Biologics in asthma
Are we turning the corner?

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Biologics in asthma - are we turning the corner?

- Allergic asthma
  - anti-IgE
Allergic airway inflammation in asthma

Biologics in asthma

• Anti - IgE
  ➢ Omalizumab
Omalizumab in severe allergic asthma

- Asthma exacerbations and hospitalizations ↓
- Reduction in inhaled steroid dose
- Improved asthma control
- Oral corticosteroid-sparing effect (?)
- Generally well tolerated, except for injection site reactions

Phenotype 'allergic asthma'

- Usually early disease onset
- Symptoms related to allergen exposure
- Allergic comorbidities
- Skin prick test positive
- Total (and specific) IgE
- Treatment response to glucocorticosteroids and omalizumab
Effects of omalizumab in allergic asthma
Biomarkers in the EXTRA study

Omalizumab n=427    Placebo n=423
Biologics in asthma

- **Anti - IgE**
  - Omalizumab
  - Ligelizumab (QGE031)
  - Quilizumab

Novartis termination letter, 21.12.2015
Biologics in asthma - are we turning the corner?

- Allergic asthma
  - anti-IgE

- Eosinophilic asthma
  - anti-IL-5 (receptor)
Airway inflammation in asthma

Allergic eosinophilic airway inflammation

Nonallergic eosinophilic airway inflammation

Blood eosinophils & asthma disease burden

• 130,248 UK asthma pts. 12-80 years

• Blood eosinophils $>$ vs. $\leq 400$ /µl

• Severe exacerbations
• Acute respiratory events
• Asthma control

• 20,929 (16%) patients had $> 400$ blood eosinophils per µL

RR / OR with blood eosinophils $>$ 400 / µl

Severe exacerbations
Acute respiratory events
Risk-domain asthma control
Overall asthma control

Severe exacerbations
RR 1.42 (1.36–1.47)*

Acute respiratory events
RR 1.28 (1.24–1.33)*

Risk-domain asthma control
OR 0.78 (0.75–0.80)*

Overall asthma control
OR 0.74 (0.72–0.77)*

Biologics in asthma

- Anti - IgE
  - Omalizumab
  - Ligelizumab (QGE031) >>
  - Quilizumab >>

- Anti - IL-5
  - Mepolizumab
  - Reslizumab
  - Benralizumab (anti-IL-5 - receptor)
Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma

135 asthma patients
HD ICS + 2nd controller + 5-35 mg prednisone/d.
≥ 150 - 300 eos./µL blood

- Mepolizumab - 100 mg s.c./4 wks.
- Placebo

20 weeks

- Reduction in the glucocorticoid dose

Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma

**Exacerbations [n]**

**Asthma symptoms (ACQ-5)**

**Mepolizumab**
- 50% reduction in glucocorticoid dose ($p = 0.007$)
- 32% reduction in rate of exacerbations ($1.44$ vs. $2.12$, $p = 0.04$)
- 0.52 point reduction of asthma symptoms (ACQ-5, $p = 0.004$)

Eosinophilic asthma (1)

- Late onset of disease
- Symptoms ↑, exacerbations ↑
- Eosinophilia in blood (± sputum)
- ± FeNO > 50 ppb
- No clinically relevant allergy
- ± Nasal polyposis
  - smell ↓ & taste ↓
- Response to (oral) glucocorticoids and anti-IL-5
'Eosinophilic' asthma (2)

- > **150** eosinophils/µl or > **300** eosinophils/µl during the 12-month period before screening *Mepolizumab phase III studies*

- > **260** eosinophils/µl *Median value in Europe*

- > **300** eosinophils/µl *FDA analysis, expert opinion*

- > **400** eosinophils/µl *Reslizumab phase III studies*
Effects of reslizumab on lung function stratified by baseline eosinophil thresholds

- 492 asthma pts. (18-65 yrs.) with an ACQ-7 score ≥ 1.5 inadequately controlled by fluticasone propionate ≥ 440 μg/day or equivalent
- 16-week double-blind (4:1 randomisation) treatment with reslizumab 3.0 mg/kg or placebo once every 4 weeks
Benralizumab for severe asthma uncontrolled with high-dose ICS and LABS (SIROCCO)

1205 asthma patients
12-75 yrs., HD ICS + LABA
≥ 2 exac./prev. year

- Benralizumab 30 mg s.c. Q4W
- Benralizumab 30 mg s.c. 3x Q4W ➔Q8W
- Placebo

48 weeks

• Exacerbation rate

Bleecker, et al. ERS London
5.9.2016, OA4832

Severe asthma

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- Guidelines
  - severe asthma

www.ginasthma.org
Stepwise asthma treatment for adults and adolescents

www.ginasthma.org

PREFERRED CONTROLLER CHOICE

STEP 1

Low dose ICS

Consider low dose ICS

STEP 2

Leukotriene receptor antagonists (LTRA)
Low dose theophylline*

STEP 3

Low dose ICS/LABA**

Med/high dose ICS/LABA

Add tiotropium*†

STEP 4

High dose ICS/LABA

Add low dose OCS

STEP 5

Refer for add-on treatment e.g.
tiotropium*†
omalizumab
mepolizumab*

RELIEVER

As-needed short-acting beta₂-agonist (SABA)

