

Severe Asthma(s): Can THEY be prevented or reversed?

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Disclosures

- Sally Wenzel, M.D.
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Umbrella Definition: Severe Asthma *Chung et al ERJ 2014*

- ...requires treatment with high dose inhaled corticosteroids (ICS) (≥ 1000 μg fluticasone propionate or equivalent) plus a second controller (and/or systemic CS) to prevent it from becoming "uncontrolled" or remains "uncontrolled" despite this therapy

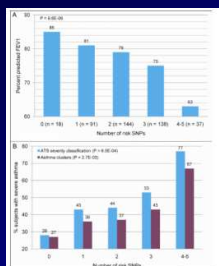
The Severe Asthmas

- Severe asthma not a single disease
- Most clear phenotypes:
 - Childhood onset allergic
 - Always severe
 - Worsening in adulthood
 - Uncommon to slowly progress to severe asthma
 - Adult onset/nasal polyposis
 - Comorbidity associated
 - Autoimmunity/asthmatic granulomatosis
- Each may require different approaches to prevention/reversal

Common Elements of Prevention

- Have normal lung function at birth and during infancy
 - Pick your parents wisely
 - Genetics of asthma/lung function
 - Make sure Mom doesn't smoke during pregnancy
 - Avoid certain viruses (RSV/RV), especially if you're premature

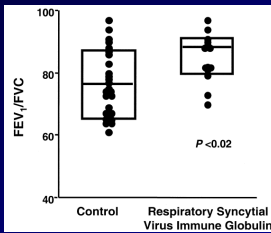
Pick your parents wisely: Genetics of lung function



- Select mutations in HHIP, PTCH1, FAM13A1, PID1, NOTCH4 associated with lower FEV1
- Additive effect of mutations in all 5 associated with lowest FEV1 and highest % severe dz

Li, X....E. Bleeker J Allergy Clin Immunol 2011

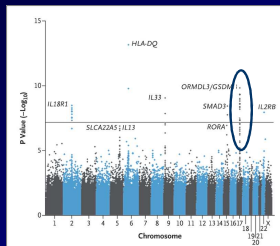
Avoid viral infections (or get preventive immunizations)



Fewer asthma attacks, school days missed
Wenzel Am J Med 2002

- Severe bronchiolitis associated with asthma risk, esp in those with asthma FH
 - Sigurs et al AJRCCM 2005
- Premature infants at risk for RSV and treated with RSV immunoglobulin had less asthma/better lung function 10 yrs later

Childhood onset allergic asthma: Genetics and presence of asthma

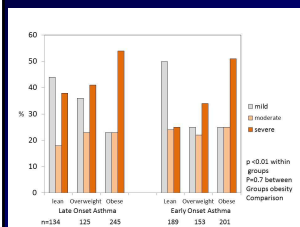


Moffatt MF et al. A Large Scale Consortium-Based Genomewide Association Study of Asthma. N Engl J Med 2010;363:1211-1221



- >10,000 asthma/16,000 controls
- Highest p-values for any region were in 17q12-21 in association with CHILDHOOD onset asthma (<16 yrs old)
- Not seen with adult onset asthma
- Gene x environment interactions: Dogs protective

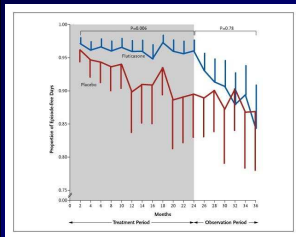
Avoid comorbid conditions



Holguin F. J Allergy Clin Immunol 2011

- Adult onset disease associated with both smoking and obesity
 - Obesity in adult onset asthma not associated with disease duration (as it is in childhood onset)
 - Holguin JACI 2011
- Obesity associated with poorly controlled asthma
- Both "preventable"

Can any treatment *prevent* severe asthma?

