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Rocatinlimab for atopic dermatitis: Rebalancing immunity by targeting pathogenic T cells

Anqi Cheng[1,2,3], Jianwei Li[1,2,3], Zhe Wang[1,2,3], Hong Liu[1,2,*]

[1]Dermatology Hospital of Shandong First Medical University, Ji'nan 27397, China

[2]Shandong Provincial Institute of Dermatology and Venereology, Shandong Academy of Medical Sciences, Ji'nan 27397, China

[3] These authors contributed equally

*** Correspondence:** hongyue2519@hotmail.com

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Atopic dermatitis (AD) is characterized by T-cell-mediated and downstream type 2 inflammation.[1] The pathogenesis is initiated when disruption of the skin barrier prompts keratinocytes to release epithelial alarmins—including thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. These alarmins coordinate the activation and clonal expansion of type 2 helper T (Th2) cells and innate lymphoid cells.[1,2] Mechanistically, the engagement of OX40 on activated T cells by OX40L recruits TNF receptor-associated factors (TRAFs), subsequently activating the NF-κB and PI3K-AKT signaling pathways. These molecular events upregulate anti-apoptotic proteins (e.g., Bcl-2 and Bcl-xL) and promote clonal expansion, thereby functioning as a pivotal 'amplifier' that sustains the robust production of downstream type 2 cytokines (IL-4 and IL-13) and perpetuates chronic inflammation.[2] Consequently, the overexpression of key type 2 cytokines, particularly IL-4 and IL-13, perpetuates disease by intensifying pruritus, reducing filaggrin expression—which further impairs the skin barrier—and promoting IgE class switching.[1] Current therapies for moderate-to-severe AD primarily focus on blocking key Th2-associated cytokines.[1] In contrast, the OX40-OX40L axis serves as a critical co-stimulatory checkpoint that regulates the survival, clonal expansion, and memory formation of pathogenic effector T cells (e.g., Th2, Th17, Th22).[2,3] Although the current IL-4Rα antagonists, such as dupilumab, provide rapid and effective symptom control by inhibiting downstream cytokine signaling,[1,4] it fails to eliminate the upstream cellular source of inflammation. Analogously, additional downstream inhibitors illustrated in Figure 1—including tralokinumab and lebrikizumab (targeting IL-13) and nemolizumab (targeting IL-31

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signaling)—have demonstrated efficacy in attenuating inflammation and pruritus, respectively.[1] However, a limitation shared by these cytokine-targeting therapies is that their efficacy is contingent upon continuous suppression; consequently, clinical symptoms typically recur upon treatment cessation due to the persistence of the pathogenic cellular source.[1] As a result, continuous treatment is generally required to prevent disease recurrence, highlighting the unmet need for durable, drug-free remission.[1] In contrast, rocatinlimab, a novel anti-OX40 monoclonal antibody, directly targets these upstream pathogenic T-cell populations. Recent Phase 3 trials have demonstrated its clinical efficacy;[5] distinct from cytokine inhibitors, rocatinlimab employs a unique T-cell rebalancing mechanism—mediated by the selective depletion of $OX40^+$ cells—to enable durable off-treatment remission.[5] This mechanistic difference positions rocatinlimab as a promising disease-modifying alternative that may complement existing downstream suppressive approaches. (Figure 1). These mechanistic distinctions underscore the necessity of a precision medicine approach to therapeutic selection. Downstream cytokine blockade (e.g., dupilumab), characterized by a rapid onset of action, remains the preferred first-line strategy for patients requiring immediate symptomatic relief and disease stabilization. Conversely, the upstream 'starvation and depletion' strategy (rocatinlimab) offers distinct clinical utility for two specific patient populations: (1) those with refractory disease exhibiting inadequate responses to downstream blockade, potentially attributable to heterogeneous T-cell drivers; and (2) those prioritizing 'disease modification'—specifically, the potential for sustained off-treatment remission.

