Immunotherapy/Biologics and Asthma

ATS Fellows Track Symposium 2020

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Introduction/Objectives

Objectives:
1. Severe asthma: defining characteristics
2. Biologics selection and assessment
3. Allergic rhinitis
4. Understanding biologics
5. Indications
6. What’s now and what’s next?
Asthma:
Inflammatory Changes in Airway Wall

Recruitment and accumulation of eosinophils, mast cells, lymphocytes

Resulting structural changes:
- Goblet cell hyperplasia
- Thickening of basement membrane
- Increased vascularity
To now a selection of therapies to a more personalized care
Case 1- 62 M  severe asthma

Initially seen at age 53 in 2011
30 yrs hx of asthma, nonsmoker
Prednisone only controls it
  On MTX weekly
NOE: osteoporosis, neuropathy

Ruled out ABPA
Optimized regimen
Bronch with 33% lymphs
25 um mm hypertrophy, goblet cells, eos

Underwent BT did much better
Case 1 - 62 M comes back

Initially seen at age 53 in 2011
- 30 yrs hx of asthma, nonsmoker
- Prednisone only controls it
  - On MTX weekly
- O/E: osteoporosis, neuropathy

Ruled out ABPA
- Optimized regimen
- Bronch with 33% lymphs
  - 1 mm mm hypertrophy, goblet cells, eos

Underwent BT did much better

Worsened again with symptoms
- Never really got off prednisone after BT
- Over months, weaned off prednisone
- Continued ICS/LABA, stopped zileuton
- Spirometry 80% without sig BDR
Case 1-what would you do next?

1) Start a biologic therapy
2) Review symptoms and reassess
3) Repeat thermoplasty (it worked before)
4) Chronic oral steroid therapy
Case 1

Revisited diagnosis, GERD uncontrolled
Sinus treatment optimized
While off steroids, CBC diff obtained
Started mepolizumab
Significantly better ACT = 20
off steroids ‘I have my life back’
Biologics for Asthma
What makes severe asthma different?

Severe asthma:
- Asthma that requires tx with high dose ICS + second controller and/or systemic corticosteroids to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy.
- Uncontrolled asthma: poor sx control, freq severe exacerbation (>=2 bursts of systemic CS in past yr,) exacerbations-1 hosp, ICU or mech vent in prior yr; FEV1< 80%

Relatively large proportion of resource expenditure although only 10% prevalence
Severe Asthma: From phenotypes to endotype

**Phenotype**

- Observable characteristics
  - Airflow limitation, age, eosinophilic, etc.
- Hereditary, early onset allergic asthma
- Poorly reversible, very severe, neutrophilic asthma
- Late onset eosinophilic asthma
- Late onset, symptom dominant obese minimal inflammation

**Endotype**

- Subtype of a condition defined by distinct functional or pathophysiological mechanism
- Biomarker, genetic element or pathobiology, stable over time which has a robust response to therapy

*Wenzel Clin Exp Allergy 2012*
## Evolving Endotypes for Asthma

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Natural Hx</th>
<th>Clinical</th>
<th>Genetics/Pathobiology</th>
<th>Biomarkers</th>
<th>Tx Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe early onset allergic</td>
<td>Childhood/progressive</td>
<td>Allergic disease</td>
<td>Th2, eos?</td>
<td>Hi Exhaled NO, IgE</td>
<td>Steroids, Th2 blockers</td>
</tr>
<tr>
<td>Late onset, persistently eosinophic</td>
<td>Adult onset</td>
<td>Sinusitis, polyps, AERD</td>
<td>Leukotriene pthway</td>
<td>Blood/pulm eos despite GC, csLT, IL-5</td>
<td>Anti-IL5, Th2 modifiers</td>
</tr>
<tr>
<td>ABPM</td>
<td>Usu adult onset, persistent</td>
<td>Cough, mucus, central b’ectasis</td>
<td>CFTR? Blood/lung eos</td>
<td>Fungus specific IgE and IgG</td>
<td>Steroids, antifungal, anti-IgE</td>
</tr>
<tr>
<td>Obese-female</td>
<td>Very late onset</td>
<td>Enhanced sx, less obstrn, hormonal</td>
<td></td>
<td>Adipokines</td>
<td>Weight loss, not steroid responsive</td>
</tr>
<tr>
<td>Neutrophilic</td>
<td>Exposures, pollution, viral</td>
<td>Fixed airway obstn</td>
<td>Neutrophilic, innate immune activation</td>
<td>BAL or sputum neutrophils, Th17, IL-18</td>
<td>Macrolides</td>
</tr>
</tbody>
</table>
Omalizumab
Severe atopic, steroid dependent asthma

