894 most variable genes). PCA analysis on the level of expression of these genes did not divide samples into distinct groups, instead yielding a continuous distribution broadly associated with baseline disease activity, as measured by DAS28CRP. Consequently, we used unsupervised clustering to allow for unbiased definition of two patient clusters (PtC): PtC1 (n=52) and PtC2 (n=22) based on their expression of these 894 genes. Pathway analysis of these genes revealed significant enrichment of immune system genes, in the *Inflammatory response* and *Rheumatoid Arthritis* pathways (gene cluster 1: GC1), B cell & plasma cell-related pathways (GC2) and metabolic processes-related genes (GC3). Interestingly, PtC1 and PtC2 were characterized by very different clinical features. More specifically, patients from the group with a strong B & plasma cell signature (PtC1) displayed higher baseline indices of all disease activity score components (median DAS28CRP: 5.56 *vs* 4.09; p-value = 0.0003). They also had higher rates of baseline radiological erosions (erosive disease in 34.6 % *vs* 10%; p-value = 0.0252) but similar rates of seropositive disease. In line with our pathway analyses, we found a higher signature (inferred relative frequency) of B & plasma cells, T cells and M1-like macrophages in PtC1 compared to PtC2 synovia. PtC2 synovia instead had relatively higher M2-like macrophage and resting mast cell signatures.
Conclusion: In this large synovial biopsy study, we found that synovial transcriptomic profiles in ERA patients distribute continuously based on the expression of inflammatory and immune cell transcriptomic pathways. These synovial transcriptomic signatures correlate strongly with systemic disease activity.
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