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REVIEW

Targeted therapeutics for severe refractory asthma: monoclonal antibodies

Christopher L. Grainge^{a,b}, Steven Maltby^a, Peter G. Gibson^{a,b}, Peter A. B. Wark^{a,b} and Vanessa M. McDonald^{a,b}

^aCentre of Excellence in Severe Asthma, Hunter Medical Research Institute and Priority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, Australia; ^bDepartment of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, Australia

ABSTRACT

Severe asthma is a complex multifactorial disease that requires specialist multidisciplinary input for optimal clinical outcomes. Following multidimensional assessment for optimisation of current therapy, self-management skills and comorbidities, all patients should be accurately phenotyped. Only after this assessment has been completed should new monoclonal antibody therapies be considered. In this review, we summarise the new antibody approaches targeting identified pathological pathways in severe refractory asthma.

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Introduction

Asthma is a common chronic inflammatory disorder of the airways affecting approximately 300 million people worldwide. Over the last three decades, there have been significant advances in the management of and outcomes for people with mild to moderate asthma. While asthma prevalence throughout the world remains high, the majority of patients with asthma can achieve effective disease control with standard guideline-based treatments [1].

However, this is not the case for a relatively small proportion between 5% and 20% of patients with asthma who have severe disease [2]. In this population, a major unmet need remains in terms of both health and economic burden. Patients with severe asthma suffer a high symptom burden and health status impairment [3], resulting in two of three severe asthma patients being unable to hold full-time employment because of their illness [4]. Severe asthma also accounts for the majority of health-care expenditure for asthma, with per patient costs 10 times that of mild disease [5], equating to approximately 50% of all asthma health-care costs.

To address the ongoing problems related to severe asthma, the European Respiratory Society and American Thoracic Society taskforce on severe asthma was formed, with goals of reviewing the definition and providing clinicians guidelines for the assessment and management of severe asthma [1]. Their definition of severe asthma is as follows:

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose inhaled corticosteroid (ICS) and long acting beta agonist (LABA) or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for $\geq 50\%$ of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy [1].

Severe asthma is characterized by disease heterogeneity as well as multiple exacerbating factors and comorbidities [6]. To identify and treat these issues, the taskforce recommended that patients undergo a systematic assessment to confirm diagnosis, assess and optimize disease management skills, triggers, and comorbidities, and that patients be characterized in terms of disease phenotypes in order to target therapies [1].

In this review, we present the currently available monoclonal antibody therapies as well as those in development for severe asthma. These are discussed along with the importance of and rationale for careful characterization of severe asthma patients to confirm and manage the disease and support the use of these targeted therapies.

Asthma phenotyping

Severe asthma is recognized as a heterogeneous disease with great variability in clinical, pathological, immunological, molecular, and physiological domains. Unbiased statistical cluster analysis has helped identify clinical phenotypes in severe asthma [7–10]. Chung [10] summarized these findings and presents the following three primary clinical severe asthma phenotypes:

- (1) Early onset severe asthma with an allergic background.
- (2) Late-onset asthma with persistence of eosinophilic inflammation, despite treatment with adequate corticosteroid therapy.
- (3) Late-onset asthma with uncontrolled symptoms, particularly in women and associated with obesity, that is less eosinophilic.

The heterogeneous nature of the disease is well recognized [7, 9, 11] and likely reflects multifactorial precipitating and driving

Table 1. Monoclonal antibodies for severe refractory asthma.

Target	Biomarkers/indications	Antibodies	Treatment subgroup/study population	Effect of treatment in clinical trials
IgE	High serum IgE (but <700 IU/mL) Atopy	Omalizumab	Currently in use for treatment of refractory allergic asthma	Improved asthma control Reduced exacerbations Reduced ICS use Improved quality of life Variable results for lung function
IL-5 and IL-5Ra	Sputum eosinophilia >3% or blood eosinophilia >0.3 × 10 ⁹ /L Frequent exacerbations	Ligelizumab Mepolizumab	Single phase I trial to date Currently in use for treatment of refractory eosinophilic asthma	Reduced circulating IgE Reduced sputum/blood eosinophils Improved asthma control Reduced exacerbations Reduced ICS use Variable results for lung function
		Reslizumab	In trials: poorly controlled eosinophilic asthmatics	Reduced exacerbations Improved lung function Improved quality of life Reduced exacerbations
		Benralizumab	Phase IIb trial: patients with baseline eosinophils >0.3 × 10 ⁹ /L	
IL-13 and IL-13R	High periostin High FeNO Increased blood eosinophil counts	Lebrikizumab	In trials: severe treatment-refractory asthma Baseline FEV ₁ reversibility >12%	Improved lung function Reduced exacerbations
		Tralokinumab	In trials: moderate-to-severe uncontrolled asthma, potential added benefit: Patients not on long-term OCS	Minor improvement in lung function Reduced beta-agonist use
IL-4Ra	High blood or sputum eosinophils	GSK679586 Dupilumab	Single trial: treatment-refractory asthma Single trial: moderate-to-severe asthma	No benefit Reduced exacerbations Improved asthma control Improved lung function
IL-17R		Brodalumab	Single study: poorly controlled moderate-to-severe asthma	Improved asthma control (‘high reversibility’ subgroup only)
IL-2		Daclizumab	Single trial: moderate-to-severe persistent asthma	Improved symptoms Improve lung function Reduced exacerbations
IL-1 TNFα		Canakinumab Infliximab Golimumab	Single safety study Single trial: moderate asthma In trials: severe asthma, add-on to anti-inflammatory	Well-tolerated Reduced exacerbations No benefit (trial discontinued)
		Etanercept	In trials: refractory asthma and moderate-to-severe asthma	Variable results
C5a		Eculizumab	Single phase II trial: mild asthmatics	Reduced late phase response (only when patients received treatment after placebo)

IgE: immunoglobulin E; ICS: inhaled corticosteroid; IL: interleukin; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in 1 second; OCS: oral corticosteroid; TNFα: tumor necrosis factor alpha; C5a: complement 5a.

factors which require a different approach to management compared to ‘usual’ asthma. Severe asthma can usefully be considered a separate disease entity to mild or moderate asthma, rather than on a continuum with these disease phenotypes. As such, detailed phenotyping of patients presenting with severe asthma enables selection of specific treatments for specific individuals. Once patients are phenotyped clinically (e.g. frequent exacerbator), pathologically (e.g. predominant eosinophilic airway inflammation), and often on the basis of biomarkers (e.g. serum immunoglobulin E [IgE]; [Table 1](#)), specific targeted therapies, including monoclonal antibodies if needed, can be selected as appropriate [12,13].

Four inflammatory airway phenotypes have been described in severe asthma: (1) eosinophilic, (2) neutrophilic, (3) mixed eosinophilic and neutrophilic, and (4) paucigranulocytic (an absence of any granulocytes) [14] ([Figure 1](#)). The eosinophilic phenotype is frequently defined as sputum eosinophils ≥3% of total sputum cells, and has been reported in approximately 55% of severe asthma patients, though estimates vary in different populations [15]. Using a cut off of >1.9%, the European U-BIOPRED adult severe asthma cohort reported eosinophilic bronchitis in approximately 60% of participants [3]. Simpson and colleagues found that 41% of patients with

asthma exhibited an eosinophilic pattern of inflammation, 20% were neutrophilic, 8% had a mixed eosinophilic/neutrophilic pattern, and the remaining 31% were paucigranulocytic [14]. The coexistence of eosinophilic and neutrophilic inflammation in asthma is associated with more severe disease [1].

Without consideration of the complexities of the multiple inflammatory processes which exist in asthma and can coexist in any single patient [16], it is likely that treatment nonresponsiveness, unnecessary escalation of inappropriate treatments, and the potential for toxic side effects will prevail. Detailed asthma phenotyping should lead to optimization of the right therapy to the right patient at the right time [13,17].

