Bimekizumab reduces systemic inflammation and cardiovascular risk gene signatures in psoriatic disease

P3189

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Objective

To understand the early molecular effects of bimekizumab (BKZ) on gene signatures related to systemic inflammation and cardiovascular (CV) risk in psoriatic disease.

Introduction

- Psoriatic disease is associated with increased CV disease (CVD) risk, which may be driven by the release of proinflammatory cytokines. An elevation of these cytokines has been detected in both psoriatic tissue and in circulation, demonstrating the systemic nature of this disease.[1–3]
- BKZ, a monoclonal antibody that selectively inhibits both interleukin (IL)-17A and IL-17F, has shown sustained differentiating efficacy in both moderate to severe plaque psoriasis (PSO) and psoriatic arthritis (PsA).[4,5]
- Analysis from phase 3 trials in PSO indicated that BKZ reduces CVD-associated systemic inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein.[6–8]

Methods

- Five CVD risk-related gene signatures were defined based on previous studies reporting genes dysregulated in the blood of patients with PSO compared with healthy controls, and affected in prevalent and incident CV events (myocardial infarction [MI], major adverse CV or limb events [MACLE]):[9,10]
  - PSO prevalent MI, PSO incident MACLE, PSO combined MI MACLE, PSO CVD key regulators, PSO+CVD (Kvist-Hansen).
- Blood bulk RNA-seq data from a previous study that compared patients with PSO to healthy controls were used to understand the extent of dysregulation of these gene signatures in blood at baseline.[11]
- Changes in these signatures post-BKZ treatment were assessed using molecular data from BKZ-treated patients with PSO and PsA.[12–14]
  - Bulk RNA-seq data were generated from a phase 2a trial in PSO (skin and blood samples at baseline and Week 8)[15] and from a phase 3 trial in PsA (blood samples at baseline and Week 16).[5]
  - Proteomics data were generated from the serum samples of patients with PSO (baseline and Week 8 in the phase 2a trial)[15] using the Olink Explore 3072 panel.

Results

- A positive correlation was observed between mean gene expression in the CVD gene signatures and NLR levels in blood at baseline (R=0.27–0.51 [PSO], R=0.42–0.69 [PsA]; FDR<0.1) (**Figure 1**).
- Baseline data from a published study[11] showed an increase in these gene signatures in the blood of patients with PSO versus healthy controls (average fold change: 1.06–1.42) (**Figure 2**).
- In the skin of patients with PSO, CVD gene signatures were rapidly normalised after BKZ treatment by Week 8 (two BKZ doses; median percentage improvement: 93–100%) (**Figure 3**).
- In blood, significant downregulation of the CVD gene signatures was observed as early as Week 8 in PSO (**Figure 4A**) and Week 16 in PsA (**Figure 4B**). This effect was associated with clinical response in PsA, with greater reduction in patients who responded to treatment compared with non-responders (**Figure 4C**). It is expected that gene dysregulation is weaker in blood than in disease tissue.[16]
- Placed in the context of baseline dysregulation in blood of PSO patients,[11] BKZ led to a median percentage improvement ranging from 33.55–39.92% (Week 8; PSO) and 55.51–60.94% (Week 16; PsA), demonstrating early reversal of CVD-related gene signatures (**Figure 5**).
- By Week 8, in the serum of patients with PSO, proteomics analysis demonstrated significant reduction[13] (FDR<0.05) of several IL-17-related proteins, some of which are also linked to CVD (e.g. PI3)[10] (**Figure 6**).

Conclusions

At early timepoints, bimekizumab treatment was associated with molecular reduction in systemic inflammation/ cardiovascular disease risk signatures in both blood and skin, which is consistent with the reduction in the neutrophil-to-lymphocyte ratio observed in clinical data.

Further studies are being undertaken to assess longer term molecular effects post-bimekizumab treatment.

