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LETTER

IL-17A blockade alleviates immune checkpoint inhibitor-associated psoriasiform rash: preclinical and clinical responses

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Psoriasiform rash is a notable immune-related cutaneous adverse event (ircAE) accounting for approximately 5% of all ircAEs[1,2]. Patients with cancer and pre-existing psoriasis face elevated risk of disease recurrence or exacerbation after receiving immune checkpoint inhibitors (ICIs). A European multicenter study has reported a reactivation rate of 28.7% in this population[3]. ICIs also trigger *de novo* psoriatic lesions, which mirror conventional lesion subtypes (plaque, guttate, erythrodermic, or pustular), and 20%–30% of patients develop psoriatic arthritis[4]. These rashes are often refractory to topical steroids and therefore require treatment modification or discontinuation. Emerging evidence suggests that IL-17A is a key driver of ICI-induced autoinflammation. Despite concerns regarding the use of biologics in patients with cancer, several case reports (**Table S1 and S2**) have demonstrated that anti-IL-17A monoclonal antibodies (mAbs) can effectively and safely manage ICI-induced psoriasiform rashes without promoting tumor progression[5-10]. Our prior studies in MSS colorectal cancer mouse models have further validated IL-17A blockade as a promising strategy that enhances anti-PD-1 efficacy by downregulating PD-L1 expression through the p65/NRF1/miR-15b-5p axis, thereby decreasing immunosuppressive myeloid-derived suppressor cells and increasing $CD8^+$ T-cell infiltration[11]. These findings highlight the dual benefit of IL-17A blockade in controlling ircAEs while potentially augmenting antitumor immunity in ICI-treated patients.

This study investigated the role of IL-17A in ICI-induced psoriasiform rash in a preclinical model and indicated that elevated IL-17A accelerates disease onset and progression. We also report our clinical experience, in which anti-IL-17A mAb effectively managed grade 2 psoriasiform rash in patients with cancer and enabled uninterrupted ICI therapy without compromising short-term oncologic outcomes. Targeting IL-17A is therefore a promising strategy for managing refractory ircAEs and increasing ICI safety.

Therapeutic efficacy of IL-17A blockade in preclinical and clinical models of immune-related psoriasiform dermatitis

To evaluate the roles of ICIs (anti-PD-1 and anti-CTLA-4 mAbs) in psoriasiform skin inflammation, we established a low-dose imiquimod (IMQ)-induced dermatitis model in mice (**Figure S1A**). Detailed experimental procedures, antibody

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administration schedules, histopathological scoring, and statistical analysis methods are provided in **Supplementary Material 1**. Compared with IgG-treated controls, ICI-treated mice exhibited markedly greater ear thickness, higher PASI scores (**Figure S1B–D**), and exacerbated histopathological features (**Figure S1E and F**). Moreover, RT-qPCR analysis further confirmed the significant upregulation of IL-17A, IL-6, IL-22, and IL-23 expression in ICI-treated skin tissues ($P < 0.01$, **Figure S1G and H**). To determine the therapeutic potential of IL-17A blockade, we administered anti-IL-17A mAb at multiple time points (D-1, D3, and D5) in mice receiving ICIs (**Figure 1A and B**). Notably, this treatment significantly ameliorated dermatitis severity in both PD-1 and CTLA-4 models, which was reflected by decreases in ear thickness and PASI scores ($P < 0.01$, **Figure 1C and D**), as well as attenuation of epidermal hyperplasia on histology ($P < 0.01$, **Figure 1E and F**). Correspondingly, mRNA levels of IL-17A, IL-6, IL-22, and IL-23 markedly decreased in treated skin (**Figure 1G and H**).