Targeted therapy and approaches to the management of refractory asthma

Due to the complexity of severe asthma, management is confounded by disease heterogeneity, symptoms that may be erroneously attributed, and comorbidities that both mimic asthma and lead to increased disease severity [18]. An essential step in the management of severe asthma is first ensuring the diagnosis of asthma is correct and subsequently that it is indeed severe asthma [1]. In studies evaluating patients

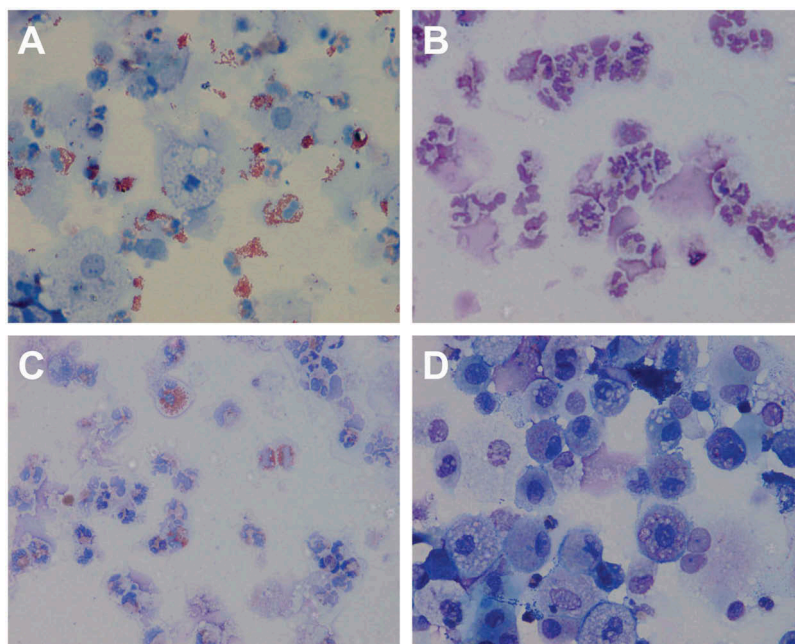


Figure 1. Inflammatory Airway Phenotypes in Severe Asthma. Assessment of induced sputum samples from patients with severe asthma can demonstrate A) eosinophilic, B) neutrophilic, C) mixed granulocytic or D) paucigranulocytic patterns of airways inflammation.

referred to a severe asthma center, 22–50% of patients who had previously been classified as severe asthma were reclassified as difficult-to-treat asthma following multidimensional and systematic assessment [18–21]. These data highlight the importance of systematic assessment in severe asthma populations. A practical guide for the assessment and characterization of severe asthma can be found at <http://www.severeasthma.org.au/tools-resources/toolkits> and [22].

Once diagnosis is confirmed, treatment must be optimized to ensure that patients are prescribed and also adherent to high-dose inhaled corticosteroids (ICSs) and long-acting beta₂-agonists. In addition, other disease management skills, including disease knowledge, inhaler technique, self-monitoring, and exacerbation management, must be optimized. Triggers and comorbidities must be identified and appropriately managed. This process requires the input of a multidisciplinary team, including specialist asthma physicians, specialist asthma nurses, physiotherapists, speech pathologists, dieticians, and ideally clinical psychologists. It is not until all correctable issues have been addressed that the addition of expensive or potentially toxic add-on therapies should be considered. These issues are of high importance; in severe asthma populations, non-adherence may be as high as 56% and inadequate inhaler technique is common [1]. Furthermore, as few as 32% of patients referred to a severe asthma clinic recalled ever having received a written asthma management plan [18].

When patients with severe asthma undergo systematic assessment within a dedicated severe asthma service, significant reductions in primary care or emergency department visits (66.4% vs. 87.8%) and hospital admissions (38% vs. 48%) can be achieved. In addition, patients use less oral corticosteroids (OCSs) and achieve improved health status [23]. We would advocate that no patients be considered for monoclonal antibody therapy in the absence of such an assessment. We would also advocate that multidimensional

assessment of clinical asthma characteristics, airway pathobiology, comorbidities, risk factors, and self-management skills as well as an individualized approach to correcting any management issues identified be standard for all patients with severe asthma (Figure 2). Only once this is achieved should monoclonal antibody therapies be trialed.

Monoclonal antibodies

Antibodies are large glycoproteins (~150 kDa) consisting of both variable and constant regions. The variable region for each antibody binds to a single target (or antigen) and provides antigen specificity. The constant region determines the antibody class. Monoclonal antibodies are produced by a single immune cell, or a genetically identical clone, and will only recognize one specific target. This affinity is used therapeutically to block target molecule function, modulate signaling pathways, or induce apoptosis of specific cells.

Constant regions vary by species, meaning that antibodies generated in different species are recognized as foreign by the human immune system. This was an issue for early monoclonal antibodies, which were manufactured in animals. Injection of these unmodified monoclonal antibodies led to host antibody formation and multiple inflammatory and immune-mediated side effects (reviewed in [25]). These problems have largely been overcome by ‘humanizing’ monoclonal antibodies, a process of replacing all but the antigen-binding site with a human amino acid sequence, or production of antibodies with fully human sequences.

Monoclonal antibody naming is governed by the World Health Organization’s International Non-proprietary Names Committee [26] and provides some information about species of origin and intended activity. The first part of the word provides a unique identifier (e.g. ‘mepo’ in mepolizumab). The next part indicates the body system being targeted (e.g. immune system is



Figure 2. Core Components For Assessment And Management In Severe Asthma. Multidimensional assessment of severe refractory asthma patients requires an integrated approach including guideline-based management, risk factor modification, self-management education and pharmacotherapy (Reproduced with permission [24]).

designated by – li(m), hence omalizumab or interleukin targeting – k(i) as lebrikizumab). The next portion reflects the degree of humanization of the antibody (partially humanized = ‘zu’ [e.g. reslizumab], fully humanized = ‘xi’ [e.g. infliximab], and fully human sequence = ‘nu’ [e.g. canakinumab]). The terminator ‘mab’ indicates the molecule is a monoclonal antibody [27].

Antibodies currently in use or under development for the treatment of severe refractory asthma are detailed in Table 1.

The IgE pathway

The IgE pathway is central to allergic asthma. B cells produce antigen-specific IgE, which then binds to specific IgE receptors. These receptors for IgE are divided into two types: low affinity and high affinity.

The high-affinity IgE receptor ($F_{c\epsilon}RI$) is present on mast cells and basophils [28]. Cross-linking of high-affinity receptors by IgE leads to release of a wide variety of proinflammatory mediators including cysteinyl leukotrienes, proinflammatory cytokines including interleukin (IL) 3, 4, and 5, and granulocyte monocyte colony-stimulating factor. These molecules promote the recruitment of eosinophils and other inflammatory cells. IgE/ $F_{c\epsilon}RI$ binding also promotes mast cell proliferation and survival (reviewed in [29]).

The low-affinity receptor ($F_{c\epsilon}RII:CD23$) is expressed on a multitude of cells, including T cells, macrophages, B cells, eosinophils, and platelets. IgE binding to low-affinity receptors mediates and regulates IgE production, the differentiation of B cells, as well as induces antigen presentation. $F_{c\epsilon}RII$ is

upregulated by IL-4 and IgE, and, though its exact role in asthma is currently unknown, genetic polymorphisms are associated with increased risk of asthma exacerbations, high serum IgE, and atopy [30]. Inhibition of IgE/ $F_{c\epsilon}RII$ binding may be more important than previously thought, as mouse models of asthma have suggested that the IgE/ $F_{c\epsilon}RII$ binding allows IgE–allergen complexes to translocate across the epithelial barrier in the lung [31,32], which implies that antibodies preventing this binding may be useful in asthma [33,34].

Anti-IgE-targeted therapy aims to reduce signaling via the IgE pathway to decrease the clinical asthma syndrome. Omalizumab targets IgE and is the first monoclonal antibody to be licensed for asthma treatment. Other anti-IgE monoclonal antibodies under development include ligelizumab.

Omalizumab

Omalizumab (Xolair; Genentech, South San Francisco, USA/Novartis, Basel, Switzerland) is a humanized monoclonal IgG1 antibody that was approved by the United States Food and Drug Administration (US FDA) in 2003 and the European Union Medicines Agency in 2005 as an add-on therapy for patients with severe, persistent asthma. Patients should have ongoing symptoms despite optimized inhaled therapy, as well as reduced lung function, high serum IgE, and a positive skin prick test result to an aeroallergen to qualify for treatment. Omalizumab is administered by subcutaneous injection every 2 or 4 weeks, depending on the dose, which is calculated

using a nomogram of body weight and serum IgE. The recommended upper and lower limits of IgE vary by country; however, few data exist in patients with IgE < 30 or >700 IU/mL. An Australian real-life data registry study compared responses to omalizumab in patients who were both within and above the recommended dosing range. Patients with high IgE, normally above the recommended upper limit for IgE, received a ceiling dose of 750 mg/month of omalizumab. In both groups, improved asthma control and improved health status were observed [22].

Omalizumab binds IgE at its CE3 domain, the same domain bound by the F_{CE}RI receptor. By binding at this site, omalizumab cannot cross-link IgE, which is fundamental to the drug's safety; cross-linking could lead to mast cell degranulation and possible anaphylaxis [35]. By binding to IgE, omalizumab reduces levels of free IgE, and through a feedback pathway, reduces F_{CE}RI expression on mast cells and basophils [36–38]. This in turn reduces cellular responses to allergen, reducing inflammatory cell influx into the lung. In addition, omalizumab has effects on dendritic cells, downregulating F_{CE}RI and reducing their ability to skew naïve T cells to a Th2 phenotype [39], and B cells, inducing anergy and reducing IgE production [40].

The effectiveness and safety of treatment with omalizumab in refractory allergic asthma is now well established, with evidence from a large number of clinical trials [38,41–54] and real-life effectiveness studies [55,56].

A recent Cochrane review of omalizumab clinical trial data reported significant benefits across multiple disease outcomes [57]. After treatment, exacerbation frequency was reduced, with an odds ratio (OR) of 0.55 (95% CI: 0.46–0.65) and an absolute reduction in risk of an exacerbation falling from 26% to 16% [57]. Hospitalizations were also reduced (OR: 0.16; 95% CI: 0.06–0.42), with the absolute risk falling from 3% to 0.5% [57]. In addition, more patients were able to cease ICS treatment [57], though whether this should be an aim of any asthma therapy is debatable. However, no significant reduction in OCS use was observed [57]. The meta-analysis from the Cochrane review did demonstrate improved quality of life and symptoms with omalizumab therapy, although no consistent improvement in lung function was seen [57].

