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

Iain B. McInnes,[1,*] Ioana Cutcutache,[2,*] Magnus Petersen,[3] Melanie Randahl Nielsen,[4] Marie Skougaard,[3,5] Victoria Svinti MacLeod,[2] Andrew Skelton,[2] Adam R. Prickett,[2] Stevan Shaw[2]

[1]College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [2]UCB, Slough, UK; [3]The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark; [4]Department of Health Technology, Section for Bioinformatics, Technical University of Denmark, Kongens Lyngby, Denmark; [5]Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark.

*Iain B. McInnes and Ioana Cutcutache jointly contributed to this study

Presenter: Irene Toruno

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

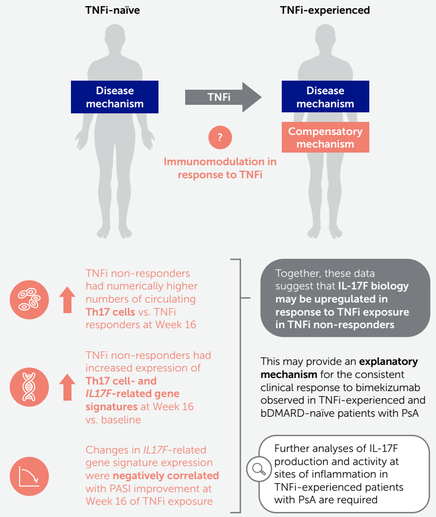
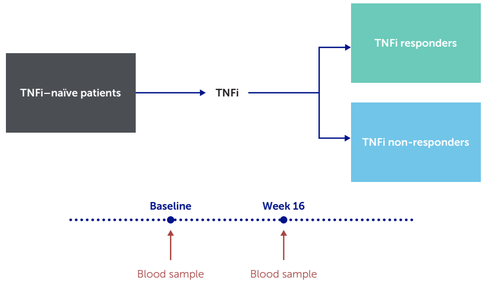
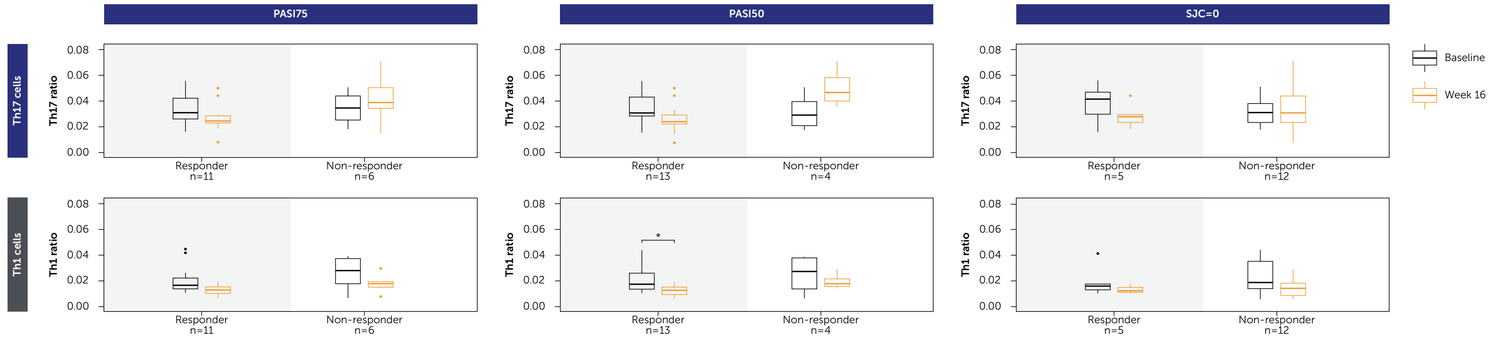


Figure 1 Study design of EXAMINe-PsA and BE OPTIMAL



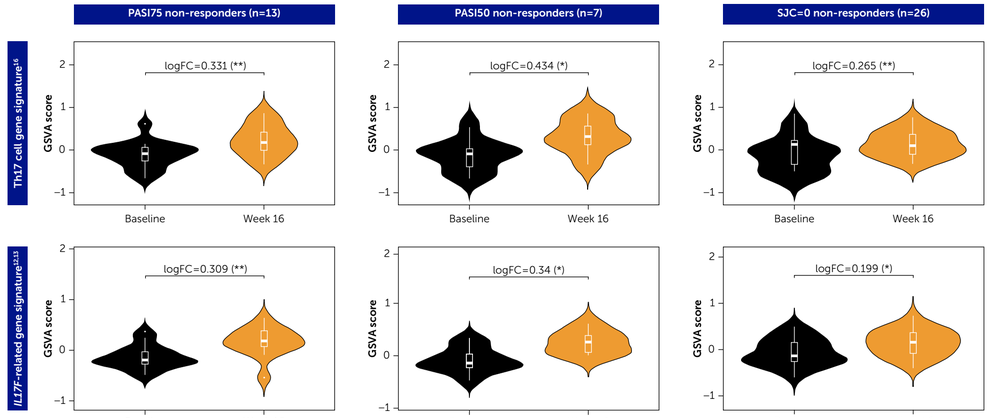
Immune signaling was assessed by examining immune cell composition and *IL17F*-related gene signatures in two separate studies (EXAMINe-PsA and BE OPTIMAL) of bDMARD-naïve patients with PsA initiating their first TNFi treatment.

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



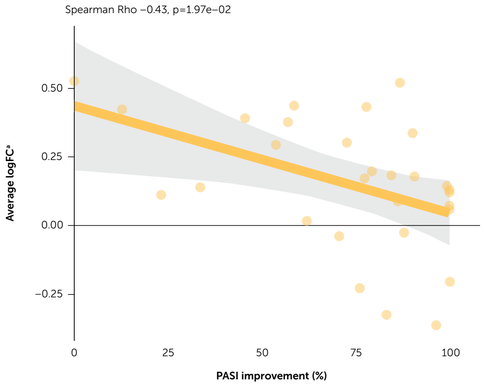
Flow cytometry analysis of CD4+ Th1 and Th17 cells in whole blood samples from patients with PsA in EXAMINe-PsA (N=17) is shown; box-and-whisker plots each present the median and interquartile range. Th1 and Th17 cells were defined by measurement of cell surface markers (Th1: CD3+CD4+CXCR3+CCR6−; Th17: 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.

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