

Evidence for phenotype-driven treatment in asthmatic patients

Sherif Gonem, Dhananjay Desai, Salman Siddiqui and Christopher C.E. Brightling

Department of Infection, Immunity and Inflammation,
Institute for Lung Health, University of Leicester,
Leicester, UK

Correspondence to Professor Christopher C.E.
Brightling, Institute for Lung Health, Clinical Sciences
Wing, University Hospitals of Leicester, Leicester LE3
9QP, UK
Tel: +44 116 258 3998; fax: +44 116 258 3950;
e-mail: ceb17@le.ac.uk

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Purpose of review

Asthma is a complex inflammatory disease and current therapy remains inadequate in many sufferers. There is phenotypic heterogeneity in its clinical expression as a consequence of gene–environment interactions and heterogeneity in response to therapy. This review summarizes the current state of knowledge on phenotype-driven treatment of asthma.

Recent findings

Evidence is accumulating that even standard therapies such as inhaled corticosteroids benefit some groups of asthmatic patients more than others. Macrolide antibiotics and antifungal agents are examples of drugs that have established indications outside the field of airways disease but which may benefit a subset of patients with asthma. Finally, new and expensive biological therapies for asthma are emerging that may be highly efficacious, but only for a selected group of patients.

Summary

The emergence of novel therapies, in particular highly specific treatments, bring the promise of improving healthcare in asthma but present the challenge of choosing the right therapy for the right patient. Phenotype-driven treatment of asthma is emerging as a potential reality and will pave the way for personalized healthcare.

Keywords

asthma, phenotype, stratified medicine

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Introduction

Asthma affects an estimated 300 million people worldwide and the burden is likely to rise substantially in the next few decades [1]. Approximately 5–10% of these asthmatics have severe asthma, whereby sufferers have persistent symptoms and exacerbations in spite of high-dose standard therapy [1,2]. Patients with inadequately controlled severe persistent asthma are at a particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life. Although this group represents a relatively small proportion of the asthma population, they consume two-thirds of the healthcare costs attributed to asthma. This disproportionate use of healthcare resources means there is a considerable unmet need to the individual patients, and to the healthcare providers.

Asthma is a complex disease characterized by typical symptoms of breathlessness, wheeze and cough together with episodes of marked worsening of symptoms known as exacerbations. These symptoms occur on a background of disordered airway physiology characterized by variable airflow limitation, airway hyperresponsiveness (AHR) and in more severe disease persistent airflow

obstruction. In spite of our increasing understanding of the immunopathogenesis of asthma, there has been a paucity of novel therapies for asthma over the last 20 years. Indeed, the mainstay of therapy for asthma remains inhaled corticosteroids (ICSs) and long-acting bronchodilators [2]. These therapies reduce, but do not eliminate, the impact of day-to-day symptoms and the frequency of exacerbations. Importantly, decline in lung function and development of airflow obstruction remain refractory to current therapy.

There is an increasing recognition that asthma encompasses several underlying pathological processes that develop as a consequence of a variety of gene–environment interactions that give rise to a clinical phenotype. Novel developments in the measurement of airway inflammation, lung physiology and imaging, coupled with emerging data utilizing ‘omic’ technology and biostatistical modelling [3,4] mean that we are now positioned to inform our understanding of the complexity of airways disease. The concept that ‘one size does not fit all’ is also exemplified by the heterogeneity in treatment response. This variability of response to therapies will be further magnified in the context of highly specific treatments. This heterogeneity is further compounded by the

increasing cost of these novel therapies, which are likely to be restricted to severe disease in which the potential health economic benefit is greatest. There is therefore a pressing need to be able to unravel the complexity of asthma in order to understand structure–function relationships, disease cause and progression.

This review will summarize current knowledge on the relationship between phenotypic variants of asthma and response to current therapy and novel treatments in early phase development.

