Year-in-Review

# Year-in-Review: Adult asthma

Department of Internal Medicine, Korea University Medical Center Anam Hospital

Byung-Keun Kim

This review will highlight new articles published I 2017. Numerous articles concerning adult asthma have been published in 2017. I have focused this review on 5 issues: (1) Epidemiology and course of asthma, (2) Asthma genetics and pathophysiology, (3) Asthma as airway disease, (4) Diagnosis of asthma, (5) Management of asthma: Focusing on corticosteroids, and (6) Management of asthma: Biologics and new treatment.

## 1. Epidemiology and course of asthma

Since the 1980's the so called 'epidemics of asthma mortality' abruptly ended with the regulatory restriction or withdrawal of high-dose, potent, poorly selective $\beta 2$ agonists. The efficacy of ICS reduced risk of mortality in the late 1980s. Ebmeier and collegues reported international trends in asthma mortality rates in the 5–34-year age group over the past decade.[1] Although in some countries and regions the asthma mortality rate has continued to fall, the estimated global asthma mortality rate has not changed since 2006.

Adult-onset asthma covers more than 50% of new diagnoses of asthma. Adult-onset asthma is associated with more eosinophilic airway inflammation and chronic sinus disease. It has also been suggested that these patients have a more rapid decline in FEV1. Coumou et al performed prospective 5-year follow-up study in 200 adults with newly diagnosed asthma.[2] Median change in post-BD FEV1 was −17.5 mL per year. Nasal polyps, blood and sputum eosinophils, BMI, and level of exhaled NO were univariably associated with decline in lung function. Only the latter two were independently associated. Also, Bowatte and colleagues reported that exposure to traffic-related air pollution increases the risk of atopy, wheeze, and lower lung function of adult asthma.[3] Especially, Individuals with the glutathione S-transferase-null genotype are at high risk of respiratory and allergic disorders.

There have been several studies on the risk factors for the occurrence of asthma. Children with chronic

asthma are more frequently born in families with significantly lower household income, have lower weight at birth, and are less often breastfed. In urban families with low socioeconomic status, maternal stress and depression during pregnancy seem to be associated with recurrent wheezing in children at age 3 years but not with allergic sensitization, enhanced T2 response, or reduced antiviral responses.[4] Preeclampsia is also weakly associated with increased use of ICS during infancy, increased bronchial hyperresponsiveness, and allergic rhinitis and eczema.[5] In a large prospective population-based cohort, pregnant women taking supplemental folic acid, combined with a diet rich in folate, associated with a slightly increased risk of asthma in children.[6]

## 2. Asthma genetics and pathophysiology

Gref et al reported that gene-environment interactions are important for asthma development.[7] They analyzed individual air pollution exposure at the birth address and performed a genome-wide interaction study for doctors' diagnoses of asthma up to 8 years in three European birth cohorts. They provided supportive evidence for interaction with air pollution for ADCY2, B4GALT5, and DLG2. Berthon et al reported that OCS response can be predicted with sputum gene expression assay.[8] The six-gene (CLC, CPA3, DNASE1L3, IL1B, ALPL and CXCR2) expression signature including eosinophil and Th2 related mast cell biomarkers showed greater precision in predicting OCS response in stable asthma. Thus, a novel sputum gene expression signature could be a useful measurement to guide OCS therapy in asthma.

Genomic analyses also underscored possible mechanistic differences between various clinical manifestations of asthma. With WGCNA, the expression of genes in airway epithelial cells related to T2 inflammation increases with the clinical severity of the disease.[9] The expression of low epithelial growth and repair and neuronal function genes is associated with severe asthma more strongly than T2 inflammation, suggesting that epithelial integrity and related processes are of primary importance in the development of asthma. Bigler et al revealed blood gene expression differences between clinically defined subgroups of patients with asthma and individuals using unsupervised cluster analyses and constructed gene co-expression networks.[10] Similarly, the U-BIOPRED "omics" assessment with bronchial biopsies and airway epithelial brushings suggested that common patterns of gene expression in the sputum and blood of children and adults are associated with clinical asthma severity.[11]