Summary

Five previously published gene signatures associated with **systemic inflammation and CVD risk** were examined

These gene signatures were **increased in the blood of patients with PSO** at baseline versus healthy controls, and were **positively correlated with NLR levels**

The effect of **BKZ** treatment on these gene signatures was examined in **skin** and **blood** of patients with PSO and PsA:

In the **skin of patients with PSO**, CVD gene signatures were **rapidly normalised** after two doses of BKZ treatment by **Week 8** (median % improvement: 93–100%)

In **blood**, **significant downregulation** of the CVD gene signatures was observed as early as **Week 8 in PSO** and **Week 16 in PsA** (median % improvement: 33.55–39.92% and 55.51–60.94%, respectively); the effect was **associated with clinical response in PsA**

Figure 1 Correlation of CVD risk-related gene signature expression with NLR in blood at baseline

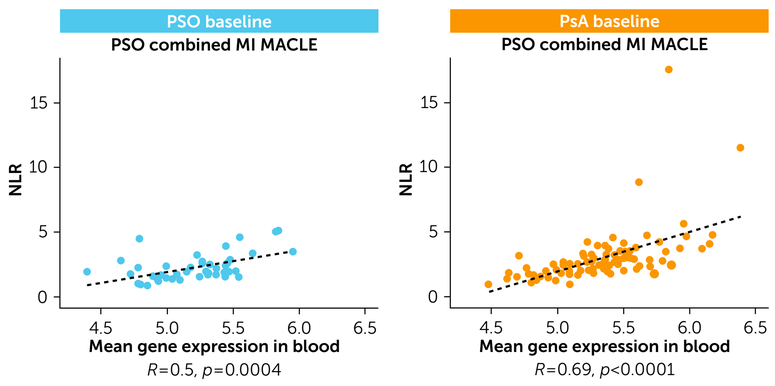
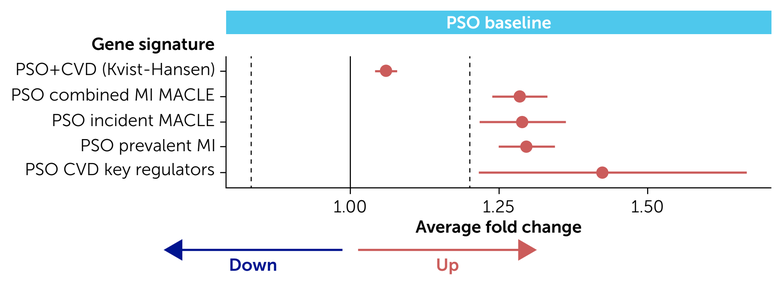


