SAT0315

ABATACEPT IN PSORIATIC ARTHRITIS: A SINGLE CENTRE, PLACEBO-CONTROLLED, CROSSOVER STUDY IN 20 PATIENTS; A PILOT PROTEOMIC FEASIBILITY STUDY

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Background: Psoriatic arthritis (PsA) is a multifaceted inflammatory disease that affects approximately 0.25% of the global population¹. A range of disease modifying drugs has been used to treat PsA including Abatacept. Unfortunately, not all PsA patients respond to Abatacept treatment and some patients may be intolerant, thus there is an urgent need for the improved selection of patients who are likely to respond Abatacept treatment.

Objectives: This pilot project seeks to demonstrate the potential with which MS based proteomics strategies might be used to discover proteins that may discriminate responders from non-responders to treatment with Abatacept. Using synovial samples collected at baseline and a label-free nLC-MS/MS strategy, candidate proteins were identified. These proteins together with other proteins identified in previous studies were further evaluated by developing multiplexed MRM assays to quantify the proteins both before and during Abatacept treatment (at 2 and 6 months).

Methods: Baseline samples from 6 patients were prepared according to the FASP protocol and analysed by Q-Exactive. MS data was analysed using MaxQuant (v. 1.4.1.2.) and Perseus (v. 1.5.0.8). For the evaluation of candidate proteins Skyline (v. 3.7.0.11317) was used to develop multiplexed MRM assays for these newly identified proteins and to analyse the MRM data acquired on high sensitivity triple quadrupole mass spectrometer (Agilent 6495).

Results: 41 proteins were shown to be differentially expressed at baseline between responders (n=5) and the non-responder (n=1). Of these proteins, 15 were elevated and 26 were reduced in the non-responder. A sub-set of the candidate proteins identified here (n=41) and some proteins identified in our previous PsA related studies² was used to develop an MRM assay targeting total 114 proteins. The MRM assay was developed using our stringent MRM assay standards. Six candidate proteins, ANXA1, ANXA2, S100A10, LMNA, CADH5 and MYL6 have been shown to be differentially expressed in synovial samples collected at 2 months when compared to 6 months. A further 5 proteins, ANXA5, RS18, TAGL, TRFL and HPT were differentially expressed between responders and non-responder at the 2 month time point but most importantly, these five proteins have shown a similar pattern of expression following four months of Abatacept treatment.

Conclusions: Although the small number of patient samples in this pilot study limits the biological significance of these findings, the data highlights some of the significant advantages of unbiased LC-MS/MS protein discovery and of multiplexed MRM assays. These advantages include reproducible and robust coverage of a large number of proteins in small synovial tissue samples and a workflow that supports rapid development of optimised multiplexed assays targeted to proteins of interest.

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SAT0316

RAPID AND SUSTAINED IMPROVEMENTS IN BOTH SKIN AND MUSCULOSKELETAL SYMPTOMS CORRELATES WITH IMPROVED QUALITY OF LIFE IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS

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Background: Psoriatic arthritis (PsA) is a chronic, systemic, autoimmune, inflammatory arthritis condition commonly associated with psoriasis. Several biologic

therapies exist for the treatment of PsA, with varying degrees of efficacy and onset of action.

Objectives: The objective of this analysis was to examine whether there is additional value to a patient's overall quality of life if efficacy is achieved early during treatment and sustained.

Methods: Data were analysed from an integrated database of 2 double-blind, phase III SPIRIT trials investigating the efficacy and safety of ixekizumab (IXE), a high-affinity monoclonal antibody selectively targeting interleukin-17A, for patients with active PsA. The integrated database consisted of patients who were biologic-naïve (SPIRIT-P1, NCT01695239) or who had an inadequate response or were intolerant to tumour necrosis factor inhibitors (SPIRIT-P2; NCT02349295). Patients were randomised to placebo (n=224) or 80 mg IXE every 4 (n=229) or 2 weeks (n=226) after a 160 mg starting dose. Patients included in this post-hoc analysis had baseline $\geq 3\%$ body surface area (BSA) and at least one visit with a Psoriasis Area and Severity Index (PASI) 75 and American College of Rheumatology (ACR) 20 response; all treatment groups were combined. During the first 24 weeks of the trial, health-related quality of life (HRQoL) was measured by Short Form-36 Health Survey (SF-36) domain scores, the EuroQoL 5 Dimensions Visual Analogue Scale (EQ-5D VAS), and the Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) activity impairment domain. Change in HRQoL at Week 24 was modelled using a response surface model with duration of consecutive PASI and ACR responses and their interaction as independent variables. Missing data were imputed using last observation carried forward and non-responder imputation for continuous and categorical endpoints, respectively.

Results: Of the 679 placebo- and IXE-treated patients in the SPIRIT trials, 215 (31.7%) had baseline $\geq 3\%$ BSA and ≥ 1 PASI75 and ACR20 response. Longer consecutive ACR20 responses correlated positively with greater HRQoL improvements, as measured by the EQ-5D VAS (figure 1). Patients with a longer consecutive number of both ACR20 and PASI75 responses had the highest improvements in EQ-5D VAS. This was consistent with 7 of 8 SF-36 domains, as well as the WPAI-SHP activity impairment domain (data not shown).

Abstract SAT0316 – Figure 1

Response surface modelling of the contribution of skin and joint improvements to patient HRQoL. (A) Three-dimensional scatterplot of skin (y-axis: PASI – consecutive response in weeks), joint (x-axis: ACR20 – consecutive response in weeks), and HRQoL (z-axis: EQ-5D – change from baseline) improvement at Week 24. A colour spectrum is applied to HRQoL improvements (blue [least improvement] to red [greatest improvement]). (B) Response surface of scatterplot estimated by smoothing spline method.

Conclusions: Early and sustained improvements in the symptoms of PSA correlated positively with improved HRQoL. The greatest HRQoL improvements were achieved when both skin and musculoskeletal symptoms improved early and were sustained.

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