Methods: 696 samples were identified from a previous genetic study in obesity where each patient was systematically examined with BMI and other related anthropometric measures were recorded. No patients had psoriasis, inflammatory arthritis or any other-articular manifestations of spondyloarthritis. Samples were genotyped using a PsA-weighted single nucleotide polymorphism (SNP) panel, representing genetic variants associated with PsA. The cohort consisted of 73% female with an average age of 49 years ± 15. The average BMI of the group was 35 ± 8 kg/m², ranging from 17 to 67 kg/m². The PsA SNP panel consists of 42 SNPs associated with PsA including IL23R, SAPT2, TNFAIP3, TNIP1, TRAF3IP2, KIR2DS2, FBXL19, REL, IL23R, IL23A, TNIPI, and TYK2. DNA (10ng/ ul) was used to prepare a PCR, followed by SAP and extension reaction with Agena iPLEX Pro kit using Agena MassARRAY. Quantitative trait analysis was performed to obtain the association between BMI and genotype of the 42 SNPs using a linear regression model. Bonferroni correction was used to adjust for multiple comparisons. The factors of age, gender, smoking and height also have been adjusted in the analysis (Table 1).

Table 1. Regression analysis between BMI and 2 significant SNPs

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Beta</th>
<th>SE</th>
<th>T</th>
<th>P</th>
<th>P (adjusted with factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10782001</td>
<td>16</td>
<td>T</td>
<td>C</td>
<td>2.227</td>
<td>0.7207</td>
<td>3.17</td>
<td>0.001596</td>
<td>5.40E-05</td>
</tr>
<tr>
<td>rs10782001</td>
<td>16</td>
<td>G</td>
<td>A</td>
<td>1.584</td>
<td>0.4347</td>
<td>3.644</td>
<td>0.00029</td>
<td>0.0007524</td>
</tr>
</tbody>
</table>

**Results:** Linear regression analysis with and without clinical factors for the two significant SNPs are presented in Table 1. Genotypes of two SNPs (rs10782001 and rs3131382) showed a difference with BMI (Table 1). The rs10782001 variant is within FBXL19 and the average BMI in the presence of GG genotype was 37.2 vs 34.3 for the AA genotype (p = 0.0007). The rs3131382 variant is within HLA-B*39:05 and the average BMI with TT genotype was 47.1 vs 35.4 for the CC genotype (p = 0.00005). Both SNPs maintained significance after correction for multiple testing (p < 0.001).

**Conclusion:** Homozygotes for the minor allele of SNPs within HLA-B*39 and FBXL19 have shown to have an increased BMI, suggesting a potential genetic link between these genes and PsA and obesity. Interestingly, it has been recently noted that miR-26 suppresses adipocyte progenitor differentiation and fat production by targeting FBXL19, leading to possible biologic possibility regarding the link between PsA-weighted genetic variants and obesity.

**REFERENCES:**

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Figure 1.
show the post-treatment deregulated miRs, hsa-miR-3691-5p and hsa-miR-3161 represent the miRs that were deregulated in both conditions. The highlighted nodes represent the most connected miRs and genes; thus, representing miRs that are the most RHO-pathway centric regulators (hsa-miR-495-3p, 16-5p, 129-5p, 520h, 520g-3p), and genes representing the most strongly regulated RHO-pathway gene products (ROCK1, RHQO, PFN2, TAOK1, DYNCL1L2, MAPRE1, PACAHB1, ARHGAAPS, MAPK1, CALM1, DIAPH2, PKN2, ITSN1). Conclusion: Pre- and post-treatment differential miRs related to IL-17A response regulate multiple genes from RHO GTPase pathway.
References:


Disclosure of Interests: Proton Rahman Speakers bureau: AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, UCB, Consultant of: AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, UCB, Grant/research support from: Janssen, Novartis, Quan Li: None declared, Dianne Codner: None declared, Aki O’Reilly: None declared, Amanda Doherty: None declared, Kari Jenkins: None declared, Dafna D Gladman Speakers bureau: AbbVie, Amgen, BMS, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, UCB, Consultant of: AbbVie, Amgen, BMS, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, UCB, Grant/research support from: AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, UCB, Vinood Chandran Speakers bureau: AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, Pfizer, UCB, Paid instructor for: AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, Pfizer, UCB, Grant/research support from: AbbVie, Amgen, Eli Lilly, Employee of: Spousal Employment Eli Lilly, Igor Jurisica: None declared.

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PROTEOMICS ANALYSIS COMPARING THE MODE OF ACTION OF UPADACITINIB BETWEEN NON-BIOLOGIC-DMARD-IR AND BIOLOGIC-DMARD-IR PsA PATIENTS IDENTIFIES DISTINCT PATHOGENIC PATHWAYS IN THE SELECT-PsA 1 AND SELECT-PsA 2 PHASE 3 STUDIES

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Background: Treatment of non-biologic-DMARD-IR (DMARD-IR) and biological-DMARD-IR (bio-IR) PsA patients with upadacitinib (UPA) at 15 mg QD, an oral JAK1 selective inhibitor, resulted in significant improvement in signs and symptoms compared to placebo.

Objectives: Using a pre-defined set of inflammation-related plasma protein biomarkers (pBM), to explore immunological pathway modulation by UPA 15 mg QD in PsA patients with active disease despite treatment with non-biologic or biologic DMARDs in the context of clinical response vs. non-response to treatment.