Eosinophils are end-stage effector cells of T2 inflammation. The contribution of eosinophils specifically, and their secondary granule proteins in lung remodeling, is not well documented. In a transgenic mouse model of chronic T2 inflammation, eosinophil-dependent T2 pulmonary remodeling and lung dysfunction were mainly driven by eosinophil-dependent IL-13 expression and not by the release of individual secondary granule proteins.[12] Airway remodeling is also one of key feature of asthma pathology. In stable asthma, activation of airway smooth muscle (ASM) matrix metalloproteinase-1 by mast cell tryptase results in

enhanced ASM proliferation, and matrix metalloproteinase-1 expression correlates with the severity of airway response to bronchoconstrictor stimuli.[13] This suggests that ASM/mast cell interactions contribute to airway remodeling and asthma severity.

There were several reports regarding the relationship between asthma and obesity / metabolic syndrome. Distinct metabolic fingerprints can be detected in exhaled breath condensate of patients with obesity, asthma, or both.[14] Adding exercise to a short-term weight-loss program improves clinical control of asthma in obese patients.[15] There were reports that medications for diabetes or metabolic syndrome such as statins,[16] or pioglitazine[17] showed efficacy in obese asthmatics.

## 3. Asthma as airway disease

Thinking about asthma and airways diseases is changing. In a Lancet commission titled “After asthma: redefining airways disease”, on which many ATS members were authors, the case was made that a change in approach is required to achieve genuine advances in this field.[18] The Commissioners argued that after reductions in the burden of asthma, especially related to hospital admissions and mortality in the 1990s and early 2000s, progress has been poor over the past decade, despite escalating treatment costs. While there is a general acceptance of the view that there is not “one asthma” and that the term asthma represents a clinical syndrome with many sub-types, the Commissioners argue that the continued use of the term “asthma” is limiting thinking and progress. This report represents that new thinking is emerging, at least in some areas.

## 4. Diagnosis of asthma

Bronchoprovocation tests requiring maximal inhalations to total lung capacity are not recommended because the bronchoprotective effect of a deep breath reduces the sensitivity of the test. Therefore, ERS task force recommended new guidelines for methacholine challenge testing reporting the test outcome as dose rather than concentration.[19] Davis et al developed a novel method for measuring 20% provocative dose (PD20) using a vibrating mesh nebulizer.[20] New nebulizer technology was simple, repeatable for conducting methacholine challenges and the method meets recommendations set out in the new guidelines. Expressing FEV1 responsiveness as % baseline spuriously suggests that responsiveness increases with the severity of respiratory impairment. Quanjer and colleagues reported that in severe airway obstruction, change of FVC should be critically evaluated as an index of clinically important relief of hyperinflation.[21] They showed that the change of FEV1% increased with the level of airflow obstruction but decreased with severe obstruction. However, change of FVC increased with the level of airflow obstruction.

Measurement of FENO concentration is a non-invasive method to estimate inflammatory processes in the

lung. Karrasch et al performed a meta-analysis concerning FENO for diagnosis of asthma.[22] The overall sensitivity was 0.65, the overall specificity 0.82, the diagnostic OR was 9.23 and the AUC was 0.80. Higher cut-off values were associated with increasing specificity. Sensitivities varied significantly within the different FENO devices, but not specificities. Neither prevalence, age, use of bronchoprovocation in >90% of participants or as exclusive reference standard test, nor risk of bias were significantly associated with diagnostic accuracy. Song and colleagues also performed a meta-analysis regarding FENO measurement in detecting cough-variant asthma (CVA) and eosinophilic bronchitis (EB) in patients with chronic cough.[23] FENO measurement had a moderate diagnostic accuracy in predicting CVA in patients with chronic cough, showing the summary AUC to be 0.87. Specificity was higher and more consistent than sensitivity (0.85 and 0.72, respectively). However, in the non-asthmatic population with chronic cough, the diagnostic accuracy to predict EB was found to be relatively lower (summary AUC, 0.81), and specificity was inconsistent.

