Markers of IL-17 Signaling in the Blood of Patients with Psoriatic Arthritis with Inadequate Response to Tumor Necrosis Factor Inhibitors

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Presenter: Cori Cooper

Objective

To test the hypothesis that immune signaling pathways, specifically interleukin (IL)-17F signaling, may be differentially regulated in patients with psoriatic arthritis (PsA) following treatment with tumor necrosis factor inhibitors (TNFis), providing a potential mechanism for the consistent clinical response observed with bimekizumab treatment across biologic disease-modifying antirheumatic drug (bDMARD)–naïve and TNFi–experienced patients.

Background

- In clinical trial and registry data from patients with PsA treated with bDMARDs that do not target IL-17F (e.g., TNFi, IL-17Ai, IL-23i), TNFi–naïve patients tended to achieve a treatment response more frequently than TNFi–experienced patients.[1,2]
- However, in clinical trials involving patients with PsA, consistent levels of response to bimekizumab (BKZ) have been observed regardless of prior TNFi exposure.[3–7]
- BKZ is a monoclonal IgG1 antibody that selectively inhibits IL-17F in addition to IL-17A.[8,9]

Methods

- Immune signaling was assessed in two studies of TNFi–naïve patients with PsA initiating their first TNFi treatment.
- In Exploring Autoimmune disease Mechanisms IN Psoriatic Arthritis (EXAMINe-PsA), changes in immune cell composition were evaluated in TNFi responders versus (vs.) non-responders who had initiated TNFi treatment in a real-world setting (**Figure 1**).[10]
  - Flow cytometry was performed on whole blood samples taken at baseline and Week 16 of TNFi exposure, and the number of CD4+ T helper type 1 (Th1) and CD4+ T helper type 17 (Th17) cells was evaluated.
- A post-hoc biomarker analysis of samples collected during BE OPTIMAL (NCT03895203) was conducted for patients who were non-responders to the TNFi adalimumab (ADA) at Week 16 (**Figure 1**).[3]
  - *IL17F*–related gene expression was assessed by bulk RNA sequencing (RNA-seq) on whole blood samples at baseline and Week 16 of TNFi exposure. As *IL17F* gene expression was not detectable by bulk RNA-seq, *IL17F*–related signatures, comprised of regulatory genes and genes specific to *IL17F*–expressing T cells,[12,13] were used to assess possible immune priming indicative of *IL17F* expression in tissue.
  - Gene set level expression analyses were performed using Gene Set Variation Analysis (GSVA) and limma statistical methods.[14,15]
- In both studies, TNFi non-responders were defined based on lack of achievement at Week 16 of Psoriasis Area and Severity Index (PASI) ≥75% improvement from baseline (PASI75), PASI ≥50% improvement from baseline (PASI50), or resolution of swollen joint count (SJC=0).

Results

- In EXAMINe-PsA, immune cell composition trended toward increased levels of circulating Th17 cells in the blood from TNFi non-responders for PASI, albeit without meeting the threshold for statistical significance (**Figure 2**).
  - The increase in circulating Th17 cells was more pronounced in PASI50 non-responders than in PASI75 non-responders.
  - No change in Th17 cell levels was observed in SJC=0 non-responders.
  - Additionally, no increase in circulating Th17 cells was observed in TNFi responders or circulating Th1 cells in any group.
- In BE OPTIMAL, expression of Th17 cell– and *IL17F*–related gene signatures increased at Week 16 of TNFi exposure in whole blood samples from TNFi non-responders (**Figure 3**).
  - GSVA analysis showed that TNFi non-responders had a significant increase in an *IL17F*–related gene signature at Week 16 compared with baseline (**Figure 3**).
  - There was a negative correlation between PASI improvements and changes in *IL17F*–related gene signature expression at Week 16 of TNFi exposure (**Figure 4**).

Conclusions

In patients with PsA treated with TNFi, non-responders had increased expression of an *IL17F*–related gene signature, providing indirect evidence that IL-17F levels may increase in non-responders following TNFi exposure. Upregulation of IL-17F expression may be a compensatory immunomodulatory mechanism following TNFi exposure and may explain the consistent level of clinical response observed with bimekizumab treatment in TNFi–experienced and bDMARD–naïve patients in phase 3 clinical trials.

Numerical differences in immune cell composition observed in TNFi responders vs. non-responders were not significant. Further analyses of IL-17F production and activity at sites of inflammation in TNFi–experienced patients with PsA are required to support these preliminary results.

