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Disclosure of Interests: Proton Rahman Speakers bureau: AbbVie, Amgen, BMS, Celgene, Eli Lily, Janssen, Merck, Novartis, Pfizer, UCB, Consultant of: AbbVie, Amgen, BMS, Celgene, Eli Lily, Janssen, Merck, Novartis, Pfizer, UCB, Grant/research support from: Janssen, Novartis, Quan Li: None declared, Dianne Codner: None declared, Darren O'Rielly: None declared, Amanda Dohey: None declared, Kari Jenkins: None declared, Dafna D Gladman Speakers bureau: AbbVie, Amgen, BMS, Eli Lily, Galapagos, Gilead, Janssen, Novartis, Pfizer, UCB, Consultant of: AbbVie, Amgen, BMS, Eli Lily, Galapagos, Gilead, Janssen, Novartis, Pfizer, UCB, Grant/research support from: AbbVie, Amgen, Eli Lily, Janssen, Novartis, Pfizer, UCB, Vinod Chandran Speakers bureau: AbbVie, Amgen, BMS, Eli Lily, Janssen, Novartis, Pfizer, UCB, Paid instructor for: AbbVie, Amgen, BMS, Eli Lily, Janssen, Novartis, Pfizer, UCB, Grant/research support from: AbbVie, Amgen, Eli Lily, Employee of: Spousal Employment Eli Lilly, Igor Jurisica: None declared
DOI: 10.1136/annrheumdis-2021-eular.1434

POS0407 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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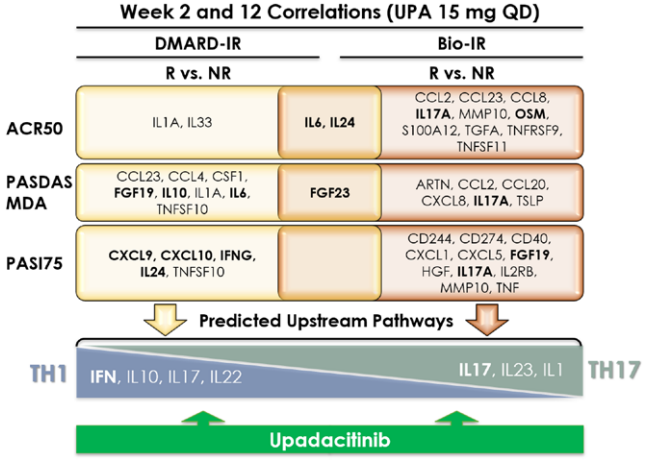
Background: Treatment of non-biologic-DMARD-IR[1] (DMARD-IR) and biologic-DMARD-IR[2] (bio-IR) PsA patients with upadacitinib (UPA) at 15 mg QD, an oral JAK1 selective inhibitor, resulted in significant improvement in signs and symptoms compared to placebo.
Objectives: Using a pre-defined set of inflammation-related 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 Log_2 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 Log_{10} (x+1) prior to the analysis. Functional pathway prediction was performed in silico with a commercial distributed software.



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-, IL6-, and TNF-related pathways in both DMARD-IR and bio-IR PsA patients. Overall effects of UPA on single pBMs 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 pBMs 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.

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Acknowledgements: AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.
Disclosure of Interests: Thierry Sornasse Shareholder of: AbbVie, Employee of: AbbVie, Jaclyn Anderson Shareholder of: AbbVie, Employee of: AbbVie, Koji Kato Shareholder of: AbbVie, Employee of: AbbVie, Apinya Lertratanakul Shareholder of: AbbVie, Employee of: AbbVie, Iain McInnes Consultant of: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi Regeneron, UCB Pharma, Grant/research support from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi Regeneron, UCB Pharma, Christopher T. Ritchlin Consultant of: AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun, UCB Pharma, Grant/research support from: AbbVie, Amgen, UCB
DOI: 10.1136/annrheumdis-2021-eular.1652

POS0408 INVESTIGATING THE ANTI-INFLAMMATORY POTENTIAL OF A NOVEL MK2 INHIBITOR IN A VITRO MODEL OF ENTHESITIS

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Background: Enthesitis or inflammation of tendon/ligament anchorage points is the cardinal lesion in spondyloarthritis (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[1]. 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/F secretion[2,3]. Attempted inhibition of p38 MAPK for inflammatory disease in the past has yielded toxicity 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 supress 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 24 hr. Supernatant was harvested and protein detected using multiplexing for panels relating to inflammation (IL-1β, IFN-α2, IFN-γ, TNF, CCL2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33) or T-cell activation (IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-17A, IL-17F, IL-22, IFN-γ 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.