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FOCUS PIGMENTARY DISORDERS

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WHAT'S NEW

Tebentafusp elicits on-target cutaneous immune responses driven by cytotoxic T-cells in uveal melanoma patients

This article is a contribution by the SKINTEGRITY.CH consortium. The work presented here was performed by Ramon Stäger and colleagues, including SKINTEGRITY.CH principal investigators Barbara Meier-Schiesser, Reinhard Dummer, Mitch Levesque and Burkhard Becher.

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Background and rationale

Bispecific T-cell engagers link tumor antigen recognition to polyclonal T-cell redirection and activation. Tebentafusp is a bispecific T-cell engager that is based on a T-cell-receptor recognizing gp100 in the context of HLA-A*02:01 on target cells with picomolar-affinity and has established the first survival benefit for patients with metastatic uveal melanoma (mUM). Clinically, tebentafusp often triggers an acute, self-limited skin eruption and late-onset vitiligo-like pigment disorders. We hypothesized that tebentafusp drives T-cells toward gp100+ cutaneous melanocytes, allowing a pharmacodynamic window into drug activity through the skin. Therefore, we profiled patient skin during treatment to test whether these events reflect on-target, off-tumor immunity and to define the underlying cellular programs.

Cohort and methods

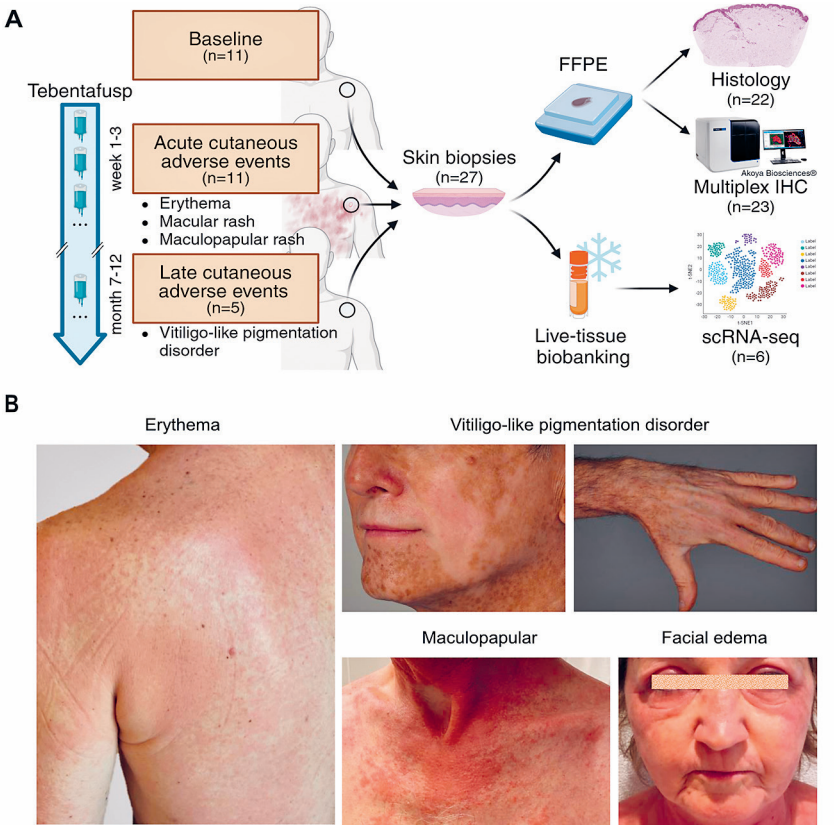
We analyzed sequential biopsies from mUM patients at baseline, during acute cutaneous adverse events (acAE) and during vitiligo-like pigment disorder (VLPD). Techniques included multiplex spatial immunophenotyping, single-cell RNA-sequencing, and gp100-dependent functional assays.

Cutaneous toxicity profile

acAE occurred in 82% of patients within 12-48 h of the first three infusions, were grade 1-2 and manageable with topical steroids and oral antihistamines and resolved before the next dose. VLPD developed in 64%, with a delayed onset (after median 6 months) and was consistently preceded by acAE. acAE presence associated with longer overall survival but this was not independent after adjustment for other baseline prognostic factors.

Spatial analysis of skin

acAE lesions showed interface dermatitis with T-cell infiltrations at the dermo-epidermal junction, basal vacuolization, keratinocyte apoptosis, and increased perivascular lymphocytes. Multiplexed spatial analysis demonstrated CD8+ enrichment in close proximity of melanocytes and a decrease in the number of melanocytes, supporting direct cytotoxic engagement.



scRNA-seq: single cell RNA sequencing. IHC: Immunohistochemistry.

(A) Overview of the experimental design. (B) Representative clinical photographs of cutaneous adverse events observed under tebentafusp.

Single-cell profiling of the inflammatory reaction

Single-cell profiling revealed proliferating T-cells and dominant CD8+ cytotoxic / IFN-γ signatures in lesional skin. CD8+ T cells upregulated LAG3 expression. *In vitro,* dual LAG3 / PD-1 blockade augmented tebentafusp-redirected CD8+ activation, nominating a rational combination strategy.

Melanocytes upregulated HLA-I antigen-processing / presentation and IFN-γ responses, downregulated pigmentation genes (*e.g.,* MITF), and showed apoptotic signaling with numeric decline. Importantly, gp100 / PMEL expression was largely maintained, arguing against antigen-loss escape.

Melanocytes and keratinocytes were major CXCL10 sources in acAE skin, consistent with earlier observations of systemic CXCL10 increases under tebentafusp and suggesting the skin as a source tissue of cytokine-release syndrome.

Implications for clinical practice

- **Mechanism-based toxicity:** The eruption seen under tebentafusp reflects on-target cytotoxicity toward gp100+ melanocytes rather than nonspecific rash.
- **Care:** Expect an erythematous sunburn-like or maculo-(papular) eruption after first doses; manage with topical corticosteroids ± oral antihistamines. Counsel patients about delayed VLPD affecting skin and hair.
- **Biomarkers and combinations:** acAE presence is a useful real-time pharmacodynamic readout but not an independent predictor. LAG3 induction highlights testable combination partners to deepen activity while monitoring skin tolerability.

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