To translate these findings to a clinical context, we evaluated therapeutic efficacy of IL-17A blockade in 5 patients with cancer who developed ICI-related cutaneous toxicity (**Table S3**). Three patients presented psoriasiform eruptions: patient 1 (with advanced hepatocellular carcinoma with pre-existing psoriasis) developed a grade 3 rash [Dermal Toxicity Assessment Scale (DTAS) score: 8] after treatment with pembrolizumab plus bevacizumab (**Table S4**). This rash was characterized by widespread erythema, desquamation, bleeding, and severe pruritus. Combination therapy with oral prednisone (30 mg/day) and secukinumab (anti-IL-17A mAb, 150 mg/week) achieved rapid symptom relief, with resolution of pruritus and pain within 24 h. Crust formation was also observed over most affected areas (**Figure 1I**). After 3 weeks, the rash subsided completely (DTAS score: 2, G1), and the patient was able to resume antitumor therapy. Moreover, imaging confirmed hepatic tumor regression and a continued decline in tumor markers (**Figure 1J**). Two additional patients with advanced gastric cancer developed grade 2 psoriasiform rashes during oxaliplatin-based chemotherapy plus sintilimab, and achieved full resolution of symptoms within 4 weeks of secukinumab treatment, without additional adverse events (**Table S5 and S6**).

Beyond these patients, 2 additional patients developed non-psoriasiform ICI-related rashes (one with hepatocellular carcinoma, G2; one with esophageal carcinoma, G2). Both showed limited responses to corticosteroids but experienced marked improvement after secukinumab monotherapy: alleviation occurred after one cycle, and near-complete remission occurred by 2 cycles (**Table S7 and S8**). Importantly, across all 5 cases, IL-17A blockade not only provided rapid and durable control of cutaneous toxicity but also well tolerated, with no tumor progression observed during treatment. Furthermore, patients who resumed ICI therapy did not experience rash recurrence.

IL-17A is a central mediator of immune and epithelial dysregulation in ICI-induced psoriasiform dermatitis

To investigate the mechanism underlying IL-17A-mediated ICI-related psoriasiform dermatitis, we analyzed immune markers through immunohistochemistry and immunofluorescence assays. Both assays demonstrated increased CD4+ T cells and IL-17A in ICI-treated skin lesions, which markedly decreased after anti-IL-17A mAb administration (**Figure S2A–F**), thus implicating IL-17A in the inflammatory phenotype of ICI-induced rash.

To further assess the IL-23-IL-17A axis, we tested anti-IL-23 mAb in ICI + IMQ mouse model. IL-23 blockade partially alleviated skin inflammation and decreased IL-17A expression, although with slightly lower efficacy than IL-17A inhibition (**Figure S3A–E**). In tumor-bearing mice, in agreement with our previous findings that IL-17A blockade enhances antitumor immunity and decreases tumor burden, IL-17A inhibition ameliorated ICI-induced psoriasiform dermatitis. (**Figure S3F–M**). These results highlight IL-17A as a central driver of skin toxicity, further supporting the therapeutic relevance of IL-17A blockade for tumor control during ICI treatment.

To further explore the molecular mechanism, we performed RNA sequencing on skin samples from mice treated with IMQ alone; IMQ + anti-PD-1 mAb; or IMQ + anti-PD-1 mAb + anti-IL-17A mAb (**Figure S4A**). Differential expression analysis revealed that PD-1 blockade in the context of IMQ exposure led to upregulation of pro-inflammatory mediators such as IL-17A and S100a8/a9, alongside downregulation of epithelial structural genes (e.g., Krt26, Krt28) and extracellular matrix regulators (Prss35) (**Figure S4B**). Notably, IL-17A blockade reversed these transcriptomic alterations, as evidenced by downregulation of IL-17A and suppression of neutrophil degranulation markers (S100a8, S100a9, and Defb3).

