Personalized medicine for asthma: Are we there yet?

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Asthma has generally been defined as a chronic disorder of the lung, with variable airway obstruction, wheeze/cough, and an underlying inflammatory process. However, considerable heterogeneity exists within the population of patients with asthma-like symptoms. Clinically, asthma is being categorized into eosinophilic, neutrophilic, atopic, non-atopic, early onset, and late onset; and aspirin- or exercise-induced in cases with known triggers.[1] The disease is currently recognized as a complex condition with variable severity, natural history, and response to treatment. Treating asthma based on phenotypes that group observable characteristics, with no direct relationship to the disease mechanisms is suboptimal, given the variability in treatment response. Endotyping, which refers to defining subpopulations of a disease based on molecular mechanisms or treatment response has shown some success in designing a more effective treatment scheme.[1-3] Lotvall *et al*., proposed endotyping asthma into seven classes: *aspirin-sensitive, allergic bronchopulmonary mycosis (ABPM), adult allergic, asthma-predictive indices-positive preschool wheezer, severe late-onset, hyperosinophilic, and cross-country skiers* asthma.[1] More recently Wenzel has described the evolving five severe asthma endotypes: *early onset allergic, persistent eosinophilia, ABPM, obese-female,* and *neutrophilic* severe asthma.[3]

Endotyping asthma serves as a stepping stone toward the practice of personalized medicine for asthma. The principle of personalized or individualized medicine is to 'bring the right drug to the right patient at the right dose', such that therapeutic efficacy is maximized and the side effects are kept to a minimum.[4,5] With the advance of the '-omic' era, physicians are getting closer to being able to 'tailor' treatment schemes, based on unique individual's biological data, such as, genomic, transcriptomic, and proteomic profiles, in addition to the conventional clinical data such as family history, symptoms, and laboratory test results. In the case of asthma, as recently reviewed by Weiss, about 11 genes have sequence variations associated with drug response, but only five have been replicated in at least one other study, and only one has validated functional effects.[6] Although the exact molecular mechanisms underlying asthma pathogenesis and treatment response are far from understood, targeting therapy based on asthma endotypes would at least allow the physicians to target treatment based on an individual's biology.

At present some success has been achieved in clinical trials when treatments are tailored to endotypes. For example,[1] anti-IgE (omalizumab) has been effective in improving the clinical outcomes, particularly in treating childhood onset allergic asthma, in which interleukin (IL)-4 and 13 signal pathways are probably the predominant underlying mechanism, as recently reviewed by Kuhl and Hanania.[7] (2) A clinical trial of an anti-IL-13 monoclonal antibody (lebrikizumab), for the treatment of severe asthma, reported improved lung function, particularly in those with high IL-13 activity indicated by high levels of the IL-13 activity biomarker periostin(49). (3) Anti-IL-5 (mepolizumab) treatment has been shown to be effective in preventing symptomatic exacerbations in persistent eosinophilic severe asthma.[8,9] (4) The new treatment option of bronchial thermoplasty to remove airway smooth muscle mass has just been approved by the US Food and Drug Administration (FDA). Clinical data support the use of bronchial theraplasty in treating individuals with extensive airway remodeling (i.e., severe refractory and severe persistent asthma).[8,10-12] Hence, although we are still far from practicing 'personalized medicine', by treating asthma based on endotypes would reduce the likelihood of prescribing the wrong drug to the wrong patient. It will also decrease the number of difficult-to-treat asthmatics, which might have important implications in reducing the cost and minimizing the burden of this chronic inflammatory disease.

Although it is naïve to think that personalized medicine for asthma is within arm's reach, putting in continuous efforts to better the endotyping of asthma is moving in the right direction.

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