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Consequently, therapeutic selection should be guided by individualized treatment objectives, balancing the imperative for rapid induction against the goal of long-term, drug-free maintenance.

The phase 3 trials demonstrated promising efficacy. At week 24, a significantly higher proportion of patients treated with rocatinlimab achieved EASI-75 and vIGA-AD 0/1 responses compared with placebo (p<0.001),[5] and a marked increase in Dermatology Life Quality Index (DLQI) scores (p<0.001).[5] The safety profile was characterized primarily by mild-to-moderate pyrexia and chills following the first dose, consistent with a mechanism-based cytokine release resulting from antibody-dependent cellular cytotoxicity (ADCC)-mediated T-cell depletion.[5] Although the clinical trial duration was limited to 24 weeks, future studies with extended follow-up are necessary to assess the long-term safety of rocatinlimab and identify any potential delayed adverse effects. Given the critical role of OX40 in T-cell differentiation and memory maintenance, theoretical concerns about the reactivation of latent viral infections, such as herpes simplex virus or Epstein–Barr virus, should also be considered. Long-term surveillance will be essential to fully define the safety profile of sustained OX40 modulation. Notably, clinical responses were not immediate but progressively improved between weeks 16 and 24.[5] This progressive response pattern—contrasting with the rapid plateau observed with downstream cytokine inhibitors like dupilumab,[4] aligns with its upstream mechanism of depleting pathogenic T-cell clones.[2,5] Although rocatinlimab did not demonstrate superior efficacy over established biologics in the trials, this may be explained by the enrollment of a substantial proportion

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(approximately 20%) of biologic-refractory patients and the use of a conservative non-responder imputation method in the primary analysis.[5] These results nevertheless indicate that rocatinlimab holds particular value for difficult-to-treat populations. Furthermore, while extended treatment may be required to attain maximal benefit, the therapy selectively reduced $OX40^+$ $CD4^+$ T cells without depleting the overall $CD4^+$ T-cell pool, supporting the maintenance of systemic immune homeostasis.[5] Therefore, as a T-cell rebalancing therapy, rocatinlimab represents a promising therapeutic strategy for diseases such as AD, working through the restoration of T-cell equilibrium. The existence of non-responders in phase 3 trials underscores the need for predictive biomarkers, particularly those reflecting OX40-dependent T-cell activation or disease endotypes driven by pathogenic T-cell memory. A validated biomarker is expected to be established to reliably predict response to OX40-targeted therapy. The upstream mechanism of targeting pathogenic T-cell survival and memory formation is fundamentally distinct from downstream cytokine blockade, which therefore raises the possibility that combining rocatinlimab with cytokine-targeting biologics, such as IL-4/IL-13 inhibitors, could provide complementary benefits by rapidly controlling inflammation while progressively rebalancing the underlying T-cell compartment. Such combination strategies remain speculative and will require careful evaluation of safety, durability, and clinical benefit in future studies.

Immune homeostasis relies on a balanced interplay between different T-cell subsets, ensuring efficient pathogen elimination while maintaining self-tolerance. Genetic

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predisposition and environmental exposures, however, can disrupt this equilibrium, leading to immune dysregulation. Such dysregulation often becomes self-sustaining: excessive production of polarizing cytokines—including IL-4, IL-13, and IL-17—not only fuels inflammation but also creates a microenvironment that undermines the stability and suppressive function of regulatory T cells (Tregs). This in turn promotes the abnormal differentiation and activation of pro-inflammatory T-cell subsets such as Th1, Th2, and Th17, while Tregs become numerically or functionally impaired.[2,3] The resulting loss of immune tolerance can trigger autoimmune reactions or uncontrolled inflammation, ultimately contributing to tissue damage. Therefore, therapies aimed at rebalancing T cells seek to restore homeostasis by correcting the imbalance between effector T cells (Teff) and Tregs.[3] Currently, three distinct interventional modalities have been established. One approach is to expand the Treg population. For example, low-dose IL-2 therapy capitalizes on the high constitutive expression of CD25 on Tregs to selectively promote their expansion and activation. This coordinated action enhances Treg-mediated suppression, promotes their migration to sites of inflammation, and concurrently inhibits the development of pro-inflammatory lineages such as Th17, thereby strengthening immune tolerance at multiple levels.[3] The second strategy, often termed co-stimulation blockade or the "starvation" approach, aims to disrupt essential survival signals for pathogenic T cells by blocking critical co-stimulatory pathways. In AD, the OX40-OX40L axis has been identified as a key checkpoint regulating effector T-cell survival and memory formation. Agents targeting this axis employ distinct mechanisms.[2] While amlitelimab (anti-OX40L)

