Received: 16 April 2024 | Revised: 12 July 2024 | Accepted: 3 August 2024

DOI: 10.1111/all.16271

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

NEWS & VIEWS

Recent Patents and Major Discoveries

Recent patents in allergy and immunology: The interleukin-2 receptor pathway agonist rezpegaldesleukin (REZPEG) for the rescue of regulatory T cells in chronic inflammatory and autoimmune diseases

Regulatory T cells (Tregs) hold a pivotal role in orchestrating immune homeostasis through their ability to modulate the activity of T helper cell subsets, but are impaired in many autoimmune and chronic inflammatory diseases including psoriasis (PsO) and atopic dermatitis (AD).[1,2] Interleukin-2 (IL-2) plays a role in controlling the proliferation and survival of Tregs,[3] with low-dose IL-2 shown to partially rescue Treg function and provide clinical benefit in autoimmune diseases.[4] Low-dose IL-2, however, has limited therapeutic practicality, including a narrow therapeutic window and short half-life, thereby requiring more frequent dosing that could, in turn, result in conventional CD4 and CD8 T cell (Tcon) induction.

The patent application[5] described herein provides therapeutically advantageous formulations, doses, and dosing regimens for rezpegaldesleukin (REZPEG), an IL-2 receptor (IL-2R) pathway agonist designed to stimulate the expansion and function of Tregs. REZPEG incorporates the approved recombinant human IL-2 (rhIL-2) aldesleukin sequence, which has been conjugated with stable, covalently attached polyethylene glycol (PEG) moieties (Figure 1). The result is a drug candidate having an extended half-life as well as a selectivity for Treg stimulation over Tcons compared with rhIL-2.[5,6] The formulations, doses, and dosing regimens described in this patent include a range of fixed unit doses and regimens for induction and maintenance dosing. The objectives of these being to achieve effective autoimmune and chronic inflammatory disease management, increased patient compliance, convenience, and tolerability while also minimizing the risk of off-target Tcon stimulation.

In two randomized, double-blind, placebo-controlled Phase 1b trials in patients with AD or PsO, REZPEG was safe and well-tolerated, demonstrating consistent pharmacokinetics (PK) and clinical efficacy, meeting the primary, secondary, and exploratory objectives in both trials (NCT04081350 and NCT04119557). Notably, AD patients receiving 24 μg/kg REZPEG every 2 weeks (q2w) demonstrated an 83% improvement in Eczema Area and Severity Index (EASI) score after 12 weeks of treatment. EASI improvement of ≥75% (EASI-75) and validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) responses were maintained for 36 weeks after the end of the treatment period in 71% and 80% of patients responding to treatment at week 12, respectively. These clinical improvements were accompanied by sustained increases in $CD25^{bright}$ Tregs over the 12-week treatment period.

We set about designing an IL-2-based biologic that could be used as a potential therapeutic to drive the proliferation and activation of Tregs over Tcons. We rejected a traditional drug discovery screening approach focused on in vitro ligand binding on our belief that it was unlikely to be successful due to the overall complexity of IL-2 biology and IL-2's known on- and off-target immunological effects in vivo. Instead, we started with the rhIL-2 protein sequence and generated structurally different drug candidates therefrom utilizing a polymer conjugate construct. Each polymer conjugate was screened in vivo to allow for simultaneous evaluation of the [A] on-target effects (e.g., magnitude and duration of elevation of Tregs), [B] off-target effects (e.g., levels of Tcons, other lymphocyte and granulocyte populations, total blood cell populations, and other measures of off-target toxicity), and [C] the PK profile. Through this screening process, REZPEG was selected as the lead drug candidate.

Subsequent in vitro biophysical characterization revealed that REZPEG had a slow association rate for IL-2R which made it surprisingly selective for proliferating Tregs over Tcons. REZPEG also exhibited a dramatically decreased clearance relative to rhIL-2. More recently, REZPEG has been evaluated in numerous clinical studies in both healthy volunteers and patients with various autoimmune diseases.[3,7,8] In these clinical studies, we observed a prolonged PK/pharmacodynamic (PD) profile that allows for REZPEG to be dosed in patient-convenient intervals (such as q2w, once every four- [q4w], or 12 week [q12w] regimens).

Administration of REZPEG resulted in promising clinical improvements as determined by physician-measured and patient-reported outcomes in AD and PsO that were sustained for an additional 36 weeks following treatment cessation. Less frequent and/or adjusted REZPEG induction and maintenance doses and