In addition to clinical trial data, there is a growing body of real-life data on omalizumab effectiveness. These data include over 4000 patients and reinforce the results of clinical trials, with omalizumab associated with improvements in both the objective and the subjective burden of asthma [56]. Again, improvements in exacerbation frequency, hospitalizations, and symptoms are demonstrated, though unlike the clinical trial data, there were also significant improvements in lung function [56,58]. Patients who demonstrated improvement following an initial 16-week therapeutic trial of omalizumab were likely to receive long-term benefit, and although the optimal duration of therapy is not known, improvements in asthma control extend up to 5 years [59]. There are conflicting reports regarding asthma control following cessation of omalizumab therapy [60,61], with full results of the xolair persistence of response after long-term therapy (XPORT) study examining this issue awaited [62]. In addition to its clinical effectiveness, the safety of omalizumab is now well

established, with an anaphylaxis incidence of 0.14% [63], a rate similar to penicillin and aspirin [64].

Omalizumab may also be effective in patients with non-allergic/nonatopic asthma. Several clinical studies, albeit small and uncontrolled in design, have demonstrated efficacy of omalizumab in patients who have not been identified as atopic [45,65–67]. The mechanisms of this are unclear and may result from treatment responses in atopic patients that test negative on standard clinical atopy diagnostics, or may indicate that omalizumab is acting via a non-IgE-mediated pathway. IgE, unlike IgG antibodies, can be produced in local tissues, rather than in germinal centers [69] and in this situation, it may be that omalizumab therapy targets this locally produced IgE despite negative skin prick testing. Another proposed mechanism is that omalizumab reduces expression of F_{CE}RI on dendritic cells, increasing the ability of the innate immune system to clear viral infections [38,69,70]. Whatever the mechanism, the issue remains of how to identify this group of patients; the current approach is to use a clinical trial of therapy for 16–24 weeks, in order to identify responders.

Given the significant clinical improvements associated with omalizumab and the decade of clinical experience using this treatment in practice, the cost-effectiveness of this expensive therapy is worthy of mention. A 2015 review [71] of omalizumab cost-effectiveness presents equivocal data. Economic evaluations conducted in Dutch and Spanish health-care settings found omalizumab to be cost-effective. However, data from economic evaluations using current willingness to pay thresholds in the UK and Japan did not demonstrate cost-effectiveness of omalizumab as an add-on to standard therapy. In subgroups of patients with more severe disease, cost-effectiveness seems to be greater.

Ligelizumab

Ligelizumab (QGE031; Novartis) is a humanized IgG1 anti-IgE antibody with 50 times greater affinity for IgE than omalizumab while still binding at the CE3 binding domain. During omalizumab therapy, greater reductions in circulating IgE are associated with greater improvements in asthma control [72], and so a more potent antibody may result in a better treatment response. In small phase I clinical trials, compared to omalizumab, ligelizumab produces a more rapid and greater reduction of circulating IgE, even in patients with initially high levels of IgE [73]. This may be particularly relevant for patients with high IgE levels (>700 IU/mL), where dosing is not recommended in some countries. A clinical trial is currently listed by Novartis for the assessment of ligelizumab in patients with asthma (NCT01716754); however, no results from this study have been reported to date.

Interleukins in asthma: an overview

Interleukins are cytokines that are produced by immune cells and modulate many immune responses. A number of interleukins have key roles in severe asthma, and targeting interleukin pathways has been proposed as a novel approach for asthma treatment (reviewed in [74]). In particular, type 2 or

Th2 cytokines (IL-4, 5, and 13) have been extensively associated with allergic and eosinophilic disease. Anti-IL5 therapy (mepolizumab) recently received marketing authorization in Europe, for the treatment of severe eosinophilic asthma, and antibodies targeting IL-13 and IL-4 are under investigation. In non-eosinophilic disease phenotypes, other interleukins play more prominent roles. IL-17 has been associated with neutrophilic disease [75,76], and anti-IL-17 therapy is under trial. IL-2 regulates T- and B-cell proliferation and the development of antibody responses and may play a role in initiation and prolongation of inflammation in asthma and is also being targeted for treatment [77]. Finally, IL-1 β levels are increased in patients with asthma [78–80], and anti-IL-1 therapies are undergoing trials.

The IL-5 pathway

Eosinophilic asthma is a common severe asthma inflammatory phenotype and airway eosinophilia has long been used as a marker of disease severity, with disease control improving when eosinophils are specifically targeted [81,82]. In addition, there is growing evidence that blood eosinophils are an excellent surrogate marker for sputum eosinophils [83–87], and one study suggests that severe asthma control may be improved with the use of an OCS dosing algorithm based on blood eosinophil levels [87]. Airway remodeling in asthma is also related to eosinophil numbers, with smooth muscle hyperplasia associated with an increased density of eosinophils [89].

IL-5 is a 115 amino acid protein homodimer that potently induces eosinophil differentiation and is a major regulatory factor for eosinophil accumulation in tissues. IL-5 is produced by both Th2 cells and type 2 innate lymphoid cells and modulates eosinophil function by mobilizing eosinophils and eosinophil precursors into the circulation and increasing both eosinophil survival and cytotoxicity. The IL-5 pathway appears particularly important in a population of eosinophilic asthmatics termed 'Th2 high' [90,91].

In mice, IL-5 leads to increased airway hyperresponsiveness, as well as airway inflammation [92], while inhibition abolishes airway hyperreactivity and eosinophilia [93]. In humans, there is a negative correlation between IL-5 protein levels in the bronchial mucosa or bronchoalveolar lavage (BAL) and asthma control [94]. Further, IL-5 inhalation increases airway eosinophils in asthmatic patients [95]. As a result of these findings, anti-IL-5 monoclonal antibodies were developed as a potential targeted asthma therapy.

Mepolizumab

Mepolizumab (Nucala®; GlaxoSmithKline, Brentford, London) is a humanized monoclonal IgG1 antibody against IL-5. Mepolizumab was initially studied in the context of experimental allergen challenge. In this setting, mepolizumab decreased blood eosinophil counts for 16 weeks and reduced blood and sputum eosinophils following allergen challenge. However, mepolizumab failed to improve the severity of either airway hyperresponsiveness or late-phase allergic responses [96]. This was followed by a clinical study of patients with poorly controlled asthma despite high-dose ICSs, assessing

end points of peak expiratory flow (PEF) rate, symptom scores, lung function, quality of life, and exacerbation frequency [97]. Mepolizumab treatment effectively decreased blood and sputum eosinophils and also reduced airway remodeling, but did not provide significant improvements in symptoms, quality of life, or exacerbation frequency [98].

Though these initial studies failed to show clinically or statistically significant benefits, they had recruited participants based on disease severity, rather than airway inflammatory phenotype. Follow-up studies assessed patients with poorly controlled asthma and sputum eosinophilia of $\geq 3\%$, despite treatment with high-dose ICSs and OCSs, based on the hypothesis that anti-IL-5 would be most beneficial in patients with eosinophilic disease. In this subset of patients, not only was there a reduction in sputum and blood eosinophils, but there were also improvements in asthma control, lung function, exacerbation frequency, and a reduction in corticosteroid dose [99]. The possibility of a personalized approach was further investigated in patients selected based on the presence of eosinophilic inflammation and recurrent exacerbations. This study demonstrated a reduction in exacerbation frequency, despite no observed change in lung function or asthma-related quality of life [100]. Further, the effect size of the observed reduction in exacerbation rates was higher in individuals with higher blood eosinophil counts. Recent larger phase III studies were conducted in patients selected based on peripheral blood eosinophilia ($>0.3 \times 10^9/\text{L}$ in the preceding year) and recurrent exacerbations (≥ 2 per year), despite optimal inhaled steroid therapy [90,91]. In this patient group, mepolizumab reduced exacerbations, improved asthma control, and improved lung function, despite a reduction in oral steroid dose [90,91].

The mepolizumab studies are important in several ways, beyond providing another therapeutic option for severe asthma. These studies highlight the importance of targeting severe asthma treatment to carefully characterize patients using biomarkers, in this case eosinophils, to guide treatment decisions. In the clinic, use of anti-IL-5 therapy should be focused on patients with a demonstrated eosinophilic phenotype and a history of frequent exacerbations, rather than a high symptom burden.

