Emerging Concepts in the Pathogenesis and Management of AERD

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Conflict of Interest

• Grant Support: NIH, Astra Zeneca, GSK
• Consulting Work: Novartis, Astra Zeneca, Allakos, Sanofi-Regeneron
Learning Objectives

• To know exactly what AERD is
• To appreciate the role of leukotrienes and why leukotriene synthesis inhibitors work so well
• To be updated on current and potential medical therapies for AERD
Questions that keep me up the long winter nights in Charlottesville

• AERD: What is it?
• Why does zileuton work and LTRAs much less so?
• Is AERD an eosinophil or mast cell disease?
• How does aspirin desensitization work?
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ASA Intolerance

- Adverse reactions to ASA first described by Hirschberg in Germany in 1902
- 1911 Gilbert notes ASA evoked asthma attack
- Widal (Widal-Abrami-Lermoyez Syndrome) in 1922
  - Asthma, Polyps, ASA intolerance
  - First describes ASA desensitization

Samter’s Triad
What Samter knew . . .

• Triad was not coincidence
  – i.e., this is a syndrome
• Bronchial asthma can develop in “middle age”
• No evidence of IgE-mediated reactivity: Atopy is generally of low prevalence
  – and when present, it is the “coincidental” occurrence of a common disease
  – do not react to salicylates
• Food reactions to alcohol, sweet corn, soft drinks
• Polypectomy and surgery alone were fruitless
Alcohol and AERD

- 74% of AERD patients have increased symptoms with alcohol consumption
  - with lower rates of intolerance in other airway disorders
- Red wine (29%) > Beer (9%) > White wine or Liquor (6%)

Cardet et al. *JACI Pract* 2014;2:208-2013
AERD Epidemiology

• 0.6-2.5% of asthmatics
• 8.7% of CRSwNP
• 14.9% of severe asthmatics

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AERD is a Disease of Constitutive CysLT Overproduction

• With a surge after exposure to aspirin / selective cox1 inhibitors
**Baseline** urinary LTE$_4$ is higher in AERD>ATA

Urinary LTE$_4$ **increases** with **aspirin reaction** in AERD

## Diagnostic Utility of uLTE4 in AERD

<table>
<thead>
<tr>
<th>[uLTE4]</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 pg/mg Cr</td>
<td>94.1 (71.3-99.8)</td>
<td>35.0</td>
<td>12.2 (7.1-19)</td>
<td>98.4 (91.4-99.9)</td>
<td>Normal values reported to be below this</td>
</tr>
<tr>
<td>80 pg/mg Cr</td>
<td>88.2 (63.5-98.5)</td>
<td>62.7</td>
<td>12.8 (10.7-28.7)</td>
<td>98.2 (93.7-99.7)</td>
<td>Another upper limit of cutoff value reported for normal</td>
</tr>
<tr>
<td>166 pg/mg Cr</td>
<td>76.5 (50.1-93.1)</td>
<td>89.3</td>
<td>40.6 (23.7-59.3)</td>
<td>97.5 (93.8-99.3)</td>
<td>Value in present analysis with best balance of diagnostic parameters</td>
</tr>
<tr>
<td>951 pg/mg Cr</td>
<td>23.5 (6.8-49.9)</td>
<td>98.9</td>
<td></td>
<td></td>
<td>Closest value to 859 pg/mg Cr, another suggest value using immunoassay</td>
</tr>
</tbody>
</table>

ROC curves

Evidence for a novel LTE4 receptor driving AERD
Responsiveness of subjects with AERD to LTE₄ pre and post desensitization


Hyperresponsiveness was not observed for LTC₄
Christie PE Eur Respir J. 1993; 6:1468-73
Changes in the number of eosinophils in the airways of subjects with asthma after inhalation of LTE\(_4\):

- Associated with increased BHR

- Not observed with inhalation of LTD\(_4\)

Effects of CysLTR deficiency on LTC4-, LTD4-, and LTE4-induced ear edema.