Anti IgE Ab: Omalizumab - 2003

Neutralization therapy

- Reduced exacerbation rate, risk of hospitalization
- IgE 30-700 IU/mL
- Recombinant mAb down-regulates IgE receptors, blunting allergic reaction

Humber M, Busse W, Hanania et al. JACI 20...
Partner with allergist

Severe asthma
  Pheno-endotype with IgE and skin test/RAST
  Optimize management

Control other factors
  Comorbidities

Consider Omalizumab and refer for AIT
  Counsel patients-disease modifying approach
Omalizumab with AIT

Omalizumab pretreatment

\(\uparrow\) safety and tolerability of cluster and rush immunotherapy schedule in pts with moderate persistent asthma and AR

More effective together than with AIT alone

Improved symptoms load and asthma control

Adding Omalizumab tx to birch and grass AIT resulted in less rescue med use and sx days c/w Omalizumab or AIT alone

Reduce rate of systemic reactions

Kopp JACI 2002, Kuehr JACI 2002
Mepolizumab- mAb directly binds IL-5

Approved 2015 for ≥12 yr and older
- 100 mg every 4 weeks
- self administration syringe July 2019

Reduces exacerbation rate (by ~ 50%)
Reduces sputum and blood eosinophils

Improves asthma control
Glucocorticoid-sparing effect (2.39 more likely with tx)

Pavord D. et al. Lancet 380 2012; Ortega H et al. NEJM 2014; Bel et al. NEJM
Anti-IL5 Reslizumab- mAb

Approved in 2016

Light-based IV
- Best response with high eosinophils and nasal polyps
- Subgroup with > 400 eos/uL:
  - significant mean $FEV_1$ increase 270 mL vs. placebo

Inhibits IL-5 from binding to IL-5 receptor on eosinophils
Reduces frequency of asthma exacerbations

Benralizumab (Anti-IL 5 receptor α mAb)

Approved in 2017
- Reduction in exacerbations by 51%
- Increased lung function, improved symptom control
- Oral steroid-sparing effect reduces OCS on avg by 75% and total discontinuation in 52%
- Reduced hospitalization by 60%

Targets IL 5 receptor α results in apoptosis of eos and lymphs via Ab-dependent cytotoxicity

Dupilumab (Anti IL-4 R α / IL-13)

Approved 2017 now mod-sev asthma

Inhibits IL-4 and IL-13 signaling

Initial indication: atopic dermatitis

Newer Indications ages ≥ 12:
  severe eosinophilic asthma
  nasal polyposis

Asthma: better control (reduced exacerbation by 50-70%)
  Improved lung function (29-33%), steroid sparing (off OCS in 50%)

Dosing variable:
  Loading dose 600mg then 300 mg q 2 weeks or 200 mg q 2 weeks SQ

Wenzel et al. Lancet 2016; Castro et al NEJ Science
logic therapy-Biomarkers for guidance
dict efficacy?

**Omalizumab** - high eos, high FeNO

**Mepolizumab** - eos ≥ 300 cells/uL

**Reslizumab** - eos ≥ 400 cells/uL

**Benralizumab** - any eos

**Dupilumab** - eos ≥ 300 cells/uL
Algorithm to guide selection advanced therapies for (severe) asthma

Adapted from Oberle Current Opinion Pulm Med 20
Case 2: Path to success(?)

54 M longstanding patient
- Developed asthma worsening in 2012, initial FEV$_1$ best was 78%
- Mucus production/thick
- Variable adherence
- + atopic with + eos
- Chronic sinusitis

Ratio 57%, FEV$_1$ 62% (proven BDR in past)
- Optimized management and treated GERD

At FU, FEV$_1$ remained at 53% and ACT = 12
- Added nebulized medications + LAMA therapy
Case 2: Path to success(?)

