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 evolvingly 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 for AD from the standpoint of disease-modifying vs. disease-suppressing capabilities.

METHODS

Literature search from academic databases:

- PubMed, Embase, Cochrane Library, Scopus, Web of Science, Clinical Trial Library

- Analysis for therapeutic targets and mechanisms in innate immunity

Figure 1. Unmet needs of treating AD

RESULTS I

Mechanisms and disease-modifying therapies for atopic dermatitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism of modification</th>
</tr>
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<tbody>
<tr>
<td>AD</td>
<td></td>
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</table>

RESULTS II

Table 1. Disease-modifying potential of current and emerging drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic (mAb)</td>
<td>Dupilumab, Tralokinumab</td>
<td>Selective inhibition of IL-4/13, blocking signaling of IL-4 and IL-13, (involved in epidermal barrier function, inflammation, microbial diversity)</td>
</tr>
<tr>
<td>JAK (mAb)</td>
<td>Abrocitinib, Ruxolitinib, Upadacitinib</td>
<td>Disruption of multiple downstream cytokine signaling pathways that regulate TH2 inflammation and filaggrin expression</td>
</tr>
<tr>
<td>Small Molecules</td>
<td>PDE4 inhibitors</td>
<td>Janus Kinase; cyclic adenosine monophosphate; suppressing</td>
</tr>
</tbody>
</table>

RESULTS III

Evidence suggesting modification of AD

- 50% of patients treated with dupilumab maintained remission for 40 weeks after discontinuation [4]
- After 16 weeks of nzmoltizumab treatment, patients maintained skin lesion and itch benefits through week 48 despite dose reductions every 4-8 weeks [6]
- After 16 weeks of lebrikizumab therapy, withdrawal or dose reduction led to maintained skin lesion and pruritus benefits at week 52 [1]
- Withdrawal or continuation of amloclitumab after 24 weeks led to maintained AD symptom reduction in 58.8% and 69.2% of patients. [5]
- AD-related biomarkers also remained reduced at week 52 in both groups [5]

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 DIRECTIONS

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.

Several agents are in development that focus on specific disease-modifying strategies:

1. Correcting dysbiosis – reduction of S. aureus colonization, increasing microbiome diversity
2. Restoring epidermal barrier function
3. Early modulation of the immune response – may halt/delay the atopic march in children
4. Altering neural structure/function and the stress response – increased cortisol and noradrenaline in neural circuits may alter the perception of itch

REFERENCES

3. Czarnowicki T, Krueger JG, Guttman-Yassky E. Therapeutic interventions for AD that not only treat pathology over time. 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. Several agents are in development that focus on specific disease-modifying strategies:
4. Correcting dysbiosis – reduction of S. aureus colonization, increasing microbiome diversity
5. Restoring epidermal barrier function
6. Early modulation of the immune response – may halt/delay the atopic march in children
7. Altering neural structure/function and the stress response – increased cortisol and noradrenaline in neural circuits may alter the perception of itch

Figure 2. A comparison of the disease-modifying and disease-suppressing mechanisms of current and emerging drugs for atopic dermatitis