Effects of CysLTR deficiency on LTC4-, LTD4-, and LTE4-induced ear edema. WT (closed squares), Cyslтр1−/− (diamonds), Cyslтр2−/− (triangles), and Cyslтр1/Cyslтр2−/− (open circles) mice received intradermal injections of LTC4 (A), LTD4 (B), or LTE4 (C) and ear thickness measured. *, P < 0.01 vs. WT mice.
gpr99 as the missing LTE$_4$ Receptor

Therapeutic Implications

• Leukotriene Modifiers
  – Leukotriene receptor antagonists (e.g., montelukast, zafirlukast) improve lung function, decrease rescue bronchodilator use, reduce symptoms, and improve qol
  – 5-LO inhibition (zileuton) – may be uniquely effective including in reducing upper and lower airway symptoms

Leukotriene Modifiers in AERD

Implications:
- Alternative 5-LO products (LTB$_4$, 5-HETE)
- Alternative CysLT receptors
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Aspirin Induces Mast Cell and Eosinophil Activation in AERD

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptase (ng/ml)</td>
<td>0.5±0.1</td>
<td>4.0±2.7</td>
</tr>
<tr>
<td>CysLTs (pg/ml)</td>
<td>29.1±1.5</td>
<td>180.6±101.6</td>
</tr>
<tr>
<td>Histamine (ng/ml)</td>
<td>0.08±0.04</td>
<td>1.81±1.19</td>
</tr>
<tr>
<td>ECP (ng/ml)</td>
<td>7.3±2.5</td>
<td>75.8±39.5</td>
</tr>
</tbody>
</table>

So, is eosinophil elimination sufficient to eradicate CRSwNPs?
Eosinophil Reduction in NPs: Dexpramipexole

Prussin C et al., AAAAI 2017, Atlanta
and how does that translate in terms of clinical benefit?

Prussin C et al., AAAAI 2017, Atlanta
So if this isn’t (just) an eosinophilic disease what else might it be?

• What is the role of mast cells (±basophils) in refractory CRS (w or wo NPs)?
Prostaglandin D$_2$

Major COX product of mast cells (and eosinophils)

Signals through:

- DP1 $\rightarrow$ Vasodilation / DC chemotaxis
- DP2 (CRTH2) $\rightarrow$ Eosinophil / Th2 / innate lymphoid type 2 cell chemotaxis/activation
- TP $\rightarrow$ Bronchoconstriction, platelet aggregation, adhesion molecule expression

Overexpression of PGD$_2$ receptors (DP and CRTH2) in sinonasal tissue

PGDS mRNA is overexpressed in CRS tissue

Mediators in Asthma / AERD: Urinary PGD$_2$

**A**

![Graph showing urinary PGD-M levels and percent fall in FEV1](chart.png)

- Baseline urinary PGD-M (ng/mg Creatinine)
  - Healthy
  - ATA
  - AERD

- Percent fall in FEV1 vs. Basal urinary PGD-M (pmol/mg Creatinine)
  - Correlation coefficient: $r = -0.506$
  - Significance: $P < 0.05$

* $P \leq 0.05$

Buchheit KM ... TM Laidlaw *J Allergy Clin Immunol* 2016;137(5):1566-76

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## Aspirin Desensitization Treatment for AERD:
Patients treated 1-3 yrs (n=29)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>ASA Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6</td>
</tr>
<tr>
<td>Sinus surgery/yr</td>
<td>0.2</td>
</tr>
<tr>
<td>Hospitalizations/yr</td>
<td>0.2</td>
</tr>
<tr>
<td>ED visits/yr</td>
<td>0</td>
</tr>
<tr>
<td>Olfaction score</td>
<td>0</td>
</tr>
</tbody>
</table>

### Asthma Response

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Median</th>
<th>Range</th>
<th>ASA Rx</th>
<th>Median</th>
<th>Range</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (mg/d)</td>
<td>7.9</td>
<td>±2.0</td>
<td>1.8</td>
<td>±0.7</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal steroid (µg/day)</td>
<td>137</td>
<td>±25.6</td>
<td>90</td>
<td>±22.3</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled steroid (µg/d)</td>
<td>640</td>
<td>±146</td>
<td>885</td>
<td>226</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA desensitization for AERD: A randomized DBPC trial

