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.

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Disclosure of Interests: None declared

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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 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.

In (%) of patients	Placebo	BKZ 16 mg	BKZ 160 mg	BKZ 160 mg (LD)	BKZ 320 mg
Week 12[a]					
ACR20	8/42 (19.0)	22/41 (53.7)**	29/41 (70.7)***	25/41 (61.0)***	21/41 (51.2)**
TNFi naive	7/33 (21.2)	20/34 (58.8)	23/33 (69.7)	23/34 (67.6)	18/33 (54.5)
ACR50	3/42 (7.1)	11/41 (26.8)*	17/41 (41.5)**	19/41 (46.3)***	10/41 (24.4)
TNFi naive	2/33 (6.1)	11/34 (32.4)	14/33 (42.4)	16/34 (52.9)	8/33 (24.2)
ACR70	2/42 (4.8)	5/41 (12.2)	8/41 (19.5)	13/41 (31.7)**	6/41 (14.6)
MDA	6/42 (14.3)	13/41 (31.7)	19/41 (46.3)	17/41 (41.5)	12/41 (29.3)
PASI75[b]	2/28 (7.1)	13/29 (44.8)**	18/28 (64.3)**	20/26 (76.9)***	14/26 (53.8)***
PASI90[b]	2/28 (7.1)	6/29 (20.7)	13/28 (46.4)**	14/26 (53.8)***	14/26 (53.8)**
TNFi naive	2/22 (9.1)	6/23 (26.1)	9/20 (45.0)	13/22 (59.1)	13/22 (59.1)
PASI100	2/28 (7.1)	5/29 (17.2)	10/28 (35.7)	13/26 (50.0)	10/26 (38.5)
TNFi naive	2/22 (9.1)	5/23 (21.7)	7/20 (35.0)	12/22 (54.5)	9/22 (40.9)
Resolution of enthesitis[c]	6/21 (28.6)	5/10 (26.3)	13/22 (59.1)	13/22 (59.1)	8/23 (34.8)

	Placebo → BKZ 160 mg	Placebo → BKZ 320 mg	BKZ 16 mg → BKZ 160 mg	BKZ 16 mg → BKZ 320 mg	BKZ 160 mg → BKZ 160 mg	BKZ 160 mg (LD) → BKZ 160 mg	BKZ 320 mg → BKZ 320 mg
Week 24[d]							
ACR20	13/20 (65.0)	15/20 (75.0)	20/22 (90.9)	16/19 (84.2)	27/40 (67.5)	29/37 (78.4)	33/41 (80.5)
ACR50	9/20 (45.0)	10/20 (50.0)	13/22 (59.1)	12/19 (63.2)	24/40 (60.0)	23/37 (62.2)	23/41 (56.1)
ACR70	5/20 (25.0)	8/20 (40.0)	8/22 (36.4)	7/19 (36.8)	13/40 (32.5)	15/37 (40.5)	11/41 (26.8)
MDA	6/20 (30.0)	11/20 (55.0)	11/22 (50.0)	12/19 (63.2)	20/40 (50.0)	22/37 (59.5)	19/41 (39.6)
PASI75[b]	10/11 (90.9)	13/15 (86.7)	12/14 (85.7)	14/15 (93.3)	22/27 (81.5)	19/23 (82.6)	21/26 (80.8)
PASI90[b]	5/11 (45.5)	11/15 (73.3)	11/14 (78.6)	11/15 (73.3)	18/27 (66.7)	18/23 (78.3)	20/26 (76.9)
Resolution of enthesitis[c]	4/10 (40.0)	7/10 (70.0)	5/10 (50.0)	7/10 (70.0)	12/22 (54.5)	14/20 (70.0)	10/23 (43.5)