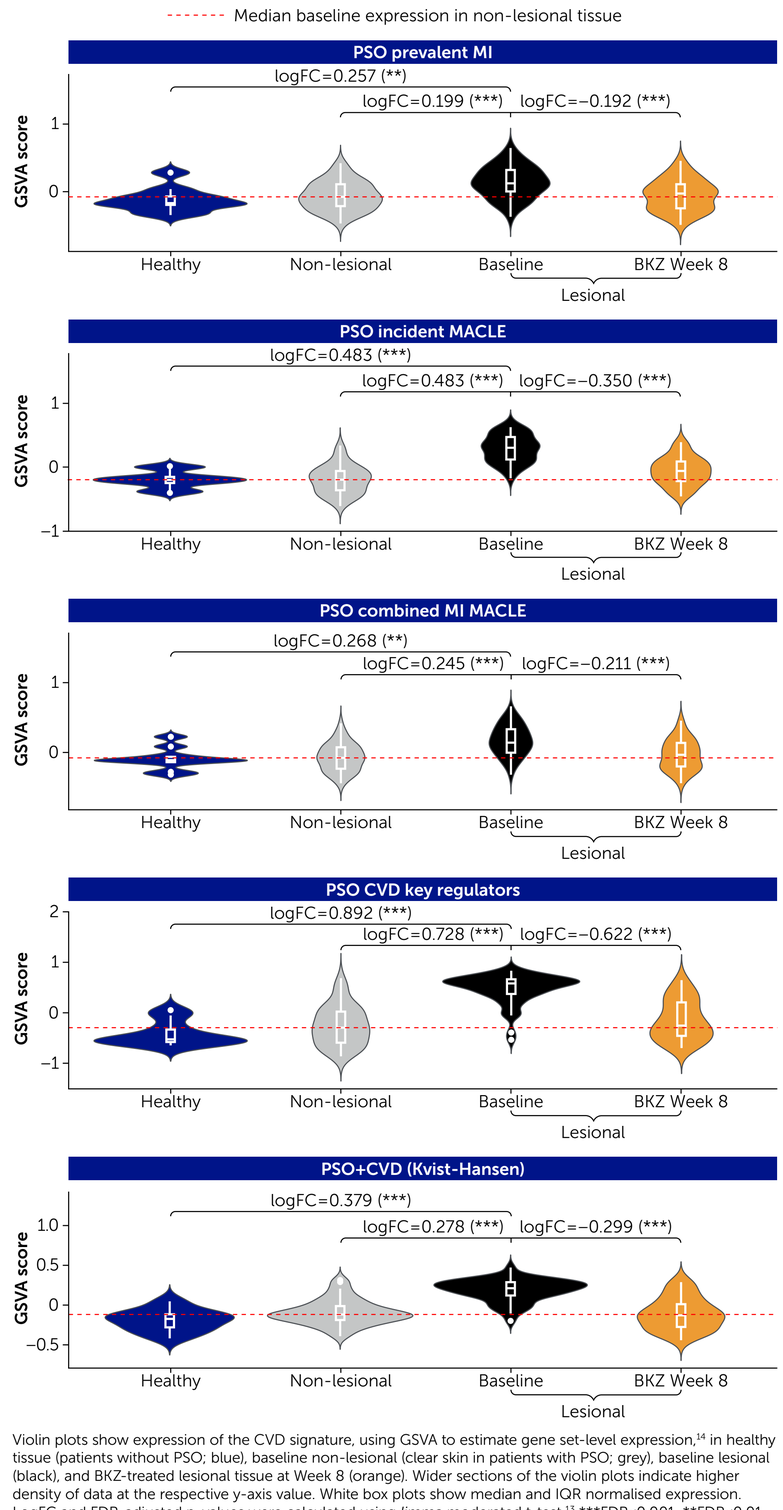
Figure shows only 'PSO combined MI MACLE' signature as an example. R is the Spearman correlation coefficient.

Figure 2 Changes in CVD risk-related gene signature expression at baseline in PSO vs healthy blood



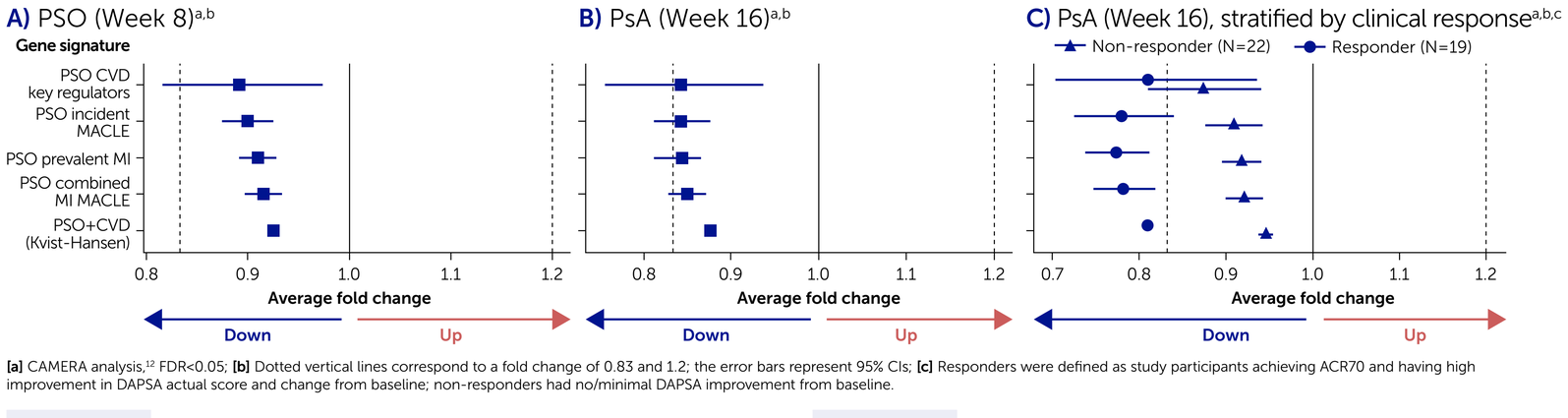
Dotted vertical lines correspond to a fold change of 0.83 and 1.2; the error bars represent 95% CIs.

