Chronic Sinusitis: From Nasal Polyps to Biologics

Rohit Katial, MD, FACAAI, FAAAAI, FACP
Professor of Medicine
National Jewish Health &
University of Colorado, Denver
US. Medical Respiratory Expert GSK
Disclosures

• Employee; Salary
  – GlaxoSmithKline

• Professor of Medicine; National Jewish Health

• “Opinions and assertions herein are not representative of either entity but are of my own opinion”
Objectives

- Understand the clinical phenotype of nasal polyposis
- Understand the CRS with and without nasal polyps
- Understand the emerging concepts in dysregulation in the Th2 pathway contributing to the pathophysiology
Pathogenesis

• Study Design
  – 40 adults with PAR
  – CT evidence of chronic sinusitis 27 (68%)
  – CT evidence of maxillary sinusitis 22 (55%)
• OMC obstruction 9 (41%)
• No OMC obstruction 13 (59%)
• Conclusion: factors other than mechanical obstruction must contribute to the development of sinusitis in patients with PAR

### Chronic Rhinosinusitis With And Without Nasal Polyposis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Chronic Sinusitis</th>
<th>Nasal Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial pain/pressure</td>
<td>Yes</td>
<td>Rarely</td>
</tr>
<tr>
<td>Facial congestion/fullness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nasal obstruction/blockage</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nasal discharge/purulence/postnasal drip</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyposmia/anosmia</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Asthma</td>
<td>Rarely</td>
<td>Often</td>
</tr>
<tr>
<td>Aspirin hypersensitivity</td>
<td>Rarely</td>
<td>Typical</td>
</tr>
</tbody>
</table>

*References: T. Van Zele et al. Allergy 2006*
## Differences In The Clinical Pattern

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Chronic sinusitis</th>
<th>Nasal polyps</th>
<th>Cystic fibrosis Nasal polyps</th>
<th>One way Anova * Fisher’s Exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>CT score (Lund &amp; Mackay)</td>
<td>0.75 (0-2)</td>
<td>6 (2-11)</td>
<td>16.3 (7-24)</td>
<td>14.5 (5-20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polyp score (Davos)</td>
<td>0</td>
<td>0</td>
<td>4.8 (2-6)</td>
<td>2.9 (0-6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>4 (3-5)</td>
<td>6.6 (4-10)</td>
<td>9.6 (3-14)</td>
<td>4.3 (0-9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1.1 (0-3)</td>
<td>1.0 (0-3)</td>
<td>2.6 (0-3)</td>
<td>2.8 (2-3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0</td>
<td>0.1 (0-1)</td>
<td>0.2 (0-2)</td>
<td>0.6 (0-2)</td>
<td>0.761</td>
</tr>
<tr>
<td>Rhinorrhee</td>
<td>0.3 (0-2)</td>
<td>1.6 (0-3)</td>
<td>1.6 (0-3)</td>
<td>1.0 (0-3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>0</td>
<td>0</td>
<td>2.3 (0-3)</td>
<td>1.0 (0-3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post Nasal Drip</td>
<td>0</td>
<td>1.4 (0-2)</td>
<td>1.3 (0-3)</td>
<td>0.6 (0-2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>0.9 (0-2)</td>
<td>2.5 (1-3)</td>
<td>1.6 (0-3)</td>
<td>1.2 (0-3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* T. Van Zele et al. Allergy 2006
Chronic rhinosinusitis (CRS)

Nasal polyps (NP)

All the same?
Chronic rhinosinusitis

Nasal polyps

- Chronic rhinosinusitis “without polyps” (CRS)
- Nasal polyps (NP)

Subgroups of nasal polyps?
Caucasian nasal polyps are more eosinophilic than Chinese nasal polyps.
Caucasian nasal polyps are more eosinophilic than Chinese nasal polyps

- Clinically comparable diseases with typical edema and pseudocyst formation.
- But:
  - In Caucasian NP eosinophil activation: ECP
  - In S-Chinese NP neutrophil activation: MPO
- Share T-cell activation
  - subsets of T-effector cells?

N Zhang, Van Zele T JACI
FIG 4. Patterns of $T_H1/T_H2/T_H17$ cytokine expression in samples from patients with CRSwNP: Benelux (A), Berlin (B), Adelaide (C), Beijing (D), Chengdu (E), and Tochigi (F).
Sinusitis/Asthma

- Newman et al (JAMA 1994;271:363) 104 sinusitis; 31/104 asthma; Calculated CT sinus scores to determine severity of disease

- PB eosinophilia - 63% wheezers versus 29% without wheezing

- 98 nasal biopsy specimens available

- Presence of tissue eosinophilia correlated with h/o wheezing, extensive disease on CT, positive RAST and PB eosinophilia
Local production of IL-5 and IL-13 in NP

NP contain increased numbers of IL-5 producing T lymphocytes.

