AUDIT, RESEARCH AND GUIDELINE UPDATE

Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK)


INTRODUCTION

The Medical Research Council has recently funded an ambitious stratified medicines programme in severe asthma (the UK Refractory Asthma Stratification Programme (RASP-UK) http://www.rasp.org.uk/). In asthma, disease stratification has traditionally followed a ‘one-size fits all’ approach, based on level of asthma control and response to ‘stepwise’ increases in corticosteroids (CS) treatment. More recently, stratification has been based on inflammatory biomarkers, with sputum analysis and transcriptomic profiling demonstrating that ~30% of patients with asthma have typical eosinophilic airway inflammation driven by ‘Type 2’ cytokines (T2 cytokines: interleukin (IL)-4, IL-5, IL-13); this T2-high asthma has been shown to respond well to CS therapy. In the remainder of patients, there is limited evidence for a major role for T2 cytokines and this has been termed ‘T2-low asthma’, where patients show little or no response to CS therapy. There is also evidence of significant disease heterogeneity in severe asthma, with only 25%–50% of patients having the prototypic T2 gene signature consistent with T2-high disease. In many cases of severe asthma, it therefore seems likely that the CS dose has been escalated inappropriately to try and manage persistent symptoms that are not CS responsive. Given the clear evidence that CS responsiveness is confined to T2-high disease, the cornerstone of the RASP-UK stratification programme is around failure of response to CS therapy in severe asthma.

We propose that in patients with severe asthma, failure to respond to high-dose CS treatment occurs for three principal reasons:

2. Impaired CS responsiveness—in some patients, despite adherence with high-dose inhaled CS, there is persistent T2-high inflammation/eosinophilia and these patients frequently require systemic CS to achieve an acceptable level of disease control.
3. Non-responsiveness to CS in patients with T2-low asthma—we believe that CS will have been escalated inappropriately in this group in clinical practice.

NON-ADHERENCE TO CS TREATMENT

Non-adherence to inhaled CS and oral CS therapy is a major clinical problem, present in 30%–50% of patients with difficult-to-control asthma. Non-adherence can be intentional or non-intentional, is poorly detected by physicians and asthma nurses and is associated with poor asthma outcomes and increased healthcare costs. Moreover, enrolment of non-adherent patients into clinical trials is believed to contribute to the frequently observed improvement in placebo arms of asthma clinical trials, complicating the interpretation of trial results and reducing statistical power. Importantly, expensive new biological therapies targeting T2-high patients can potentially be used inappropriately in
patients who would often be controlled with improved adherence to inhaled CS. Patients with difficult-to-control asthma and fractional exhaled nitric oxide (FeNO) >45 ppb have a high risk of exacerbation and the key clinical question is whether failure to control their disease is because of non-adherence to inhaled CS treatment or whether they have relative CS-resistant T2-high asthma and, thus, require additional treatment with drugs that target T2 mechanisms (eg, anti-IL-5 and anti-IL-13 treatments). RASP-UK will therefore use biomarker-based assessments of inhaled CS exposure and response in biomarker-high patients (‘FeNO suppression test’—reference 4 online supplementary data) using remote monitoring technologies to define CS responsibility and thus optimise inhaled CS where appropriate.

IMPAIRED CS RESPONSIVENESS

In some patients with severe asthma, despite adherence with high-dose inhaled CS, there is persistent T2-high inflammation and airway eosinophilia and these patients frequently require systemic CS to achieve disease control. The availability of many new biological therapies targeting T2-high disease in the next 5 years will generate many interesting questions, including differential efficacy between monoclonal antibodies targeting IL-5/IL-5R (mepolizumab, bendralizumab, relizumab), IL-13 (lebrikizumab, tralokinumab) and IL-4Rα (dupilumab). Other strategies targeting the T2-axis, including anti-CrTh2 and novel anti-IgE therapies (quilizumab, Medi-4212, QGE031), will also be targeting overlapping patient groups; identifying which patients respond better to different classes of drugs may require ‘head-to-head’ studies. Many of these new therapies are expected to come to market with a companion diagnostic or predictive biomarker(s) of clinical response.

NON-RESPONSIVENESS TO CS

Inhaled CS remain the mainstay of asthma treatment, controlling disease through suppression of T2/eosinophilic inflammation in the airway. However, not all symptoms in severe asthma respond to CS, and CS responsiveness is minimal in the absence of T2 inflammation. Therefore, new algorithms for guiding CS treatment in patients with severe asthma are needed, which are not solely based on clinical symptoms and lung function and which can be delivered in the clinic. Titrating CS against sputum eosinophilia improves asthma control by reducing asthma exacerbations but this strategy is difficult to deliver in real-world clinical settings. FeNO is straightforward to measure, but when used as a single biomarker, it has been disappointing in titrating CS in patients with moderate asthma. Periostin is a secreted matricellular protein from a number of tissues including airway epithelial cells and is upregulated by T2 cytokines (IL-4 and IL-13) and is associated with airway eosinophilia in patients with severe asthma. An assay for serum periostin is being developed to help identify a periostin-high responder population for the anti-IL-13 antibody structure/function/symptom relationships. This will include transcriptomic and microbiomic profiling compared with age and gender matched patients with refractory eosinophilic asthma and stable asthma controlled with low-dose inhaled CS. These groups will be followed up for 12 months to identify their exacerbation pattern and stability of the phenotype. Previous research has focused on eosinophilia as a prognostic for exacerbation, but ‘non-eosinophilic cohorts’ also experience exacerbations and potent anti-eosinophilic therapies have not eradicated severe exacerbations in clinical trials. A better understanding of the mechanism and phenotype of exacerbations in this T2-low cohort is fundamental to targeting exacerbations in this group.

CONCLUSION

RASP-UK is a logical, clinically focused, stratification programme which will develop a clinical model to assess and phenotype patients with severe asthma (figure 1). It will identify appropriate patients for novel biological treatments that target the T2-cytokine axis (T2 biomarker high when adherent to high dose inhaled CS), will optimise CS treatment so that excessive CS exposure does not cause unnecessary morbidity and will facilitate a research focus and better understanding in a major area of ‘unmet need’, specifically non-T2/non-CS responsive severe asthma. Harmonised protocols for patient phenotyping will also allow stratified patient groups to enter proof of concept clinical trials which target the biology of their disease rather than using the usual broad inclusion criteria, where many of the patients are unlikely to respond; this will streamline and reduce size for early drug development in severe asthma. The RASP-UK Consortium vision is to effect a paradigm shift in asthma care through a logical stratified approach to severe asthma and to establish a long-term collaborative infrastructure for translational research excellence in the UK.
Figure 1 Flow diagram for the RASP-UK Clinical Stratification Programme. ATS, American Thoracic Society; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; FP, Fluticasone Propionate; RASP-UK, UK Refractory Asthma Stratification Programme.

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