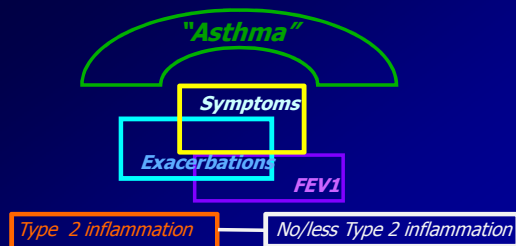


Guilbert TW et al. *N Engl J Med* 2006;354:1985-1997.

- Early ICS Rx does not prevent asthma progression in children
 - Those who best responded to ICS suffered the most on withdrawal
- Trials of specific biologics at very early age are needed

THE NEW ENGLAND JOURNAL OF MEDICINE

Reversal: Type-2 Hi vs Not?



The promise of biologics?

What does it mean to reverse?

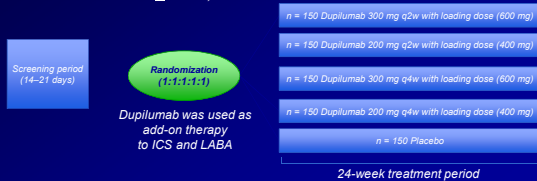
- Prevent progression
- Bring poorly controlled asthma back to well controlled asthma
- Permanently improve lung function or remodeling elements
- Improve asthma control AND reduce medication requirements

Likely only modest evidence to suggest can bring poorly controlled asthma back to well controlled

Anti-IL-4Rα in Eos/T2Hi Asthma

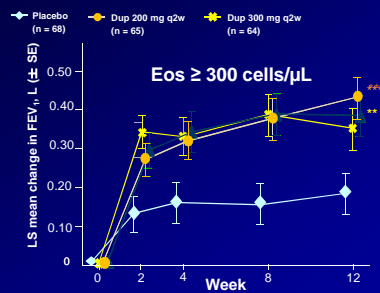
Multinational, randomized, placebo-controlled study in patients with uncontrolled asthma despite background therapy with medium- to high-dose ICS and LABA

- Patients stratified by blood eosinophil count
- Hi Eos defined as $\geq 300/\mu\text{L}$, Lo Eos all others



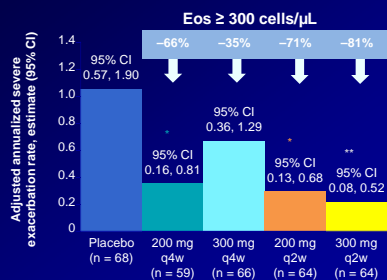
Wenzel, Castro, Corren et al Lancet e-pub 2016

Primary endpoint: Change in FEV₁ in patients with ≥ 300 eos/ μL



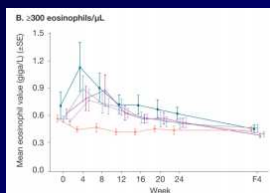
Wenzel, Castro, Corren et al Lancet e-pub 2016

~75% reduction in steroid requiring asthma exacerbations (6mos)



Wenzel, Castro, Corren et al Lancet e-pub 2016

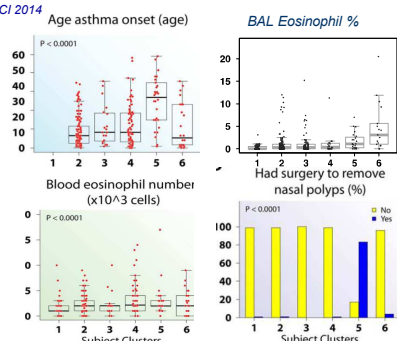
Could there be immune modification as well?



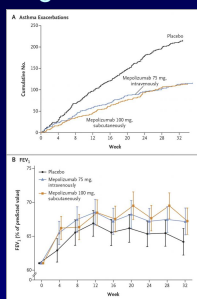
- Dupilumab increases blood eos, esp in those with high #s
- However, after 4-5 mos on Rx, they are back to baseline and perhaps even lower
 - Associated decrease in T2 biomarkers
- *Could* inhibition of IL-4R reduce T2 activity?

