

Workshop 19: Controversies Surrounding Long-Acting Beta Agonists (LABAs) in Asthma: Step-Up Therapy.

Presenter: Homer Boushey, MD, University of California San Francisco.

Outline: (not for citation or publication)

- **Goals of therapy:**

1. Reduce impairment.
 - Reduce symptom burden
 - Improve functional capacity
 - Improve pulmonary function
2. Reduce risk:
 - Of exacerbations
 - Of progressive loss of pulmonary function
 - Of toxicities of treatment

- **Current options:** All measures of impairment and frequency of exacerbation reduced by 4x-increase in ICS dose or by addition of LABA to baseline ICS dose. Exacerbation frequency reduced by Anti-IgE Mab therapy in atopic asthmatics and by Bronchial Thermoplasty in severe, high-dose ICS-dependent asthma, but both are expensive, cumbersome therapies.
- **Tiotropium as add-on therapy:** Review of ACRN trial showing addition of Tiotropium to ICS more effective than 2X increase in ICS dose and not inferior to addition of salmeterol. Subsequent studies show efficacy in improving FEV1 in asthmatics homozygous for Arginine at B16 locus, and in asthmatics taking ICS+LABA.
- **Tailoring therapy to phenotypic features:** Earlier trials with anti-IL5 MAb therapy did not show efficacy in unselected asthmatics, but recent studies with two different anti-IL-
- **“Molecular Phenotypes” of Asthma.** The pattern of gene expression in bronchial epithelial cells from asthmatic subjects not taking an ICS and from healthy controls shows upregulation of Periostin, CICA-1, and Serpin B-2 in only half of the asthmatics. These genes are upregulated by addition of IL-13 to epithelial cells *in vitro* and so is referred to as the “Th2-molecular phenotype. This phenotype differed from the non-Th2 phenotype in responding to ICS treatment (the non-Th2 subjects did not) and tended to have greater blood eosinophilia, higher total IgE and more + skin tests, but there was overlap between the groups. Because periostin is secreted from the basal aspect of epithelial cells, it is increased in the circulation of Th2-high asthmatics, and a recent trial has shown Lebrikizumab, an anti-IL-13 antibody, to be significantly more effective in improving FEV1 in the periostin high subgroup of the asthmatic subjects studied.
- **Sputum eosinophilia as a distinct phenotypic marker of ICS responsiveness in mild asthma?**
Analysis of the previously published IMPACT study showed that 10 days of intense combined treatment with prednisone, an LTRA, and high-dose budesonide improved FEV1 only in subjects with intermittent or persistent sputum eosinophilia (>2%)
- **Unmet needs and future directions:**
 1. Identification of mechanisms of “Th2- negative” and/or “eosinophil negative” asthma.
 2. Identification of easily assessable phenotypic features predicting responsiveness to different therapies.