

EDITORIAL

The role of IgE in difficult-to-treat asthma. Of compliance and competence

DOI:10.1111/j.1398-9995.2011.02740.x

Asthma is a heterogeneous disease, not only in its clinical expression and course but also in its response to treatment (1). While most patients on inhaled corticosteroids and beta-2-agonists do well and are clinically stable, a substantial part of the asthma population develops exacerbations even during the course of treatment (2). It is those exacerbations and the difficult-to-treat asthmatics that, in the long run, represent the greatest burden on the health system. Foremost, it is extremely disturbing for patients to go through exacerbations despite treatment. If this would not be bad enough, these patients are often suspected by their physician not to adhere to treatment and not to comply with the doctor's good advice.

The study by Ellen Koster et al. published in the previous issue of *Allergy* (3) suggests that it is worth having a second look at these patients before drawing improper conclusions: It may be genetics rather than bad compliance driving some of these patients into exacerbations. Specifically, a genetic variation in the low-affinity IgE receptor (FCER2) seems to be associated with increased exacerbation rates in children treated with steroids in two large and independent populations: one from the Netherlands and one from Scotland. Carriers of the risk-associated allele at polymorphism T2206C are more than twice as likely to have uncontrolled asthma and asthma-related hospital visits despite a significantly increased steroid dose.

This study is intriguing beyond genetic association as the polymorphism under investigation is located in a gene not naturally coming to one's mind when thinking about 'steroid resistance'. A FCER2 polymorphism had previously been shown to be associated with IgE levels in a single study (4), but in recent GWAS, this SNP was not one of the major determinants of total serum IgE levels (5). However, functional evidence exists that support a role of the T2206C polymorphisms in regulating the expression of FCER2. In turn, the authors argue that altered levels of FCER2 may affect an individual's reaction to IgE or even affect IgE levels indirectly. Thus, FCER2 may not be associated with pharmacological steroid resistance in its narrow definition but with uncontrolled disease symptoms potentially mediated by IgE-related mechanisms despite steroid treatment in increasing doses.

Is it worth and ethically justifiable to perform genetic testing for this variant in a clinical setting to predict exacerbation risk for asthma patients under treatment? Well, at least there is a significant chance that this may be feasible. The

major question that needs to be answered is formulated as a hypothesis by the authors of the study when they discuss the impact of their finding: Could testing for T2206C in FCER2 help to better identify patients that may profit from IgE antibody therapy and spare these patients excessively high steroid doses as well as unnecessary exacerbations? This needs to be answered in prospective clinical trials taking genotypes into account. If this is the case, it would indeed be a leap toward personalized medicine that would help to employ health resources better than in the past.

With an increased understanding of disease mechanisms, more advanced therapeutics are becoming available. In asthma and allergy, a number of biologicals have already entered the market. Anti-IgE is the most prominent of these biologicals, probably because it is the least specific (6). Others are the cytokine antagonists anti-IL-5 and anti-IL-13. Anti-IL-5 seemed to be effective when patients were selected on specific characteristics (7). For effective anti-IL-13 therapy (8), patients with an IL-13-related phenotype were selected for a trial.

The more we know about complex diseases (or think to know about the diseases), the more specific the therapy will become. At the same time, it is important to understand that pathomechanisms may vary considerably between asthmatics. Certain immunological cascades may drive one form of asthma but may be secondary in others, mirroring the heterogeneity of asthma (a fact that is also visible in the heterogeneity of asthma genetics results). While Koster and colleagues show that the 'one therapy fits all' concept is not even true for inhaled corticosteroid therapy, the broadest possible anti-inflammatory weapon, this is even more so for biologicals. It is a selected few that will profit the most from a therapy targeted against a specific form of asthma. Once this fact is acknowledged, the next logical consequence is that patients treated with biological need to be matched the best possible way with a specific therapy to optimize treatment success and to avoid serious side-effects. Genetics will be one of the tools for matching; others will be immunological and clinical profiling. Most likely, a mix of these approaches will be successful (9, 10). Considering treatment costs of biologicals, matching is necessary and cost-effective. It will increase acceptance of these expensive treatments with patients and the public.

Many or even most patients do and will do very well on current therapies such as inhaled steroids or leukotriene antagonists and additional reliever medication if needed. It is

those that are not covered by these standard therapies that need special attention. At the end, patients with 'steroid-resistant' asthma may not be difficult to treat if you treat them with what they actually need.

Conflict of interest

The author has no conflict of interest to declare.

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