Anti-Cytokine Therapy for Severe CRS/Nasal Polyposis

Fig. 1 The three steps of personalised (precision) medicine (modified from [2])


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Ghent University Hospital, Belgium
Karolinska Institute, Stockholm, Sweden
AERD (Aspirin-exacerbated respiratory disease)

Male patient, 46 y
CRSwNP since 12 y, 3x “FESS”
Nasal obstruction, continuous secretions and PND, no smell, “heavy head”
Polyp grade: Davos 3 bilateral
Severe asthma since 5 y, inhal. and oral GCS
Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis (AFRS)- a bacterial presence coexisting with fungal disease? J Allergy Clin Immunol 2013;132:487-

[Images of medical scans and an endoscopic view of the nasal cavity]
Phenotype: any observable characteristic or trait of a disease, such as morphology, development, biochemical or physiological properties, or behavior, without any implication of a mechanism.

Endotype: a subtype of a condition, which is defined by a distinct functional or pathobiological mechanism.

The definition of an endotype may provide information on the prognosis of the patient, the optimal management of the disease or innovative approaches to its treatment.

T helper cells currently provide the best approach to define endotypes.
Derycke L et al,
PLOS ONE 2014
Diversity of T cell repertoires

**Benelux-CRSwNP**
- N=45
- IL-5+: 62%
- IL-5+IL-17+: 16%
- IL-5+IFN-γ+: 7%
- IL-5+IL-17+IFN-γ+: 4%
- IL-17+: 2%
- IFN-γ+: 2%
- ALL-: 5%

**Beijing-CRSwNP**
- N=95
- IL-5+: 19%
- IL-5+IL-17+: 18%
- IL-5+IFN-γ+: 15%
- IL-5+IL-17+IFN-γ+: 10%
- IL-17+: 9%
- IFN-γ+: 5%
- ALL-: 4%

**Chengdu-CRSwNP**
- N=69
- IL-5+: 57%
- IL-5+IL-17+: 16%
- IL-5+IFN-γ+: 10%
- IL-5+IL-17+IFN-γ+: 9%
- IL-17+: 4%
- IFN-γ+: 4%
- ALL-: 0%

**Adelaide-CRSwNP**
- N=33
- IL-5+: 82%
- IL-5+IL-17+: 9%
- IL-5+IFN-γ+: 9%
- IL-5+IL-17+IFN-γ+: 0%
- IL-17+: 0%
- IFN-γ+: 0%
- ALL-: 0%

WANG XD et al, 2016
Co-morbid asthma in nasal polyps: Categorical and continuous data analysis

C. Bachert, Nan Zhang, et al. JACI 2010
<table>
<thead>
<tr>
<th></th>
<th>IL5</th>
<th>IgE</th>
<th>ECP</th>
<th>MPO</th>
<th>IL8</th>
<th>IL6</th>
<th>IL17</th>
<th>IL22</th>
<th>IFN-g</th>
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<td>10</td>
<td>SE-IgE</td>
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</tbody>
</table>

- **IL5 - negative**
- **IL5 - positive**
  - **IL5 - high**
  - S. aureus Super-antigens

**Th2**

**IgE**

**eosinophils**

**SE-IgE**

Tomassen P et al, JACI 2016
### TABLE I. Reported studies with hmAbs in nasal polyposis

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Target</th>
<th>Year</th>
<th>Therapeutic effects</th>
<th>Limitations</th>
<th>Status of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>2013</td>
<td>Significant reduction of polyp and CT scores, improvement of symptoms of upper and lower airways and quality of life</td>
<td>No reduction of serum or nasal secretion mediators, frequent rhinopharyngitis</td>
<td>PoC</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>2011</td>
<td>Significant reduction of polyp score, reduction of blood eosinophil count, as well as ECP and IL-5Rα levels, in serum</td>
<td>No significant improvement of symptoms, frequent rhinopharyngitis</td>
<td>Clinical trial, phase 3</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>2006</td>
<td>Significant reduction of polyp score, reduction of blood eosinophil counts, as well as ECP levels, in serum</td>
<td>No significant improvement of symptoms</td>
<td>PoC</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>2015</td>
<td>Significant reduction of polyp and CT scores, improvement of smelling, symptoms, and quality of life (SNOT-22); improvement of pulmonary function (FEV₁) and asthma control test score (ACQ5)</td>
<td>Side effects include headache, rhinopharyngitis, and reaction at injection site</td>
<td>PoC</td>
</tr>
</tbody>
</table>