Reslizumab

Reslizumab (Cinquil®; Teva, Petah Tikva, Israel) is an IgG4k humanized monoclonal antibody that also targets IL-5. Similar to mepolizumab, early reslizumab studies in severe persistent asthma failed to demonstrate improvements in lung function or symptom scores, despite significant reductions in blood eosinophils [101]. Subsequent studies stratified patients on ICS and long-acting beta-agonist (LABA) according to sputum eosinophils ($>3\%$) and, in this subgroup, demonstrated an improvement in asthma control and lung function, with a trend toward a reduction in exacerbation frequency [102]. Two parallel phase III studies recruited a large population (953 patients) with poorly controlled asthma, at least one exacerbation in the preceding year and blood eosinophils $>0.4 \times 10^9/\text{L}$. Treatment with 3 mg/kg intravenous reslizumab monthly reduced exacerbations as well as improved lung function, quality of life, and symptom scores [103]. The FDA's

Pulmonary-Allergy Drugs Advisory Committee recommended approval of reslizumab in December 2015, and regulatory action is expected by March 2016, while a decision from the European Medicine Agency is expected later in 2016.

Benralizumab

Benralizumab (MEDI-563; MedImmune, Gaithersburg, MD, USA/AstraZeneca, London, England) is an IgG1 antibody directed against the IL-5 receptor (IL-5R α), as an alternative approach to block IL-5 signaling. Similar to anti-IL-5 antibodies, benralizumab depletes blood and airway eosinophils [104]. In addition to blocking the effect of IL-5 on eosinophils, basophils also express IL-5R α and are hence targeted by benralizumab. As a result, benralizumab induces antibody-mediated cell cytotoxicity of eosinophils and basophils [105]. Theoretically, this could result in greater reductions in eosinophil and basophil numbers, compared to reslizumab or mepolizumab. However, the clinical differences are yet to be demonstrated with only a single, dose-ranging phase IIb study reported for benralizumab, which demonstrated a reduction in exacerbation frequency in patients with baseline blood eosinophils of $>0.3 \times 10^9/L$ [106]. Larger phase III studies assessing benralizumab are awaited.

The IL-13 pathway

IL-13 is linked to multiple aspects of asthma pathophysiology (reviewed in [107]). IL-13 promotes inflammation and airway hyperresponsiveness [108], in part, by increasing eosinophil migration, inducing macrophage activation, and stimulating goblet cell hyperplasia and mucus overproduction [109,110]. IL-13 is also important in directing antibody class-switching of B cells to produce IgE [111]. Elevated IL-13 levels are present in sputum from a subset of asthma patients, including patients with severe uncontrolled asthma [112].

A number of drugs have been designed to block IL-13 function *in vivo*. Both lebrikizumab and tralokinumab are humanized monoclonal antibodies that bind IL-13 and inhibit its function, which have been assessed in patients with asthma [113], while GSK679586 is a humanized monoclonal antibody that targets the IL-13 receptor. GSK679586 has been assessed in a single study of 237 patients with treatment refractory asthma, but failed to improve asthma outcomes [114]. Anrukinzumab is a monoclonal antibody that blocks interaction of IL-13 with the IL-4R α receptor, but has only been assessed for the treatment of ulcerative colitis [115].

Lebrikizumab

Initial dose-ranging studies of lebrikizumab (TNX-650; Roche, Basel, Switzerland) targeted 212 patients with mild asthma not receiving ICS treatment [116]. Patients received placebo or lebrikizumab (125, 250, or 500 mg s.c. every 4 weeks for 12 weeks, with an 8-week follow-up). Forced expiratory volume in 1 second (FEV₁) changes following treatment were higher, but failed to achieve statistical significance. Lebrikizumab-treated patients had reduced rates of treatment failure at all treatment doses, compared to placebo controls. No significant differences were observed between the varying

lebrikizumab doses or when patients were subgrouped based on periostin levels. Adverse events were reported by a similar number of patients in the treatment and placebo groups. The first clinical trial of lebrikizumab conducted in severe asthma patients who remained poorly controlled despite high-dose inhaled glucocorticoid therapy recruited 219 participants. Patients were treated with lebrikizumab (250 mg/dose s.c. every 4 weeks) for 20 weeks and followed until week 32. Patients demonstrated a greater improvement in FEV₁ from baseline to week 12 than placebo controls [117]. In a subgroup of patients with high periostin levels, a further increase in FEV₁ was observed [113,117].

In a follow-up trial, 29 patients with uncontrolled asthma were randomized to either placebo control or lebrikizumab treatment (1–5 mg/kg s.c. every 4 weeks for 12 weeks). The late asthmatic response to allergen challenge was decreased, but failed to reach statistical significance and patients with higher levels of peripheral blood eosinophils, serum IgE, and periostin exhibited the greatest response to treatment. In addition, lebrikizumab treatment reduced serum IgE and CCL13/17 levels [118].

The LUTE and VERSE studies were initiated as phase III clinical trials in a total of 463 patients with uncontrolled asthma despite medium-to-high-dose ICS therapy and an additional controller medication [119]. Patients received placebo or different doses of lebrikizumab (37.5, 125, or 250 mg s.c. every 4 weeks, initially planned for 52 weeks). However, the trials were discontinued as a precautionary measure and downgraded to phase IIb, following detection of impurities in the drug preparation. As a result, patient follow-up lengths were variable, with median treatment duration of 24.1 weeks. Asthma exacerbations were reduced following treatment across all groups. In a high periostin subgroup (>50 ng/mL), exacerbations were reduced by 60% and FEV₁ measurements were improved by 9.1%, compared to placebo controls. The 'low periostin' subgroup experienced exacerbation and FEV₁ improvements between 5% and 2.6%, respectively. Biomarker assessment for high fractional exhaled nitric oxide (FeNO) (>21 ppb) and increased peripheral blood eosinophil counts ($>0.24 \times 10^9/L$) was predictive for responses to lebrikizumab treatment. Treatment was well tolerated and no safety issues were identified [119].

Tralokinumab

Tralokinumab (CAT-354; AstraZeneca/MedImmune) was first evaluated in a phase II trial of 194 patients with moderate-to-severe uncontrolled asthma [120]. Participants received placebo control or different doses of tralokinumab (150, 300, or 600 mg s.c.) every 2 weeks for 12 weeks. At 13 weeks, treatment had no effect on Asthma Control Questionnaire (ACQ-6) scores, the primary study end point. Treatment resulted in modest dose-dependent improvements in FEV₁, which only reached statistical significance in the high-dose treatment group (600 mg) though the increased FEV₁ persisted through to week 24, 12 weeks after treatment cessation. Reduced short-acting beta₂-agonist use occurred in all treatment groups, at weeks 13 and 24, compared to placebo control. No serious adverse effects were noted from treatment.

A further randomized, double-blind, placebo-controlled, parallel-group phase IIb study of 452 patients with severe uncontrolled asthma was reported [121]. Patients received placebo control or tralokinumab (300 mg s.c. every 2 weeks for 52 weeks, or every 2 weeks for 12 weeks followed by every 4 weeks until week 52). Patients also received high-dose fluticasone and salmeterol and any pre-study controller therapies. FEV₁ measurements were significantly increased in patients that received biweekly treatment, but not patients receiving treatment every 4 weeks, compared to placebo control. *Post hoc* subgroup analysis did reveal significant improvements in FEV₁, ACQ-6 scores, and asthma quality of life questionnaire scores (AQLQ[S]), for a subset of patients not on long-term OCS and with baseline FEV₁ reversibility >12%. Similar exacerbation rates were reported for all groups after 1 year. No significant safety concerns were reported.

The IL-4Ra pathway

IL-4 signaling in T cells controls Th2 differentiation and induces IgE production by B cells [122]. Importantly, both IL-4 and IL-13 signal through a receptor containing the IL-4Ra subunit. By blocking this interaction, dupilumab effectively blocks signaling from both IL-4 and IL-13, to dampen allergic responses.

Dupilumab

Dupilumab (Regeneron) treatment has been assessed in a single trial of 104 patients with moderate-to-severe asthma and blood eosinophil counts $\geq 0.3 \times 10^9/L$ or sputum eosinophils $\geq 3\%$ that were on treatment with medium-to-high-dose ICS plus LABA [123]. Dupilumab, or placebo, was administered (300 mg s.c.) weekly for 12 weeks, with patients discontinuing LABAs on week 4 and tapering ICS from weeks 6–9. In the treatment group, an 87% reduction in exacerbations was observed. While none of the patients in either group experienced an exacerbation requiring hospitalization, reductions were seen in significant but less severe exacerbations, defined by a $\geq 30\%$ reduction in morning PEF from baseline on 2 consecutive days, the requirement for ≥ 6 additional inhalations of short-acting beta-agonist in a 24-h period relative to baseline on 2 consecutive days or the need for systemic corticosteroids. The secondary end points of asthma control (ACQ-5) and lung function (improvement in FEV₁, morning PEF) also improved. Treatment also reduced biomarkers associated with Th2 inflammation, including reduced FeNO and reduced serum CCL26 and IgE. The overall rates of reported adverse events were similar between groups, with no serious adverse reports resulting from the study drug.

The IL-17 pathway

In addition to Th2-driven subtypes of asthma, there is growing recognition that IL-17 (and Th17) responses can recruit eosinophils and neutrophils to the lung and contribute to airway hyperresponsiveness [75,76]. IL-17 expression is increased in animal models of asthma [124] and increased levels of IL-17A and IL-17F are observed in the lungs of

patients with asthma, particularly those with severe neutrophilic disease [75,125–128]. IL-25 (IL-17E) also signals through the IL-17 receptor (IL-17R) and contributes to asthma through the activation of Th2 pathways, increasing secretion of IL-4, 5, and 13 [129]. By blocking interactions with the IL-17R, brodalumab effectively blocks both IL-17 and IL-25 signaling. Brodalumab has previously been assessed in rheumatoid arthritis, psoriasis, psoriatic arthritis, and Crohn's disease, and showed promising results in a phase II study of plaque psoriasis [130].