As-needed SABA or low dose ICS/formoterol#

*Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol for maintenance and reliever therapy.
†Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations (not for children <12 years)
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Definition of severe asthma

Asthma which requires treatment with high dose ICS and LABA ± systemic CS for ≥ 50% of the previous year to prevent it from becoming uncontrolled or is uncontrolled despite this therapy

- **Poor symptom control:** ACQ > 1.5, ACT < 20 (or “not well controlled” by NAEPP/GINA guidelines)
- **Frequent severe exacerbations:** ≥ 2 bursts of systemic CS (> 3 days each) in the previous year
- **Serious exacerbations:** ≥ 1 hospitalisation, ICU stay or mechanical ventilation in the previous year
- **Airflow limitation:** FEV1 < 80% after appropriate bronchodilator withhold, FEV1/FVC < lower limit of normal
- **Controlled asthma that worsens on tapering of treatment**

Morbidity associated with oral corticosteroids in severe asthma

• 93% of patients with severe asthma had one or more condition linked to systemic corticosteroid exposure

Compared with mild/moderate asthma

• Diabetes (type II)  10% vs. 7%  OR=1.46, p<0.01
• Osteoporosis       16% vs. 4%  OR=5.23, p<0.001
• Dyspeptic disorders 65% vs. 34%  OR=3.99, p<0.001
• Cataracts          9% vs. 5%  OR=1.89, p<0.001

Lefebvre, et al. JACI 2016
Choo & Pavord. Thorax 2016
Biologics in asthma - are we turning the corner?

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• Guidelines
  ➢ severe asthma

• New biologics
Biologics in severe asthma

- **Anti - IgE**
  - Omalizumab
  - Ligelizumab (QGE031) >>
  - Quilizumab >>

- **Anti - IL-5**
  - Mepolizumab
  - Reslizumab
  - Benralizumab (anti-IL-5 - receptor)

- **Anti - IL-13**
  - Lebrikizumab >>
  - Tralokinumab ?

Roche Media Release LAVOLTA, 29.2. 2016  
Biologics in severe asthma

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  - Omalizumab
  - Ligelizumab (QGE031) >>
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- **Anti - IL-5**
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- **Anti - IL-13**
  - Lebrikizumab >>
  - Tralokinumab ?

- **Anti - IL-4 / IL-13**
  - Dupilumab (anti-IL-4/IL-13 - receptor)

Airway inflammation in asthma

ILC2: Type 2 innate lymphoid cells

IL-4 and IL-13 receptors

JAK = Janus kinase; STAT = Signal transducer and transcription activator; Tik2 = Tyrosin kinase 2  Vatrella, et al. J Asthma Allergy 7:123-130, 2014

Dupilumab, a fully human anti-IL-4 receptor-α monoclonal antibody, inhibits IL-4 and IL-13 signaling

JAK = Janus kinase; STAT = Signal transducer and transcription activator; Tik2 = Tyrosin kinase 2  Vatrella, et al. J Asthma Allergy 7:123-130, 2014
Dupilumab in uncontrolled asthma despite ICS + LABA

776 asthma patients
MD-HD ICS + LABA
≥ 1 exacerbation in previous year

- Dupilumab
  200 or 300 mg s.c.
every 2 or 4 weeks
- Placebo

24 weeks

- Lung function
- Exacerbations

Effect of dupilumab on nasal polyps

60 patients with nasal polyposis refractory to intranasal corticosteroids

Mometasone nasal spray plus
• Dupilumab
300 mg s.c. weekly
• Placebo

16 weeks

• Endoscopic nasal polyp score

Endoscopic nasal polyp score

Dupilumab in uncontrolled asthma despite ICS + LABA

- FEV1 ↑
- Exacerbations ↓
- Nasal polyps ↓
- Atopic dermatitis ↓

Simpson, et al. NEJM 2016 [epub]
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• Guidelines
  ➢ severe asthma

• New biologics

• Biologics by inhalation
  ➢ DNAzymes

Structure and properties of 10-23 DNAzymes

- Single strand DNA molecule
- Central catalytic domain with conserved DNA sequence (15 bases), flanked by 2 binding domains (9-12 bases each)
- Binding domain binds corresponding target mRNA sequence via Watson-Crick base pairs
- Catalytic domain with RNA endonuclease activity

Mechanism of action of 10-23 DNAzymes

DNAzyme binds to target mRNA

DNAzyme cuts target mRNA

Destruction of target structure
DNAzyme binds new target mRNA

Reduce protein translation

www.sterna-biologicals.com
GATA-3 as master transcription factor of type 2 immune responses

Inhaled GATA-3 specific DNAzyme in allergic asthma

39 asthma patients with allergic early and late reaction

- SB010 (GATA-3-specific DNAzyme)
- Placebo

28 days

Allergic reaction [AUC, %]

SB010
Placebo

- Early reaction:
  - SB010: -21%
  - Placebo: -35%

- Late reaction:
  - SB010: -35%
  - Placebo: -35%

Biologics in asthma
- Precision medicine -

• Successful inhibition of strategic mediators in asthma

• Personalized, targeted asthma treatment based on phenotype-specific diagnosis and biomarkers
  ➢ allergic asthma
  ➢ eosinophilic asthma
  ➢ ...