Abstract

Prostaglandin D2 (PGD2) is a potent prostanoid released from activated mast cells during atopic responses. CRTh2 (Chemotactactant Receptor-homologous molecule expressed on Th2 lymphocytes; a.k.a. DP2), a PGD2 receptor, mediates chemotaxis and mast cell-dependent activation of basophils, eosinophils and Th2 lymphocytes. Preclinical data and emerging clinical results suggest CRTh2 antagonists may have utility in allergic diseases. ARRY-005 is a potent, selective, orally bioavailable competitive antagonist of CRTh2 (binding IC50 = 1 nM). ARRY-005 inhibits i) PGD2-mediated chemotaxis of isolated human basophils, ii) PGD2-induced eosinophil shape change in human whole blood and iii) PGD2-induced CRTh2 receptor internalization in human whole blood. In a model of atopic dermatitis (AD) utilizing NC/Nga mice that spontaneously develop symptoms of AD, oral administration of ARRY-005 at 30mg/kg (QD) inhibited ear edema, erythema, oozing, crust formation, hemorrhaging and pruritus and showed trends in improved skin histopathology. The selective CRTh2 antagonist, ARRY-005, is a potent inhibitor of basophils and eosinophils in vitro and exhibited significant protective activity in a model of dermatitis.

[Acknowledgement: Dr. Wenbin Ying, MD (Bio-Quant, San Diego, CA)]

Background

• Local antigen challenge stimulates PGD2 production in the skin of atopic dermatitis patients
  - Corticosteroids have no inhibitory effect on this event1
• Increased levels of circulating CRTh2-positive lymphocytes have been detected in blood from AD patients2
• CRTh2 KO mice have diminished responses to allergic challenge with decreased IL-4, IL-13, IgE, mucus production, eosinophil migration & airway hyperresponsiveness
• CRTh2 is expressed on eosinophils, basophils & Th2 T cells
  - CRTh2 activation results in chemotaxis
  - CRTh2 stimulation yields IL-4, 5 & 13 from Th2 T cells
• There are reports of CRTh2 involvement in dermatitis models3
• A weak, non-selective CRTh2 antagonist with modest efficacy, is approved for allergic rhinitis in Japan (Ramatroban®)
• Selective CRTh2 antagonists are in clinical development4

Murine Model of Atopic Dermatitis

• NC/Nga mice: inbred mouse strain that develops a spontaneous AD-like pathology in non-sterile housing conditions5
• Dosing started at ~4 weeks of age; microscopic disease present
• Groups:
  - Vehicle (Labrafac, BID, po) x 30 days
  - ARRY-005 (30 mg/kg, QD, po) x 30 days in CMC/SDS
  - Protopic® (0.03% Tacrolimus) cream (10 mg/cm2, BID, topical) x 30 days
• Assessments:
  - Twice weekly ear thickness measure
  - Weekly clinical scoring
  - Assessments: Mild epidermal hyperplasia (E) Minimal orthokeratotic hyperkeratosis Minimal epithelial necrosis
• Skin samples taken for histopathology at conclusion of study

Unmet Medical Needs in Atopic Dermatitis

• Topical corticosteroids are typically effective but there are concerns with side effects particularly among pediatric patients
• Topical immunosuppressants are effective but have a black box warning

We hypothesize that an oral agent possessing efficacy similar to topical steroids and immunosuppressants but with a superior safety profile would provide benefit to patients

Profile of ARRY-005

<table>
<thead>
<tr>
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<th>ARRY-005</th>
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<tbody>
<tr>
<td>Human CRTh2 Binding</td>
<td>1 nM</td>
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<tr>
<td>Human CRTh2 Binding</td>
<td>35 nM</td>
</tr>
<tr>
<td>(4% HSA)</td>
<td></td>
</tr>
<tr>
<td>Selectivity vs. 30 GPCR's, Ion Channels and Transporters</td>
<td>No significant activity at 500 nM</td>
</tr>
<tr>
<td>CRTh2 FLIPR Calcium Mobilization</td>
<td>5 nM</td>
</tr>
<tr>
<td>Human Isolated Basophil Chemotaxis</td>
<td>1 nM</td>
</tr>
<tr>
<td>Human Whole Blood Eosinophil Shape Change</td>
<td>33 nM</td>
</tr>
<tr>
<td>Human Whole Blood Receptor Internalization</td>
<td>22 nM</td>
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</tbody>
</table>

Results

Ear Swelling

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>ARRY-005</th>
<th>Protopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear thickness (Mean ± SEM) Day 0</td>
<td>1.60</td>
<td>0.50</td>
<td>1.60</td>
</tr>
<tr>
<td>Ear thickness (Mean ± SEM) Day 30</td>
<td>0.50</td>
<td>0.50</td>
<td>1.60</td>
</tr>
</tbody>
</table>

Oozing/crusted/hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
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<th>Protopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oozing score (Mean ± SEM) Day 0</td>
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<td>0.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Oozing score (Mean ± SEM) Day 30</td>
<td>0.00</td>
<td>0.00</td>
<td>1.50</td>
</tr>
</tbody>
</table>

Histopathology

Vehicle treated skin section
- Marked epidermal hyperplasia (E)
- Mild dermal inflammation (D)
- Excessive keratin (arrow)
- Moderate perivascularitis
- Marked orthokeratotic hyperkeratosis
- Panniculitis muscularis (P)

ARRY-005 treated skin section
- Mild epidermal hyperplasia (E)
- Mild dermal inflammation (D)
- Excessive keratin (arrow)
- Minimal perivascular infiltrate
- Minimal orthokeratotic hyperkeratosis
- Minimal epidermal inflammation

Summary

A potent, selective CRTh2 antagonist ameliorates several aspects of disease severity including pruritus via oral dosing in a mouse model of atopic dermatitis

References


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