Brodalumab

Responses of 302 poorly controlled, moderate-to-severe patients with asthma were assessed using three doses of brodalumab (140, 210, and 280 mg; Amgen, Thousand Oaks, CA, USA/AstraZeneca/Valeant Pharmaceuticals, Laval, Canada) or placebo control. In the overall study population, no significant differences were observed in asthma control (ACQ), FEV₁, symptom scores, or symptom-free days. However, in a 'high reversibility' patient subgroup, slightly improved ACQ scores were observed [131]. A subsequent phase IIb study in this patient subpopulation has been discontinued due to lack of efficacy.

The IL-2 pathway

IL-2 is released by antigen-stimulated T cells, inducing the proliferation of T cells and B cells and also increasing antibody production by B cells; it may also directly promote eosinophil recruitment [132,133]. Increased levels of IL-2 and soluble IL-2 receptor are found in the airways of patients with severe asthma. It is possible that IL-2 contributes to the initiation and prolongation of inflammation in asthma, as well as contributing to airway remodeling [77].

Daclizumab

Daclizumab (Zenapax®; Roche) is a humanized monoclonal antibody that binds the alpha subunit of the IL-2 receptor, blocking IL-2 signaling. A small trial of daclizumab in 115 moderate-to-severe persistent asthma patients demonstrated an improvement in symptoms, lung function (FEV₁), and exacerbation frequency [134]. Despite these positive initial findings, no further trials are registered examining the effects of daclizumab in asthma.

The IL-1 pathway

The therapeutic options for eosinophilic asthma are growing; however, few exist for neutrophilic asthma. Innate immune activation appears to be important in both neutrophilic asthma and virus-induced asthma exacerbations, with a proposed role for the IL-1 β axis in both acute and chronic neutrophilic asthma. IL-1 is secreted by macrophages, monocytes, fibroblasts, and dendritic cells in response to bacterial infection, injury, and cellular activation [135]. Preliminary studies using inhaled lipopolysaccharide endotoxin to induce innate immune activation demonstrated that administration of the IL-1R antagonist anakinra effectively reduced neutrophilic airway

inflammation and reduced the inflammatory cytokines IL-1 β , IL-6, and IL-8 [136]. Blockade of IL-1 β in mice reduces airway inflammation and airway hyperresponsiveness [137]. Both *IL-1 β* and *IL-1 α* genes are associated with asthma risk [138], and IL-1 β levels are increased in BAL, sputum, and airway epithelium in asthmatics [78,79].

Canakinumab

Canakinumab (Ilaris®; Novartis) is a high-affinity human anti-IL-1 β monoclonal IgG1k antibody. The drug was developed to treat a rare group of disorders, the cryopyrin-associated periodic disorders, which are caused by an overproduction of IL-1 β . In airways disease, IL-1 β has been implicated in both epithelial and systemic inflammation [139,140] and may be an appropriate treatment target in both asthma and chronic obstructive pulmonary disease (COPD). While the drug has orphan drug approval via the FDA, and there is one reported small study in mild asthma [141], there are no ongoing clinical trials in airways disease.

Other molecules in severe asthma

In addition to interleukins, other molecules have been implicated in severe asthma pathogenesis. Tumor necrosis factor alpha (TNF α) is a proinflammatory cytokine that is present in sputum from severe steroid-resistant asthma patients [142]. The complement system is part of the immune system that enhances the ability of antibodies and immune cells to destroy pathogens. Complement 5 (C5), a protein in the complement pathway, has also been implicated in asthma. C5 is increased in asthmatic patients [143] and can induce a number of disease pathways associated with asthma. Targeted antibody treatment against each of these molecules is being assessed in asthma.

TNF α pathway

TNF α is a proinflammatory cytokine produced primarily by activated monocytes/macrophages, but also by T cells, mast cells, eosinophils, and epithelial cells [144]. TNF α release induces fever and inflammation, and also promotes neutrophil recruitment [145]. TNF α levels are increased in induced sputum samples from patients with asthma [146,147], in particular those with severe steroid-resistant disease [142].

Infliximab and golimumab are monoclonal antibodies that specifically bind and neutralize TNF α [148,149]. Blocking TNF α function has been demonstrated as an effective therapy in patients with rheumatoid arthritis [150], ankylosing spondylitis [151], Crohn's disease [152], and psoriasis [153]. In mouse models of acute asthma, infliximab treatment effectively decreased numbers of BAL fluid neutrophils and eosinophils and a range of inflammatory cytokines, suggesting potent anti-inflammatory effects [154].

While not technically a monoclonal antibody, we also draw attention to the use of etanercept in severe asthma. Etanercept is an engineered recombinant protein that blocks both TNF α and lymphotoxin- α function [155].

Infliximab

The effects of infliximab (Remicade®; Janssen Biotech, Horsham, PA, USA) were assessed in 38 patients with moderate asthma (5 mg/kg) by i.v. infusion on weeks 0, 2, and 6. Clinical responses were assessed by monitoring lung function, symptoms, and inhaled β_2 -agonist usage [156]. The results indicated that while treatment failed to alter morning PEF, treatment did decrease exacerbations and sputum TNF α levels [156,157]. Assessment of infliximab in severe asthma patients may yield more promising results; however, these studies have not been performed to date.

Golimumab

Golimumab (Simponi®; Janssen Biotech) treatment was assessed in a group of 309 severe asthma patients, as an add-on anti-inflammatory treatment [158]. Patients were randomized into placebo control ($n = 78$) or golimumab groups (50, 100, 150, or 200 mg/dose s.c. every 4 weeks for 52 weeks). End points were changes in FEV $_1$ (% predicted) and the number of exacerbations by week 24. At week 24, there were no significant effects of treatment, although two treatment groups (100 and 200 mg) trended toward decreased exacerbations. This trial was discontinued due to reported adverse events. The overall rates of adverse events were similar between groups. However, patients receiving golimumab experienced increased incidence of infections and malignancies. Golimumab treatment did not appear to have a causal role in malignancies, but was proposed to be a risk factor for increased tumoral aggressivity in elderly subjects [159]. *Post hoc* analysis demonstrated that patients with better lung function and who were receiving higher doses of treatment were less likely to experience exacerbations at week 24. This study suggests that anti-TNF treatments may increase infection risk in severe asthma, but may have some clinical benefit in a subset of patients.

Etanercept

Etanercept (Enbrel®; Amgen) treatment was first assessed in a pilot study of 10 patients with refractory asthma [160]. Ten weeks of treatment resulted in an increased methacholine concentration required for bronchial hyperresponsiveness (BHR), improve AQLQ scores, and an increase in FEV $_1$. In a second study, etanercept treatment (over 12 weeks) in 39 patients with severe corticosteroid refractory asthma resulted in a small reduction in ACQ scores, but no difference in AQLQ scores, lung function, PEF, BHR, or exacerbation rates [161]. In a phase II trial of etanercept treatment (12 weeks) of 132 individuals with moderate-to-severe asthma, treatment failed to identify any improvements in lung function (FEV $_1$), morning PEF, exacerbations, methacholine provocation responses, or ACQ/AQLQ scores [162]. Minor adverse effects of treatment were reported following etanercept treatment [161].

The C5 pathway

C5 is increased in asthmatic patients [143] and in the lungs of mice in experimental models of asthma [163]. C5a can induce

smooth muscle contractions, mucus secretion, microvascular permeability, and immune cell migration and activation, in particular mast cell release of histamine (reviewed in [164,165]). In animal models of allergic airways disease, inhibition of C5 suppresses allergic responses to a variety of allergens [163,166].

Eculizumab

Eculizumab (Soliris®; Alexion Pharmaceuticals, New Haven, CT, USA) is a humanized monoclonal antibody that targets C5 and prevents cleavage into the active C5a/b forms. It was initially approved for the treatment of paroxysmal nocturnal hemoglobinuria [167], at a cost of >400,000 USD/year. More recently, it has also been approved in the United States for the treatment of atypical hemolytic uremic syndrome [168].

Eculizumab treatment for asthma has only been tested in one clinical asthma trial to date. In a phase II trial, the impact of a single dose (600 mg) of eculizumab on the late asthmatic response was assessed in mild asthmatic patients in a crossover study [169]. Treatment blunted the late asthmatic response, but only when given after placebo in the crossover allocation. This may suggest that the drug, though effective, was not cleared during the 4-week washout period. No further trials have been performed.

Expert commentary

Severe asthma is a complex multifactorial disease. Effective management of severe asthma requires careful and systematic multidimensional and multidisciplinary characterization of patients to confirm diagnosis, identify areas of suboptimal disease management, comorbidities, and aggravating factors, and also to identify disease phenotypes. Often, careful assessment and management using standard therapy is sufficient to control even severe asthma following detailed characterization. If standard therapy is not sufficient, then meticulous characterization of individual patients enables selection of targeted therapies most likely to be of benefit. Monoclonal antibody therapies target specific pathways in severe asthma and offer promise for effective therapy.