54 M longstanding patient
- Developed asthma worsening in 2012
- Mucus production/thick
- Variable adherence
- + atopic with + eos
- Chronic sinusitis

Ratio 57%, FEV₁ 62% (*proven BDR in past*)
- Optimized management and treated GERD

FEV₁ stayed at 53% and ACT = 12 *and then as low as 40%*
- Added nebulized medications + LAMA therapy

STILL NOT BETTER

Only prednisone helped
What would you do next?

1) Bronchoscopy to evaluate severe asthma
2) CT chest
3) Initiate Omalizumab therapy
4) Evaluate for sinus surgery
How we got to 65%

CT chest progressive worse from prior:
- diffuse central/periph bronchial wall thickening, mucoid impactions, GT

Agreed to omalizumab → duration of stability
- 1 yr later, unsatisfactory results, started benralizumab

Stagnant lung function (low) at 35-40%
- Bronch no sig eos (benra) but PMNs 53 - PCR mycoplasma/chlamydia neg
- EBBx: BM thickening, smooth muscle hypertrophy
- possible ABPA/SAFS – added vori did better, however d/c’d (↑d LFTs)

After 8 doses of benralizumab switched to dupilumab
- Hx of nasal polyposis and chronic rhinosinusitis
Emerging therapies

Target receptors
- Toll-like receptor activator
- Chemoattractant receptor homologous molecule on TH2 (CRTH2)
- Proteinase-activated receptor 2 (PAR-2)
- Calcium sensing receptor (CaSR) antagonism
- H4 receptor antagonism

Transcription Factors

• Biologics
  - Anti-IL5, 13, IL4Rα
  - Anti-IL17
  - Anti-TNF
  - Anti-TSLP

• Enzymatic Targets
  - Rho-kinase inhibitor
  - PDE4 Inhibitor (roflumilast)
  - iNOS and arginase inhibitor
Tezepelumab (anti-TSLP)
Targets upstream cytokine

Anti-TSLP
- Expression higher in asthma airways
- IgG2 mAB, binds prevents interaction with TSLP complex → increased cytokines Th2 cells

Tx demonstrated lower rates asthma exacerbation, regardless baseline eos counts, Th2 status
- Substantial decreases in eos and FeNO
- influencing more than a single downstream pathway
- Phase 3 trials underway

Corren et al NEJM 2017
Guidelines

EPR4

ERS/ATS

GINA

Consensus / Workshop documents
NHLBI/EPR4

Did not specifically have recommendations on biological therapy (IgE/IL-5)

Suggested reference: ERS/ATS

Draft Report for Public Comment, December 2019

Notes for Individuals Ages 12+ Years Discount

- Abbreviations: ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist; EIB, exercise-induced bronchoconstriction; PRN, as needed
- "A" is updated based on the 2020 guidelines.
- "I" - The term "pets" in the diagram refers to mice and cockroaches. These were specifically examined in the evidence reviewed.
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Review the Integration of the New Recommendations into Asthma Care section of the guideline for guidance on how to use the diagram.
- Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol.
- If there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings and spirometry, FeNO concentration is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessments.
- Bronchial thermoplasty was evaluated in step 6. The outcome was a conditional recommendation against the therapy.
- "The evidence-based reviews that informed the GRADE methodology employed in this report did not include studies that examined the role of anti-IgE or more recently FDA-approved biologics (anti-IL-5, anti-IL-5R, anti-IL-4R/IL-13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6. Readers are referred to a recently released guideline on the management of severe asthma that also used GRADE methodology for further information (Holguin F, Calvi JC, Chung KF, et al. Management of Severe Asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2019, in press [https://doi.org/10.1183/13993003.00588-2019]).
<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Quality of evidence</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>We suggest an anti-IL-5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>We suggest that a blood eosinophil cut-point ≥150 µL⁻¹ can be used to guide anti-IL-5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>3</td>
<td>We suggest using a blood eosinophil cut-off ≥260 µL⁻¹ to identify adolescents (&gt;12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>4</td>
<td>We suggest using a $F_{ENO}$ cut-off ≥19.5 ppb to identify adolescents (&gt;12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>5</td>
<td>For children, adolescents and adults with severe asthma uncontrolled despite GINA step 4–5 or NAEPP step 5 therapies, we recommend the addition of tiotropium</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>We suggest dupilumab as add-on therapy for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels</td>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>

