Eosinophil activation in Aspirin Exacerbated Respiratory Disease (AERD)

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Today’s topics are...

1. The clinical features of AERD
2. Eosinophil activation in upper and lower airway mucosa
3. Molecular genetic mechanism of eosinophil activation
4. Management of upper and lower airway inflammation
Clinical characteristics of the **AERD** patients in a Korean cohort

<table>
<thead>
<tr>
<th></th>
<th>AERD (n=267)</th>
<th>ATA (n=449)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy (positive)</td>
<td>114 (53.3%)</td>
<td>175 (60.8%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Log_total IgE</td>
<td>2.23±0.55</td>
<td>2.22±0.64</td>
<td>0.773</td>
</tr>
<tr>
<td>FEV1 (% Pred)</td>
<td>79.65±26.07</td>
<td>84.89±21.67</td>
<td>0.018</td>
</tr>
<tr>
<td>Metacholine_PC20</td>
<td>4.35±7.66</td>
<td>6.76±8.94</td>
<td>0.003</td>
</tr>
<tr>
<td>Rhinosinusitis (positive)</td>
<td>127 (75.6%)</td>
<td>198 (58.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal polyp (positive)</td>
<td>78 (48.4%)</td>
<td>14 (6.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma duration (year)</td>
<td>6.15±5.85</td>
<td>4.9±5.97</td>
<td>0.045</td>
</tr>
</tbody>
</table>

ATA; aspirin-tolerant asthma,

**Male to Female ratio is 1:2, 24% of them had severe asthma**

**Present more severe symptoms and higher prevalence of RS/nasal polyps**

*Palike N & Park HS. Yonsei Med J, 2009;50:744*
Eosinophils were found in airway mucosa and secretion.
Eosinophils are more activated in nasal polyp tissue of the **AERD** patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th><strong>AERD</strong></th>
<th><strong>ATA</strong></th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP (ng/mg)</td>
<td>366.5 ± 89.1</td>
<td>59.0 ± 14.0</td>
<td>0.005</td>
</tr>
<tr>
<td>MMP-9 (ng/mg)</td>
<td>53.7 ± 21.1</td>
<td>27.8 ± 6.3</td>
<td>0.70</td>
</tr>
<tr>
<td>MMP-2 (ng/mg)</td>
<td>134.1 ± 30.5</td>
<td>81.9 ± 14.1</td>
<td>0.29</td>
</tr>
<tr>
<td>TIMP-1 (ng/mg)</td>
<td>42.7 ± 12.3</td>
<td>11.1 ± 4.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ECP in nasal polyp tissue homogenate was higher in AERD than in ATA, while other parameters were not significantly different.

*Eotaxin-2 level in the polyp tissues from ATA and AERD*

Eotaxin-2 is a major chemokine involved in eosinophil activation of AERD patients.

*Lee YM et al. J Kor Med Sci 2003;18:97*
Pathogenic mechanism of AERD

Cell membrane phospholipids

ASA/NSAIDs

COX-2

COX-1

Arachidonic acid

5-LO

LTA₄

LTC₄S

LTC₄

LTD₄

LTE₄

PGG₂

PGH₂

PGE₂

EP-R

CYSLTR1 / CYSLTR2

Reduction of PGE2/overproduction of CysLT increased expression of CysLTR1
1. The levels of LTE4 and PGE2, PGD2 metabolites were measured before and after the ASA challenges in AERD patients compared to ATA.

2. Baseline level of LTE4 were significantly higher in AERD than in ATA, while PGE2 was significantly lower in AERD.

3. CysLTE4 and PGD2 metabolites increased significantly after the ASA challenges in AERD, while no significant changes were noted in ATA.

These finding indicates mast cell as well as eosinophil is a key cell to activate eosinophil in AERD.
How mast cell and eosinophil are activated after ASA exposure in AERD patients

ASA exposure

Mast cell

Early response

Chronic RS/Nasal Polyp

CysLTs

PGD2

Eosinophil

Late response

Lower airway symptoms
Targeted genes for AERD

1. HLA and LT related genes: HLA class II, 5-LO, LTC4S, CysLTR1, CysLTR2
2. COX-1/PG related genes: PGE2R, PGE4R, TXA2R
3. Mast cell activation genes: FceRIβ, ADORA
4. Eosinophil activation genes: CCR3, CRTH2, IL13
5. Others: IL10, TGFβ1

Palike N & Park HS. J Allergy, 2011
The 12/15-LO pathway in AERD

→ 15-LO pathway and eosinophil activation
1. The prevalence of serum specific IgE to Staphylococcal superantigen was higher in AERD patients.

2. The AERD patients with specific IgE to superantigen had lower FEV1 and more severe AHR.

3. Several studies demonstrated sIgE response could involve in Th2 and eosinophil activation.

- These finding indicates sIgE response to superantigen may have a key role in eosinophil activation in AERD.
Eosinophil receptors

- **FcγRI- IgA**
- **FcεRI,II- IgE**

**Fc receptors**

**Complement receptors**

**Cytokine receptors**

**Chemokine receptors**

**Histamine receptors**

**Other receptors**

**CysLTR1, P2RY**

**Granular proteins**

**ECP, EDN EPO**

**Active oxygen species**

**Tissue damage**

**Lipid mediators**

**Granular proteins**

**ECP, EDN EPO**

**Active oxygen species**

**Tissue damage**

**Migration and activation of immunocompetent cells**

- Mucus production
- Increase of vessel permeability

**CCR3, CRTh2, RANTES**

**IL-3, IL-4, IL-5, IL-6, TNF-α, GM CSF**

**IL-3, IL-4, IL-5, IL-6, TNF-α, GM CSF**
Management

1. Avoidance from ASA and cross reacting drugs of COX-1

2. Pharmacologic treatment

3. Management of RS/nasal polyp

- ICS and INS could suppress upper and lower airway inflammation including eosinophils

- Biologics: Anti-IgE antibody or anti-IL 5 antibody
Thank You

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