Severe asthma therapy is guided by outcomes from clinical trials; however, trials in severe asthma, as in most diseases, are conducted on a highly selected group of patients. The entry criteria for trials are extremely stringent, and becoming more so as therapies target ever more specific subgroups of disease. Less than 10% of patients in severe asthma clinics are eligible for trial entry [170], and this raises various issues. First, these entry criteria affect recruitment to and the feasibility of clinical trials, especially when multiple trials are aiming to recruit the same disease subpopulations. Second, management of patients in 'real life', which should ideally be directed by clinical trial data, instead requires highly nuanced experience and expertise. Third, most studies trialing monoclonal antibodies have and continue to target allergic or eosinophilic disease phenotypes, while other phenotypes are not well catered for.

Another issue in clinical trials of severe asthma is the prevalent use of exacerbations as a primary end point. While this end point is binary (exacerbation or not) and, therefore, a useful clinical trial metric, many patients do not exacerbate frequently, and rather are burdened by daily life-limiting symptoms and quality-of-life impairment. These impacts are difficult both to measure and to control. Clinical trial metrics that specifically measure the impacts of treatment on everyday symptoms, health status, and treatment requirement including OCSs would provide more nuanced data on the impacts of treatment and improve the ability to verify response to treatment in the clinic.

The requirement of dedicated specialist teams for patients with severe or chronic respiratory disease is well established in cystic fibrosis and lung transplantation. The same degree of multidisciplinary input is required to ensure best possible outcomes in severe asthma, and severe asthma centers are best equipped to provide this. The reluctance to embrace this concept is, in part, due to the fact that asthma can exist in mild or moderate forms, which do not require such intensive medical input. However, severe asthma is most usefully considered as a separate disease entity, rather than on a continuum with milder forms of disease.

Five-year view

The first monoclonal therapy approved for severe asthma (omalizumab) is now widely used in clinical practice and recently, a second molecule, mepolizumab, has been approved for use in the United States and Europe. Many more therapies are at advanced stages of development and will provide much needed treatment options for severe asthma.

These new therapies will raise a number of challenges relating to patient management, which impact the individual patient, clinic structure, and health-care expenditure levels. In order to use advanced therapies, detailed patient characterization is vital, meaning that severe asthma centers will need support and development. Although the high direct costs of these therapies are apparent, there is also a significant indirect health-care cost. The requirement for skilled administration and monitoring of treatment will require systems of health care that can cope with the increasing prevalence of advanced therapy. It may be that following an initial period of administration and stabilization, responsibility for ongoing therapy can be shared with primary care groups or specialized administration centers, in much the same way as community dialysis units have been organized.

Finally, new research into biomarker discovery and validation programs in severe asthma is required, in order to improve clinicians' ability to target therapies to achieve optimal health and economic benefit. Single-dimensional assessments of disease phenotypes (e.g. serum IgE levels) will not be sufficient to predict patient responses to treatment or select therapy. To overcome this challenge, algorithms will need to be developed that consider multiple biomarkers of disease and inform the optimal therapy option for each individual with severe asthma.

Key issues

- Severe asthma is a complex multifactorial disease requiring specialist input.
- Patients with severe asthma should be treated in severe asthma centres by multidisciplinary teams conducting multidimensional assessments.
- It is vital that severe asthma patients have management optimised on the basis of multidimensional assessment, including pathological phenotype, prior to the addition of targeted monoclonal antibody therapy.
- Airway Inflammatory phenotypes in asthma include eosinophilic, neutrophilic, paucigranulocytic and mixed granulocytic.
- Monoclonal antibody therapies target specific pathological pathways in severe asthma that drive symptoms and exacerbations of the disease.
- Omalizumab (anti-IgE) reduces exacerbations in patients with severe allergic asthma.
- Mepolizumab (anti-IL-5) reduces exacerbations, improves asthma control and lung function in patients with severe eosinophilic asthma.
- Increasing use of monoclonal antibodies will result in financial and, clinic design and management issues, which need to be addressed to maintain services in the future.
- New monoclonal antibody therapies will become available in the next few years, leading to the need for further phenotyping of patients.
- Treatments that target non-eosinophilic asthma and its molecular pathways are needed.

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ORCID

Steven Maltby  <http://orcid.org/0000-0003-1240-5964>

Peter G. Gibson  <http://orcid.org/0000-0001-5865-489X>

Peter A. B. Wark  <http://orcid.org/0000-0001-5676-6126>

References

Papers of special note have been highlighted as:

- of interest
 - of considerable interest
1. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. **2014**;34(2):343–373.
 - **An evidence-based guideline for severe asthma management.**
 2. Chung KF, Bel EH, Wenzel SE. Difficult-to-treat severe asthma. *Eur Respir Soc Monogr*. **2011**;15:51.
 3. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. **2015**;46(5):1308–1321.
 4. Heaney LG, Brightling CE, Menzies-Gow A, et al., British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax*. **2010**;65(9):787–794.
 5. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J*. **2010**;17(2):74–80.
 6. McDonald VM, Gibson PG. Exacerbations of severe asthma. *Clin Exp Allergy*. **2012**;42(5):670–677.
 7. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. **2010**;181(4):315–323.
 - **An important study for severe asthma. This study described the results of an early cluster analysis that has improved severe asthma phenotyping.**
 8. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. **2008**;178:218–224.
 - **One of the first studies to use statistical cluster analysis to describe clinical asthma phenotypes.**
 9. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. **2007**;119(2):405–413.
 10. Chung K. Inflammatory biomarkers in severe asthma. *Curr Opin Pulm Med*. **2012**;18(1):35–41.
 11. Hastie AT, Moore WC, Meyers DA, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. *J Allergy Clin Immunol*. **2010**;125:1028–1036.e13.
 12. Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. *J Intern Med*. **2016**;279(2):192–204.
 - **An informative review highlighting the importance of phenotyping on severe asthma and therapies for severe asthma that are targeted to phenotypes.**
 13. Gibson PG, Marks G, Sly P, et al. Case for action proposal: targeted therapy for asthma. Submitted by the NHMRC Research Translation Faculty Asthma Steering Group; **2015** [cited 2015 Feb]. Available from: www.nhmrc.gov.au/research/research-translation/research-translation-faculty/ideas-research-translation-faculty-cases
 14. Simpson JL, Scott R, Boyle M, et al. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology*. **2006**;11:54–61.
 15. Schleif F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med*. **2014**;108(12):1723–1732.
 16. McDonald VM, Higgins I, Wood LG, et al. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? *Thorax*. **2013**;68(7):691–694.
 17. Britten N, Pope C, Halford S, et al. What if we made stratified medicine work for patients? *Lancet Respir Med*. **2016**;4(1):8–10.
 18. McDonald VM, Vertigan AE, Gibson PG. How to set up a severe asthma service. *Respirology*. **2011**;16(6):900–911.
 - **A practical guide for setting up and management of a severe asthma specialist center.**
 19. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. *Eur Respir J*. **2003**;22(3):478–483.

