The Translational Revolution in Atopic Dermatitis, and How It Also Translates to Other Inflammatory Skin Diseases

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Atopic dermatitis (AD) is the most common inflammatory skin disease in both adults and children.[1] Unfortunately, the current treatment armamentarium is largely confined to topical calcineurin inhibitors, topical and systemic steroids, phototherapy, cyclosporine (not approved by the US Food and Drug Administration for AD), and other oral immunosuppressants.[2] The availability of partially helpful and highly toxic treatments creates a huge unmet need for more effective and safer treatments, particularly for patients with moderate to severe AD who often require systemic approaches.

Recent extensive translational (bench top to bedside and back) investigations in skin of AD patients has shown that skin phenotype is characterized by increased T-cell infiltration and related inflammatory cytokines as well as epidermal abnormalities (eg, hyperplasia, aberrant differentiation).[3] Clinical improvement of AD has been demonstrated with broad T-cell targeted therapeutics, such as cyclosporine and narrowband UVB, coupled with decreases of T-cell infiltrates and inflammatory gene products as well as improvement of the pathologic epidermal phenotype.[4,5]

In the past, AD was conceptualized as a T helper cell T_H2 (acute disease)/T_H1 (chronic disease) bipolar cytokine disorder.[6] Acute lesions are characterized by high T_H2, T_H22, and some T_H17 signals, with intensification of these axes and T_H1 augmentation orchestrating the chronic phenotype.[7] The identification of the inflammatory pathways underlying AD has led to the development and testing of more than 10 broad or targeted therapeutics (Table).[8] Phase 1 and phase 2 studies of dupilumab (targeting IL-4Rα) have shown not only tremendous AD improvement (~70%) but also tissue reversal of the immune and barrier abnormalities, including inflammatory cytokines and epidermal hyperplasia.[9-11] As a result, other T_H2 axis inhibitors (anti–IL-13/tralokinumab, anti–IL-31RA/CIM 331) are now in clinical trials. The identification of IL-22 in AD lesions has prompted trials with an anti–IL-22 (ILV 094) and an IL-12/IL-23p40 (ustekinumab) inhibitor.[12] For psoriasis, ustekinumab showed 75% improvement in approximately 70% of patients,[13] but for AD, despite clear clinical and molecular effects, differences compared to placebo were not statistically significant,[12] probably due to underdosing of the drug in an excessively immune-activated disease[14] as well as allowing topical steroids in patients, which may minimize the differences in treatment effect between drug and placebo.

The developments seen in AD are now moving into other inflammatory skin diseases, particularly

Therapeutics on the Horizon for AD

Drug	Molecular Target
AMG 157	TSLP
Apremilast	PDE4
Baricitinib	Jak1, Jak2
BMS 981164	IL-31
CIM-331	IL-31RA
Dupilumab	IL-4Rα
ILV 094	IL-22
MK 8226	TSLPR
OC 000459	CRTH2
QGE 031	IgE
Tralokinumab	IL-13RA
Ustekinumab	IL-12/IL-23p40

Abbreviations: AD, atopic dermatitis; TSLP, thymic stromal lymphopoietin; PDE4, phosphodiesterase 4; Jak, Janus kinase; TSLPR, TSLP receptor; CRTH2, chemoattractant receptor-homologous molecule expressed on T helper cell 2 (T_H2).

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Dr. Czarnowicki reports no conflict of interest. Dr. Guttman-Yassky is an advisory board member and accepted grant support from Regeneron Pharmaceuticals, Inc.
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alopecia areata (AA), a T-cell–mediated disease that shares phenotypic similarities with AD and often is associated with it.[15] There is a paucity of effective, remission-sustaining treatments of AA, particularly for patients with severe disease who rarely experience spontaneous hair regrowth and who have a limited response to topical interventions.[16,17] Our clinical experience showed that successfully treating patients with concurrent AD and AA has led to hair regrowth. Inspired by these clinical observations and by results obtained in AD,[9-12] studying AA skin showed an upregulation of not only the traditionally suspected culprit T_H1 but also T_H2 and T_H9 axes, IL-23 cytokines, and phosphodiesterase 4.[18] Subsequently, a pilot study of 3 patients with extensive AA treated with ustekinumab showed that all 3 patients not only experienced hair regrowth but also had a reduction in inflammatory markers in scalp lesions.[19] Although these results are promising, AA is an immunologically complex disease and it is yet to be determined if therapeutically targeting 1 (eg, IL-4) rather than a wide array of cytokines can reverse disease phenotype. There are ongoing clinical trials directed at different pathogenic targets (eg, Jak inhibitors, IL-13 antagonist, IL-17 antagonist, phosphodiesterase 4 antagonist); some showed some efficacy in small studies.[20,21]

The finding of a commonly upregulated T_H2 pathway in both AD and AA will pave the way for studies with T_H2 antagonists in AA patients. Future targeted therapeutic studies will shed light on the pathogenic pathways of this devastating skin disease and answer the extensive unmet therapeutic need it presents.

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