patients we have used it intravenously, and in higher doses, where the half-life is shorter and twice daily dosing is required. Anakinra was well tolerated and its short half-life makes it ideal for use in suspected sepsis-driven HLH. One case was managed entirely steroid-free using anakinra. This allowed for the identification of an underlying lymphoma which may have missed had high-dose steroids been used. Larger studies will help us ascertain whether earlier anakinra use may spare steroid and chemotherapy side-effects and improve patient outcomes.

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THU0052

USTEKINUMAB AND GUSELKUMAB TREATMENT RESULTS IN DIFFERENCES IN SERUM IL17A, IL17F AND CRP LEVELS IN PSORIATIC ARTHRITIS PATIENTS: A COMPARISON FROM USTEKINUMAB PH3 AND GUSELKUMAB PH2 PROGRAMS

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Background: Ustekinumab (UST) is a monoclonal antibody (mAb) that binds the p40 epitope which is shared by IL12 and IL23, whereas guselkumab (GUS) is a mAb that selectively binds the p19 subunit of IL23. In recent studies, both UST (Phase 3 programs)¹ and GUS (Phase 2 program)² have demonstrated a reduction in musculoskeletal clinical signs and symptoms and improvement of psoriatic lesions in patients with active psoriatic arthritis (PsA), implicating the IL12/23 pathway in disease pathogenesis.

Objectives: To explore the post-treatment pharmacodynamic changes of IL17A, IL17F, and CRP with GUS and UST in the context of PsA.

Methods: Serum protein levels of IL17A, IL17F, and CRP were measured in 142 subjects and 38 matched healthy controls from the GUS Ph2 study² at Weeks 0, 4, and 16. In the UST Ph3 studies¹, biomarkers were assayed at Weeks 0, 4, and 24 as follows: IL17A (n=474), IL17F (n=237), CRP (n=927). IL17A and IL17F were assayed using Single Molecule CountingTM Human Immunoassay Kits (formerly Singulex). CRP was measured using CardioPhase hsCRP assay (UST studies) or Meso Scale Discovery Platform (GUS study).

Results: At baseline, the Th17 effector cytokines IL17A and IL17F were elevated in the serum of PsA subjects in the GUS Ph2 cohort compared to healthy controls. IL17A and IL17F levels significantly correlated with affected skin body surface area, but not swollen or tender joint scores, in both studies. While none of the baseline levels of evaluated cytokines were associated with American College of Rheumatology (ACR) or Psoriasis Area Severity Index (PASI) clinical responses to UST, baseline IL17F levels were modestly associated with ACR20 response to GUS at week 24. Both UST and GUS treatment resulted in pharmacodynamic decreases in IL17A, IL17F, and CRP levels, with GUS treatment restoring IL17A and IL17F levels to that of healthy controls by week 16. Consistent with being a component of ACR scores, CRP changes were significantly associated with ACR20 responses to both UST and GUS treatment. Weeks 4 and 16 changes in IL17F with GUS treatment were significantly associated with ACR20 response at week 24. Week 24 PASI75 response to GUS was significantly associated with week 4 changes in IL17A, with a similar trend observed at Week 16.

Conclusion: These results underscore the relevance of the IL23/Th17 pathway in PsA, with GUS treatment providing a stronger suppression of the pathway than UST treatment. The significant associations of changes in IL17A and IL17F levels with GUS treatment with PASI75 and ACR20 response, respectively, support the importance of the IL23/Th17 pathway for both skin and joint pathologies. The associations of reduction in CRP levels with both UST and GUS treatment also reinforce the role of acute phase inflammation in joint pathology.

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THU0053

APREMILAST INHIBITS THE TGFβ1 MEDIATED TRANSITION OF CULTURED HUMAN SKIN FIBROBLASTS INTO PROFIBROTIC MYOFIBROBLASTS: IN VITRO STUDY

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Background: Fibroblast-to-myofibroblast transition and extracellular matrix (ECM) overproduction represent fundamental events in chronic inflammation, that characterise several diseases, including psoriasis (1,2). Transforming growth factor-β1 (TGFβ1), plays an important role as a profibrotic mediator (3).

Phosphodiesterases (PDE)4 act as proinflammatory enzymes via degradation of cAMP. PDE4 are expressed in normal skin fibroblasts (Fbs) and overexpressed in psoriatic skin Fbs and myofibroblasts (2).

Objectives: This study investigated how apremilast (an oral PDE4 inhibitor small molecule used for the treatment of psoriasis and psoriatic arthritis) might interfere with intracellular signalling for the fibroblast-to-myofibroblast transition and the synthesis of profibrotic ECM proteins induced by TGFβ1 in primary cultures of healthy human skin Fbs.

Methods: Human skin Fbs were isolated from 7 voluntary healthy subjects after signing informed consent and EC approval. The cultured Fbs were stimulated with TGFβ1 10ng/ml alone or in combination with apremilast 1μM and 10μM for 4, 16 and 24 hours. Other aliquots of Fbs were also previously stimulated with TGFβ1 for 4 hours and then treated with apremilast 1μM and 10μM for 4, 16 and 24 hours always in the presence of TGFβ1. Genes and related protein expression of α-smooth muscle actin (αSMA), type I collagen (COL-1) and fibronectin (FN) were investigated by qRT-PCR and Western blotting (WB). Smad proteins (the main signal transducers for receptors of TGFβ1) and extracellular signal-regulated kinases (ERKs), which are implicated in mediating TGFβ1 effects, were investigated by WB after 15, 30 and 60 minutes of apremilast treatment combined with TGFβ1 stimulation.

Results: Apremilast significantly downregulated the phosphorylation of Smad 2 and 3, at 15 minutes, and that of Erk1/2, after 30 minutes (p<0.05), both induced by TGFβ1 stimulation in cultured skin Fbs. Apremilast significantly downregulated the TGFβ1-induced increase in the gene expression of αSMA, COL-1 and FN at 4 and 16 hours, and the related protein synthesis at 24 hours (p<0.05) in cultured skin Fbs (treated in combination with TGFβ1). Similar effects were observed in differentiated myofibroblasts treated with apremilast.

Conclusion: Apremilast inhibited the fibroblast-to-myofibroblast transition *in vitro*, as well as the profibrotic activity induced by TGFβ1 in cultured skin Fbs by downregulating specific intracellular signalling pathways Smad 2/3 and Erk 1/2. These results might partially explain some of the downregulating effects on skin Fbs overactivity during treatment of skin lesions of psoriasis and that of psoriatic patients with apremilast.