*ACQ5*, Five-item Asthma Control Questionnaire; *ECP*, eosinophil cationic protein; *IL-4Rα*, IL-4 receptor α; *IL-5Rα*, IL-5 receptor α; *PoC*, proof of concept; *SNOT-22*, Sino-Nasal Outcome Test.
Study design

Objective: To assess the therapeutic potential of SC injections of anti-IgE Omalizumab (XOLAIR) in NP with asthma

Study design: Double blind, randomized, placebo controlled trial

Investigator initiated trial: Ghent University (Prof P Gevaert)
KULeuven (Prof P Hellings)

24 Subjects Severe nasal polyps with asthma

Dosing: Xolair® 75 to 375mg is administered every 2 to 4 weeks (3 m) following official drug leaflet (total serum IgE and body weight)
Improvement in total nasal polyp score
Omalizumab (n=15) versus placebo (n=8)

Results of mixed model (Compound Symmetry covariance matrix):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.004</td>
</tr>
<tr>
<td>Time</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time*Treatment</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

F_{4,84} = 5.15
CT-scans before and after Anti-IgE
Allergic versus non allergic patients

Allergy skin prick test

<table>
<thead>
<tr>
<th></th>
<th>SPT-</th>
<th>SPT+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Allergic vs non allergic poliepscore: change from baseline

**Receptor Types**

Type I
- B cells activation and expansion
- Class switching to IgE
- Th2 cell differentiation
- Recruitment of monocytes, eosinophils

Type II
- Epithelial cell activation
- Goblet cell hyperplasia
- Mucus secretion
- B cell activation
- IgE synthesis
- Homing and lifespan of mast cells and eosinophils

**Signaling Pathways**

- IL-4
  - IL-4Rα
  - JAK1
  - STAT6
  - IRS1/2
  - PI3K

- IL-13
  - IL-13Rα1
  - JAK1
  - TYK2
  - STAT6
  - STAT3

- sIL-13Rα2

**Signaling Activity Debated**
Dupilumab Demonstrated Efficacy in a Phase 2a Study in CSwNP Patients

• In a proof of concept study, dupilumab on a background of mometasone fumarate nasal spray (MFNS) has shown to improve patient reported outcomes and to reduce nasal polyp burden
• The most common adverse events were nasopharyngitis, injection-site reactions, and headache
• Original paper: JAMA 2016;315:469-479
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

**Study Treatment**
- Placebo + MFNS\(^a\) (n = 30)
- Dupilumab 600 mg SC loading dose on Day 1 then 300 mg SC weekly + MFNS\(^a\) (n = 30)

**Off-treatment follow-up**
- Safety and efficacy
- MFNS\(^a\)

\(^a\)100 μg MFNS in each nostril twice daily.

Bachert C et al, JAMA 2016

MFNS, mometasone furoate nasal spray; SC, subcutaneous.
Primary and secondary endpoints: nasal polyp score, PNIF, SNOT22 and UPSIT

In patients with asthma: pronounced reduction of polyp score, change in 5-ACQ and lung function (FEV1 percent predicted)

Significant reductions in Type 2 biomarkers: Serum IgE, TARC, Eotaxin-3, but not blood eosinophils.

In nasal biopsies, Dupilumab also reduces ECP significantly.
## Treatment-emergent Adverse Events

<table>
<thead>
<tr>
<th>Patients With TEAEs(^a), n (%)</th>
<th>Placebo/MFNS (n = 30)</th>
<th>Dupilumab/MFNS (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any TEAE</strong></td>
<td>25 (83.3)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>TEAEs reported in &gt; 10% of patients in either treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (33.3)</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2 (6.7)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (16.7)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (13.3)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

\(^a\)TEAEs were defined as events occurring from the first administration of study medication to the end of the post-treatment period; Medical Dictionary of Regulatory Activities (MedDRA) preferred term.
Currently no indication for CRSwNP

Open questions:

In whom?
- Disease recurrence
- asthma
- biomarker?

Which?

Place in management?

Mepolizumab
Reslizumab
Omalizumab
Dupilumab
Prof Dr Claus Bachert
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