Alternative Type-2: adult onset-nasal polyp/eosinophilic disease

Wu, JACI 2014



Mepolizumab consistently effective in 3 large trials of eosinophilic patients

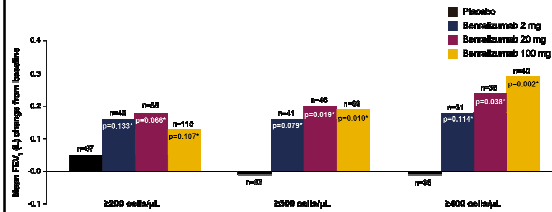


- Targeted patients with blood eosinophils >~280/ml
- Reductions in exacerbations of 40-50%
- Recent studies show impact on FEV1/ACQ as well
- Responses improve with increasing eosinophils (and likely nasal polyposis/sinus dz)
- Recently approved by FDA
- Similar data with reslizumab, benralizumab (anti-IL5Receptor antibody) *Castro Lancet Resp Med 2014 and 2015*

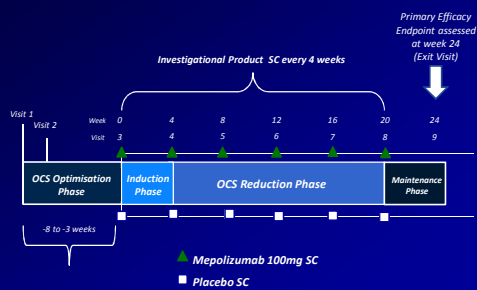
Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.



The more blood eos present the better the response (anti-IL5R)

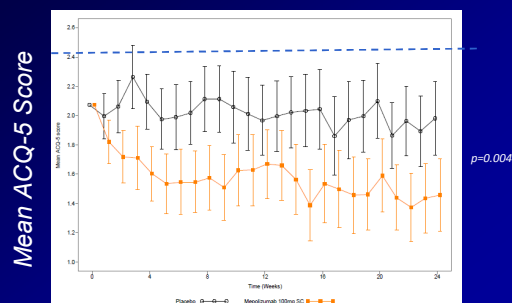


Anti-IL-5 as CS sparing agent

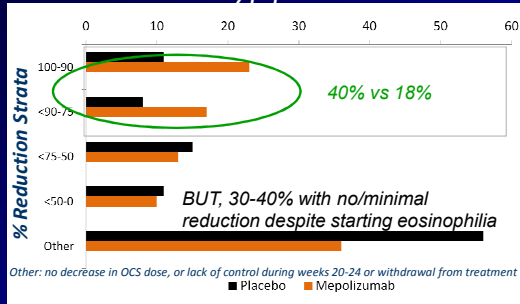


Bel E, et al, N Engl J Med, Sept 2014

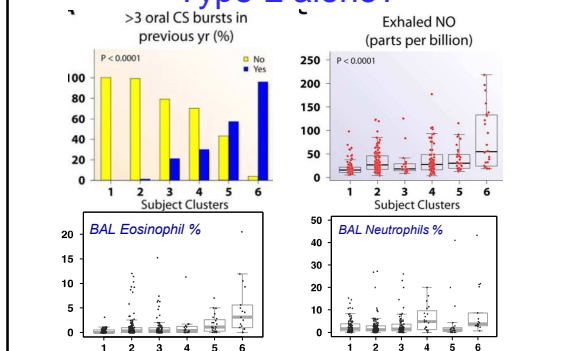
Improvement in asthma control despite reduction in corticosteroids



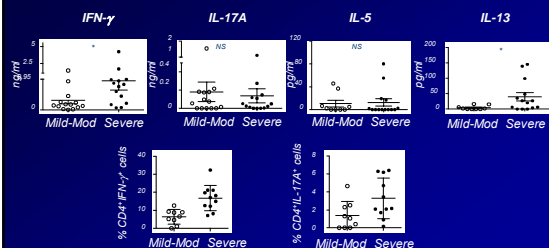
Despite persistent eos, >1/3 of SA could not reduce CS dose
% study population



Very severe disease: Beyond Type-2 alone?