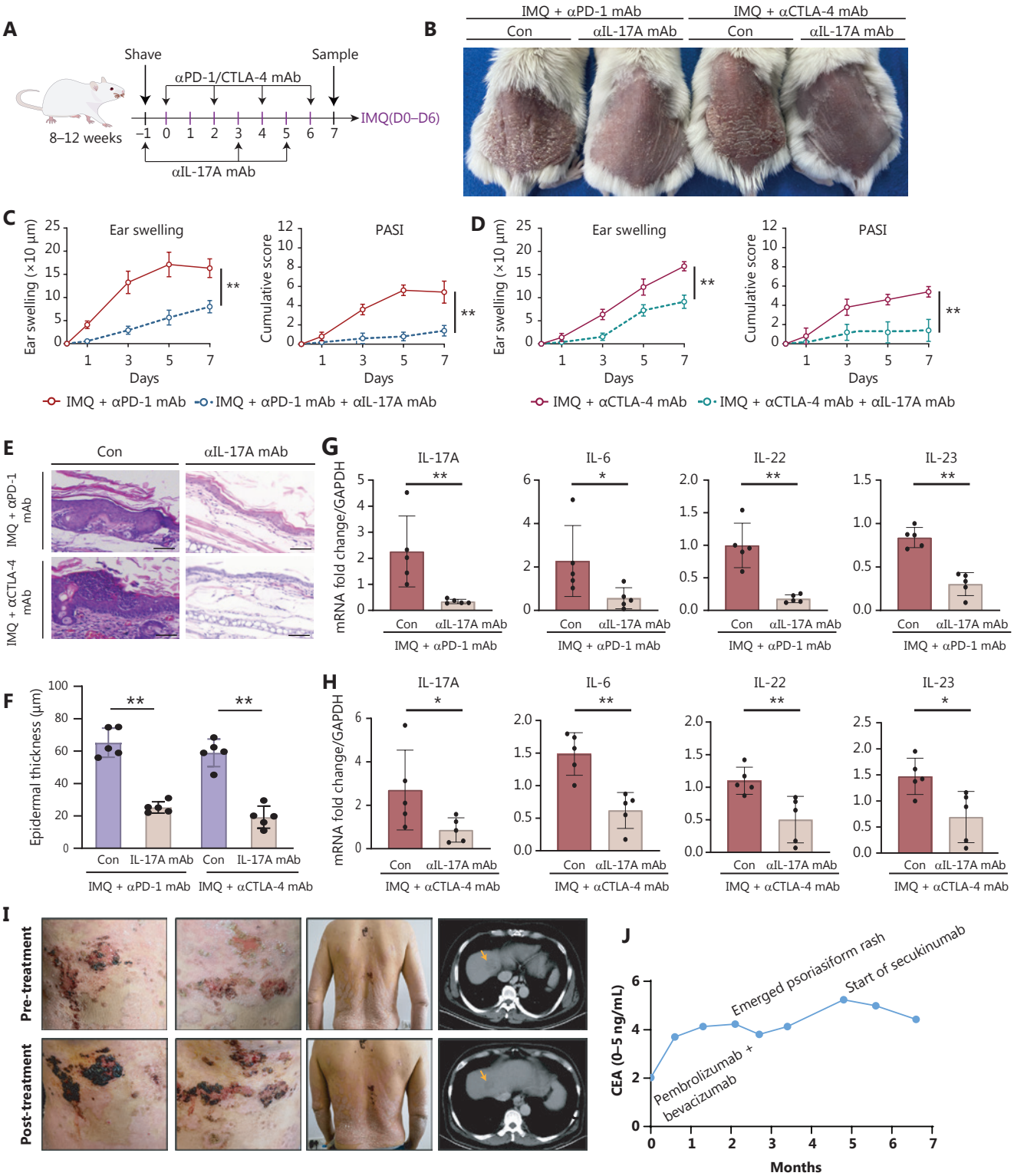

Figure 1 Therapeutic efficacy of IL-17A blockade in preclinical and clinical models of immune-related psoriasiform dermatitis. (A) Schematic timeline of anti-IL-17A mAb administration. Mice were pretreated with anti-IL-17A mAb or IgG control on days −1, 3, and 5, then treated with IMQ and ICIs (anti-PD-1/CTLA-4 mAb). Skin inflammation was evaluated on day 7. (B) Clinical presentation of the psoriasiform dermatitis model under various antibody treatments. (C and D) Ear thickness (× 10 μm) and cumulative PASI scores in IMQ + anti-PD-1 mAb-treated and

