Industry Perspective on the Clinical Development of Systemic Products for the Treatment of Atopic Dermatitis in Pediatric Patients with Inadequate Response to Topical Prescription Therapy

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Industry Presenters

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Overview of Atopic Dermatitis (AD)
Atopic Dermatitis Overview

- Chronic inflammatory itchy skin condition that develops in early childhood
- It is relapsing/remitting by nature
- Significantly impairs quality of life due to vicious cycle of intense itching & scratching, insomnia, depression and anxiety
- Increased susceptibility to bacterial, viral, and fungal infections
Atopic Dermatitis Overview

- Complex interaction of genetic and environmental factors
- Lesional skin characterized by:
  - Impaired protective barrier
  - Deficient innate immune response
  - Predominantly Th2 mediated inflammation
    - ~80% of AD patients have elevated serum IgE levels and increased allergen specific responses
- Common dermatitis triggers e.g. irritants, allergens, microbes, weather changes, etc.
Atopic Dermatitis Overview

• ~30% of children with AD will develop asthma and/or allergic rhinitis (including hayfever)\(^1\)
  o This sequence of events is referred to as the ‘atopic march’

\(^1\) Hanifin 2007
Atopic Dermatitis Overview

• AD persists in 80+% of US children and adolescents\(^2\)

• Many AD cases clear or improve during childhood, whereas others persist into adulthood
  
  o Up to 70% of children who develop AD between 6 months-5 years of age, have spontaneous remission before adolescence\(^3\)

• Evidence suggest prevalence of AD decreases as age increases in children\(^4,5\)

• Severity tends to increase with age\(^6\)
  
  o Children with severe disease are more likely to have a protracted disease course and a significantly worse quality of life compared with those with more mild disease

\(^2\) Margolis 2014; \(^3\) Bieber 2008; \(^4\) Furue 2011; \(^5\) Shaw T, et al; \(^6\) Silverberg and Simpson 2014
Target Population Prevalence

• There are very little demographic data available on children with AD who are inadequately treated with topical or systemic treatment.

• It can be extrapolated from older data that a proportion of moderate and severe patients will respectively represent those who inadequately respond to topical treatment or those who receive systemic treatment.
# Severity in US Pediatric AD Population

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Atopic Dermatitis Severity</th>
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<tbody>
<tr>
<td></td>
<td>Mild (N=7198)</td>
</tr>
<tr>
<td></td>
<td>Percent (95% CI)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>76.9 (69.9-84.0)</td>
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<tr>
<td>1 - 3</td>
<td>76.2 (72.2-80.2)</td>
</tr>
<tr>
<td>3 - 7</td>
<td>67.7 (63.3-72.2)</td>
</tr>
<tr>
<td>7 - 13</td>
<td>63.1 (59.0-67.3)</td>
</tr>
<tr>
<td>13 - 17</td>
<td>62.6 (57.4-67.7)</td>
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Silverberg and Simpson 2014
Age-related Differences in Disease Manifestation

• AD occurs in three main age-related stages
  o Infants (0-2 years): highly pruritic, red, scaly crusted, weeping patches on cheeks and extensor surfaces of extremities; scalp
  o Childhood (2 to 12 years): xerosis, papulation frequently in flexural surfaces of extremities; thickened plaques, excoriation
  o Adolescence/Adulthood: flexural surfaces, facial, hands, feet

<table>
<thead>
<tr>
<th>Infants (0-2 years)</th>
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<tr>
<td>• Extensor surfaces of extremities</td>
</tr>
<tr>
<td>• Face (forehead, cheeks, chin)</td>
</tr>
<tr>
<td>• Neck</td>
</tr>
<tr>
<td>• Scalp</td>
</tr>
<tr>
<td>• Trunk</td>
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Childhood (2 years to puberty)

| • Flexural surfaces of extremities |
| • Neck |
| • Wrists, ankles |

Adolescence/adulthood

| • Flexural surfaces of extremities |
| • Hands, feet |

7Rudikoff 1998; 8Table adapted from Wasserbauer N, Ballow M, 2009
Challenges in AD – Definitions\(^9\)

- Lack of universally accepted, formal definition of “inadequate response,” “intolerance,” “refractory” and “resistance” in AD

- One interpretation:

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<tr>
<th><strong>Intolerance to topical treatment</strong>: patient’s opinion after at least 2 weeks of therapy with a new topical treatment, because of worsening of lesions or any difficulty to apply the drug (ointment not supported, pain, burning or any uncomfortable sensation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resistance to topical treatment</strong>: physician’s opinion after at least 2 weeks of therapy with an appropriate dosage of the treatment which has not changed or has aggravated the clinical score</td>
</tr>
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</table>

\(^9\)Darsow U et al 2010
Challenges in AD – Disease Severity Scales

• AAD identified 28 different scales
• No gold standard identified
• Common Scales:
  o SCORing Atopic Dermatitis (SCORAD) index
  o Eczema Area and Severity Index (EASI)
  o Static Investigator’s Global Assessment (sIGA)
  o Six Area, Six Sign Atopic Dermatitis (SASSAD)
• Lack of uniformity in scales
• Differences in requirements between health authorities
American Academy of Dermatology (AAD)
American Academy of Dermatology Guidelines\textsuperscript{10}

• In general, no differentiation in use of agents made between adults and pediatrics
• Currently, no FDA approved treatment for patients with AD who inadequately respond to topical therapy are recommended
• Majority of patients with AD achieve improvement and control of symptoms using combination of
  o Nonpharmacologic interventions (e.g. emollients, bleach baths)
  o Conventional topical therapies (e.g. corticosteroids, calcineurin inhibitors)
  o Lifestyle and/or environmental modifications
American Academy of Dermatology Guidelines

• If not controlled by previous methods, phototherapy recommended
• If still not adequately controlled, systemic immunomodulating agents recommended (all “off-label” use)
• Systemic corticosteroids should generally be avoided
  o Some are FDA approved for control of severe or incapacitating AD to conventional treatments, but not recommended
  o Unfavorable risk-benefit profile in both short- and long-term use
  o Rebound of AD following discontinuation is an important reason to avoid systemic CS
  o Not recommended unless used to manage comorbid conditions (e.g. asthma)

10 AAD guidelines 2014 Part 3
American Academy of Dermatology Guidelines

- Systemic immunomodulating agents recommended by AAD (all “off-label” use)
  - Cyclosporine A
    - Generally reserved for refractory disease
    - Both pediatric and adult patients treated with CSA experience a reduction in signs and symptoms of AD
    - For both short-term and long-term use (up to 12 months)
  - Azathioprine
    - Use in recalcitrant disease or when disease causes significant social impact
    - Patients experience a reduction in AD disease activity
  - Methotrexate
    - Treatment effect in refractory AD is unclear
  - Mycophenolate mofetil
    - Use as alternative therapy for patients with AD, treatment effect variable
    - “…should be considered a relatively safe alternative systemic therapy for pediatric patients with refractory AD.”
# Systemic Agents: Adverse Effects

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<tr>
<th>Systemic Agent</th>
<th>Black Box Warnings/Adverse Effects</th>
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| Cyclosporine A          | Risk of infection  
Malignancy, hypertension, nephrotoxicity and structural renal damage, hypertrichosis, gingival hyperplasia, and paresthesia. |
| Azathioprine            | Chronic immunosuppression with increased malignancy risk  
Increased infection risk, hepatotoxicity (elevation in liver enzymes), and bone marrow suppression.                                                             |
| Methotrexate            | Bone marrow suppression, skin and kidney toxicities  
Anemia/pancytopenia, elevated transaminases, liver fibrosis/failure and teratogenic.                                                                               |
| Mycophenolate mofetil   | Fetal-risk and lymphoma  
Nausea, vomiting, diarrhea, leukopenia, hypertension and nephrotoxicity.                                                                                     |
Past and Potential Concerns in Pediatrics
Tumor Necrosis Factor (TNF) α blockers\textsuperscript{11}

- Risk of malignancies in adults were identified from clinical trials after initial drug approvals in autoimmune diseases

- Evidence that treatment with TNF α blockers in children may increase the risk of malignancies
  - Rate of malignancy in pediatrics receiving infliximab was $\sim$4X the estimated background rate in general US population

- For some agents appropriate safety evaluation in adults may be warranted before use in children

\textsuperscript{11}Diak, Peter et al 2010
Secukinumab (Cosentyx™) for Psoriasis

“Serious safety signals have been observed... in adult patients, and the Agency has determined that pediatric studies should be deferred until after adult studies have been completed.”