20. Heaney LG, Conway E, Kelly C, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax*. 2003;58(7):561–566.
21. Bracken M, Fleming L, Hall P, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child*. 2009;94(10):780–784.
22. Mark Hew AG, Sutherland M, Wark P, et al. Clinical effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria. *Clin Exp Allergy*. Forthcoming 2016.
23. Gibeon D, Heaney LG, Brightling CE, et al. Dedicated severe asthma services improve health-care use and quality of life. *Chest*. 2015;148(4):870–876.
24. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376(9743):803–813.
25. Chames P, Van Regenmortel M, Weiss E, et al. Therapeutic antibodies: successes, limitations and hopes for the future. *Br J Pharmacol*. 2009;157(2):220–233.
- **A review of the history and key issues relating to monoclonal antibody therapies in general.**
26. Jones TD, Carter PJ, Pluckthun A, et al. The INNs and outs of antibody nonproprietary names. *MAbs*. 2016;8(1):1–9.
27. General policies for monoclonal antibodies. P.o.I.N.N. (INN), editor. Geneva: World Health Organization (WHO); 2009.
28. Ishizaka K, Tomioka H, Ishizaka T. Mechanisms of passive sensitization. I. Presence of IgE and IgG molecules on human leukocytes. *J Immunol*. 1970;105(6):1459–1467.
29. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med*. 2012;18(5):693–704.
30. Chan MA, Gigliotti NM, Aubin BG, et al. FCER2 (CD23) asthma-related single nucleotide polymorphisms yields increased IgE binding and Egr-1 expression in human B cells. *Am J Respir Cell Mol Biol*. 2014;50(2):263–269.
31. Palaniyandi S, Liu X, Periasamy S, et al. Inhibition of CD23-mediated IgE transcytosis suppresses the initiation and development of allergic airway inflammation. *Mucosal Immunol*. 2015;8(6):1262–1274.
32. MacGlashan D Jr. IgE receptor and signal transduction in mast cells and basophils. *Curr Opin Immunol*. 2008;20(6):717–723.
33. Shiung YY, Chiang CY, Chen JB, et al. An anti-IgE monoclonal antibody that binds to IgE on CD23 but not on high-affinity IgE Fc receptors. *Immunobiology*. 2012;217(7):676–683.
34. Rosenwasser LJ, Busse WW, Lizambri RG, et al. Allergic asthma and an anti-CD23 mAb (IDEC-152): results of a phase I, single-dose, dose-escalating clinical trial. *J Allergy Clin Immunol*. 2003;112(3):563–570.
35. Corne J, Djukanovic R, Thomas L, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. *J Clin Invest*. 1997;99(5):879–887.
36. Djukanovic R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med*. 2004;170(6):583–593.
37. Oliver JM, Tarleton CA, Gilmartin L, et al. Reduced FcεpsilonRI-mediated release of asthma-promoting cytokines and chemokines from human basophils during omalizumab therapy. *Int Arch Allergy Immunol*. 2010;151(4):275–284.
38. Chanez P, Contin-Bordes C, Garcia G, et al. Omalizumab-induced decrease of FcεRI expression in patients with severe allergic asthma. *Respir Med*. 2010;104(11):1608–1617.
39. Schroeder JT, Bieneman AP, Chichester KL, et al. Decreases in human dendritic cell-dependent T(H)2-like responses after acute in vivo IgE neutralization. *J Allergy Clin Immunol*. 2010;125(4):896–901.e6.
40. Chan MA, Gigliotti NM, Dotson AL, et al. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. *Clin Transl Allergy*. 2013;3(1):29.
41. Bardelas J, Figliomeni M, Kianifard F, et al. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma*. 2012;49(2):144–152.
42. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184–190.
43. Hanania NA, Alban O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573–582.
44. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364(11):1005–1015.
45. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110–6 e1.
46. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632–638.
47. Ohta K, Miyamoto T, Amagasaki T, et al. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology*. 2009;14(8):1156–1165.
48. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254–261.
49. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy*. 2004;59(7):709–717.
50. Massanari M, Holgate ST, Busse WW, et al. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. *Respir Med*. 2010;104(2):188–196.
51. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60(3):309–316.
52. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N Engl J Med*. 1999;341(26):1966–1973.
53. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108(2):E36.
54. Lanier B, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210–1216.
55. Gibson PG, Taramarcaz P, McDonald VM. Use of omalizumab in a severe asthma clinic. *Respirology*. 2007;12(Suppl. 3):S35–S44.
56. Abraham I, Alhossan A, Lee CS, et al. 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy*. 2015. doi:10.1111/all.12815. [Epub ahead of print].
57. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1:CD003559.
- **A systematic review of all clinical trial data relating to the use of omalizumab (anti-IgE) for asthma.**
58. Korn S, Thielen A, Seyfried S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med*. 2009;103(11):1725–1731.
59. Zazzali JL, Raimundo KP, Trzaskoma B, et al. Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results. *Allergy Asthma Proc*. 2015;36(4):283–292.
60. Nopp A, Johansson SG, Adedoyin J, et al. After 6 years with Xolair; a 3-year withdrawal follow-up. *Allergy*. 2010;65(1):56–60.
61. Kuprys-Lipinska I, Kuna P. Loss of asthma control after cessation of omalizumab treatment: real life data. *Postepy Dermatol Alergol*. 2014;31(1):1–5.
62. Busse W, Trzaskoma B, Omachi T, et al. Evaluating omalizumab persistency of response after long-term therapy (XPORT). *Eur Respir J*. 2014;44(Suppl 58).
63. Corren J, Casale TB, Lanier B, et al. Safety and tolerability of omalizumab. *Clin Exp Allergy*. 2009;39(6):788–797.
64. Hendeles L, Sorkness CA. Anti-immunoglobulin E therapy with omalizumab for asthma. *Ann Pharmacother*. 2007;41(9):1397–1410.
65. Grimaldi-Bensouda L, Zureik M, Aubier M, et al. Does omalizumab make a difference to the real-life treatment of asthma

- exacerbations? Results from a large cohort of patients with severe uncontrolled asthma. *Chest*. 2013;143(2):398–405.
66. de Llano LP, Vennera Mdel C, Alvarez FJ, et al. Effects of omalizumab in non-atopic asthma: results from a Spanish multicenter registry. *J Asthma*. 2013;50(3):296–301.
 67. Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest*. 2013;144(2):411–419.
 68. Dema B, Suzuki R, Rivera J. Rethinking the role of immunoglobulin E and its high-affinity receptor: new insights into allergy and beyond. *Int Arch Allergy Immunol*. 2014;164(4):271–279.
 69. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804–811.
 70. Schroeder JT, Bieneman AP, Xiao H, et al. TLR9- and FcεpsilonR1-mediated responses oppose one another in plasmacytoid dendritic cells by down-regulating receptor expression. *J Immunol*. 2005;175(9):5724–5731.
 71. CADTH rapid response reports, in omalizumab treatment for adults and children with allergic asthma: a review of the clinical effectiveness, cost-effectiveness, and guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright (c) 2015 Canadian Agency for Drugs and Technologies in Health; 2015.
 72. Lowe PJ, Tannenbaum S, Gautier A, et al. Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. *Br J Clin Pharmacol*. 2009;68(1):61–76.
 73. Arm JP, Bottoli I, Skerjanec A, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy*. 2014;44(11):1371–1385.
 74. Chung KF. Targeting the interleukin pathway in the treatment of asthma. *Lancet*. 2015;386(9998):1086–1096.
 75. Barczyk A, Pierzchala W, Sozanska E. Interleukin-17 in sputum correlates with airway hyperresponsiveness to methacholine. *Respir Med*. 2003;97(6):726–733.
 76. Kudo M, Melton AC, Chen C, et al. IL-17A produced by αβ T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. *Nat Med*. 2012;18(4):547–554.
 77. Park CS, Lee SM, Chung SW, et al. Interleukin-2 and soluble interleukin-2 receptor in bronchoalveolar lavage fluid from patients with bronchial asthma. *Chest*. 1994;106(2):400–406.
 78. Konno S, Gonokami Y, Kurokawa M, et al. Cytokine concentrations in sputum of asthmatic patients. *Int Arch Allergy Immunol*. 1996;109(1):73–78.
 79. Broide DH, Lotz M, Cuomo AJ, et al. Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol*. 1992;89(5):958–967.
 80. Fu JJ, McDonald VM, Baines KJ, et al. Airway IL-1β and systemic inflammation as predictors of future exacerbation risk in asthma and COPD. *Chest*. 2015;148(3):618–629.
 81. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*. 2002;360(9347):1715–1721.
 82. Green RH, Brightling CE, Woltmann G, et al. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax*. 2002;57(10):875–879.
 83. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax*. 2015;70(2):115–120.
 84. Khatry DB, Gossage DL, Geba GP, et al. Discriminating sputum-eosinophilic asthma: accuracy of cutoffs in blood eosinophil measurements versus a composite index, ELEN. *J Allergy Clin Immunol*. 2015;136(3):812–814.e2.
 85. Westerhof GA, Korevaar DA, Amelink M, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J*. 2015;46(3):688–696.
 86. McGrath KW, Icitovic N, Boushey HA, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med*. 2012;185(6):612–619.
 87. Schleich FN, Manise M, Sele J, et al. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. *BMC Pulm Med*. 2013;13:11.
 88. Wark PA, McDonald VM, Gibson PG. Adjusting prednisone using blood eosinophils reduces exacerbations and improves asthma control in difficult patients with asthma. *Respirology*. 2015;20(8):1282–1284.
 89. Elliot JG, Jones RL, Abramson MJ, et al. Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. *Respirology*. 2015;20(1):66–72.
 90. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189–1197.
 91. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198–1207.
 92. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol*. 2000;105(4):651–663.
 93. Foster PS, Hogan SP, Ramsay AJ, et al. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. *J Exp Med*. 1996;183(1):195–201.
 94. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *N Engl J Med*. 1990;323(15):1033–1039.
 95. Shi HZ, Xiao CQ, Zhong D, et al. Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. *Am J Respir Crit Care Med*. 1998;157(1):204–209.
 96. Leckie MJ, Ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet*. 2000;356(9248):2144–2148.
 97. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003;112(7):1029–1036.
 98. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med*. 2007;176(11):1062–1071.
 99. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360(10):985–993.
 - **The first assessment to demonstrate that mepolizumab (anti-IL-5) could effectively improve asthma control, when administered to a patient subgroup selected for poorly controlled disease and high eosinophil numbers.**
 100. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651–659.
 101. Kips JC, O'Connor BJ, Langley SJ, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med*. 2003;167(12):1655–1659.
 102. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184(10):1125–1132.
 103. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355–366.
 104. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol*. 2013;132(5):1086–1096.e5.
 105. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol*. 2010;125(6):1344–1353.e2.

106. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med*. 2014;2(11):879–890.
107. Thomson NC, Patel M, Smith AD. Lebrikizumab in the personalized management of asthma. *Biologics*. 2012;6:329–335.
108. Wills-Karp M, Luyimbazi J, Xu X, et al. Interleukin-13: central mediator of allergic asthma. *Science*. 1998;282(5397):2258–2261.
109. Zhu Z, Homer RJ, Wang Z, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest*. 1999;103(6):779–788.
110. Brandt EB, Zimmermann N, Muntel EE, et al. The $\alpha 4\beta 7$ -integrin is dynamically expressed on murine eosinophils and involved in eosinophil trafficking to the intestine. *Clin Exp Allergy*. 2006;36(4):543–553.
111. Van der Pouw Kraan TC, Van der Zee JS, Boeijs LC, et al. The role of IL-13 in IgE synthesis by allergic asthma patients. *Clin Exp Immunol*. 1998;111(1):129–135.
112. Saha SK, Berry MA, Parker D, et al. Increased sputum and bronchial biopsy IL-13 expression in severe asthma. *J Allergy Clin Immunol*. 2008;121(3):685–691.
113. Maselli DJ, Keyt H, Rogers L. Profile of lebrikizumab and its potential in the treatment of asthma. *J Asthma Allergy*. 2015;8:87–92.
114. De Boever EH, Ashman C, Cahn AP, et al. Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. *J Allergy Clin Immunol*. 2014;133(4):989–996.
115. Reinisch W, Panes J, Khurana S, et al. Anrakinumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. *Gut*. 2015;64(6):894–900.
116. Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol*. 2013;132(3):567–574.e12.
117. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med*. 2011;365(12):1088–1098.
118. Scheerens H, Arron JR, Zheng Y, et al. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. *Clin Exp Allergy*. 2014;44(1):38–46.
119. Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 2015;70(8):748–756.
120. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J*. 2013;41(2):330–338.
121. Brightling CE, Chanez P, Leigh R, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2015;3(9):692–701.
122. Ishizaka A, Sakiyama Y, Nakanishi M, et al. The inductive effect of interleukin-4 on IgG4 and IgE synthesis in human peripheral blood lymphocytes. *Clin Exp Immunol*. 1990;79(3):392–396.
123. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455–2466.
124. Hoshino H, Lotvall J, Skoogh BE, et al. Neutrophil recruitment by interleukin-17 into rat airways in vivo. Role of tachykinins. *Am J Respir Crit Care Med*. 1999;159(5 Pt 1):1423–1428.
125. Molet S, Hamid Q, Davoine F, et al. IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. *J Allergy Clin Immunol*. 2001;108(3):430–438.
126. Al-Ramli W, Prefontaine D, Chouiali F, et al. T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol*. 2009;123(5):1185–1187.
127. Sergejeva S, Ivanov S, Lotvall J, et al. Interleukin-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *Am J Respir Cell Mol Biol*. 2005;33(3):248–253.
128. Chakir J, Shannon J, Molet S, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol*. 2003;111(6):1293–1298.
129. Rickel EA, Siegel LA, Yoon BR, et al. Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. *J Immunol*. 2008;181(6):4299–4310.
130. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med*. 2012;366(13):1181–1189.
131. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med*. 2013;188(11):1294–1302.
132. Nelson BH. IL-2, regulatory T cells, and tolerance. *J Immunol*. 2004;172(7):3983–3988.
133. Rand TH, Silberstein DS, Kornfeld H, et al. Human eosinophils express functional interleukin 2 receptors. *J Clin Invest*. 1991;88(3):825–832.
134. Busse WW, Israel E, Nelson HS, et al. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. *Am J Respir Crit Care Med*. 2008;178(10):1002–1008.
135. Sims JE, Smith DE. The IL-1 family: regulators of immunity. *Nat Rev Immunol*. 2010;10(2):89–102.
136. Hernandez ML, Mills K, Almond M, et al. IL-1 receptor antagonist reduces endotoxin-induced airway inflammation in healthy volunteers. *J Allergy Clin Immunol*. 2015;135(2):379–385.
137. Kim SR, Kim DI, Kim SH, et al. NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation. *Cell Death Dis*. 2014;5:e1498.
138. Gohlke H, Illig T, Bahnweg M, et al. Association of the interleukin-1 receptor antagonist gene with asthma. *Am J Respir Crit Care Med*. 2004;169(11):1217–1223.
139. Fu JJ, McDonald VM, Baines KJ, et al. Airway IL-1 β and systemic inflammation as predictors of future exacerbation risk in asthma and COPD. *Chest*. 2015;148(3):618–629.
140. Sundaram K, Mitra S, Gavrilin MA, et al. House dust mite allergens and the induction of monocyte interleukin 1 β production that triggers an I κ B ζ -dependent granulocyte macrophage colony-stimulating factor release from human lung epithelial cells. *Am J Respir Cell Mol Biol*. 2015;53(3):400–411.
141. Pascoe S, Kannies F, Bonner J, et al. A monoclonal antibody to IL-1 β attenuates the late asthmatic response to antigen challenge in patients with mild asthma. *Annu Congr Eur Resp Soc*. 2006;752.
142. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax*. 2005;60(12):1012–1018.
143. Krug N, Tschernig T, Erpenbeck VJ, et al. Complement factors C3a and C5a are increased in bronchoalveolar lavage fluid after segmental allergen provocation in subjects with asthma. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1841–1843.
144. Thomas PS. Tumour necrosis factor- α : the role of this multi-functional cytokine in asthma. *Immunol Cell Biol*. 2001;79(2):132–140.
145. Brightling C, Berry M, Amrani Y. Targeting TNF- α : a novel therapeutic approach for asthma. *J Allergy Clin Immunol*. 2008;121(1):5–10; quiz 711–712.
146. Keatings VM, Jatakanon A, Worsdell YM, et al. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med*. 1997;155(2):542–548.
147. Obase Y, Shimoda T, Mitsuta K, et al. Correlation between airway hyperresponsiveness and airway inflammation in a young adult population: eosinophil, ECP, and cytokine levels in induced sputum. *Ann Allergy Asthma Immunol*. 2001;86(3):304–310.
148. Vilcek J, Feldmann M. Historical review: cytokines as therapeutics and targets of therapeutics. *Trends Pharmacol Sci*. 2004;25(4):201–209.
149. Hutas G. Golimumab, a fully human monoclonal antibody against TNF α . *Curr Opin Mol Ther*. 2008;10(4):393–406.
150. Feldmann M, Maini RN. Anti-TNF α therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol*. 2001;19:163–196.

151. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet*. 2002;359(9313):1187–1193.
152. Conroy CA, Cattell R. Infliximab treatment for Crohn's disease. *Postgrad Med J*. 2001;77(909):436–440.
153. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349(21):2014–2022.
154. Deveci F, Muz MH, Ilhan N, et al. Evaluation of the anti-inflammatory effect of infliximab in a mouse model of acute asthma. *Respirology*. 2008;13(4):488–497.
155. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999;340(4):253–259.
156. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. *Am J Respir Crit Care Med*. 2006;174(7):753–762.
157. Edwards CJ, Polosa R. Study of infliximab treatment in asthma. *Am J Respir Crit Care Med*. 2007;175(2):196; author reply 196–197.
158. Wenzel SE, Barnes PJ, Bleecker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med*. 2009;179(7):549–558.
159. Antoniu SA. Golimumab for severe asthma. *Expert Opin Investig Drugs*. 2009;18(9):1421–1423.
160. Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med*. 2006;354(7):697–708.
161. Morjaria JB, Chauhan AJ, Babu KS, et al. The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax*. 2008;63(7):584–591.
162. Holgate ST, Noonan M, Chanez P, et al. Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised, controlled trial. *Eur Respir J*. 2011;37(6):1352–1359.
163. Peng T, Hao L, Madri JA, et al. Role of C5 in the development of airway inflammation, airway hyperresponsiveness, and ongoing airway response. *J Clin Invest*. 2005;115(6):1590–1600.
164. Catley MC, Coote J, Bari M, et al. Monoclonal antibodies for the treatment of asthma. *Pharmacol Ther*. 2011;132(3):333–351.
165. Smith SG, Watson B, Clark G, et al. Eculizumab for treatment of asthma. *Expert Opin Biol Ther*. 2012;12(4):529–537.
166. Baelder R, Fuchs B, Bautsch W, et al. Pharmacological targeting of anaphylatoxin receptors during the effector phase of allergic asthma suppresses airway hyperresponsiveness and airway inflammation. *J Immunol*. 2005;174(2):783–789.
167. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355(12):1233–1243.
168. Lapeyraque AL, Fremeaux-Bacchi V, Robitaille P. Efficacy of eculizumab in a patient with factor-H-associated atypical hemolytic uremic syndrome. *Pediatr Nephrol*. 2011;26(4):621–624.
169. Gauvreau G, Boulet L, Severino B, et al. The effect of C5 inhibition by eculizumab on allergen-induced asthmatic responses. *Allergy*. 2009;64:16.
170. Brown T, Rupani H, Barber C, et al. Dissociation between clinical trial inclusion and exclusion criteria for trials in severe asthma and the reality of the patient population. *Eur Respir J*. 2014;44(Suppl 58).