OP0107

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

Marie-Louise Frémond[1], Alice Lepelley[1], Carolina Uggenti[2], Maria José Martin-Niclos[1], Marine Depp[2], Vincent Bondet[3], Darragh Duffy[3], Gillian I Rice[4], Mary Brennan[5], Caroline Thumerelle[6], Siham Boulisfane[6], Marie Legendre[7], Serge Amselem[7], Thierry Molina[8], Nadia Nathan[9], Yanick Crow[1,2]. [1]*Imagine Institute, Laboratory of Neurogenetics and Neuroinflammation, Paris, France*; [2]*Institute of Genetics and Molecular Medicine, Centre for Genomic and Experimental Medicine, Edinburgh, United Kingdom*; [3]*Institut Pasteur, Immunobiology of Dendritic Cells, Paris, France*; [4]*Manchester Academic Health Science Centre, Division of Evolution and Genomic Sciences, Manchester, United Kingdom*; [5]*Royal Hospital for Sick Children, Department of Paediatric Rheumatology, Edinburgh, United Kingdom*; [6]*CHU de Lille, Pediatrics Department, Lille, France*; [7]*Trousseau Hospital-APHP and Sorbonne Université, Genetic Department and Inserm UMR S933, Paris, France*; [8]*Necker Hospital-APHP, Pathology Department, Paris, France*; [9]*RespiRare, Trousseau Hospital-APHP and Sorbonne Université, Inserm UMR S933 and Pediatric Pulmonology department and Reference Centre for Rare Lung Diseases, Paris, France*

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:

[1] Watkin et al, Nat Genet 2015;47:654-60.
[2] Volpi et al, Clin Immunol 2018;187:33-36.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.4158

THURSDAY, 13 JUNE 2019

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

Christopher T. Ritchlin[1], Arthur Kavanaugh[2], Joseph F. Merola[3], Georg Schett[4], Jose U. Scher[5], Richard B. Warren[6], Deepak Assudani[7], Thomas Kumke[8], Barbara Ink[7], Iain Mcinnes[9]. [1]*University of Rochester Medical Centre, Rochester, United States of America*; [2]*UC San Diego School of Medicine, La Jolla, United States of America*; [3]*Harvard Medical School, Brigham and Women's Hospital, Boston, United States of America*; [4]*Friedrich Alexander University Erlangen-Nurnberg, Erlangen, Germany*; [5]*NYU Langone Medical Center, Department of Medicine, New York, United States of America*; [6]*The Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom*; [7]*UCB Pharma, Slough, United Kingdom*; [8]*UCB Pharma, Monheim am Rhein, Germany*; [9]*University of Glasgow, Glasgow, United Kingdom*

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.

n (%) 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)	18/34 (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)**	18/26 (64.3)***	20/26 (76.9)***	19/26 (73.1)***
PASI90[b]	2/28 (7.1)	6/29 (20.7)	13/26 (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)	10/26 (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)	5/19 (26.3)	13/22 (59.1)	13/22 (59.1)	8/23 (34.8)
Week 24[d]					
	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
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)	13/19 (63.2)	24/40 (60.0)	23/37 (62.2)	22/41 (53.7)
ACR70	5/20 (25.0)	6/20 (30.0)	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)	26/40 (65.0)	22/37 (59.5)	15/41 (36.6)
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)	2/9 (22.2)	12/22 (54.5)	14/20 (70.0)	10/23 (43.5)
Week 48[e]							
	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
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)	23/40 (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)	18/41 (39.0)
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)	13/15 (80.0)	12/14 (85.7)	13/15 (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)	16/23 (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)	14/20 (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). †nominal p<0.05, ††nominal <0.01. ‡Full analysis set, all randomised patients who received ≥1 dose of study medication and had a valid measurement of the primary efficacy variable at baseline. §dose-blind set, all patients who started the dose-blind period and received ≥1 dose of bimekizumab during the dose-blind period. ¶PASI response evaluated in patients with psoriasis involvement of ≥3% BSA at baseline. #resolution of enthesitis was evaluated in patients with enthesitis at baseline using the MASEI 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.
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, Janssen, Lilly, LEO, Novartis, Pfizer, UCB Pharma, Consultant for: AbbVie, Almirall, Amgen, Boehringer-Ingleheim, Celgene, Janssen, LEO, Lilly, Novartis, Pfizer, Sanofi, UCB, Xenoport, Deepak Assudani Shareholder of: UCB Pharma, Employee of: UCB Pharma, Thomas Kumke Employee of: UCB Pharma, Barbara Ink Shareholder of: GSK, UCB Pharma, Employee of: UCB Pharma, Iain McInnes Grant/research