-from FDA BLA Approval letter (January 2015) for Cosentyx™
Children’s Development
Safety Concerns

• Normal growth and development, 4 periods\textsuperscript{12}:
  1. Infancy
  2. Preschool years
  3. Middle childhood years
  4. Adolescence

• Care should be taken not to negatively impact the normal growth and development process

• The developing immune system may be particularly sensitive to systemic therapies
  o Neutrophil maturation during infancy\textsuperscript{13}
  o Innate immune system maturation before preschool years with full capacity reached only at adolescence\textsuperscript{13}
  o Intensive shaping of adaptive immune system \textsuperscript{14}

\textsuperscript{12} Textbook of Pediatrics 19\textsuperscript{th} Ed 2011; \textsuperscript{13} Ygberg et al 2012; \textsuperscript{14} Ygberg et al. 2011
Considerations for Timing of Pediatric Studies
Pediatric Safeguards: 21 CFR 50 Subpart D

• Direct benefit should justify risks
  o Potential risks posed by novel systemic agents particularly immunomodulatory agents generally exceed a minor increase over minimal risk
  o Risk justified by anticipated benefit
  o Consider alternative therapies available which may offset the direct benefit of the new treatment
ICH E11 Guidance

• “...timing of pediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternatives”
  o Disease:
    • AD can be severe and debilitating
  o Safety:
    • Uncertainties of novel agents must be taken into consideration
  o Alternative therapies:
    • Exist and they are recommended by AAD for pediatric use
    • Benefits and risks are known
Accelerating Development in Pediatrics

- ICH and 21 CRF 50: special attention needs to be given to development in pediatrics

- At the same time, there is a need to carefully accelerate development

- Safety cannot be compromised
Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar (1) disease progression and (2) response to intervention?

No to either ➔ Yes to both

Is it reasonable to assume a similar ER in children when compared to adults?

No ➔ Is there a PD measurement that can be used to predict efficacy in children?

Option A: Conduct PK studies to establish dosing, and then safety and efficacy trials in children.

Yes ➔ Conduct (1) PK studies in children aimed at achieving drug levels similar to those for adults then (2) safety trials at the proper dose.

Option B: Conduct (1) PK/PD studies to establish an ER in children for the PD measurement, (2) PK studies to achieve target concentrations based on ER, then (3) safety trials at the proper dose.

Option C

15Dunne et al, 2011
ER: Exposure-Response
Extrapolation and Timing

• If extrapolation can be based on exposure-response or PK/PD, then there is potential for pediatric safety data to be submitted with adult data for approval.

• If extrapolation is not possible (e.g. exposure–response not expected to be similar or no PD marker):
  o Both safety and efficacy trials are required in pediatrics.
Consideration for Timing of Pediatric Studies

• Acknowledgement that there is a true need to develop safe and effective therapies in pediatric patients with AD with inadequate response to topical therapies

• Potential to study adolescents (>12 years old) with adult study

• Careful consideration for appropriate timing to study in younger pediatrics (≤12 years old)
Evaluation on Case-by-Base Basis

- Risk/benefit profile of the product
- Availability of data to support direct benefit to pediatrics to justify risk
- Ability to extrapolate from adult data is dependent on particular drug/biologic
- Consider alternative therapies available
- Practical considerations for the time needed to recruit younger population
A Proposal for Timing of Pediatric Studies

• Potential inclusion of adolescents with adult population

• Deferral for 2-12 years old
  o Evaluate efficacy and/or safety in adults and adolescents prior to exposing younger population to potential risk

• Waiver for pediatric patients <2 years old
  o Consider antibody therapies which can have unpredictable effects in pediatrics under 2 years old (ICH E11)
  o Studies may be impractical
Summary

• There is a need for safe and effective therapies for the treatment of AD that is inadequately responsive to topical therapies.

• Timing of pediatric studies should be considered on a case-by-case basis based on risk/benefit of each product.

• Novel therapies have an opportunity to provide safe and effective therapies.
References


References


Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. The Institution for Woman and Child Health, Unit of Clinical Pediatrics, Karolinska Institute, 2011