Editorial

Towards precision drug therapy in asthma

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For novel asthma drugs to receive market authorization, randomised controlled trials need to show a drug's beneficial effects on relevant clinical outcomes such as lung function or exacerbations (1). Notably, when assessing whether or not a drug "works", differences in trial endpoints are usually determined based on mean effect differences between the intervention and the control group. However, within these groups, large inter-individual differences in actual drug response can exist. Some patients may show an extremely large response ["super responders" (2)] and some may show no effect, or even worse, have harmful outcomes (3). Exactly these differences are observed in real-world daily practice, when healthcare professionals have to deal with the treatment of individual patients with asthma. As such, there is an increased need to personalize the treatment we are providing.

Within asthma management, most commonly used drugs include inhaled corticosteroids (ICS), short and long-acting beta2 agonists (e.g., salmeterol, formoterol) and leukotreine antagonists (e.g., montelukast). Furthermore, in severe asthma, long-acting muscarinic antagonists or biologic therapy can be considered (4). Various factors can contribute to the observed variability in response to any of these drugs, including both biological and behavioural factors (5). Examples include age, gender, smoking, diet, severity of disease, comorbidities, and interactions with other drugs (6). Moreover, even factors preceding the administration of the drug to the body may be a cause of variability. Here, we should consider the choice physicians make regarding the exact drug within particular drug classes, dose, dosing regimens and administration route. Notably, most asthma drugs are administered through the inhaled route, i.e., using inhalers. Even when standardizing the drug, its dose, its regimen and its inhaler, some patients may have difficulties with inhaler technique or medication adherence, resulting in lower drug deposition in the lungs and as such, potentially poorer effects. After this behavioural cause of drug response variability, biological factors start playing a role. Indeed, at the point when the drug reaches the body, pharmacokinetic and pharmacodynamic factors become more important, causing further variability (7). Notably, pharmacokinetics describes how a drug will be absorbed, distributed among body tissue, metabolized and eventually excreted from the body. In the meantime, the drug may temporarily bind to one of its target receptors where its pharmacodynamic effect takes place (7). The "journey" of a drug through the body is modulated by different receptors and proteins (e.g., transporters and enzymes) that come in different genetic variants. This genetic variability makes them perform "better" or "worse" regarding their function, e.g., being it transporting the drug, degrading the drug or putting in motion its pharmacologic mode of action. The study of the impact of genetic variations on pharmacology is called "pharmacogenomics".

Previous reviews have provided overviews of the role of pharmacogenomics in asthma (8,9), yet given the fast developments in the field, an up-to-date review would be very welcome. In this edition of the *Annals of Translational Medicine*, Li and Qiu provide a state-of-the-art overview of recent pharmacogenomic studies in asthma focusing on beta-agonists, ICS and leukotreine modulators (10). Notably, these three classes of drugs are among the most widely used in the management of asthma (4). Besides providing an overview of the increased number of single

nucleotide polymorphisms of genes identified for these three drug classes, the authors highlight the limitations of the studies performed so far and the challenges that need to be overcome, including small sample sizes and limited reproducibility. Given the complex interactions of multiple genes, we should also consider advanced statistical analyses to fully understand genetic data.

Following this review, one of the other unanswered questions is whether a pharmacogenetically driven approach would actually be of benefit in daily clinical practice? Interestingly, a recent pragmatic randomised controlled trial in the United Kingdom (11) enrolled 241 children with asthma and assessed whether personalizing their treatment based on the Arg16Gly genotype (i.e., GG genotypes receiving twice daily inhaled salmeterol and AA and AG genotypes receiving once daily oral montelukast) would result in better quality of life. Although a statistical significant difference was observed in favor of the pharmacogenetically driven group, it was deemed below a clinically relevant threshold. Indeed, it is one of the first pharmacogenetic intervention trials showing actual differences in real-world asthma outcomes, yet whether the observed difference was caused by intrinsic differences in pharmacologic effects or due to variation in route of administration (orally *vs.* inhaled) and associated adherence variation could not be determined (5). More research is needed to better understand the complex interplay, not only between genes, but also between genes and behaviour and environment. A second question regarding implementation of pharmacogenomics in daily practice is whether patients with asthma and/or their parents (in case of children) would accept the sharing of (pharmaco)genetic data. Here we have seen some variation in willingness to share this type of data, varying between around 50% and 80% (12) and this requires further exploration of perceived privacy issues.

Looking forward, we should keep looking for better understanding of the role of pharmacogenomics regarding asthma therapies and further explore its optimal, cost-effective application in daily clinical practice. Particular attention should be paid to diversity in patient populations, including people from different descents in pharmacogenetic cohorts (13). Lastly, we should not overlook the tools we already have available to further personalize asthma treatment. This personalization goes beyond genetics alone and does also include tailoring treatment based on patients' preferences, disease characteristics, behaviour, bacteria and biomarkers. Currently, our arsenal for practicing precision drug therapy is expanding and already includes different emerging biomarkers such as FeNO and blood eosinophils (14) and exploration of the microbiome (15). Another option is therapeutic drug monitoring where drug concentrations are measured in body fluids (e.g., blood, sputum, urine) and used to adjust individual drug dosing accordingly (16,17). Other developments include electronic inhalers that may help to further understand individual dosing patterns (18) and inform the subsequent provision of personalized medication adherence support (19) and follow-up treatment.

In conclusion, to maximize therapeutic effects and minimize side effects in asthma, we need to provide the right treatment in the right dose to the right patient. As such, there is an increased need for precision drug therapy, with promising developments in the field of pharmacogenomics ahead of us.

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