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RESEARCH LETTER

WILEY

Differential dynamics of TARC during JAK-inhibitor therapy compared to biological therapies targeting type 2 inflammation

To the editor,

Atopic dermatitis (AD) is a complex inflammatory skin disease whose pathogenesis is primarily driven by CD4+ T helper (Th)2 cell-mediated responses. One of the involved type 2 chemokines is thymus and activation-regulated chemokine (TARC)/CCL17 which is constitutively expressed in the thymus, and mainly produced by dendritic and endothelial cells. It is therefore highly expressed in the dermis of both acute and chronic AD lesions.[1] Consequently, higher serum TARC levels are found in AD patients compared to healthy controls, and levels significantly correlate with disease severity.[2] Moreover, serum TARC levels significantly decrease during AD treatment including dupilumab and tralokinumab.[3,4] TARC is therefore identified as most reliable severity biomarker for AD.[2] Janus kinase (JAK) inhibitors (JAKi) baricitinib, upadacitinib and abrocitinib, targeting multiple cytokine pathways, have recently entered the market and have shown to be effective treatments for AD.[5] Two recently published studies reported that serum TARC levels substantially decrease during upadacitinib and abrocitinib treatment.[6,7] However, in our clinical practice, we found persistently high or increased serum TARC levels in AD patients despite disease improvement during JAKi treatment. Therefore, we determined serum TARC levels, which were measured during routine diagnostics, of AD patients treated with JAKi at the University Medical Center Utrecht, and compared those with serum TARC levels of AD patients treated with biologicals (i.e. dupilumab or tralokinumab). All patients participated the Dutch BioDay registry and visited the outpatient clinic at baseline and after 4, 8 (only JAKi) and 16 weeks of treatment and then every 3 months, between October 2017 and July 2023. Clinical effectiveness was measured by the Eczema Area Severity Index (EASI). TARC was also measured in plasma in a subgroup of JAKi patients ($n = 10$) and a dupilumab control group ($n = 5$), at baseline and week 8 or 16. Furthermore, platelet, lymphocyte and monocyte counts were determined. All patients provided written informed consent.

A total of 95 AD patients with 134 baricitinib, upadacitinib or abrocitinib treatment episodes, 622 AD patients with 643 dupilumab episodes and 60 tralokinumab treated patients, were included. Gender and age were equally distributed between the treatment groups (JAKi patients: 63.2% male, median age 33.0 years [interquartile range (IQR) 26–49]; dupilumab patients: 57.1% male, median age 43.0 years [IQR 30–56]; tralokinumab patients: 46.7% male, median age 40.0 years [IQR 29–52]). The baseline EASI was 13.0 (IQR 8.0–18.9) in the JAKi patients, and 14.0 (IQR 9.4–20.8) and 10.2 (IQR 6.6–16.5) in dupilumab and tralokinumab patients, respectively. In the JAKi cohort, the median EASI decreased during 52 weeks of treatment with all medians beneath the cutoff score (EASI ≤ 7), indicating mild disease. However, median serum TARC levels either remained relatively stable or demonstrated a propensity to increase, which persisted during long-term treatment. In contrast, in the dupilumab and tralokinumab group both EASI and serum TARC levels substantially decreased during treatment (Figure 1).

So far, we have not found an explanation for the high serum TARC levels in AD patients treated with JAKi. Recently the European Medicines Agency (EMA) issued a warning stating that JAKi treatment may lead to an increased risk of thrombo-embolic events. Platelets have been demonstrated to store and release TARC, however, mean platelet counts were within normal range at baseline and follow-up measurements.[8] Also, serum/plasma TARC ratios were stable and similar in both JAKi and dupilumab subgroups, indicating that the JAKi did not influence TARC levels by affecting the platelet population. In addition, no changes in lymphocyte (i.e. binds TARC to CCR4) or monocyte (i.e. produces TARC) counts were found during JAKi treatment.[1]

It is known that interleukin (IL)-4 and IL-13 are highly expressed in active AD skin.[5] One could hypothesize that the effect of JAKi on these TARC-inducing cytokines might be less effective. For example, JAK1 inhibition alone may not be sufficient to completely block IL-4 and IL-13 signaling. While JAK1 is involved in the signaling pathways of these cytokines, they also rely on other JAKs, such as JAK3 (IL-4) and JAK2 (IL-13). Therefore, baricitinib (JAK1/2 inhibitor), upadacitinib and abrocitinib (both selective JAK1 inhibitors) likely do not provide a comprehensive blockade of TARC-inducing cytokines. Dupilumab and tralokinumab, both monoclonal antibodies specifically and strongly inhibiting IL-4 and/or IL-13 receptor binding, might therefore be more effective in reducing serum TARC levels.[2,3,5] Larger studies are needed to confirm our findings as in contrast to our study, two previous

studies reported a decrease in serum TARC levels during upadacitinib and abrocitinib treatment in AD patients.[6,7] Interestingly, a phase 3 clinical trial with nemolizumab, an IL-31 receptor alpha antagonist, also reported that serum TARC levels increased while AD severity decreased. However, this was only found in the first 16 weeks, whereas in our study, it remained up to at least 52 weeks of treatment.[9] Another hypothesis could be that despite disease improvement, remission at immune level is limited in some patients (i.e. subclinical response), leading to persistently high serum TARC levels. These patients might be prone for relapsing of the disease, and serum TARC would then still be an adequate biomarker of persistent immune dysregulation.

