More options for managing severe asthma in adults

Chang, Anne; Beasley, Richard

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reduction in exacerbation frequency is not trivial, although it is lower than that anticipated in a population of patients with type 2-high allergic asthma when compared with the effects seen with biologics. In less selected severe asthma populations, such improvements in exacerbation frequency and FEV_1 have formed the basis for the registration of new, long-acting inhaled drugs for asthma.[7,8] Similarly, in chronic obstructive pulmonary disease, such reductions of 15–25% in exacerbation frequency are deemed worthwhile, and led to guideline recommendations for these drugs.

Why does the overall effect seem to be as good in non-eosinophilic populations as in those with eosinophilia (>250 cells per µL)? Prostaglandin D_2 has broader chemoattractant activity, activating human Th2 cells and macrophages to secrete neutrophil chemokines, and contributes to neutrophilic inflammation in animal models.[9,10] Not all cases of severe asthma or severe exacerbations are eosinophilic, as there are probably multiple pathways towards eosinophilia, and it is conceivable that the activity in the neutrophil pathway at least partially explains the 22% overall exacerbation rate reduction observed in the LUSTER trials. Unfortunately, sputum cell eosinophils and neutrophils were not measured at baseline or during exacerbations in the LUSTER trials. Such information could have proven useful to understanding the results observed.

Perhaps, we should not yet close the book on prostaglandin D_2 antagonism, but instead consider adding a new chapter.

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*Huib A M Kerstjens, Reinoud Gosens
h.a.m.kerstjens@umcg.nl

Department of Pulmonology (HAMK), University of Groningen and University Medical Center Groningen, and Department of Molecular Pharmacology (RG), University of Groningen, Groningen, Netherlands; and Groningen Research Institute for Asthma and COPD, Groningen, Netherlands (HAMK, RG)

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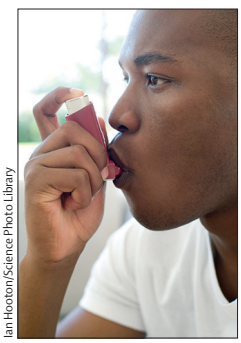
Personalised medicine for various diseases including asthma has been advocated for decades. Although the initial focus on β_2-adrenoceptor genotypes proved to be impractical and largely failed,[1] the focus on type-2 (T2) airway inflammation biomarkers has had more success, particularly with high-cost biologics (eg, interleukin[IL]-4, IL-5, and IL-13 inhibitors); however, many questions remain.[2] Two novel, well-conducted, randomised controlled trials[3,4] have assessed whether incorporation of T2 biomarkers might provide clinicians with more options when managing adults with uncontrolled or severe asthma without the use of biologics.

Liam Heaney and colleagues[4] compared use of a standardised symptom–risk-based algorithm (control) with a biomarker strategy (composite score of T2 biomarkers: fractional exhaled nitric oxide [FENO], blood eosinophils, and serum periostin), to adjust oral or inhaled corticosteroid doses. This single-blinded randomised controlled trial[4] (4:1 allocation; n=240:61) with a superiority-design (power=80% to find 20% intergroup difference for proportion of patients with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oral or inhaled corticosteroid dose reduction) did not meet its primary or any of its secondary endpoints by means of intention-to-treat analysis. However, the per-protocol analysis (n=121) found that, compared with the controls, a higher proportion in the T2-biomarker group achieved corticosteroid dose reduction at week 48 (30·7% *vs* 5·0%; adjusted odds ratio 11·48 [95% CI 1·35–97·83]; p=0·026) but that there was no intergroup difference for any secondary outcomes.[4] Reasons for the large non-adherence to the protocol (T2-biomarker group=42%, controls=33%),[4] and especially the reluctance to alter corticosteroid doses when advised to do so, are unknown. In light of data showing that patients' asthma management preferences are "influenced by the impact asthma had on their life, health beliefs, emotional consequences of asthma and perceived barriers to asthma management",[5] it is probable that the participants' preference not to alter their current treatment is at least, in part, because of their high level of asthma symptoms in terms of frequency and severity. This reluctance to reduce high corticosteroid doses under clinical guidance suggests that it might be important to measure predictive biomarkers of therapeutic response before increasing corticosteroid doses in patients with severe asthma.

The industry-sponsored CAPTAIN trial[3] of 2439 adults with inadequately controlled asthma compared the efficacy of once daily single-inhaler triple therapy (fluticasone furoate plus umeclidinium plus vilanterol [FF/UMEC/VI]; doses of 100–31·25–25 µg, 100–62·5–25 µg, 200–31·25–25 µg, and 200–62·5–25 µg) with FF/VI (doses of 100–25 µg and 200–25 µg) in improving FEV_1 (primary outcome) and annualised moderate or severe exacerbation rate (main secondary outcome). Consistent with two randomised controlled trials of the single-inhaler triple-therapy (beclomethasone/formoterol/glycopyrronium), which were of similar design,[6] Ian Pavord and colleagues[3] found significantly improved mean FEV_1 (by approximately 82–110 mL at week 24) in those who received additional UMEC, a long-acting antimuscarinic antagonist (LAMA). However, there was no significant effect of UMEC on moderate or severe exacerbation rates, and no clinically relevant effect on measures of asthma control, health status, or rescue medication use,[3] leading to uncertainty about its clinical importance. Whereas the pooled analysis showed that the addition of 62·5 µg UMEC improved FEV_1 irrespective of blood eosinophil and FENO levels, the response to increasing the dose of FF was influenced by T2-biomarker status, whereby doubling the FF dose (to 200 µg/day) resulted in an improvement in FEV_1 of 127 mL and a 65·2% exacerbation risk reduction in those with blood eosinophil counts of 300 cells per µL or more and FENO of more than 50 ppb.[3]