IL: interleukin; R: receptor; $F_{ENO}$: exhaled nitric oxide fraction; GINA: Global Initiative for Asthma; NAEPP: National Asthma Education and Prevention Program.
Assess and treat severe asthma phenotypes

5. Assess the severe asthma phenotype and factors contributing to symptoms, quality of life and exacerbations.

6a. Consider non-biologic treatments

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

Type 2 inflammation

- Blood eosinophils ≥150/μL and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
  - Consider bronchial thermoplasty (+ registry)

Investigate for comorbidities/differential diagnoses and treat/refer as appropriate

- Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins, CXR and/or HRCT chest, DLCO
- Skin prick testing or specific IgE for relevant allergens, if not already done
- Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

Consider need for social/psychological support

Involve multidisciplinary team care (if available)

Invite patient to enroll in registry (if available) or clinical trial (if appropriate)
Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

## Anti-IgE

Is the patient eligible for anti-IgE for severe allergic asthma?
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

- no → no

## Anti-IL5 / Anti-IL5R

Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
- Exacerbations in last year
- Blood eosinophil ≥300μL

- no → no

## Anti-IL4R

Is the patient eligible for anti-IL4R for severe eosinophilic/Type 2 asthma?
- Exacerbations in last year
- Blood eosinophils ≥150μL or FeNO ≥25 ppb
  - or because of need for maintenance OCS?

- Eligible for none? Return to section 6a

Check local eligibility criteria for specific biologic therapies as these may vary from those listed
Severe T2-high asthma in the biologics era: European experts’ opinion

Ian Pavord¹, Thomas Bahmer², Fulvio Braido³, Borja G. Cosío⁴,⁵, Marc Humbert⁶,⁷, Marco Idzkos⁶ and Lukasz Adamk⁸

1 Important concerns in the management of severe asthma identified at the European Asthma Biologics Forum

- What biomarkers and phenotypes be best identified and utilised in daily clinical practice?
- Does ACQ the right tool for monitoring the response to biologics?
- How can response assessed using the ACQ related to the effect of treatment on exacerbations?
- How awareness be raised among patients and non-specialists regarding the burden of oral corticosteroids and the potential of new treatments available?
- Are corticosteroids effective in patients having exacerbations while on biological therapies?
- Should patients start and stop taking a biologic?
- Should patients be switched from one biologic to another?

Asthma Control Questionnaire.

- Early access to specialty referral
- Earlier consideration of biologics
- No consensus on length of wait time before deeming non-responder—does it lack effectiveness?
- Switch if not able to reduce OCS use
- Biologics hope to function as disease modifiers
- Focus on composite phenotypes/treatable traits (sx, pfts, AHR, OCS, HCoV)
Practical considerations…. regardless of intervention

Essential to monitor and see the patient
- When they feel better, they may disappear
- Home administration may make monitoring more difficult

Registries help with severe asthma management

Discuss therapeutic contract:
- Continue FU
- Maintain asthma meds
- Before stopping or reducing to let us know
- Provide educn and guidelines on stopping prednisone therapy

Leverage virtual care
ATS/ERS and European Expert Panel guidelines— switch vs. continue

- Individualized decision
- Case-by-case
- Determine goal of therapy
- Biomarkers/treatable traits
- Move beyond FEV$_1$
- Side effect profile
- Minimum 3 months; often 6-12

- Flexibility of criteria*
- Monitor every 3 months while initiating therapy**
- Need head-to-head
- No assumption of a superior agent for any individual

*Some with fewer eos benefit
**adherence/comorbidities reinf
How to switch-real world panel studies

- Direct switch from omalizumab to mepolizumab (within 2-4 wks of last dose) with no adverse tolerability issues
- Also need to consider overlapping biologic therapies
- No head to head trials
Side effects/adverse reactions

**Malizumab**
- Injection rxn 45%
- Resp infn 20%
- Sinusitis 16%
- HA 15%
- Pharyngitis 11%

Initial concern for malignancy, not substantiated

Systemic anaphylaxis 0.1-0.2% within 1st 3 injection and within 2 hrs administration
  - Epipen

**Mepolizumab**
- HA 29%
- Worsening asthma 27%
- Bronchitis 21%
- Injection site rxn 12%

- Well tolerate peds age
- Long term safety studies reassuring
- Shingles / zoster
Side effects/adverse reactions