In conclusion, we found persistently high and increased serum TARC levels in AD patients treated with baricitinib, upadacitinib or abrocitinib despite a good clinical response, implying a limitation of the use of TARC as clinical biomarker in these patients. Translational research on TARC levels in both blood and AD skin is essential to gain insight into the underlying mechanism and to evaluate the safety of these JAKi.

Summary box

- Elevated TARC levels were found in AD patients treated with JAK inhibitors despite a good clinical response.
- The use of TARC as a clinical biomarker in these patients is therefore questionable.

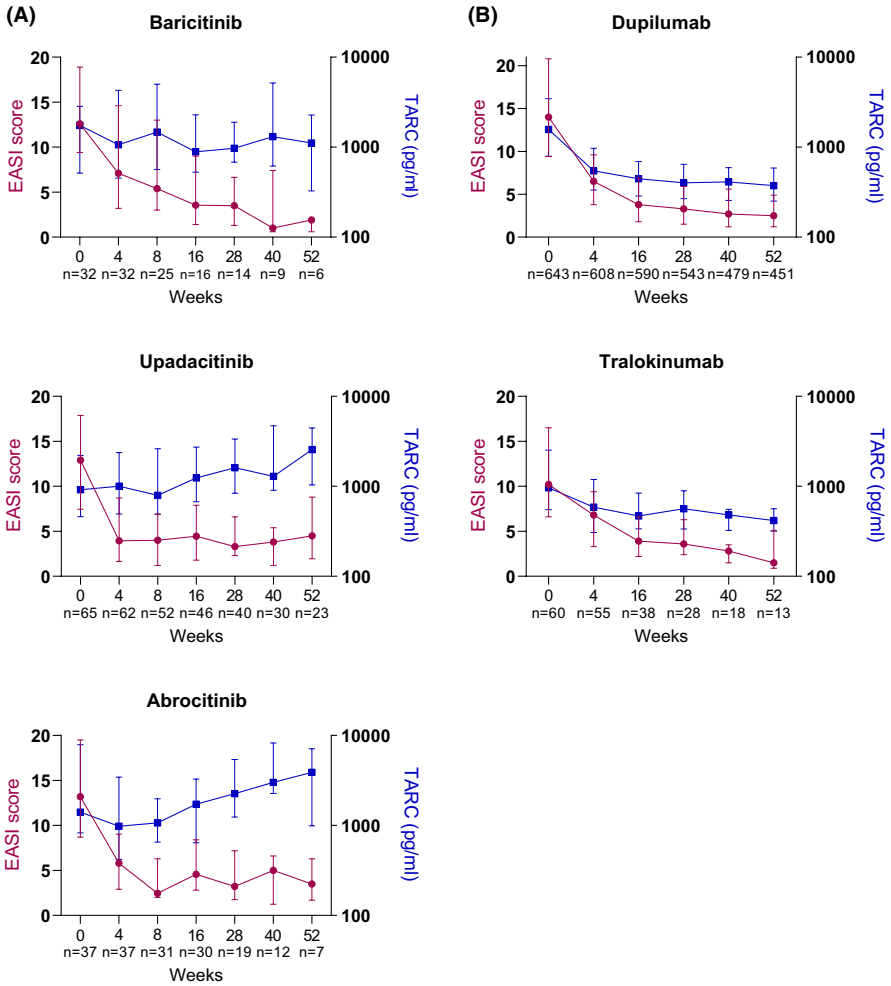

FIGURE 1 (A) Median EASI and serum TARC levels in AD patients up to 52 weeks of baricitinib, upadacitinib or abrocitinib treatment. (B) Median EASI and serum TARC levels in AD patients up to 52 weeks of dupilumab or tralokinumab treatment. TARC levels were log-transformed, and bars represent interquartile ranges. EASI, Eczema Area and Severity Index; TARC, Thymus and activation-regulated chemokine; *n*, number of treatment episodes.

AUTHOR CONTRIBUTIONS

Conceptualization: CB, DS, MG, EK, MdBW, FvW; Formal Analysis: CB; Funding Acquisition: MG, MdBW; Investigation: CB, DS, MG, MdBW; Methodology: CB, MdBW, FvW; Resources: CB; Supervision: MG, EK, MdBW, FvW; Visualization: CB, EK, MdBW, FvW; Writing—Original Draft Preparation: CB; Writing—Review and Editing: DS, MG, EK, MdBW, FvW.

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CONFLICT OF INTEREST STATEMENT

C.M. Boesjes is a speaker for AbbVie and Eli Lilly and Company. Dr. D.S. Bakker is a speaker for Sanofi and LEO Pharma. Dr. E.F. Knol is a speaker and/consultant for Sanofi, Thermo Fisher Scientific and GSK. Dr. M. de Graaf is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals and Sanofi. Prof. F. van Wijk is a speaker and/or a consultant for Janssen, Johnson&Johnson and Takeda and has received grants from Regeneron Pharmaceuticals, Leo Pharma, Sanofi, BMS, Galapagos and Takeda. Prof. Dr. M. S. de Bruin-Weller is a consultant, advisory board member and/or a speaker for AbbVie, Almirall, Aslan, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron Pharmaceuticals and Sanofi.

IRB STATEMENT

The study was part of the BioDay registry which was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18–239) and was performed according to the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request from the corresponding author.

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