Corticosteroids

ICS have been the mainstay of anti-inflammatory treatment for asthma since the 1970s, and a number of placebo-controlled trials have convincingly demonstrated a reduction in exacerbation frequency across the spectrum of severity, as recently reviewed [5]. However, there remains the possibility that this benefit may be largely confined to a subgroup of asthmatic patients, and indeed recent studies have shown that the major benefit occurs in patients with eosinophilic airway inflammation [6], whereas the subgroup with predominantly neutrophilic airway inflammation respond poorly [7]. Thus, it appears logical to titrate corticosteroid therapy using a marker of eosinophilic airway inflammation as a guide.

Three randomized controlled trials [8*,9,10] have compared standard guideline-based asthma management with sputum-based management in which ICS dose was titrated according to the sputum eosinophil count. A meta-analysis [11] of these studies concluded that sputum-based strategies were effective in reducing exacerbations in adults with asthma without a net increase in mean ICS dose. Furthermore, Haldar *et al.* [3] showed that the sputum-based strategy was of particular benefit in certain subgroups of asthmatic patients. Most notably, a ‘discordant inflammation’ group was identified in whom eosinophilic inflammation occurred in the absence of severe symptoms. Uptitration of ICS in order to control sputum eosinophilia resulted in a markedly reduced exacerbation rate. Conversely, the ‘discordant symptom’ group were severely symptomatic despite the absence of eosinophilic airway inflammation. ICS could be reduced in this group without an increase in exacerbation rate.

Management strategies based on exhaled nitric oxide (FeNO), a surrogate marker of eosinophilic airway inflammation, have been less successful. A recent meta-analysis [12*] of six randomized controlled trials (two in adults and four in children/adolescents) concluded that a FeNO-based strategy did not result in a significantly different exacerbation rate compared with standard management.

Key points

- Asthma is a complex condition with heterogeneity of response to both current and emerging treatments.
- Inhaled corticosteroids appear to particularly target eosinophilic airway inflammation, and dose titration according to the sputum eosinophil count is an effective clinical strategy.
- Biological therapies such as omalizumab may be highly efficacious but their benefit is often restricted to particular subgroups of asthmatic patients.
- Macrolide antibiotics, antifungal agents and long-acting anticholinergic agents are established therapies for conditions other than asthma but may have a role in certain phenotypes of asthma.
- Phenotype-driven treatment for asthma is of proven efficacy and its importance will continue to grow with the current emergence of targeted biological therapies.

Biological therapies

Accurate disease phenotyping has assumed greater importance with the advent of expensive biological therapies that target very specific components of the immune response. These treatments are likely to be effective only in a subset of patients with asthma.

Omalizumab is a humanized anti-IgE monoclonal antibody. A systematic review [13] of eight placebo-controlled trials of omalizumab in moderate or severe allergic asthma showed that omalizumab reduced exacerbation frequency and facilitated corticosteroid withdrawal. The use of omalizumab is currently restricted to patients with severe uncontrolled allergic asthma with raised IgE levels and a positive skin prick test to a perennial allergen [14]. Although a recent case report [15] suggested that benefit may not be restricted to patients with positive skin prick tests, this has not been confirmed in larger-scale studies.

Interleukin-5 (IL-5) is known to be a major player in eosinophilic airway inflammation through its actions of promoting eosinophil production, maturation, activation and survival. An initial randomized controlled trial [16] of mepolizumab, a monoclonal anti-IL-5 antibody, in 362 unselected patients with persistent asthma found no statistically significant clinical benefit although there was a trend towards a reduction in exacerbation rates. However, two later trials [17*,18] found that in patients with refractory eosinophilic asthma despite high-dose inhaled or oral corticosteroids, mepolizumab significantly reduced rates of exacerbations, improved Asthma Quality of Life Questionnaire (AQLQ) scores [17*] and allowed oral prednisolone doses to be successfully reduced [18].

Airway wall thickening assessed by computed tomography improved following mepolizumab therapy [17[•]] suggesting that modulating eosinophilic inflammation may impact upon airway remodelling and importantly that imaging may be an important tool to stratify patients and to assess clinical outcomes.