	Placebo → BKZ 160 mg	Placebo → BKZ 320 mg	BKZ 16 mg → BKZ 160 mg	BKZ 16 mg → BKZ 320 mg	BKZ 160 mg → BKZ 160 mg	BKZ 160 mg (LD) → BKZ 160 mg	BKZ 320 mg → BKZ 320 mg
Week 48[d]							
ACR20	13/20 (65.0)	14/20 (70.0)	19/22 (86.4)	17/19 (89.5)	28/40 (70.0)	27/37 (73.0)	31/41 (75.6)
TNFi naive	10/16 (62.5)	10/16 (62.5)	16/18 (88.9)	14/16 (87.5)	21/32 (65.6)	24/30 (80.0)	26/33 (78.8)
ACR50	8/20 (40.0)	14/20 (70.0)	11/22 (50.0)	16/19 (84.2)	22/40 (55.0)	21/37 (56.8)	26/41 (63.4)
TNFi naive	5/16 (31.3)	10/16 (62.5)	10/18 (55.6)	13/16 (81.3)	19/32 (59.4)	19/30 (63.3)	22/33 (66.7)
ACR70	8/20 (40.0)	8/20 (40.0)	6/22 (27.3)	10/19 (52.6)	17/40 (42.5)	17/37 (45.9)	19/41 (46.3)
MDA	8/20 (40.0)	11/20 (55.0)	9/22 (40.9)	15/19 (78.9)	24/40 (60.0)	20/37 (54.1)	19/41 (46.3)
PASI75[b]	11/11 (100)	12/15 (80.0)	12/14 (85.7)	12/15 (80.0)	21/27 (77.8)	21/23 (91.3)	22/26 (84.6)
PASI90[b]	11/11 (100)	11/15 (73.3)	10/14 (71.4)	12/15 (80.0)	19/27 (70.4)	19/23 (69.6)	22/26 (84.6)
TNFi naive	10/10 (100)	8/11 (72.7)	8/11 (72.7)	9/12 (75.0)	13/19 (68.4)	14/19 (73.7)	18/22 (81.8)
PASI100	8/11 (72.7)	8/15 (53.3)	9/14 (64.3)	12/15 (80.0)	18/27 (66.7)	14/23 (60.9)	19/26 (73.1)
TNFi naive	7/10 (70.0)	6/11 (54.5)	7/11 (63.6)	9/12 (75.0)	13/19 (68.4)	12/19 (63.2)	15/22 (68.2)
Resolution of enthesitis[c]	4/10 (40.0)	7/10 (70.0)	4/10 (40.0)	4/9 (44.4)	15/22 (68.2)	7/10 (70.0)	13/23 (56.5)

Non-responder imputation accounted for missing values at Weeks 12, 24 and 48; *denotes significant difference versus placebo (pairwise comparison with logistic regression at Week 12); *p<0.05, **p<0.01, ***p<0.001. [a]all analyses set, all randomised patients who received ≥1 dose of study medication and had a valid measurement of the primary efficacy variable at baseline; [b]dose-blind set, all patients who started the dose-blind period and received ≥1 dose of treatment during the dose-blind period; [c]TNFi response evaluated in patients with psoriasis involvement of ≥3% BSA at baseline; [d]solution of enthesitis evaluated in patients with enthesitis at baseline using the MASES index; BKZ, bimekizumab; BSA, body surface area; LD, loading dose; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index; TNF, tumour necrosis factor.

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, 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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OP0109   EFFICACY OF FILGOTINIB VS PLACEBO IN ACTIVE PSORIATIC ARTHRITIS: PATIENT-LEVEL DATA FROM EQUATOR, A RANDOMIZED, PHASE 2 STUDY

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Background: Filgotinib (FIL) is an oral, selective Janus kinase 1 inhibitor in development for the treatment of several inflammatory diseases. In the phase 2 EQUATOR trial (NCT03101670), FIL was efficacious vs placebo (PBO) in patients with active psoriatic arthritis (PsA), and was well tolerated [1].

Objectives: To evaluate the onset and maintenance of response to FIL vs PBO in EQUATOR by evaluating patient–level response over time.

Methods: EQUATOR was a 16-week, multicenter, double-blind study in which patients with active PsA were randomized 1:1 to FIL 200 mg or PBO once daily [1]. Disease activity was assessed at screening, day 1 and weeks 1, 2, 4, 8, 12 and 16, and the primary efficacy endpoint was the proportion of patients achieving 20% American College of Rheumatology (ACR20) response. The onset of response was assessed by calculating the median time to ACR20 response using the Kaplan-Meier method and compared between FIL and PBO using the log-rank test. Maintenance of response was assessed by analysing ACR20 response patterns over time in the FIL and PBO groups.