With recent guidelines, there are not any confirmatory test for diagnosing asthma. Wi et al. tested the accuracy of an existing natural language processing (NLP) algorithm that can extract information from narrative text automatically using predefined asthma criteria (PAC).[24] They tested the NLP-PAC on 500 children from the Mayo Clinic birth cohort. The algorithm identified 158 subjects meeting asthma criteria whereas manual chart review identified were identified by both methods. Importantly manual chart review took 384 hours for asthma ascertainment from 430 subjects whereas it took 22 minutes to run NLP-PAC for the same subjects. Also, Almoguera et al. ascertained subjects with and without asthma using an EMR-based algorithm that searched for subjects who fulfilled pre-defined criteria and diagnosed with at least one ICD9 code of asthma or documented wheeze or asthma on multiple occasions in the EMR.[25] Both internal and external validation of the algorithm showed excellent results with positive predictive values of 95.8% for both cases and controls.

## 5. Management of asthma: Focusing on corticosteroids

Sobieraj and colleagues performed two meta-analysis concerning treatment strategy of asthma. The use of single maintenance and reliever therapy (SMART) was associated with a lower risk of asthma exacerbations.[26] Also, the use of LAMA as add-on therapy to ICS was associated with a lower risk of asthma exacerbations.[27] However, the association of LAMA with benefit may not be greater than that with LABA. Triple therapy was not associated with a lower risk of exacerbations. Post hoc analysis of the START showed that 3-year budesonide treatment reduced serious asthma-related events and lung function decline and improved symptoms even in patients with symptoms less than twice a week.[28] This result for mild asthma reflected in the new GINA 2018 guideline. A 2016 Cochrane review concluded that it is unlikely that increasing the dose of ICS reduces the odds of systemic glucocorticoid use or hospitalization

or shortens recovery time. McKeever et al performed pragmatic, unblinded randomized trial to examine the efficacy of quadrupling ICS dose.[29] Personalized self-management plan that included a temporary quadrupling of the dose of ICS when asthma control started to deteriorate resulted in fewer severe asthma exacerbations than a plan in which the dose was not increased.

Two studies provided information regarding step-down of pharmacologic therapy in patients with asthma. Guidelines generally recommend considering stepping-down asthma medication after asthma is controlled for at least 3 months. Usmani et al reported in a 12-week randomized, controlled, pragmatic, open label trial, that stepping down from high-dose to medium dose ICS/LABA combination was non-inferior regarding asthma control and asthma exacerbations in patients with stable asthma for 3 months.[30] However, patients with 1 or 2 asthma exacerbations in the year before stepping-down had more asthma exacerbations when stepped-down. Another approach to stepping-down asthma medications was reviewed by Demoly et al.[31] The authors identified 5 mite allergen immunotherapy studies (2 SCIT and 3 SLIT) supported the efficacy of these treatments to aid in stepping-down asthma medications. Specifically, for dust mite-induced asthma, the report highlighted the potential value of specific allergen immunotherapy in moderate, rather than mild, asthma to help step down ICS dosage from GINA step-care levels 3 or 4.

The burden of chronic OCS use defined as more than 2.5 mg/day was studied by Zeiger et al in a retrospective observational study from 2009 to 2011.[32] Chronic OCS use was associated with significantly more asthma specialist care, GINA step 4 and 5, excess SABA use, more than 2 asthma exacerbations, and asthma ED or hospitalizations. Compared with those without chronic OCS use, patients with chronic OCS use had increases in the frequency of comorbidities: obesity, rhinitis, hypertension, chronic sinusitis, gastrointestinal reflux disease, anxiety, pneumonia, fractures, nasal polyp disease, and cataracts. The major significant adjusted predictors for future chronic OCS use were prior chronic OCS use, nasal polyp disease, asthma specialist care, GINA steps 4 and 5, theophylline use, and excess SABA dispensed.