Pitrakinra, an interleukin-4 variant, reduced the allergen-induced late-phase response and the need for rescue medication in asthmatic patients [19]. Recent evidence in a phase 2 study suggests that efficacy is greatest in those with eosinophilic inflammation. AMG-317 is a fully human monoclonal antibody to IL-4R α that blocks both IL-4 and IL-13 pathways and was administered to mainly healthy adults and a smaller number of asthmatic adults, and earlier studies have established bioavailability and safety. Recently, a phase 2, randomized, double-blind, placebo-controlled study [20[•]] of AMG-317 in 147 moderate-to-severe asthmatics showed an improvement in the number and time to exacerbation in the treatment arm. The study failed to meet its primary endpoint of improvement in asthma control (ACQ). The drug was, however, well tolerated and there was improvement in those patients with poor control as baseline. Whether IL-4 and IL-13 strategies need to target eosinophilic, atopic or poorly controlled patients is uncertain, but it remains likely that there are subpopulations who may respond well to these therapies and there remains a need to identify biomarkers of response.

Tumour necrosis factor-alpha (TNF- α) is a proinflammatory cytokine that has been implicated in the pathogenesis of asthma. In particular, there is evidence that mast cell-derived TNF- α may modify airway smooth muscle contractile function, resulting in AHR [21]. Currently available anti-TNF- α therapies include infliximab, etanercept, adalimumab and golimumab, and a number of clinical trials have been carried out in patients with asthma. The largest and most recent of these was a randomized controlled study [22[•]] of golimumab in 309 patients with severe persistent asthma. This showed no difference between placebo and treatment groups with respect to either of the co-primary endpoints, namely the FEV₁ and the number of severe exacerbations. Furthermore, the study was discontinued at 24 weeks because of excess cases of malignancy and serious infections in the treatment group, including one case of tuberculosis reactivation and one death. Thus, current evidence suggests that the risk/benefit ratio for the use of anti-TNF- α therapy in asthma is unfavourable. However, it is possible that the benefit of treatment may be greater in certain subgroups of asthmatic patients. Subgroup analysis of the golimumab study showed greater efficacy in patients with late-onset asthma and those with greater than 12% bronchodilator reversibility on study entry.

Furthermore, a previous study [23[•]] of etanercept in patients with refractory asthma showed that efficacy in reducing AHR was greatest in patients with high expression of membrane-bound TNF- α by peripheral blood monocytes.

Long-acting beta-2 adrenergic agonists

The safety of long-acting β_2 adrenergic agonists (LABAs) in patients with asthma has been a subject of recent debate since the publication of the Salmeterol Multicentre Asthma Research Trial (SMART) in 2006 [24]. In this study, the addition of salmeterol to usual asthma therapy was associated with a small but significant increase in asthma-related deaths compared with placebo. A recent meta-analysis [25] of 215 clinical trials comparing salmeterol with a non-LABA comparator drug concluded that salmeterol monotherapy was associated with an excess mortality, and that this risk was reduced in patients also taking an ICS. However, the authors found no evidence of an increase in mortality in patients taking a combination salmeterol/fluticasone inhaler.

There is some evidence that polymorphisms in the β_2 -adrenoceptor gene may affect the clinical response to LABAs. The most common polymorphisms within the coding region of the gene are at codons 16 (Arg16Gly) and 27 (Gln27Glu) [26]. Patients who are Arg/Arg homozygous at codon 16 may be at increased risk of exacerbations, particularly when treated with LABAs [27,28]. In contrast, a recent randomized controlled trial [29] found no evidence that variation in β_2 -adrenoceptor genotype affected the response to salmeterol, as measured by morning peak flow. However, this latter study only lasted 16 weeks and did not assess the rate of exacerbations.