Methods: Patients from the SELECT-PsA 1 (DMARD-IR) and the SELECT-PsA 2 (bio-IR) studies were randomly selected (PBO, n=100; UPA 15 mg QD, n=100 for each study). The levels of 92 inflammation related protein biomarkers (pBM) were analyzed using a multiplexed Proximity Extension Assay platform in plasma samples collected at baseline, week 2, and 12; change from baseline in protein levels was expressed as Log2 Fold Change; A Repeated Measure Mixed Linear Model was used to identify pBM modulated by UPA compared to Baseline, and those differentially modulated between responders (R) and non-responders (NR) according to ACR50, PASDAS Minimal Disease Activity, and PASI75 at week 12. Correlation of disease activity measures with relative levels of pBM were derived using Pearson’s correlation: PASI score was transformed as Log10(x+1) prior to the analysis. Functional pathway prediction was performed in silico with a commercially distributed software.

Week 2 and 12 Correlations (UPA 15 mg QD)

<table>
<thead>
<tr>
<th></th>
<th>DMARD-IR</th>
<th>Bio-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R vs. NR</strong></td>
<td><strong>LC3B, IL-1β</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IL-1A, IL-23</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACR50</strong></td>
<td><strong>CCL23, CCL2, IL-17A, MAP3K, TIMP-1, TNFα</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PASDAS</strong></td>
<td><strong>ATG12, CCL2, CCL3, IL-17A, TSLP</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MDA</strong></td>
<td><strong>CCL2, CCL4, CCL5, CCL6, CCL11, CCL20, IL-18, IL-2, IL-6, IL-10, TNFα</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PASI75</strong></td>
<td><strong>ATG12, CCL2, CCL3, CCL4, CCL6, IL-18, IL-2, IL-6, IL-10, TNFα, IFNγ, IL-12, IL-17A, IFNγ</strong></td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS:**
At baseline, the relative levels of 37 pBM correlated with at least one baseline disease activity measure, with a marked positive correlation of IL6 with musculoskeletal end points (PASDAS and DAS28CRP), and a strong positive correlation of IL20, IL17A, IL17C, and TGFA with baseline PASI.
At the single pBM-level, treatment with UPA 15 mg QD resulted in a down modulation of pBM associated with T cells, myeloid cells, and IFN-γ, IL-6, and TNF-related pathways in both DMARD-IR and bio-IR PsA patients. Overall effects of UPA on single pMBS were broadly similar between DMARD-IR and bio-IR patients. However, analysis of pBMs differentially modulated by UPA in R vs NR indicated that favorable clinical response (achievement of ACR50, PASDAS MDA, and PASI75) in DMARD-IR patients was associated with the down modulation of pMBS predicted to be linked to IFN, IL10, IL17, IL22, and IL27 pathways; while favorable clinical response in bio-IR patients was associated with the down modulation of multiple pBM predicted to be linked to the IL17, IL23, and IL1 pathways.

**Conclusion:** UPA effects in both DMARD-IR and bio-IR PsA patients likely stem from the direct and indirect inhibition of multiple biological pathways belonging to the adaptive and innate immune systems. Responder/Non-Responder analysis suggests a possible shift from a TH1 biased biology in DMARD-IR PsA patients to a more TH17 biased biology in bio-IR PsA patients. This apparent change in the disease biology of PsA patients after inadequate response to prior therapy could be attributed to the actual alteration of the disease biology, treatment outcome based patient selection, or both. Considering the clinical efficacy of UPA in both DMARD-IR and bio-IR PsA patients, this observation highlights the importance of targeting multiple pathways with drugs such as UPA for the treatment of a broad range of PsA patients.

References:


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INVESTIGATING THE ANTI-INFLAMMATORY POTENTIAL OF A NOVEL MK2 INHIBITOR IN A VITRO MODEL OF ENTHESIS

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Background: Enthesitis or inflammation of tendon/ligament anchorages points is the cardinal lesion in spondyloarthritids (SpA). Through the use of cytokine targeting biologics and also murine models, several key mediators have been shown to have a role in enthesitis, such as IL-23/17 axis and TNF. We have previously shown that the human enthesis contains myeloid cells capable of IL-23 and TNF production and range of T-cells capable of IL-17A secretion. Attempted inhibition of either or both MAPK for inflammatory disease in the past has failed to add additional therapeutic issues. The MAPK-associated protein kinase 2 (MK2) is situated downstream of p38 MAPK, relaying the phosphorylation signal to the nucleus, and is thus a promising target.

Objectives: To determine if a novel MK2 inhibitor (MK2i) could suppress innate and adaptive immune responses in an in vitro human enthesis model.

Methods: Normal spinous process enthesis was obtained from patients undergoing spinal decompression or surgery for scoliosis correction. Following enzymatic digestion, entheseal cells (n=5) were harvested and stimulated either with LPS/IFNγ (Entheseal myeloid cell activator) or anti-CD3 (Entheseal T-cell activator) with and without MK2i (1, 0.1 and 0.01μM) for 24h. Supernatant was harvested and protein detected using multiplexing for panels relating to inflammation (IL-1β, IFNα2, IFN-γ, TNF, CCL2, IL-6, IL-8, IL-10, IL-17p10, IL-17A, IL-17B, IL-23, and IL-33) or T-cell activation (IL-2, IL-4, IL-5, IL-9, IL-10, IL-13, IL-17A, IL-17F, IL-22, IFNγ and TNF).

Results: Following LPS/IFNγ stimulation of entheseal cells, 1μM MK2i significantly attenuated secretion of TNF, IFNα, IL-6, IL-10, IL-8 and CCL2.