Background: Upadacitinib (UPA), an oral JAK inhibitor selective for JAK1, demonstrated efficacy in patients with active ankylosing spondylitis (AS) with an inadequate response (IR) to nonsteroidal anti-inflammatory drugs (NSAID) therapy in the SELECT-Axis 1 trial.

Methods: A subgroup of patients from the SELECT-Axis 1 study, with available baseline and at least one follow up plasma sample during the placebo-controlled period, were selected for analysis (PBO, n=65; UPA 15 mg QD, n=63). The levels of 92 inflammation related protein biomarkers (BioMs) were analyzed using the Olink® platform; change from baseline were expressed as Log₂ Fold Change; a repeated measure mixed linear model identified BioMs differentially modulated by UPA. Relationship between change in BioMs and change in clinical disease activity measures were derived using Pearson's correlation (ASDAS-CRP, BASDAI, and CRP) and Spearman's correlation (MRI Spine SPARC). Pathway analysis was performed with Ingenuity® Pathway Analysis (Qiagen Inc.).

Results: Treatment with UPA 15 mg QD reduced the levels of BioMs associated with IFNγ, IL6, IL7, IL8, IL10, IL17, and TNFα, indicating the inhibition of key functional pathways such as leukocyte activation and mobility, inflammation and tissue damage which are known to be dysregulated in AS.

Conclusion: Treatment of AS patients with UPA 15 mg QD resulted in the coordinated decrease in multiple BioMs associated with the innate and adaptive immune responses, and in the increase in BioMs generally associated with tissue repair and hematopoiesis. In silico pathway prediction indicates that treatment with UPA directly inhibits JAK1-dependent and indirectly JAK1-independent pathways, resulting in the down modulation of functional pathways related to tissue repair and hematopoiesis, and decrease in BioMs associated with inflammation. Based on this observation and on the correlation of change in BioMs with change in clinical measures, we hypothesize that both increase in BioMs associated with tissue repair (FGF5, DNER [Delta/Notch Like EGF Repeat Containing]) and those of BioMs associated with tissue repair and hematopoiesis, the Type of pathways, inferred in silico based on BM data, suggests that UPA exerts broad inhibitory activity directly on multiple JAK1-dependent (IFNγ, IFNβ, IL6, IL8, IL7, IL8, and OSM) and indirectly on JAK1-independent upstream pathways (IL1, IL2, IL5, IL7, and OSM) and TNFα, resulting in the inhibition of key functional pathways such as leukocyte activation and mobility, inflammation and tissue damage. Improvement in ASDAS-CRP, BASDAI, and MRI spine SPARC correlated with increase in BioMs associated with tissue repair (FGF5, DNER [Delta/Notch Like EGF Repeat Containing]) and hematopoiesis (FLTL3LG and SCF/KITLG), while improvement in ASDAS-CRP and CRP correlated with decrease in CCL23, CSF1, IL-6, and MMP1; and reduction in only CRP correlated with decrease in IFNγ- and of TNFα-related BioMs. (Data tables will be presented)

Conclusion: Treatment of NSAID-IR AS patients with UPA 15 mg QD resulted in the coordinated decrease in multiple BioMs associated with the innate and adaptive immune responses, and the increase in BioMs generally associated with tissue repair and hematopoiesis. In silico pathway prediction indicates that treatment with UPA directly inhibits JAK1-dependent and indirectly JAK1-independent pathways, resulting in the down modulation of functional pathways related to tissue repair and immune damage which are known to be dysregulated in AS.

Based on this observation and on the correlation of change in BioMs with change in clinical measures, we hypothesize that both increase in BioMs associated with tissue repair and hematopoiesis, and decrease in BioMs associated with inflammation may contribute to the clinical activity of UPA in AS patients.

REFERENCES:

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