Considered together, these randomised controlled trials[3,4] offer a new treatment paradigm in adults with severe asthma (ie, by use of composite T2 strategies to step up and step down corticosteroids when prescribed ICS/long-acting-β_2-agonist (LABA) or ICS/LABA/LAMA. The strategy potentially lowers the need to use long-term, high-dose corticosteroids and in doing so, minimises the considerable adverse events associated with its use and the economic cost (US$29 000 per annum in high-dose users [>15 mg/day]).[7] The clinical importance of corticosteroid reduction in severe asthma is illustrated in the trial by Heaney and colleagues,[4] in which approximately 33% of patients had depression or anxiety, or hypertension, approximately 20% had osteoporosis, and approximately 10% had diabetes or cataracts.

However, the how to, cutoffs, and clinically meaningful changes of such strategies remain to be defined in adults, let alone children. The how-to steps require consideration; LAMA was a step in the control group of Heaney and colleagues' trial[4] but not in the T2-biomarker strategy group. While strategies tailoring corticosteroids based on FENO levels alone decrease the risk of asthma exacerbations (although they have no effect on symptoms),[8] the addition of blood eosinophil counts probably enhances performance, whereas periostin measurements are impractical and unlikely to play a future role. Further, more investigation is required to determine the appropriate cutoff points of FENO[9,10] and blood eosinophil counts to define eosinophilic airway inflammation and responsiveness to corticosteroid therapy. A randomised controlled trial that makes use of the T2-strategy[4] as a guide to step up therapy (as opposed to step down) also needs to be done. Such a trial has the potential to prevent patients from being unnecessarily placed on high corticosteroid doses and is arguably important because once patients are on high doses, altering their treatment regimen can be problematic.[4] Furthermore, in real-life practice,

patients' asthma management preferences (likely to affect adherence) are one of the most important factors to consider. With this further knowledge, clinicians might be able to better practice personalised medicine, using the option of biomarker-directed treatment for the benefit of patients with severe asthma.

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*Anne B Chang, Richard Beasley
anne.chang@menzies.edu.au

Centre for Healthcare Transformation, Queensland University of Technology and Department of Respiratory and Sleep Medicine, Queensland Children's Hospital, Brisbane, QLD, Australia (ABC); Child Health Division, Menzies School of Health Research, Darwin, NT, Australia (ABC); and Medical Research Institute of New Zealand, Wellington, New Zealand (RB)

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Treatment of systemic sclerosis-associated interstitial lung disease: a work in progress

In 2014, two randomised controlled trials were published showing that nintedanib and pirfenidone can slow lung function decline in patients with idiopathic pulmonary fibrosis,[1,2] prompting an era of antifibrotic therapy for this devastating disease. Overlapping features between idiopathic pulmonary fibrosis and other fibrosing interstitial lung diseases (ILDs) naturally led clinicians to wonder whether antifibrotic therapy could effectively treat a broad range of conditions that result in pulmonary fibrosis. The Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial suggested as much after nintedanib effectively slowed the decline in lung function in patients with systemic sclerosis-associated ILD (SSc-ILD).[3] Despite a relatively small treatment effect compared with that reported in studies of idiopathic pulmonary fibrosis,[1,2] nintedanib was approved for the treatment of SSc-ILD in several countries throughout Asia, North America, and Europe.

Whereas no effective therapies were previously available for idiopathic pulmonary fibrosis, the SENSCIS trial was run against the backdrop of two previous randomised controlled trials showing that immunosuppressive therapy effectively slows the progression of SSc-ILD. The Scleroderma Lung Study (SLS) I first found cyclophosphamide to effectively slow the decline in forced vital capacity (FVC) in SSc-ILD compared with placebo.[4] Then, a decade later, SLS II showed mycophenolate mofetil to be as effective and better tolerated than cyclophosphamide in this patient population.[5] Accordingly, mycophenolate mofetil has become a cornerstone of SSc-ILD management in many countries throughout North America and Europe, despite the paucity of a placebo-controlled phase 3 clinical trial supporting this approach. This reality was sure to affect the interpretation of the SENSCIS trial results, because nearly half of trial participants were treated with mycophenolate (mofetil or sodium) at the time of enrolment. Indeed, heterogeneity in FVC decline was observed in stratified analysis of SENSCIS treatment groups by mycophenolate exposure, leading SENSCIS investigators to conclude that mycophenolate might provide benefit in addition to nintedanib.[3]


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