Unmet needs of managing atopic dermatitis: where do we stand in modifying vs. suppressing disease?

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**Introduction:** Atopic Dermatitis (AD) is a chronic relapsing inflammatory skin condition that is evolvably perceived as a systemic disease, particularly when severe. The therapeutic ladder for managing AD has undergone substantial expansion in the last decade as new pathways are revealed, yet 75\% of patients are not satisfied with their management of AD. While patients may report symptom relief, AD often requires ongoing treatment, increased dosage, or alternating regimens. For those patients who appear to respond well over a prolonged period, it is unclear whether they will tolerate treatment cessation.

**Objective:** To evaluate the current therapeutic options available for AD from the standpoint of their disease-modifying vs. disease-suppressing capabilities.

**Methods:** A systematic review of the literature was performed using academic research databases including PubMed and Embase between 1994 and 2024. The studies extracted from the search included, but were not limited to, randomized placebo-controlled trials, systematic
reviews, cross-sectional studies, observational studies, case series, case reports, and retrospective studies. Current and emerging therapies for the treatment of AD were assessed for their ability to modify underlying disease mechanisms, and/or induce disease remission.

**Results:** Although several of the drugs that are currently approved for AD target the pathogenic Th2 axis, Janus Kinase (JAK) inhibitors have the most supporting evidence for their ability to modify underlying disease mechanisms. Inhibiting distinct JAK families hinders the downstream effects of multiple cytokines involved in AD at once. In some case reports, patients treated with selective JAK-1 inhibitors for up to 6 months did not experience disease recurrence following cessation during a several-month follow-up period. Similar studies of certain biological agents have shown prolonged periods of remission after discontinuation of dupilumab, tralokinumab, and lebrikizumab. This suggests that they may also drive long-lasting cellular changes, especially when implemented in early disease. Targeting OX40 or its ligand, the OX40L, may also hold promise for modifying AD. Studies have additionally indicated that there may be a therapeutic window of opportunity for maximal treatment impact in AD. Early intervention shortly after pediatric onset of disease may lead to improved long-term control and reduced comorbidity development. Novel disease-modifying strategies are currently being investigated in clinical trials for their capacity to correct skin and gut dysbiosis, restore epidermal barrier integrity, and alter innate and adaptive immune responses.

**Conclusions:** Recent progress in drug development has greatly advanced symptom control in patients with AD. However, only a few, if any, therapeutic strategies have demonstrated long-term disease modification. There is an unmet need to study the rate of recurrence upon cessation
of current AD therapies. Future research should prioritize the development of therapeutic interventions for AD that not only treat symptoms but also modify the underlying disease pathology over time.

**Keywords:** disease-modifying therapy, JAK inhibitors, biologics, microbiome, immune response

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