Summary

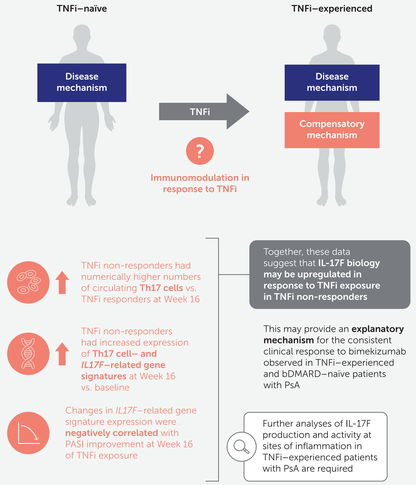
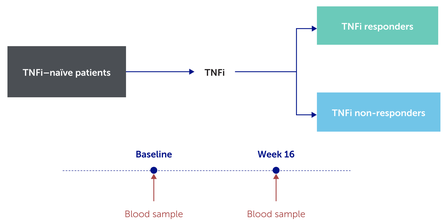
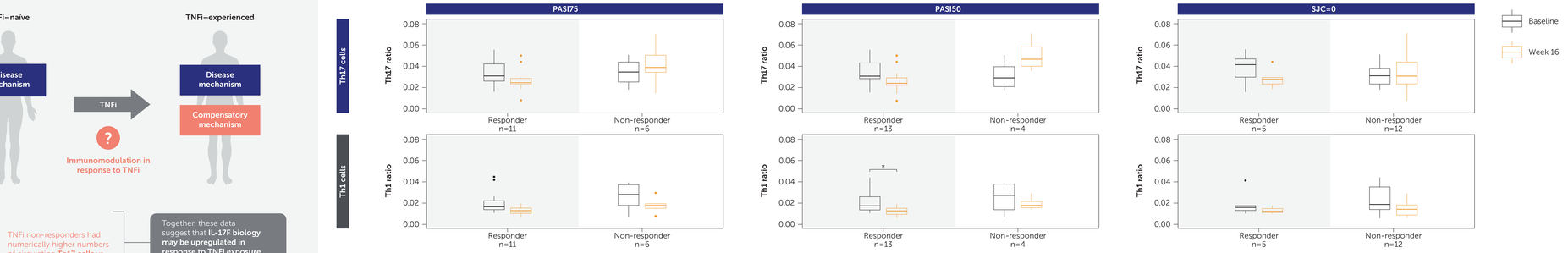


Figure 1 Study design of EXAMINe-PsA and BE OPTIMAL



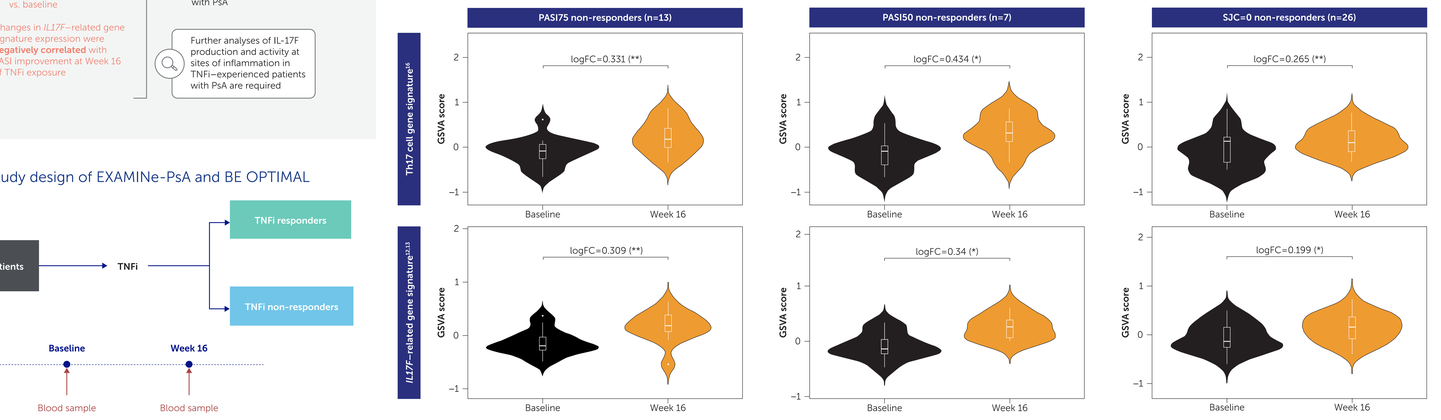
Immune signaling was assessed by examining immune cell composition and *IL17F*–related gene signatures in two separate studies (EXAMINe-PsA and BE OPTIMAL) of bDMARD–naïve patients with PsA initiating their first TNFi treatment.

Figure 2 Changes in immune cell composition in blood samples of TNFi responders and non-responders from EXAMINe-PsA



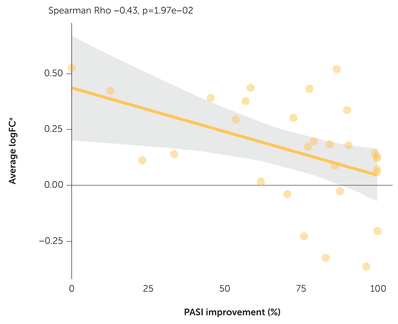
Flow cytometry analysis of CD4+ Th1 and Th17 cells in whole blood samples from patients with PsA in EXAMINe-PsA (N=17) is shown; box-and-whisker plots each present the median and interquartile range. Th1 and Th17 cells were defined by measurement of cell surface markers (Th1: CD3+CD4+CXCR3+CCR6–; Th17: CD3+CD4+CXCR3–CCR6+).[11] Blood samples were taken at baseline and Week 16. *p<0.05 for baseline vs. Week 16 within each group.

