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Anti-IL-15 neutralizing antibody counteracts vitiligo in a humanized mouse model

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Introduction & Objectives:

Vitiligo is a common skin depigmentation disorder, characterized by loss of skin pigment with an estimated prevalence of 0.5-2% worldwide. It is believed that vitiligo is caused by cytotoxic T cells infiltrating the epidermis. Indeed, melanocyte specific CD8+ resident memory T (TRM) cells are enriched in the perilesional skin of vitiligo patients (Cheuk S. et al, Immunity 2017, Boniface K. et al, J Invest Dermatol 2018). These cells constitute a reservoir of cytotoxic T cells that attack melanocytes, causing depigmentation of the skin. Since TRMs are long-lived cells, they are presumed to be responsible for the perpetual nature of this disease.

The formation and survival of TRMs are regulated by cytokine IL-15 (Mackay L.K. et al, Nat Immunol 2013, Mackay L.K. et al, Immunity 2015). Indeed, high levels of IL-15 and the IL-15 receptor a subunit (IL-15Ra) have been detected in vitiligo patients, and the levels of IL-15 correlated with disease severity. We developed TEV-53408, a human anti-IL-15 antibody that specifically binds and neutralizes IL-15. The present study evaluated the effect of TEV-53408 on TRMs and skin depigmentation in a humanized IL-15 knock-in (hIL-15KI) mouse model of vitiligo.

Materials & Methods:

A vitiligo model was established in hIL-15KI mice by immunization with a peptide derived from the melanocyte-specific enzyme tyrosinase-related protein 2 (TRP2), along with immune stimulants (You S. et al, Clin Exp Immunol 2013). Immunization was performed in the foot pad and subsequently intradermally in the tail skin and resulted in depigmentation of the tail skin and accumulation of CD8+ TRMs in the skin.

TEV-53408 was administered subcutaneously to hIL-15KI mice, starting 2 weeks following the last immunization, as 3 weekly injections at 5 mg/kg. The mice were euthanized 24 hours after the last TEV-53408 administration. Depigmentation of the tail skin was assessed, and T cell analysis was performed.

Results:

TEV-53408 attenuated depigmentation of the tail skin and suppressed the accumulation of skin TRMs in vitiligo-induced hIL-15KI mice. Furthermore, ex vivo stimulation of skin-localized CD8+ T cells with TRP2 peptide revealed that treatment with TEV-53408 reduced levels of IFNg+ activated CD8+ T cells compared to cells derived from saline-treated mice. This assay demonstrated the melanocyte-specific immune response that was developed in this model, and its inhibition by TEV-53408.

Conclusion:

TEV-53408 is a potent and specific neutralizing antibody, that has demonstrated on-target efficacy in a vitiligo hIL-15KI mouse model. These findings support the rationale for clinical development of this novel IL-15 antagonist as a treatment for vitiligo.