Long-acting anticholinergic agents

There is growing evidence that long-acting anticholinergic agents (LAMAs) may have a role in achieving control in cases of refractory asthma. Most notably, a recent study [30[•]] of 210 asthmatic patients taking ICS showed that tiotropium bromide, a LAMA currently licensed for use in chronic obstructive pulmonary disease, was superior to a doubling of ICS dose and noninferior to the addition of salmeterol with respect to morning peak flow measurements. A small-scale study [31] of 17 patients with severe asthma found a positive correlation between the proportion of neutrophils in induced sputum and the increase in FEV₁ following 4 weeks of treatment with tiotropium bromide. A further study [32] of 138 patients with severe asthma and reduced pulmonary function found that the addition of tiotropium bromide to conventional asthma medications resulted in a greater than

15% increase in FEV₁ in 33% of patients. In this study, the Arg16Gly polymorphism in the β_2 -adrenoceptor gene was found to predict response to therapy.

Antifungal agents

Allergic bronchopulmonary aspergillosis (ABPA) is a relatively uncommon condition in which long-term colonization of the airways with, and sensitization to, the fungus *Aspergillus fumigatus* results in airway inflammation and bronchiectasis, usually in association with asthma. Previous studies [33–35] have shown that treatment with itraconazole is beneficial in this group of patients. More recently, it has been hypothesized that ABPA may form just one end of a spectrum of airway disease associated with fungal sensitization, and that severe asthma with fungal sensitization (SAFS) may be a distinct asthma phenotype with therapeutic implications [36]. *A. fumigatus* IgE sensitization and airway colonization are associated with reduced FEV₁ in patients with asthma [37]. A randomized controlled trial [38^{*}] of itraconazole in 58 patients with SAFS but not ABPA showed a significant improvement in the AQLQ scores in the treatment arm, as well as in the rhinitis scores and morning peak flow readings.

Macrolide antibiotics

Macrolides are known to possess anti-inflammatory properties over and above their antimicrobial activity [39], and they are of proven benefit in diffuse panbronchiolitis [40]. Clinical trials of macrolides in asthma have yielded conflicting results with no definite overall benefit [41]. However, there is evidence that macrolides may specifically target neutrophilic airway inflammation. A recent study [42] of 45 patients with refractory asthma found that 8 weeks of treatment with clarithromycin (500 mg twice daily) resulted in significantly reduced levels of sputum IL-8, reduced airway neutrophil numbers and improved quality-of-life scores compared with placebo. These differences were more marked in the subgroup of patients with noneosinophilic asthma, suggesting that macrolides may be employed as a targeted therapy in this group.

Antileukotriene drugs

Antileukotriene drugs have an adjunctive role in the management of chronic asthma and are used as add-on therapies in patients who are not controlled on ICS (Step 3 of the British Thoracic Society guidelines) [2]. The most commonly used drug is montelukast, a cys-LT₁ receptor antagonist. There is evidence that antileukotriene drugs may be particularly effective in particular subgroups of asthmatic patients. For instance, it is known that leukotrienes have a prominent role in exercise-

induced bronchoconstriction and that antileukotriene drugs can ameliorate this [43]. Furthermore, there is some evidence that antileukotriene drugs may be of particular value in asthmatic patients who are exposed to tobacco smoke [44,45]. Leukotrienes are thought to play a prominent role in the pathogenesis of aspirin-intolerant asthma (AIA) and so antileukotriene drugs may be particularly indicated in this group of patients. Although they are certainly effective as add-on therapies in AIA patients already taking ICS, it is not known whether their efficacy is any greater in AIA than in the general asthmatic population [46].

Conclusion

The paradigm of phenotype-driven strategies for asthma now has proven efficacy and has been adopted in current guidelines for some current therapies. To date, this has largely been confined to single biomarkers that reflect only one domain of the disease such as inflammation or physiology. Novel developments in the characterization of the disease from the genome to clinical expression together with the assessments of environmental exposure to pathogens and allergens over time presents us with new opportunities to apply a systems biology approach to systems medicine. The potential predictive capability of these strategies over the forthcoming decade will turn stratified and personalized healthcare from an aspiration to a reality.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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