- IL-5 producing cells in NP:
  - 68% T cells
  - 18% eosinophils
  - 14% mast cells

- IL-5 is the principal survival-promoting cytokine in NP.
- IL-5 promotes eosinophil entry into tissues.
- IL-5 facilitates the action of eotaxin.

- Both allergic and nonallergic NP have an increase in IL-13-positive cells

Sinusitis/Asthma

- Bresciani et al (JACI 2001;107:73) 35 severe SD asthmatics, 34 mild-moderate, rhinosinusitis same in both groups
- CT scores higher in severe asthmatic group (p<.0005)
Sinusitis/Asthma

• Ten Brinke et al (JACI 2002;109:621-6)
• Correlate sinus inflammation with asthma
• 89 severe asthmatics, non-smokers
• Measured lung function, eos (sputum & PB), exhaled NO
Chronic Rhinosinusitis: Th1 Polarization

- TNF-α upregulation in tissue homogenates
- IFN-γ upregulation in tissue homogenates
- TGF-β1 upregulation in tissue homogenates

Pro-inflammatory:
- TNF-α up
- IL1-β up

T-cell immune response:
- IL2sR-α up
- CD3 up
- Th1: IFN-γ up

TGF-β1 upregulation
- Increased fibrosis
- T-reg activity

T. Van Zele et al. Allergy 2006
Nasal Polyps: Eosinophilic Inflammation With Th2 Polarization

Eosinophils
HE staining

IL-5
in tissue homogenates

IgE
in tissue homogenates

Eosinophilic inflammation:
• HE positive cells↑
  • ECP↑
  • Eotaxin↑

T-cell immune response:
• IL2sR-α↑
  • CD25↑
  • Th2: IL-5↑

Immunoglobulin production
• plasmacells (CD138)↑
  • IgE↑

T. Van Zele et al. Allergy 2006
Derycke L et al, PLOS ONE 2014
Different types of defense and inflammation in sinus disease

ARS: remodelling
Th1 inflammation

CRS: remodelling
Th1 inflammation

Chinese and Cystic fibrosis
NP: neutrophils
Th1 inflammation

NP: eosinophils
Th2 inflammation

ASTHMA (+ASA)

Try to ERADICATE

Pathogens

Superantigens

If you can’t eradicate, make a barrier and tolerate!
IL-4

- Previous data from Borish and colleagues has shown IL-4 induces cysteinyll leukotriene receptors on both T and B cells.

- Additionally, same group recently reported in an in-vitro model (monocyte culture) that aspirin inhibits IL-4 nuclear extracts that engage STAT6 binding sites, thus blocking the inducible expression of STAT6.

IL-4 Regulates IgE-dependent CysLT production by Mast Cells: Profound Induction of LTC₄ Synthase expression by IL-4:

Effect of IL-4 priming of human MCs on IgE mediated CysLT release


Effect of IL-4 priming on 5-LO/LTC₄S pathway protein expression by hMCs
The effect of aspirin desensitization on novel biomarkers in aspirin-exacerbated respiratory diseases

Rohit K. Katial, MD, Matthew Strand, PhD, Theerapol Prasertsuncharasai, MD, Roxanne Leung, MD, Weihong Zheng, MD, and Rafeul Alam, MD, PhD

Denver, Colo

Editorial

Does suppression of IL-4 synthesis by aspirin explain the therapeutic benefit of aspirin desensitization treatment?

Andrew A. White, MD, and Donald D. Stevenson, MD

La Jolla, Calif
Eligibility

Inclusion Criteria
1. Subjects > than 18 years of age
2. Physician diagnosis of asthma
3. Chronic sinusitis
4. Nasal polyps
5. Aspirin induced respiratory reaction
6. Subjects willing to take 650 mg ASA bid.

Katial et al. JACI 2010;126(4):738-44.
Study Design

• Screen for inflammatory mediators in induced sputum
  – Tryptase
  – IL-4
  – MMP-9, TIMP-1
  – FLT3 Ligand
• Immunocytochemistry
  – IL-4, Tryptase

Katial et al. JACI 2010;126(4):738-44.
IL-4 action in AERD

Membrane phospholipids → cPLA2 → Arachidonic acid

- 15-lipoxygenase → 15 (S)-HETE
- Cyclooxygenases (COX-1/COX-2)
- 5-lipoxygenase FLAP

Prostaglandins:
- Thromboxanes
  - PGD2 Synthase
  - PGD2
  - PGF2
  - PGI2
- Prostaglandins Synthase
  - PGE2
  - 5-HPETE → 5-HETE → 5-oxo-ETE → OXE receptor

- 5-lipoxygenase
  - LTC4 Synthase
  - LTC4
  - LTD4
  - LTE4

- CysLT1 and CysLT2 receptors

LTA4 → LTB4
- LTA4 hydrolase
  - BLT1 and BLT2 receptors

IL-4 stimulates expression
IL-4 inhibits expression
IL-4: Baseline to Six months

Katial et al. JACI 2010;126(4):738-44.

