OP0107

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) was reported in blood 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 quantification in plasma, STAT1 phosphorylation and RNA expression of ISGs in whole blood from patients. *In vitro* 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-resident STING remains to be investigated.

REFERENCES:

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

OP0108

DUAL NEUTRALISATION OF IL-17A AND IL-17F WITH BIMEKIZUMAB IN PATIENTS WITH ACTIVE PSA: OVERALL AND TNF-INHIBITOR-NAÏVE 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 (NCT02969525) was to assess the dose response, long-term efficacy and safety of bimekizumab (BKZ), a mAb that potentially and selectively neutralises IL-17A and IL-17F, over 48 weeks in patients (pts) with active PsA.

Methods: 206 pts with active PsA, $\geq 3/76$ swollen joint count, $\geq 3/78$ 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 end-point was ACR50 response at Week 12.

n (%) of patients	Week 12*					
	Placebo	BKZ 16 mg	BKZ 160 mg	BKZ 160 mg (LD)	BKZ 320 mg	
ACR50	8/62 (12.9)	25/61 (41.0)**	28/61 (45.9)**	25/61 (41.0)**	21/61 (34.4)**	
TNFi naïve	7/23 (30.4)	20/34 (58.8)	23/33 (69.7)	23/34 (67.6)	19/33 (57.6)	
TNFi naïve	3/62 (4.8)	11/61 (18.0)**	17/61 (27.9)**	18/61 (29.5)**	10/61 (16.4)**	
ACR50	3/33 (9.1)	11/34 (32.4)	14/32 (43.8)	14/34 (41.2)	8/32 (25.0)	
TNFi naïve	2/11 (18.2)	5/11 (45.5)**	8/11 (72.7)**	8/11 (72.7)**	4/11 (36.4)**	
MDA	6/62 (9.7)	13/61 (21.3)**	18/61 (29.5)**	17/61 (27.9)**	12/61 (19.7)**	
PASI75	2/33 (6.1)	13/34 (38.2)**	18/33 (54.5)**	16/34 (47.1)**	10/33 (30.3)**	
PASI90	2/33 (6.1)	6/33 (18.2)**	13/33 (39.4)**	14/33 (42.4)**	14/33 (42.4)**	
TNFi naïve	2/22 (9.1)	6/22 (27.3)**	9/22 (40.9)**	9/22 (40.9)**	13/22 (59.1)**	
PASI75	2/22 (9.1)	6/22 (27.3)**	9/22 (40.9)**	9/22 (40.9)**	13/22 (59.1)**	
TNFi naïve	2/22 (9.1)	6/22 (27.3)**	9/22 (40.9)**	9/22 (40.9)**	13/22 (59.1)**	
Resolution of enthesitis	6/21 (28.6)	5/19 (26.3)	13/22 (59.1)**	13/22 (59.1)**	8/21 (38.1)**	

n (%) of patients	Week 24*					
	Placebo	Placebo	BKZ 16 mg	BKZ 160 mg	BKZ 160 mg (LD)	BKZ 320 mg
ACR50	13/33 (39.4)	15/33 (45.5)	20/32 (62.5)**	18/32 (56.3)**	27/32 (84.4)**	33/61 (54.1)**
ACR50	6/23 (26.1)	10/33 (30.3)	13/32 (40.6)**	14/32 (43.8)**	23/32 (71.9)**	33/61 (54.1)**
ACR70	9/33 (27.3)	10/33 (30.3)	16/32 (50.0)**	17/32 (53.1)**	25/32 (78.1)**	33/61 (54.1)**
MDA	8/33 (24.2)	10/33 (30.3)	15/32 (46.9)**	16/32 (50.0)**	25/32 (78.1)**	33/61 (54.1)**
PASI75	10/33 (30.3)	12/33 (36.4)	17/32 (53.1)**	18/32 (56.3)**	27/32 (84.4)**	33/61 (54.1)**
PASI90	5/33 (15.2)	11/33 (33.3)	14/32 (43.8)**	15/32 (46.9)**	25/32 (78.1)**	33/61 (54.1)**
Resolution of enthesitis	4/10 (40.0)	7/10 (70.0)	5/10 (50.0)	2/10 (20.0)	14/20 (70.0)	10/21 (47.6)**

n (%) of patients	Week 48*					
	Placebo	Placebo	BKZ 16 mg	BKZ 160 mg	BKZ 160 mg (LD)	BKZ 320 mg
ACR50	13/33 (39.4)	14/33 (42.4)	19/32 (59.4)**	18/32 (56.3)**	27/32 (84.4)**	33/61 (54.1)**
ACR50	6/23 (26.1)	10/33 (30.3)	13/32 (40.6)**	14/32 (43.8)**	23/32 (71.9)**	33/61 (54.1)**
ACR70	9/33 (27.3)	10/33 (30.3)	16/32 (50.0)**	17/32 (53.1)**	25/32 (78.1)**	33/61 (54.1)**
MDA	8/33 (24.2)	10/33 (30.3)	15/32 (46.9)**	16/32 (50.0)**	25/32 (78.1)**	33/61 (54.1)**
PASI75	10/33 (30.3)	12/33 (36.4)	17/32 (53.1)**	18/32 (56.3)**	27/32 (84.4)**	33/61 (54.1)**
PASI90	5/33 (15.2)	11/33 (33.3)	14/32 (43.8)**	15/32 (46.9)**	25/32 (78.1)**	33/61 (54.1)**
Resolution of enthesitis	4/10 (40.0)	7/10 (70.0)	5/10 (50.0)	2/10 (20.0)	14/20 (70.0)	10/21 (47.6)**

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 $\geq 3\%$; 160–320mg doses) (table). ACR20/50/70, 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 through 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 naïve to TNFi achieved ACR20/50 and PASI90/100 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.

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