Figure 3 Normalisation of CVD risk-related gene signatures in psoriatic skin following BKZ treatment



Violin plots show expression of the CVD signature, using GSVA to estimate gene set-level expression,[14] in healthy tissue (patients without PSO; blue), baseline non-lesional (clear skin in patients with PSO; grey), baseline lesional (black), and BKZ-treated lesional tissue at Week 8 (orange). Wider sections of the violin plots indicate higher density of data at the respective y-axis value. White box plots show median and IQR normalised expression. LogFC and FDR-adjusted p-values were calculated using *limma* moderated t-test.[13] ***FDR<0.001, **FDR<0.01.

Figure 4 BKZ treatment effects on CVD risk-related gene signatures in blood of patients with PSO and PsA



[a] CAMERA analysis,[12] FDR<0.05; **[b]** Dotted vertical lines correspond to a fold change of 0.83 and 1.2; the error bars represent 95% CIs; **[c]** Responders were defined as study participants achieving ACR70 and having high improvement in DAPSA actual score and change from baseline; non-responders had no/minimal DAPSA improvement from baseline.

Figure 5 Median percentage improvements in CVD risk-related gene signatures

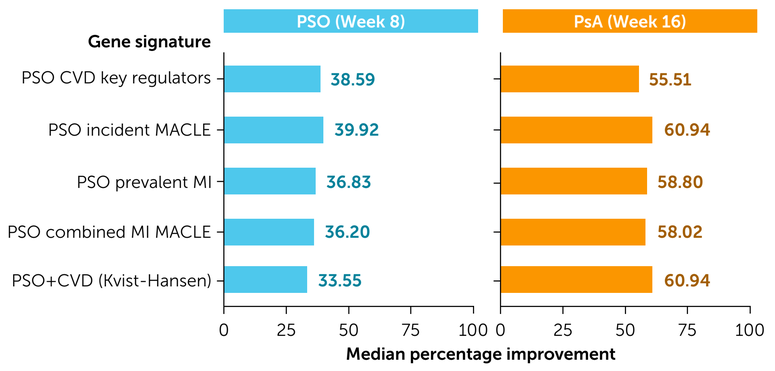
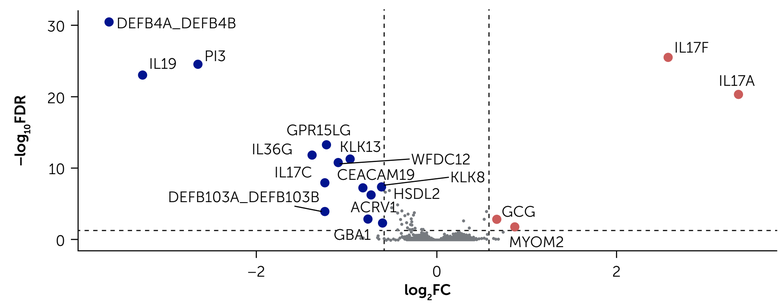


Figure 6 Effects of BKZ treatment on serum proteins in patients with PSO[a]



All proteins with $|\log_2 FC| \geq \log_2(1.5)$ and FDR<0.05 are labelled. LogFC and FDR-adjusted p-values were calculated using *limma* moderated t-test.[13] **[a]** Measured IL-17A and IL-17F in serum are the antibody-bound proteins and are expected to be increased post-treatment due to target engagement.