* P=0.0007
MMP-9 6 mos After Desensitization

Zymogram

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td>6hr</td>
<td>254.2</td>
</tr>
<tr>
<td>5ng/mL</td>
<td>6hr</td>
<td>222.6</td>
</tr>
<tr>
<td>20ng/mL</td>
<td>6hr</td>
<td>259.4</td>
</tr>
<tr>
<td>50ng/mL</td>
<td>6hr</td>
<td>341.3</td>
</tr>
<tr>
<td>(-)</td>
<td>24hr</td>
<td>638.7</td>
</tr>
<tr>
<td>5ng/mL</td>
<td>24hr</td>
<td>570.3</td>
</tr>
<tr>
<td>20ng/mL</td>
<td>24hr</td>
<td>530.1</td>
</tr>
<tr>
<td>50ng/mL</td>
<td>24hr</td>
<td>578.6</td>
</tr>
</tbody>
</table>
Tryptase vs. MMP-9

$r=0.63$ ($p=0.03$)

Katial et al. JACI 2010;126(4):738-44
MMP-9 After Desensitzation

Katial et al. JACI 2010;126(4):738-44.
AERD have increased IL-4 induced pSTAT6 expression than ATA and healthy controls.

pSTAT6 Inhibition

Nasal Polyps

**Polyps: MMP-9/TIMP-1**

Table 2. Full Slide Immunofluorescent Staining for Expression of MMP-9 and TIMP-1

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>AT</th>
<th>Control</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP—subjective</td>
<td>1.35 (1.92)</td>
<td>1.35 (1.92)</td>
<td>1.73 (2.10)</td>
<td>.77</td>
</tr>
<tr>
<td>TIMP subjective</td>
<td>0.63 (1.43)</td>
<td>1.35 (1.62)</td>
<td>1.20 (1.57)</td>
<td>.02</td>
</tr>
<tr>
<td>MMP/TIMP subjective</td>
<td>2.14 (1.90)</td>
<td>1.00 (1.55)</td>
<td>1.45 (2.05)</td>
<td>.13</td>
</tr>
<tr>
<td>MMP objective</td>
<td>22.65 (1.70)</td>
<td>18.92 (1.54)</td>
<td>27.11 (5.37)</td>
<td>.84</td>
</tr>
<tr>
<td>TIMP objective</td>
<td>0.82 (4.48)</td>
<td>9.78 (1.54)</td>
<td>13.74 (2.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMP/TIMP objective</td>
<td>27.66 (3.53)</td>
<td>1.93 (1.60)</td>
<td>1.95 (4.26)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Th1/Th2 Cytokine Signature in Chronic Sinusitis (qPCR)

Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis

Philippe Gevaert, MD, PhD, a* Nicholas Van Bruaene, MD, a* Tom Cattaert, PhD, b,c Kristel Van Steen, PhD, b,c Thibaut Van Zele, MD, PhD, a Frederic Acke, MD, a Natalie De Ruyck, MSc, a Katrien Blomme, MSc, a Ana R. Sousa, PhD, d Richard P. Marshall, MD, PhD, d and Claus Bachert, MD, PhD a  Ghent and Liège, Belgium, and Stevenage, United Kingdom

Anti-IL5 Improves total nasal polyp score in 50% of patients

Gevaert P et al. (JACI 2011)
Blinded CT-scan evaluation: baseline vs. 8 weeks

Gevaert P et al. (JACI 2011)
Conclusion

Two injections of 750mg Anti-IL-5 mAb (Mepolizumab) showed a significant improvement over placebo on:

- **Primary endpoint:** Total endoscopic nasal polyp score
  - ✓ 12/20 (60%) at w8
- **CT scan:** 11/20 (55%) with improvement on CT scan
- **PNIF:** AUC better compared to placebo
- **Symptom scores:** Congestion, smell and PND: trend

Responders 12/20: **Phenotyping**

Significant improvement in total polyp score for 36 weeks

*Gevaert P et al. (JACI 2011)*
Bachert et al. JACI 2017, in press
Study Design

Multicenter, international, randomized, double-blind, phase 2 study (ClinicalTrials.gov Identifier: NCT01920893)

Run-in period
4 weeks

Study treatment
16 weeks

Off-treatment follow-up for safety and efficacy
16 weeks

MFNS, mometasone furoate nasal spray; SC, subcutaneous.