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inhibits signaling without depletion, rocatinlimab (anti-OX40) uniquely leverages ADCC to selectively deplete $OX40^+$ pathogenic T cells. Unlike conventional biologics that merely suppress downstream cytokines, this depletion strategy targets the 'immunological scar'—specifically, the persistent pathogenic memory clones. By abrogating requisite secondary signals, this strategy arrests the chronic inflammatory cycle, demonstrating disease-modifying potential evidenced by durable remission.[5] The third paradigm, immune reset, utilizes agents such as alemtuzumab or rituximab to induce profound lymphodepletion, effectively dismantling established pathogenic immune memory circuits. Subsequently, immune reconstitution can then facilitate the reprogramming of the immune system toward a tolerogenic state, achieving sustained disease control.[3] Functioning through such upstream immunomodulation, the therapeutic potential of rocatinlimab likely extends beyond dermatology. Given that OX40 is broadly upregulated on activated effector T cells (including Th1, Th2, Th17, and Tfh subsets) independent of tissue localization, this starvation and depletion strategy is theoretically applicable to a broad spectrum of systemic pathologies.[2,3] For instance, in allergic asthma, targeting the OX40 axis may impair the persistence of pathogenic Th2 memory cells, mirroring mechanisms observed in AD.[3] In alopecia areata (AA), where disease is driven by IFN-γ–producing $CD8^+$ T cells, OX40 blockade may attenuate the cytotoxic attack on hair follicles, given the molecule's role in optimal $CD8^+$ T-cell expansion and effector function.[3] Furthermore, given the critical role of OX40 in sustaining Tfh cells, which coordinate germinal center reactions and drive B-cell differentiation into plasma cells—this approach provides a

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compelling rationale for treating antibody-mediated autoimmune disorders such as systemic lupus erythematosus (SLE) or pemphigus.[3] Additionally, in transplantation, blocking OX40 co-stimulation has also shown potential in mitigating graft-versus-host disease (GVHD) by restraining the expansion of alloreactive T cells.[2] Ultimately, clinical studies across these diverse disease contexts will be necessary to validate the efficacy and safety of this mechanistic approach. In the treatment of AD, in addition to Tregs, other immune cells such as myeloid-derived suppressor cells (MDSCs), dendritic cells, NK cells, macrophages, and B cells also play important roles in immune regulation. Targeted therapies aimed at these cells are continuously being developed. Enhancing NK cell function or targeting their receptors also contributes to immune regulation. These targeted strategies can effectively modulate the immune response, reduce excessive immune activation, and help alleviate inflammation and allergic reactions, offering new possibilities for precision medicine in AD.

In conclusion, the Phase 3 clinical trials demonstrate the promising therapeutic efficacy of rocatinlimab in moderate-to-severe AD.[5] This agent represents a pivotal therapeutic alternative, particularly for patients refractory to prior biologic therapies or JAK inhibitors. Beyond addressing unmet clinical needs in refractory AD, the clinical validation of rocatinlimab substantiates T-cell rebalancing as a viable therapeutic paradigm, thereby catalyzing further investigation into upstream immunomodulatory strategies.