IMQ + anti-CTLA-4 mAb-treated mice, with or without anti-IL-17A mAb intervention. (E) Images of HE staining exhibiting the characteristic features of ear samples in the psoriasiform dermatitis model treated with anti-IL-17A mAb on the 7th day. Scale bar: 60 μm. (F) Epidermal thickness quantification in IMQ + anti-PD-1 mAb or IMQ + anti-CTLA-4 mAb-treated mice. (G and H) RT-qPCR analysis of IL-17A, IL-6, IL-22, and IL-23 mRNA levels (normalized to GAPDH) in IMQ + anti-PD-1/CTLA-4 mAb-treated mice, with or without anti-IL-17A mAb treatment. (I) Representative clinical images showing the progression and resolution of ICI-induced psoriasiform rash, accompanied by CT scans demonstrating liver improvement after IL-17A-targeted therapy. (J) Longitudinal measurement of CEA levels over time. *P < 0.05; **P < 0.01. CT, computed tomography; CTLA-4, cytotoxic T lymphocyte-associated protein 4; CEA, carcinoembryonic antigen; DTAS, Dermatologic Toxicity Assessment Score; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IgG, immunoglobulin G; IMQ, imiquimod; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PASI, Psoriasis Area and Severity Index; HE, hematoxylin and eosin; RT-qPCR, reverse transcription quantitative polymerase chain reaction.

In contrast, the expression of skin barrier-associated genes (Stk32b) was restored (**Figure S4C**). Additionally, KEGG pathway analysis demonstrated that PD-1 blockade activated the IL-17, TNF, and Th17 signaling pathways (**Figure S4D**). In contrast, anti-IL-17A therapy significantly suppressed these inflammatory cascades (**Figure S4E**). Consistent results were obtained through GSEA, thereby reinforcing the role of IL-17A in mediating immune activation and epithelial hyperproliferation (**Figure S4F**). Protein–protein interaction network analysis also identified IL-17A as a central hub among upregulated inflammatory genes (**Figure S4G**). Cytokine profiling revealed that anti-IL-17A mAb decreased IL-17A and suppressed upstream drivers, including IL-23A, IL-6, and TNF, thus reflecting broad immunomodulatory effects (**Figure S5A and B**). Furthermore, immune deconvolution with EPIC indicated that PD-1 blockade increased cytotoxic lymphocyte infiltration (CD8+ T cells and NK cells). In comparison, IL-17A neutralization restored these populations to baseline, and markedly decreased Th17 cell enrichment and neutrophil presence (**Figure S5C**). Collectively, IL-17A blockade is a promising precision strategy for managing ICI-aggravated psoriasiform dermatitis without impairing antitumor efficacy.

Our integrated data establish IL-17A as the central driver of ICI-exacerbated psoriasiform dermatitis. In mouse models, ICI blockade synergistically amplified IMQ-induced inflammation by upregulating IL-17A, thus leading to epidermal hyperplasia and heightened cytokine responses (IL-6, IL-22, and IL-23). Transcriptomic analysis also confirmed that IL-17A prominently regulated psoriasis-associated signaling (IL-17/TNF/NF-κB) and immune dysregulation, both of which were reversed after IL-17A blockade. Clinically, secukinumab rapidly resolved ICI-induced rashes in 5 patients with cancer and consequently enabled uninterrupted immunotherapy and sustained tumor control over 6 months.

One key limitation of this study is the small patient cohort, with a case series of only 5 patients. Although IL-17A blockade did not impair short-term antitumor efficacy, its long-term effects remain unclear. To address these limitations, we are conducting a prospective clinical trial to assess the long-term safety and efficacy of secukinumab in ICI-induced psoriasiform rash. Additionally, because of the limited patient samples, we were unable to perform simultaneous analysis of inflammatory cytokine profile of serum and skin tissue from the same individuals. Moreover, the lack of *in vitro* experimental validation limited the mechanistic insights of our findings. Future studies will be aimed at overcoming these limitations by expanding clinical sample collection and conducting functional experiments. Overall, our preclinical and clinical findings support the therapeutic potential of secukinumab for ICI-induced psoriasiform rash, without compromising antitumor efficacy. However, well-designed prospective clinical studies are needed to confirm its efficacy and safety (**Supplementary Material 2**).

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Chao Liu, Yanqiao Zhang.
Collected the data: Yuli Ruan, Mengde Shi.
Contributed data or analysis tools: Yue Ma, Bojun Wang.
Performed the analysis: Ming Ma.
Wrote the paper: Yuli Ruan, Mengde Shi.

Data availability statement

The datasets supporting the conclusions of this article are included within the article and its supplementary files. The raw sequencing data have been deposited in the Genome Sequence Archive in the BIG Data Center, Beijing Institute of Genomics, Chinese Academy of Sciences (GSA) under accession code CRA024268.

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