MFNSa

Duplicumab 600 mg SC loading dose on Day 1 then 300 mg SC weekly + MFNSa (n = 30)

Placebo + MFNSa (n = 30)

MFNSa


a100 μg MFNS in each nostril twice daily.
<table>
<thead>
<tr>
<th><strong>Key Inclusion and Exclusion Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
</tr>
<tr>
<td>• Adult aged ≥ 18–65 years</td>
</tr>
<tr>
<td>• Bilateral nasal polyposis (NP) despite INCS treatment ≥ 2 months, with NP score (NPS) ≥ 5 (out of 8)</td>
</tr>
<tr>
<td>- ≥ 2 for each nostril</td>
</tr>
<tr>
<td>• ≥ 2 rhinosinusitis symptoms</td>
</tr>
<tr>
<td>- Nasal obstruction or discharge</td>
</tr>
<tr>
<td>- Facial pain or pressure</td>
</tr>
<tr>
<td>- Reduction or loss of smell</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td>• 22-item sinonasal outcome test (SNOT-22) score &lt; 7</td>
</tr>
<tr>
<td>• INCS drops within 2 months of screening</td>
</tr>
<tr>
<td>• Systemic corticosteroids within 2 months before screening or scheduled during study period</td>
</tr>
<tr>
<td>• Monoclonal antibody and immunosuppressive treatment, within 2 months or anti-IgE therapy (omalizumab) within 130 days of screening</td>
</tr>
<tr>
<td>• Surgery within 6 months before screening or &gt; 2 surgeries for NP in the past</td>
</tr>
<tr>
<td>• For patients with asthma: exacerbation within 3 months of screening, high-dose inhaled corticosteroid (&gt; 1,000 μg), or predicted forced expiratory volume in 1 second (FEV₁) ≤ 60%</td>
</tr>
</tbody>
</table>

Efficacy Endpoints: Change From Baseline at Week 16

**Primary Endpoint**
- Change in bilateral endoscopic NPS

**Secondary Endpoints**
- SNOT-22 score
- University of Pennsylvania Smell Identification Test (UPSIT)
- Change in Lund-Mackay total CT score
- Percent of maxillary sinus volume occupied by disease
- Nasal peak inspiratory flow (NPIF)
- Sinusitis symptoms severity (VAS)
- Sinusitis signs and symptoms (AM)

**Additional Exploratory Endpoints in Patients With Comorbid Asthma**
- Change in lung function
  - FEV$_1$
  - Percent predicted FEV$_1$
- Change in asthma control
  - Asthma Control Questionnaire-5 (ACQ5) score

Primary Endpoint: Mean Change in NPS at Week 16

Placebo/MFNS

Dupilumab/MFNS

Bilateral score range 0–8 (0 = no polyps, 4 = large polyps causing complete obstruction of the inferior nasal cavity).

LS, least squares; SE, standard error.

Mean Change in NPS Over Time

**No. of Patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo/MFNS</th>
<th>Dupilumab/MFNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Week 4</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Week 8</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Week 12</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Week 16</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

*Bilateral score range 0–8 (0 = no polyps, 4 = large polyps causing complete obstruction of the inferior nasal cavity); P value for dupilumab/MFNS vs placebo/MFNS.*

Chronic rhinosinusitis (CRS) without polyps

Nasal polyps

Chronic rhinosinusitis “without polyps” (CRS)

Nasal polyps (NP)

Chinese NP
Caucasian NP
NP with asthma
NP with ASA

Spectrum of sinus disease

Th1
INFγ, TGFβ, Neutr

Modulating Factors?

Th2
IgE, Eos

Severe
More recurrences
Major phenotypes of rhinosinusitis

- **Common cold and ARS**
  - Th1 inflammation
  - IL-8↑, INFγ↑
  - SHEDDING
  - Self limiting
  - Evt. Antibiotics

- **CRS: remodelling**
  - Th1 inflammation
  - INFγ↑
  - TGFB↑
  - Nasal corticoids

- **Chinese and basic NP**
  - Th1 inflammation
  - IL-8
  - TGFβ
  - INFγ
  - MPO
  - Long term macrolides or doxycycline

- **Cauc NP (asthma & ASA)**
  - Th2 inflammation
  - IL-5
  - IgE
  - Eotaxin
  - ECP
  - Anti-IL-5

**Phenotyping**
• Thank You