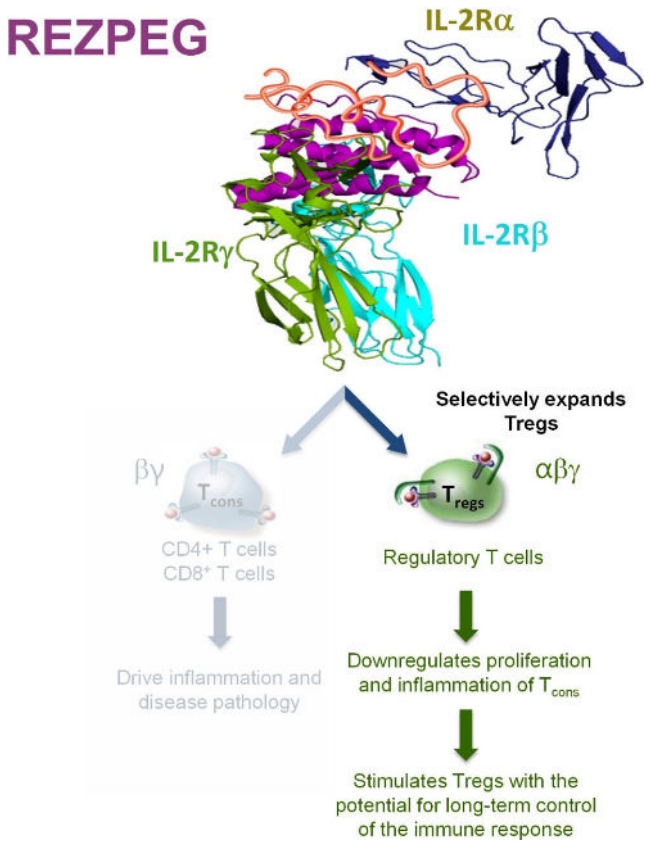

FIGURE 1 REZPEG structure and mechanism of action. REZPEG is a PEG-conjugated rhIL-2 that selectively induces Tregs and their suppressive activity. Compared with native IL-2, PEG conjugation increases the half-life and alters the binding profile of REZPEG, eliciting a lower binding affinity for all IL-2 receptor subunits. This imparts selectivity for the stimulation of Tregs constitutively expressing IL-2Rαβγ receptors over effector and conventional T cells expressing IL-2Rβγ chains. IL-2, interleukin-2; IL-2Rαβγ, interleukin-2 receptor composed of alpha, beta, and gamma chains; PEG, polyethylene glycol; REZPEG, rezpegaldesleukin; rhIL-2, recombinant human interleukin-2; Tcons, conventional T cells; Tregs, regulatory T cells.

dosing regimens provide advantageous means for the treatment of chronic inflammatory and autoimmune diseases. Consequently, improvements in clinical tolerability, enhanced patient compliance, convenience, and disease management are expected. Administration of REZPEG using q2w, q4w, and q12w regimens is currently being evaluated in an ongoing Phase 2b trial in AD (NCT06136741).

ACKNOWLEDGMENTS

Medical writing/editorial assistance was provided by Jaime S. Horton of CD Chunn & Associates and was funded by Nektar Therapeutics according to the Good Publication Practice guideline.

FUNDING INFORMATION

This research was sponsored by Eli Lilly and Company and Nektar Therapeutics.

CONFLICT OF INTEREST STATEMENT

JZ and CF are employees and stockholders at Nektar Therapeutics.

DATA AVAILABILITY STATEMENT

Supporting data are available from the corresponding author upon reasonable request.

Christie Fanton
Jonathan Zalevsky

Nektar Therapeutics, San Francisco, California, USA

Correspondence
Jonathan Zalevsky, Nektar Therapeutics, San Francisco, CA, USA.
Email: jzalevsky@nektar.com

REFERENCES

1. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. *Annu Rev Immunol*. 2020;38:541-566. doi:10.1146/annurev-immunol-042718-041717
2. Nedoszytko B, Lange M, Sokołowska-Wojdyło M, et al. The role of regulatory T cells and genes involved in their differentiation in pathogenesis of selected inflammatory and neoplastic skin diseases. Part II: the Treg role in skin diseases pathogenesis. *Postepy Dermatol Alergol*. 2017;34(5):405-417. doi:10.5114/ada.2017.71105
3. Fanton C, Furie R, Chindalore V, et al. Selective expansion of regulatory T cells by NKTR-358 in healthy volunteers and patients with systemic lupus erythematosus. *J Transl Autoimmun*. 2022;5:100152. doi:10.1016/j.jtauto.2022.100152
4. Abbas AK, Trotta E, Simeonov DR, et al. Revisiting IL-2: biology and therapeutic prospects. *Sci Immunol*. 2018;3(25):eaat1482. doi:10.1126/sciimmunol.aat1482
5. Ashrafzadeh A, Dodd SW, Jackson KA, et al. Dosing regimens for selective Treg stimulator RUR20kD-IL-2 and related compositions. WO2023/114833. PCT/US2022/081541.
6. Dixit N, Fanton C, Langowski JL, et al. NKTR-358: a novel regulatory T-cell stimulator that selectively stimulates expansion and suppressive function of regulatory T cells for the treatment of autoimmune and inflammatory diseases. *J Transl Autoimmun*. 2021;4:100103. doi:10.1016/j.jtauto.2021.100103
7. Forman S, Schmitz C, Budelsky A, et al. P1611: efficacy and safety of a selective regulatory T-cell inducing IL-2 conjugate (LY3471851) in the treatment of psoriasis: a phase 1 randomised study. *Presented at Eur Acad Dermatol Venereol Annaul Meeting*; 2022. https://doi.org/10.1007/s13224-023-01916-y
8. Silverberg J, Rosmarin D, Chovatiya R, et al. LBA 6685: efficacy and safety of single agent Rezpegaldesleukin, a selective regulatory T-cell-inducing Interleukin-2 conjugate, in the treatment of atopic dermatitis: final results from a randomized phase 1b study. *Presented at Eur Acad Dermatol Venereol Annual Meeting*; 2023.