ACR70: ≥70% improvement in American College of Rheumatology response; **BKZ:** bimekizumab; **CI:** confidence interval; **CV:** cardiovascular; **CVD:** CV disease; **DAPSA:** disease activity in psoriatic arthritis score; **FC:** fold change; **FDR:** false discovery rate; **GSVA:** gene set variation analysis; **IL:** interleukin; **IQR:** interquartile range; **MACLE:** major adverse CV or limb events; **MI:** myocardial infarction; **NLR:** neutrophil-to-lymphocyte ratio; **PI3:** peptidase inhibitor 3; **PsA:** psoriatic arthritis; **PSO:** plaque psoriasis; **RNA-seq:** ribonucleic acid sequencing.

References: [1]Garshick MS et al. J Am Coll Cardiol 2021;77:1670–80; [2]Korman NJ Br J Dermatol 2020;182:840–8; [3]Polachek A et al. Arthritis Care Res (Hoboken) 2017;69:67–74; [4]Reich K et al. N Engl J Med 2021;385:142–52 (NCT03536884); [5]McInnes IB et al. Lancet 2023;401:25–37 (NCT03895203); [6]Warren RB et al. EADV 2023; Poster 2549; [7]Angkananard T et al. Biomed Res Int 2018;11:2703518; [8]Løfblad L et al. Sci Rep 2021;11:15644; [9]Garshick MS et al. J Eur Acad Dermatol Venereol 2023;37:1361–5; [10]Kvist-Hansen A et al. Int J Mol Sci 2021;22:10818; [11]Garshick MS et al. J Invest Dermatol 2022;141:308–15; [12]Wu D et al. Nucleic Acids Res 2012;40:e133; [13]Ritchie ME et al. Nucleic Acids Res 2015;43:e47; [14]Hänzelmann S et al. BMC Bioinformatics 2013;14:714; [15]Oliver R et al. Br J Dermatol 2022;186:652–63 (NCT03025542); [16]Dolcino M et al. PLoS ONE 2015;10:e0128262. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **IC**, **VSM**, **FV**, **JR**, **AK**, **JGK**, **MP**, **SSh**; Drafting of the publication, or reviewing it critically for important intellectual content: **IC**, **VSM**, **FV**, **JR**, **AK**, **JGK**, **MP**, **SSh**; Final approval of the publication: **IC**, **VSM**, **FV**, **JR**, **AK**, **JGK**, **MP**, **SSh**. **Author Disclosures:** **IC**, **JR**, **AK**, **SSh:** Employees and shareholders of UCB. **VSM**, **FV:** Employees of UCB. **JGK:** Grants paid to institution from AbbVie, Akros, Allergan, Amgen, Avillion, Biogen MA, Boehringer Ingelheim, Botanix, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Exicure, Incyte, Innovaderm, Janssen, LEO Pharma, Novan, Novartis, Parexel, Pfizer, Regeneron, Sienna, UCB, and Vitae; personal fees from AbbVie, Aclaris, Allergan, Almirall, Amgen, Arena, Aristea, Asana, Aurigne, BiogenIdec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Escalier, Galapagos, LEO Pharma, Menlo, Nimbus, Novartis, Pfizer, Sanofi, Sienna, Sun Pharma, UCB, Valeant, and Ventyx. **MP:** Employee and shareholder of UCB at the time the work was conducted; current employee of Relation Therapeutics. **Acknowledgements:** This study was funded by UCB. 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 Inés Dueñas Pousa, UCB, Madrid, Spain for publication coordination, Esme Nias, BSc, Costello Medical, London, UK, Yasha Najafi, BSc, Costello Medical, Cambridge UK for medical writing support and editorial assistance, Claire Osgood, MSc, Costello Medical, London, UK for editorial assistance and the Costello Medical Creative team for design support. All costs associated with development of this poster were funded by UCB.

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