HETEROZYGOUS MUTATIONS IN COPA ARE ASSOCIATED WITH ENHANCED TYPE I INTERFERON SIGNALLING

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Background: Heterozygous mutations in COPA encoding coatomer protein subunit alpha, cause an autosomal dominant inflammatory syndrome associating lung, joint and renal disease, showing some overlap with STING-associated vasculopathy with onset in infancy (SAVI). Mutations were originally described to cause endoplasmic reticulum (ER) stress and priming of a T helper 17 response. More recently, increased transcription of interferon (IFN)-stimulated genes (ISGs) has been reported in blood and circulating cells of affected individuals. However, the precise pathophysiology of this disease remains unclear.

Objectives: To better decipher the mechanism of COPA syndrome.

Methods: We studied 8 patients from 3 unrelated families, each segregating a heterozygous mutation in COPA. We assessed type I IFN status by IFNα ultra-sensitive digital quantitation in plasma, STAT1 phosphorylation and RNA expression of ISGs in whole blood from patients. Pathway assays also were performed in HEK293T and THP-1 cells to study IFN signalling in the context of COPA mutations.

Results: We observed commonalities in the lung pathology between COPA and SAVI, as well as an IFN signature, raised levels of IFNα protein in the serum and phosphorylation of STAT1 in patient T cells. In a cellular model of HEK293T, phosphorylation of IRF3 and increased ISG expression were observed in cells co-transfected with wild type STING and mutant COPA plasmids. In THP-1 cells, short hairpin RNA knockdown of COPA induced IFN signalling that was abrogated in the absence of STING.

Conclusion: Our data suggest that mutations in COPA lead to constitutive activation of type I IFN signalling through STING. Based on these results, one patient has been treated with the JAK1/2 inhibitor ruxolitinib for the last 12 months. How COPA interacts with ER-resistant STING remains to be investigated.

REFERENCES:

Disclosure of Interests: None declared

THURSDAY, 13 JUNE 2019

Psoriatic arthritis: old and new drugs and how to deal with them?

DUAL NEUTRALISATION OF IL-17A AND IL-17F WITH BIMEKIZUMAB IN PATIENTS WITH ACTIVE PSA: OVERALL AND TNF-INHIBITOR-NAIVE POPULATION RESULTS FROM A 48-WEEK PHASE 2B RANDOMISED STUDY

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Background: IL-17F shares structural homology and pro-inflammatory function with IL-17A. Preclinical and early clinical data support neutralisation of IL-17F, in addition to IL-17A, as a novel targeting approach in psoriatic disease.

Objectives: The objective of this Phase 2b study (NCT029869525) was to assess the dose response, long-term efficacy and safety of bimekizumab (BKZ), a mAb that potently and selectively neutralises IL-17A and IL-17F, over 48 weeks in patients (pts) with active PsA.

Methods: 206 pts with active PsA, ≥3/76 swollen joint count, ≥3/78 tender joint count and CASPAR score ≥3, were randomised (1:1:1:1:1) to receive subcutaneous BKZ 16mg, 160mg, 160mg with 320mg loading dose (160mg (LD), 320mg or placebo (PBO) Q4W, for 12 weeks (double-blind period). After Week 12, pts receiving PBO or BKZ 16mg were re-randomised (1:1) to BKZ 160mg or 320mg; all other pts continued on their initial dose (dose-blind period). The primary endpoint was ACR50 response at Week 12.

Results: 203/206 and 189/206 pts completed the double- and dose-blind periods, respectively. Overall, demographics and baseline disease characteristics were balanced across groups. 19% of pts had prior exposure to TNF inhibitors (TNFi). There was a statistically significant (p<0.05) dose-response at Week 12 for ACR50 response rates. At Week 12, significantly more pts receiving BKZ versus PBO achieved ACR50 (primary endpoint: 16–160mg (LD) doses), ACR20 and PASI90 (in those pts with baseline body surface area >3%; 160–320mg doses) (table). ACR20/50/70 and PASI75/90/100, MDA and resolution of enthesitis response rates increased between Week 12 and Week 24 in those continuing on their initial BKZ dose; Week 24 responses were maintained throughout the study; responses were similar across the three highest dose groups at Week 48 (PASI100 analyses were post hoc). Rapid improvements were observed across all response criteria in pts re–allocated to BKZ 160 or 320mg (table). BKZ-treated pts naive to TNF achieved ACR20/50 and PAS90/100 at comparable rates to the overall population at Week 12 and 48. There was no apparent relationship between dose and TEAEs. Serious AEs were reported by 9/206 (4.4%) pts up to Week 48 (8/206 [3.9%] patients were receiving BKZ). The most common TEAE up to Week 48 was nasopharyngitis 25/206 [12.1%]). Oral candidiasis was reported at Week 48 by 10/206 (4.9%) pts (all cases during BKZ treatment). No deaths, or cases of IBD or MACE were reported.

Conclusion: Dual neutralisation of IL-17A and IL-17F with BKZ provided substantial improvements in both musculoskeletal and skin outcomes; response rates increased after Week 12 (primary analysis) and were sustained from Week 24 to 48, with a safety profile consistent with previous BKZ studies. These data provide further support that neutralising IL-17F in addition to IL-17A with BKZ is a promising therapeutic approach in pts with active PsA.

Acknowledgement: Funded by UCB Pharma.

Disclosure of Interests: Christopher T. Ritchlin Grant/research support from: AbbVie, Amgen, UCB Pharma, Consultant for: AbbVie, Amgen, Lilly, Novartis, Pfizer, UCB Pharma, Arthur Kavanaugh Grant/research support from: UCB Pharma, Joseph F. Merola Consultant for: Biogen IDEC, Abbvie, Amgen, Eli Lilly and Company, Novartis, Pfizer, Janssen, UCB, Samumed, Celgene, Sanofi, Regeneron, Merck, and GSK, Georg Schett: None declared, Jose U. Scher Consultant for: BMS, Janssen, Novartis, UCB Pharma, Richard B. Warren Grant/ research support from: AbbVie, Almirall, Amgen, Celgene, Jansen, Lilly, LEO, Novartis, Pfizer, UCB Pharma, Consultant for: AbbVie, Almirall, Amgen, Boehringer-Ingleheim, Celgene, Jansen, LEO, Lilly, Novartis, Pfizer, Sanofi, UCB, Xeroport, Deepak Assudani Shareholder of: UCB Pharma, Employee of: UCB Pharma, Thomas Kume Employee of: UCB Pharma, Barbara Ink Shareholder of: GSK, UCB Pharma, Employee of: UCB Pharma, lain Mounes Grant/research support from: AbbVie, Amgen, UCB, Novartis, Pfizer, UCB Pharma, Consultant for: Amgen, UCB, AbbVie, Novartis, Pfizer, UCB Pharma, Employee of: UCB Pharma.