- 34 subjects
- Aspirin 650 mg bid for 6 months

# Aspirin Desensitization: A Systematic Review of the Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Maintenance Dose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havel 2013</td>
<td>105, 84</td>
<td>500 mg qd</td>
<td>improvement in symptoms, endoscopy</td>
</tr>
<tr>
<td>Katial 2010</td>
<td>21</td>
<td>625 mg bid</td>
<td>improvement in symptoms</td>
</tr>
<tr>
<td>Rozsasi 2008</td>
<td>14</td>
<td>100 or 300 mg qd</td>
<td>improvement in rhinomanometry, endoscopy, symptoms</td>
</tr>
<tr>
<td>Lee 2007</td>
<td>137</td>
<td>325 or 650 mg bid</td>
<td>improvement in symptoms, corticosteroid use, surgery</td>
</tr>
<tr>
<td>Berges-Gimeno 2003</td>
<td>38</td>
<td>650 mg bid</td>
<td>improvement in symptoms, corticosteroid use</td>
</tr>
<tr>
<td>Berges-Gimeno 2003</td>
<td>172</td>
<td>650 mg bid</td>
<td>improvement in symptoms, corticosteroid use, surgery</td>
</tr>
<tr>
<td>Gosepath 2001</td>
<td>30</td>
<td>100 mg qd</td>
<td>suggested improvement in polyp recurrence, symptoms (no statistics performed)</td>
</tr>
</tbody>
</table>

Xu, JJ et al. *Int Forum Allergy Rhinol* 2013;3:915-20
Benefits of high-dose aspirin therapy

• Suppressed polyp regrowth
• Improved sinus symptom scores
• Reduction in number of polypectomies
• Decreased oral steroid use
• Decreased sinus infections
• Improved quality of life

McMains KC, Kountakis SE. AM J Rhinol 2006;20:573-76.
Questions that keep me up the long winter nights in Charlottesville

• Why does zileuton work and LTRAs much less so?
  – A:
  – 5-LO products that do not engage the CysLT1R, e.g., LTE₄

• How does aspirin desensitization work?
  - A:
  - Surprise!:
  - Inhibition of COX
    • reduced $\text{TxA}_2$
    • reduced $\text{PgD}_2$
Effect of ASA therapy

And the most important reason to consider aspirin desensitization?

So our patients can start drinking again!

<table>
<thead>
<tr>
<th>Helpfulness</th>
<th>n</th>
<th>%</th>
<th>95% CI (% range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely</td>
<td>17</td>
<td>45.9</td>
<td>29.8-62.0</td>
</tr>
<tr>
<td>Very</td>
<td>10</td>
<td>27.0</td>
<td>12.7-41.3</td>
</tr>
<tr>
<td>Somewhat</td>
<td>6</td>
<td>16.2</td>
<td>4.3-28.1</td>
</tr>
<tr>
<td>Slightly</td>
<td>3</td>
<td>8.1</td>
<td>68.4-93.6</td>
</tr>
<tr>
<td>Not at all</td>
<td>1</td>
<td>2.7</td>
<td>0-8.0</td>
</tr>
</tbody>
</table>

Glicksman JT et al. *Int Forum Allergy Rhinol* 2018;8:1093-7
## Other personalized considerations for your AERD patients

<table>
<thead>
<tr>
<th>Target</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IgE</td>
<td>Anecdotally effective in AERD</td>
</tr>
<tr>
<td>IL-5 / IL-5R*</td>
<td>Anecdotally effective in AERD – depends on extent to which this is a mast cell or eosinophil disease</td>
</tr>
<tr>
<td>IL-4 / IL-13†</td>
<td>Promising proof-of-concept studies – will target both mast cells and eosinophils</td>
</tr>
<tr>
<td>CRTH2 antagonists</td>
<td>RCTx underway</td>
</tr>
</tbody>
</table>

*Tuttle KL et al. *JACI Practice* 2018;6:1046
†Laidlaw TM et al. *JACI Practice* 2019**

**under review
Dupilumab in AERD

Summary

• AERD is associated with upregulation of traditional CysLT pathways
• With additional involvement of other eicosanoid pathways:
  – CysLTs acting through previously unknown LTE$_4$R
  – prostaglandin D$_2$
• Despite all those eosinophils, mast cells may have central importance
• Might aspirin improve AERD by inhibiting PgD$_2$/TxA$_2$ expression?
  – promising role(s) for biologics
  – could specific receptor (CRTH2) blockers accomplish the same benefit (and without the risks of desensitization and long-term aspirin administration)?