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AUTHOR CONTRIBUTIONS

Anqi Cheng was responsible for the data collection and drafting of the initial manuscript. Jianwei Li conducted conceptualization, visualizing the mechanism figure

and drafting of the initial manuscript. Zhe Wang contributed to writing of the manuscript and data collection. Hong Liu engaged in discussions, and revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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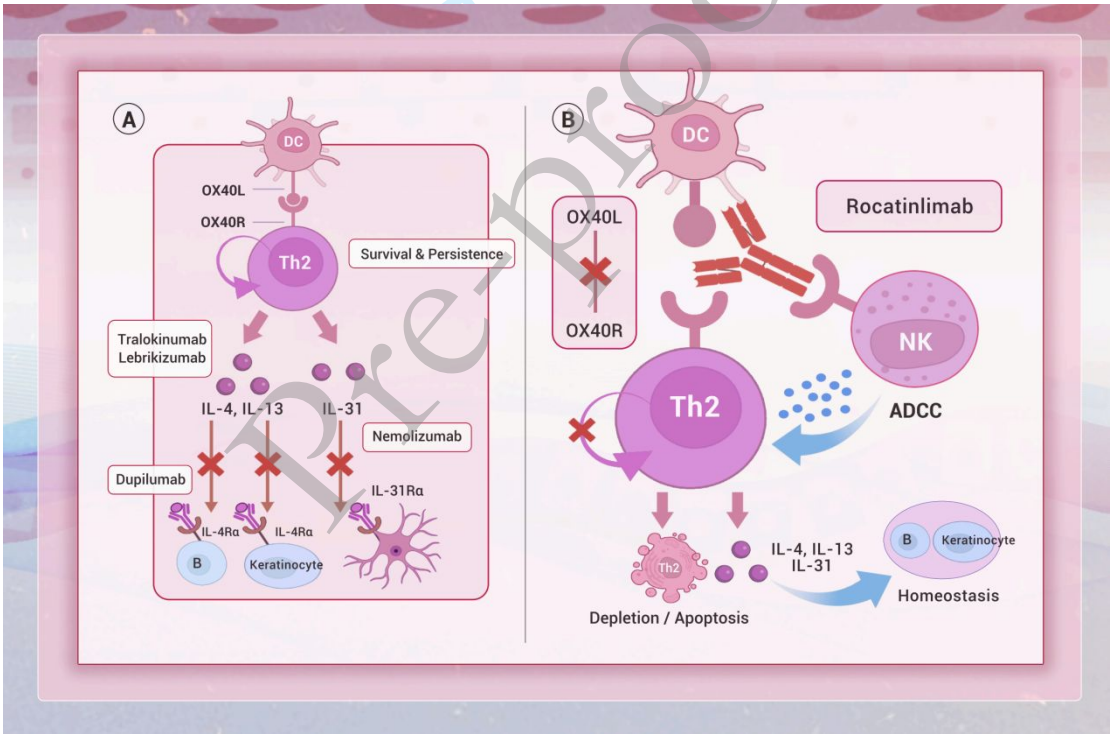

Figure 1. Mechanistic comparison of therapeutic paradigms in atopic dermatitis: Downstream cytokine blockade versus upstream T-cell rebalancing

(A) **Downstream Cytokine Blockade (Standard of Care):** Conventional biologics target downstream effector pathways. Agents such as dupilumab (anti-IL-4Rα), tralokinumab, and lebrikizumab inhibit IL-4 and IL-13 signaling on effector cells (e.g.,

B cells, keratinocytes) and sensory neurons, effectively attenuating barrier dysfunction, inflammation, and pruritus. However, the upstream cellular source—activated pathogenic memory Th2 cells—persists with retained self-renewal capacity (depicted by the "Survival & Persistence" loop), potentially predisposing patients to disease recurrence upon treatment cessation.