Results: Of 131 patients randomized (FIL: n=65; PBO: n=66), 124 (95%) completed the study. Demographics and baseline disease characteristics were similar between groups. The onset of response to FIL was early, with a median (95% confidence interval) time to first ACR20 response of 4.07 weeks (2.29, 4.14) in the FIL group compared with 12.29 weeks (12, not reached) in the PBO group (p<0.0001; Figure 1). ACR20 responses were achieved at week 16 in 80.0% (52/65) and 33.3% (22/66) of patients in the FIL and PBO groups, respectively, using the non-responder imputation method, and 86.7% (52/60) and 34.4% (22/64), respectively, using observed cases. The number of patients who presented with a stable ACR20 response (i.e. the response was maintained once initially achieved regardless of the time point at which the patient first became a responder) among those who were responders at week 16 (i.e. the primary endpoint) was higher in the FIL group than in the PBO group (80.8% [42/52] vs 68.2% [15/22]) (**Figure 2**). Similar trends were observed for other efficacy endpoints representing various manifestations of PsA.

Conclusion: In general, patients treated with FIL achieved an ACR20 response earlier than those on PBO and these responses appeared to be more stable. In the PBO group, there were more occurrences of the response being lost over time and fewer cases of regaining a lost response.
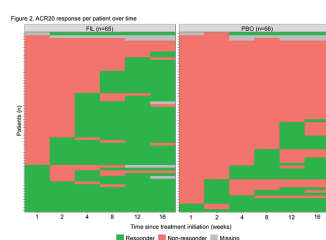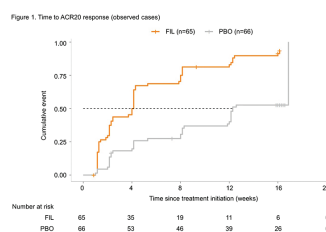
REFERENCE:
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Figure 1. Time to ACR20 response (observed cases)

Figure 2. ACR20 response per patient over time

OP0110   IXEKIZUMAB IMPROVES SIGNS AND SYMPTOMS OF PSORIATIC ARTHRITIS IN PATIENTS WHO HAVE HAD INADEQUATE RESPONSE TO 1 OR 2 TUMOR NECROSIS FACTOR INHIBITORS

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Background: Psoriatic arthritis (PsA) is a progressive, chronic inflammatory disease often treated with tumor necrosis factor inhibitors (TNFi) when conventional treatments fail. Patients with inadequate response to TNFi represent a more difficult-to-treat population.

Objectives: To report the efficacy of ixekizumab (IXE), a monoclonal antibody that selectively targets interleukin-17A, in patients with inadequate response to 1 TNFi or 2 TNFi.

Methods: In a Phase 3 study (SPIRIT-P2; NCT02349295), patients who had an inadequate response or intolerance to 1 or 2 TNFi were randomized to receive subcutaneous IXE 80 mg every 2 weeks (IXEQ2W; N=123) or every 4 weeks (IXEQ4W; N=122), after a 160-mg starting dose, or placebo (PBO; N=118) for up to 24 weeks. At Week 16, patients not meeting predefined criteria (<20% improvement in tender joint count [TJC] and swollen joint count [SJC]) received rescue therapy and were imputed as nonresponders at Weeks 20 and 24. At Week 24, PBO patients were rerandomized to IXEQ2W or IXEQ4W through Week 52 and excluded from the 52-week analysis. At Week 32 or any subsequent visit, patients were discontinued if they did not reach ≥20% improvement from baseline in both TJC and SJC. These ad-hoc data were derived from patients in the intent-to-treat population with prior inadequate response to TNFi; intolerant patients were excluded from the analysis. Efficacy was measured by percentage of patients who attained ≥50% improvement in American College of Rheumatology response criteria (ACR50), an improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) ≥0.35, minimal disease activity (MDA), Disease Activity Score 28 – C-reactive protein (DAS28-CRP) EULAR Good Response criteria, and Disease Activity in Psoriatic Arthritis (DAPSA) ≤14.

Results: At baseline, 1-TNFi inadequate responders were, on average, 52 years of age with a PsA diagnosis for 10 years; 40% were using MTX, and HAQ-DI was 1.2. 2-TNFi inadequate responders were 52 years of age with a PsA diagnosis for 11 years; 42% were using MTX, and HAQ-DI was 1.3. Regardless of inadequate response to 1 or 2 TNFi, at Week 24 significantly more patients receiving Q4W or