Figure 3 *IL17F*–related gene signature expression in whole blood samples from TNFi non-responder patients with PsA in BE OPTIMAL following 16 weeks of TNFi exposure



Data are reported for patients who were non-responders at Week 16; violin plots each present the data distribution, while the box-and-whisker plots each present the median and interquartile range. Th17 cell–related Dolcino gene signature contains *CCL20, CCR6, LY9, IL12RB1,* and *IL6ST*.[16] *IL17F*–related gene signature contains *IL17F* regulatory genes and genes that are specific to IL-17F–producing T cells based on single-cell data: *IL2, IL7, IL15, IL1A, IL1B, IL12A, IL12B, IL18, IL7R,* and *TRBV7-6*.[12,13] **P<0.01 and *p<0.05.

Figure 4 Correlation between PASI improvements and changes in *IL17F*–related gene signature expression at Week 16 of TNFi exposure in BE OPTIMAL



Each point represents a patient from BE OPTIMAL. Two points corresponding to patients with PASI improvement <0% are outside the plotting area; these patients were excluded from the statistical analysis shown here. *IL17F*–related gene signature contains IL-17F regulatory genes and genes that are specific to IL-17F–producing T cells based on single-cell data: *IL2, IL7, IL15, IL1A, IL1B, IL12A, IL12B, IL18, IL7R,* and *TRBV7-6*.[12,13] [a] Average logFC is the average logFC of gene expression between baseline and Week 16 across all genes in the signature.

ADA: adalimumab; **bDMARD:** biologic disease-modifying antirheumatic drug; **BKZ:** bimekizumab; **EXAMINe-PsA:** Exploring Autoimmune disease Mechanisms IN Psoriatic Arthritis; **FC:** fold change; **GSVA:** Gene Set Variation Analysis; **IL:** interleukin; **PASI:** Psoriasis Area and Severity Index; **PASI50:** PASI ≥50% improvement from baseline; **PASI75:** PASI ≥75% improvement from baseline; **PsA:** psoriatic arthritis; **RNA-seq:** RNA sequencing; **SJC:** swollen joint count; **Th1:** CD4+ T helper type 1; **Th17:** CD4+ T helper type 17; **TNFi:** tumor necrosis factor inhibitor; **vs.:** versus.

References: [1]Xie Y. Clin Exp Dermatol 2022;47:1627–1635; [2]Merola JF. Semin Arthritis Rheum 2017;47:29–37; [3]McInnes IB. Lancet 2023;401:25–37; [4]Merola JF. Lancet 2023;401:38–48; [5]Mease PJ. Rheumatol Ther 2024;11:1363–1382; [6]Strober B. JAAD 2024;91:Supplement (Abstract S267S); [7]Magrey M. Ann Rheum Dis 2023;82:876–877 (Abstract POS1107); [8]Glatt S. Ann Rheum Dis 2018;77:523–532; [9]Adams R and Maroof A. Front Immunol 2020;11:1894; [10]Hajgaard P. BMJ Open 2016;6:e010650; [11]Maecker HT. Nat Rev Immunol 2012;12:191–200; [12]Cutcutache I. ISDS 2023 (Poster 187); [13]Cole S. J Allergy Clin Immunol 2023;152:783–798; [14]Hänzelmann S. BMC Bioinformatics 2013;14:7; [15]Ritchie ME. Nucleic Acids Res 2015;43:e47; [16]Dolcino M and Ottria A. PLoS ONE 2015;10:e0128262. **Author Contributions:** All authors had substantial contributions to the study conception/design or acquisition/analysis/interpretation of data, drafted the publication or reviewed it critically for important intellectual content, and approved the final publication. **Author Disclosures: IBM:** Consulting fees and honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Cabaletta, Causeway Therapeutics, Celgene, Janssen, Eli Lilly and Company, MoonLake Immunotherapeutics, Montai, Novartis, Pioneering Medicines, and UCB, research support from Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, Novartis, and UCB. **IC, AS, SS, ARP:** Employees and shareholders of UCB. **MP:** Student internship at LEO Pharma; research support from LEO Pharma. **MRN:** None. **MS:** Research funding from Eli Lilly and Company, Pfizer, and UCB; speaker fees from Janssen. **VSM:** Employee of UCB. **Presenter Disclosures: CC:** Employee of UCB. **Acknowledgments:** We would like to thank the patients and their caregivers in addition to all the investigators and their teams who contributed to this study. The authors acknowledge Leon Eyrich Jessen, PhD, Department of Health Technology, Section for Bioinformatics, Technical University of Denmark, Kongens Lyngby, Denmark for contribution to the original study and study publication, Heather Edens, PhD, UCB, Smyrna, Georgia, USA for publication coordination, Orla Woodward, PhD, Costello Medical, London, UK, for medical writing and editorial assistance, and the Costello Medical Creative Team for design support. This study was funded by UCB. All costs associated with development of this poster were funded by UCB.

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