**Reslizumab**
- Similar to placebo
- Nasopharyngitis
- Sinusitis 8%
- URI 10%
- HA 7%

Anaphylaxis 0.3% as early as 2\textsuperscript{nd} dose, during or within 20 min after infusion
- Close monitoring in-office

**Benralizumab**
- any AE = 65-75%
- Nasopharyngitis 12-21%
- Worsening asthma 11-13%
- Hypersensitivity 3%

- No report of helminthic infections
- ? Vaccinate vs zoster?
55 M with severe asthma, 
- Sinus disease w polyps 
- FEV$_1$ at 58% + 12% BDR 
- FeNO 136 ppb 
Benralizumab without improvement after 18 months 

Switched to dupilumab
Case 3 – Problems below the diaphragm

55 M with severe asthma, flares every 2 months
- Sinus disease w polyps
- FEV₁ at 58% + 12% BDR
- FeNO 136 ppb

Benralizumab without improvement after 18 months...

Switched to dupilumab

Tolerated loading dose 600 mg

2nd dose with profound abdominal pain
What would you do next?

1) RUQ ultrasound
2) Bloodwork: CBC diff
3) Desensitize before next administration
4) CT abdomen
Patient: “Good to read the package insert”

Aabd: Soft tissue stranding and wall thickening predominantly involving celiac artery, short segment of the suprarenal aorta, common hepatic artery, and left gastric artery. Findings suggestive of vasculitis versus less likely malignancy.

WU

ANCA neg

Abs Eos 4200

epolizumab at higher dose indication

EGPA
Dupilumab adverse effects

Different mechanism
Home administration and good safety profile
Transient eosinophilia $\geq 3000$ cells/uL from inhibition of migration from circulation to the tissues
Consequences rare (eosinophilic pneumonia, EGPA)
Ocular complications from lacrimal gland excretion (2-28% with conjunctivitis)
important to have a core set of relevant asthma outcomes to inform guidelines

Review of 117 studies / clinical trials

117 studies, and 111 outcomes identified

Asthma control, symptom severity, some PROs

With growing number of clinical trials a core outcome set from stakeholders needed to evaluate pooled outcomes

Head-to-head comparisons are not available

• Cost, risks short term, long term
• Ongoing research and development needed b/c of gaps / non-responders

Tejwani et al. Journal of Asthma 202
COVID and asthma / biologics

No evidence asthmatics at greater risk with SARS-CoV-2,
- Prevalence of infection may be underestimated
- 3 pts who had exacerbation the prior week treated with systemic steroids admitted to ICU*

General consensus: **AAAAI, ACAAI, GINA, ERS, BTS**
- Continue treatment/maintenance therapy for best control
- No suggestion that immune response will be impaired with COVID
- Home administration recommended
- Continue biologics even if treatment initiated for COVID

*Bhatraju et al NEJM 2020
Cleveland Clinic
Every life deserves world class care.
Other/combined indications
Case: 18 y/o tennis player

8 y/o with hx of asthma
Symptoms pre-match SABA does not sustain sx
Chest tightness worsening
Increased phlegm, muffled voice/throat
Increasing controller therapy doubling ICS, LTRA, ACT still at 15
Moderately prolonged systemic steroid course resulting in Cushing
Spiro mild obstruction with sig BDR
Worsening reflux after increasing asthma meds: ICS/LABA, LTRA, antihistamine, PPI, H2 blocker
Pursued EGD demonstrated esophageal bx with significant eosinophilia

B. PROXIMAL ESOPHAGUS, BIOPSY:
MULTIPLE SEGMENTS OF SQUAMOUS MUCOSA SHOWING DIFFUSE EPITHELIAL REPAIR AND EOSINOPHILIA.

COMMENT: No columnar epithelium is identified on Alcian Blue/PAS stain. Foci containing at least 40 eosinophils per high power field can be identified suggesting eosinophilic esophagitis over simple reflux.

C. DISTAL ESOPHAGUS, BIOPSY:
SQUAMOUS MUCOSA SHOWING PATCHY EPITHELIAL REPAIR AND EOSINOPHILIA.

COMMENT: No columnar epithelium identified on Alcian Blue/PAS stain. No Helicobacter pylori organisms identified on Giemsa stain. At least focally, greater than 40 eosinophils per high power field can be identified again suggesting eosinophilic esophagitis.