(B) **Upstream Pathogenic T-Cell Depletion (Rocatinlimab):** The OX40 receptor is preferentially upregulated on activated pathogenic effector and memory T cells. Rocatinlimab targets this checkpoint via a dual mechanism: (1) blockade of OX40-OX40L co-stimulatory signaling ("Starvation") and (2) recruitment of natural killer (NK) cells to mediate antibody-dependent cellular cytotoxicity (ADCC). This results in the selective depletion of pathogenic T-cell clones. By abrogating cytokine production at the cellular source, this strategy facilitates the restoration of systemic immune homeostasis, offering disease-modifying potential characterized by durable off-treatment remission.

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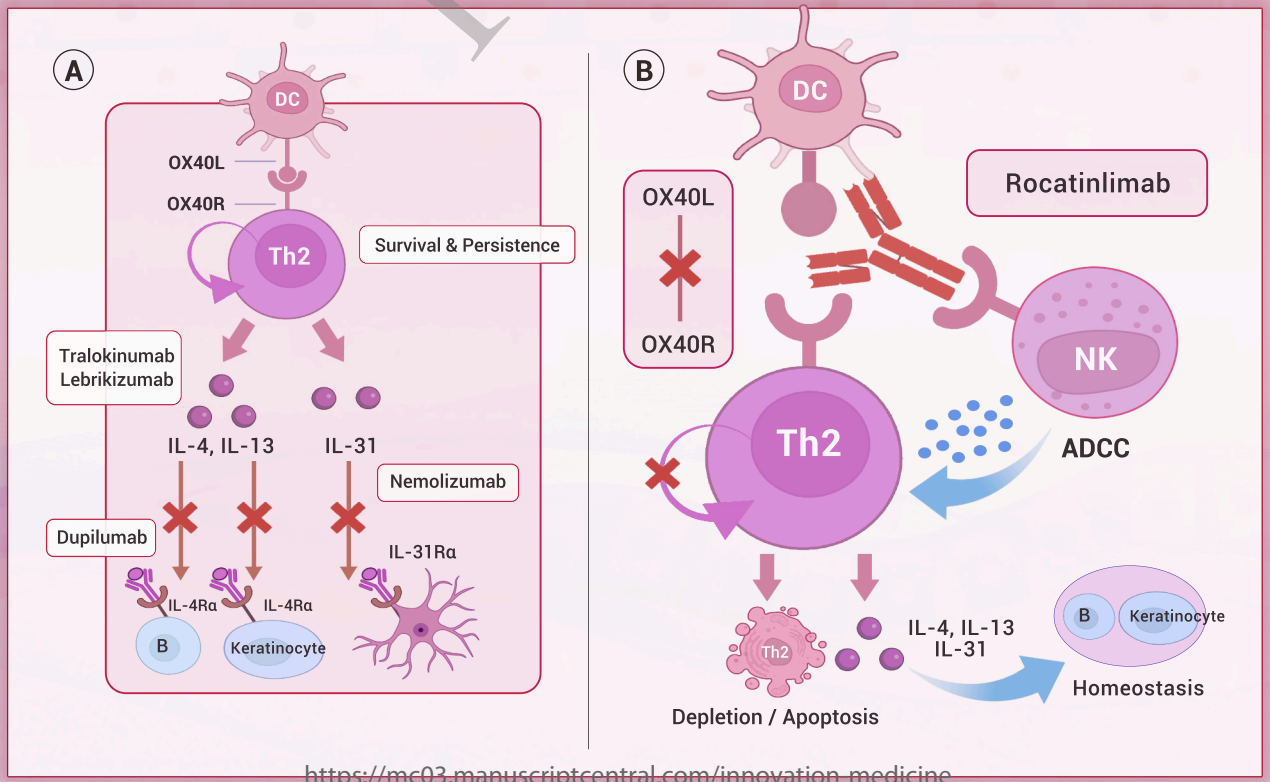
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OX40L
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