## 6. Management of asthma: Biologics and new treatment

A meta-analysis of 25 “real-life” observational effectiveness studies of omalizumab treatment confirmed the efficacy findings of randomized placebo-controlled trials.[33] Significant improvements were observed in good excellent treatment responders in spirometry and asthma specific quality of life, with reductions in exacerbations, asthma hospitalizations, and use of ICS and OCS. Maltby et al reported that omalizumab improve improves asthma control and health-related quality of life not only in severe asthma but also in overlapping COPD.[34] However, omalizumab treatment did not improve lung function in populations of asthma-COPD overlap. Iribarren et al reported the relationship of omalizumab and cerebrovascular(CV) or cerebrovascular (CBV) events in a post-marketing observational cohort (EXCELS).[35] Although it was not statistically significant, omalizumab-treated patients had a higher rate of CV/CBV serious adverse events.

(13.4 vs. 8.1 per 1,000 person-years [PYs]). The ATE rates per 1,000 PYs were 6.66 and 4.64 in the omalizumab and the non-omalizumab cohort. After control for available confounding factors, the hazard ratio was 1.32. However, differences in asthma severity between cohorts likely contributed to this imbalance.

The anti-IL-5 monoclonal antibodies mepolizumab and reslizumab and the anti-IL-5R antibody benralizumab already proved its efficacy in patients with severe, uncontrolled eosinophilic asthma. There were several additional studies in 2017. Mepolizumab approximately halved exacerbations requiring hospitalization and/or emergency room visits compared with placebo in patients with severe eosinophilic asthma.[36] Mukherjee et al compared treatment response of weight-adjusted IV reslizumab in patients previously treated with 100-mg SC mepolizumab.[37] Decrease in percent sputum eosinophil was greater with reslizumab (by 42.7% vs. 5.0%) and this was associated with greater improvement in asthma control questionnaire. The long term safety and continued efficacy of reslizumab for moderate-to-severe eosinophilic asthma over a 2-year period was reported in an open-label extension study, providing additional assurances with this new biologic agent.[38] In 2016, SIROCCO and CALIMA study revealed the effectiveness of benralizumab in severe eosinophilic asthma. Nair et al reported that benralizumab showed significant, clinically relevant benefits on oral glucocorticoid use and exacerbation rates and these effects occurred without a sustained effect on the FEV1.[39] There were also reports to explain why some patients does not response to anti-IL-5 monoclonal antibodies. The study by Kelly et al. highlighted the dichotomy between eosinophil number and function.[40] Treatment with mepolizumab reduced eosinophil influx to the airways following a segmental allergen challenge but did not reduce their functional activity. Segmental allergen challenge after mepolizumab reduced circulating eosinophil levels by 80% and reduced the number of eosinophils in the BAL. However, there was no reduction in the IL-5 responsive activation markers CD23, CD44 or CD69. Furthermore, there was no reduction in the receptors for IL-5, IL-3 or GM-CSF.

Corren et al reported the result of phase 2, randomized, double-blind, placebo-controlled trial of tezepelumab, humanized anti-TSLP monoclonal antibody.[41] Among patients treated with LABA and medium-to-high doses of ICS, those who received tezepelumab had lower rates of clinically significant asthma exacerbations than those who received placebo, independent of blood eosinophil counts. Mast cells are associated with poor quality of life and inadequate asthma control. Stem cell factor and its receptor, KIT, are central to mast-cell homeostasis. Cahill and colleagues performed a proof-of-principle trial to evaluate the effect of imatinib, a KIT inhibitor, on airway hyperresponsiveness.[42] Imatinib treatment reduced airway hyperresponsiveness than placebo. At 6 months, the methacholine PC20 increased in the imatinib group more than the placebo group. Imatinib also reduced levels of serum tryptase.

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