Higher IFN- γ /Th1 protein in Severe Asthma Compared to Milder Asthma



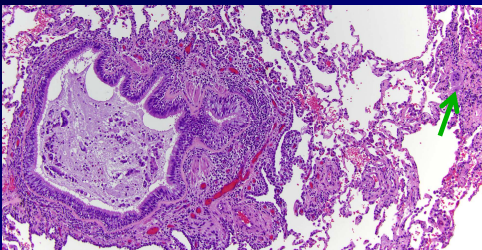
Voraphani Mucosal Immunol 2013, Raundhal et al J Clin Invest 2015

Complex (Autoimmune?) Type- 2 reactive airway disease

- First reported "Asthmatic Granulomatosis" 2012
- 10 "severe asthma" pts (now ~35) who met asthma diagnosis (reversibility or + methacholine)
 - All on systemic corticosteroids (10 mg or above)
- Often adult onset or adult worsening
- Modest obstruction with decrease in FVC and DLCO
- Hi FeNO (and blood eos) despite systemic CSs
- Associated with autoimmune family history in ~70%
- All underwent VATS surgical biopsies

Wenzel Am J Resp Crit Care Med 2012

Small airway inflammation and granulomas: complex immunity



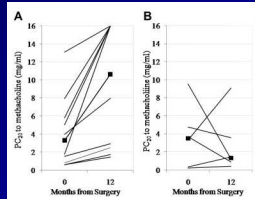
When associated with personal or family history of autoimmunity respond well to azathioprine Doberer ATS 2015

"Type 2-Lo Asthma"

- Much less well defined than Type-2 HI
 - Defined as "apparent" absence of Type 2
 - No definite endotypes, but many confounders including obesity, post infectious, smoking, long disease duration likely to play a role
 - 'omics may provide some clues
- All associated with poor CS response
 - Macrolides, thermoplasty, weight loss

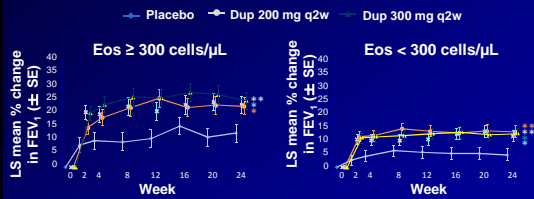
Type 2-Lo late onset obese asthma “reverses” to weight loss

- 23 obese asthmatics evaluated before and 12 mos after bariatric surgery
- Roughly phenotyped patients by median IgE levels (25 vs 305 IU/ml)
 - Late onset asthma=Lower IgE
- Later onset/low IgE obese asthmatics improved PC20 while no effect seen in low IgE/early onset
- Suggest weight loss will be more effective in some phenotypes



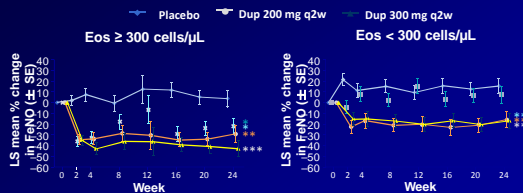
Dixon AE et al J Allergy Clin Immunol 2011

Unlike anti-IL5, anti-IL-4R α effective in those with low eos...”low” Type-2??



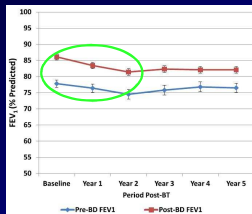
Efficacy of α IL-4R blockade in absence of Type-2 biomarker suggests better biomarkers required!!

Reduction in FeNO, even in low eos patients on ICS, supports suppression of ongoing Type-2 inflammation



Suggests residual, corticosteroid responsive Type-2 inflammation in large % of patients

Thermoplasty: Disease modifying?



Wechsler JACI 2013

- Short term data reports improvement in AQLQ, possibly exacerbations
- Longterm data without control group
- FEV1 *declines* in 1st 2 yrs (no statistics given for decline from Baseline to Year 2)

Conclusions

- Prevention of severe asthma(s) is likely dependent on aspects that are difficult to control although maintaining healthy weight in adult hood and never smoking are likely to be helpful
- Reversal depends on definition
- Biologics may get us closer by greatly improving outcomes, but ultimate disease modification not yet observed
