Abstract

Background: Elucidation of the critical immune pathways involved in allergic inflammation has identified, apart from IgE, therapeutic targets in the cytokine network suitable for intervention by biological therapies.

Objective: The drugs that target the cytokine networks pertinent to asthma and allergic diseases are reviewed and some illustrative case histories presented. The overview proposes a framework to use when deciding which monoclonal antibody (mAb) to select for treatment of severe asthma based on total IgE concentration, peripheral blood eosinophil count, induced sputum analysis and measurement of fractional exhaled nitric oxide (FENO).

Methods: Internet-based literature search including PubMed for studies on biological therapies targeting IgE and the cytokine network in allergic inflammation focusing on asthma with and without rhinosinusitis and nasal polyposis, eczema, urticaria and food allergies. Lists of pivotal trials published in the peer reviewed literature and pertaining to their own mAb products were also provided by GSK, AstraZeneca and Sanofi. Therapeutic agents licensed or in advanced stages of development (Phase 2b and 3) were selected for discussion.

Results: The survey identifies a number of mAbs with substantial potential for the future targeted treatment of asthma with and without rhinosinusitis and nasal polyposis, eczema, urticaria and food allergies uncontrolled by existing therapies. A pragmatic framework is proposed for selecting the optimal mAb for initial use in individual patients with severe asthma.

Conclusions: Launch of these new biologicals may revolutionise the treatment of allergic diseases if employed in an endotype-specific fashion, heralding an unprecedented era of personalised medicine.

Key words: Asthma, Allergy, Cytokines, Biologicals, Precision Medicine

Introduction

Specific humanised monoclonal antibodies (mAbs or ‘biologicals’) have been widely used worldwide for the treatment of cancers, rheumatological disorders, inflammatory bowel diseases and a wide spectrum of immunological disorders. The introduction of new mAbs and discovery of hitherto unknown indications for use of existing mAbs will likely revolutionise the treatment of allergic diseases in the context of targeted therapy and personalised healthcare.

The article discusses mAbs that are already licensed and others that are in advanced development, which have substantial potential for the future treatment of five common diseases, namely asthma with and without rhinosinusitis with nasal polyposis, eczema, urticaria and food allergies, which are unresponsive to other therapies. (Figure 1)
### A Biological Treatments For Disease

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Rhinosinusitis with nasal polyposis</th>
<th>Eczema</th>
<th>Urticaria</th>
<th>Food allergies</th>
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<tbody>
<tr>
<td>omalizumab, mepolizumab, benralizumab, dupilumab, reslizumab, tezepelumab</td>
<td>IL-5 mepolizumab, reslizumab</td>
<td>dupilumab, lebrilizumab, tralokinumab, fezakinumab</td>
<td>omalizumab, ligelizumab</td>
<td>omalizumab, etokimab</td>
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<tr>
<td>IgE omalizumab, ligelizumab</td>
<td>IL-5 receptor benralizumab</td>
<td>IL-4/13 receptor dupilumab</td>
<td>IL-13 tralokinumab, lebrikizumab</td>
<td>Tezepelumab</td>
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<td>IL-22 fezakinumab</td>
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<td>IL-33 etokimab</td>
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### Cytokine regulation of allergic inflammation

A simplified summary of cytokine regulation of allergic inflammation is shown in Figures 2 and 3. Historically it was hypothesised that Th2 cell responses and the Th2 cytokine microenvironment were central to driving the allergic phenotype.1,2 (Figure 2) Dendritic cells were required for activation of naïve T cells andOX40L was an essential co-stimulatory mediator of Th2 responses. Prior to activation and maturation, DCs expressed very low levels of Major Histocompatibility Complex (MHC) and co-stimulatory molecules of their surfaces. However when allergen was internalized and processed by DCs the expression of MHC class II molecules, Cluster of Differentiation (CD)40 and B7 (required for T cell activation) were upregulated. The primed DCs migrated to regional draining lymph nodes to activate naïve T cells through an interaction with the counter co-stimulatory molecules on T cells that included CD28 and CD40 ligand (CD40L).

Activation of naïve T cells in an atopic individual was driven down the pathogenic Th2, as distinct from the Th1 pathway. Activated Th2 cells released Interleukin (IL)-4 and IL-13 in the presence of CD40L to promote IgE synthesis by primed B cells. The allergen-specific IgE bound to mast cells via the high affinity IgE receptor (FceRI), which in turn released their inflammatory mediators upon cross linking of membrane-bound IgE by allergen. Th2 cells also produced IL-5 which increased eosinophil differentiation, growth and maturation in the bone marrow and primed them for activation. Th2 derived IL-4, IL-9 and IL-13 stimulated epithelial cells and smooth muscle to undergo structural remodelling and mucus hypersecretion as well as to contribute to the production of eosinophilic chemokines, such as CCL11 (eotaxin), thereby amplifying the inflammatory reaction.

However, more recently, a number of mechanisms have been discovered which have necessitated a reconsideration of the classical Th2 hypothesis. For instance, it has become abundantly clear that many innate immune cells, especially innate, type 2 lymphocytes (ILC2) also produce Th2-type cytokines and that these can promote differentiation of Th2-like T cells by inducing local OX40L expression on DCs and local class switching of B cells to IgE synthesis. (Figure 3) These ILCs are activated by the alarmins (alarm signalling molecules),3 namely Thymic Stromal Lymphopoietin (TSLP),4 IL-335 and IL-25,6,7 Alarmins are expressed in epithelial cells, endothelial cells and lymphoid organs and released in response to stimuli that include pollutants, viruses and proteins with protease activities acting on protease-activated receptors (PARs), such as house dust mites. Alarmins not only cause Th2 T cell differentiation but also elicit structural remodelling. (Figure 3) TSLP activates immature DCs by binding to the TSLP receptor (TSLPR) and the alpha chain of IL-7 receptor (IL-7R). IL-33 acts through the suppression of tumorigenicity 2 (ST2) receptor on ILC2 to release IL-5 and IL-13. ILC2 cells, in contrast to Th2 cells, are resistant to inhibition to glucocorticoids and in the relatively prednisolone-resistant patients, it is likely that ILC2 cells are the predominant source of IL-5 and IL-13 that contribute to eosinophil recruitment.8,9 IL-25 (IL-17E) supports the Th2 immune response and induces the production of Th2 cytokines. Against the background of this cytokine network, new immune targets for the development of mAbs can be identified. (Figure 1)

### ANTI IgE

Omalizumab (Xolair) binds to the 3rd constant region of the IgE molecule and prevents free IgE from interacting with the high and low-affinity IgE receptors (FceRI and FcεRI). The drug is effective regardless of allergen specificity. It rapidly reduces free but not total serum IgE concentrations by over 95% and also reduces IgE receptor density on mast cells or basophils. In addition it may restore impaired, innate anti-viral immunity through enhanced IFN-alpha responses in plasmacytoid DCs (pDCs) by decreasing allergen bound IgE on pDCs.

Dependent on the patient’s weight (40–120 kg) and total serum IgE concentration (30–1500 kU/L) omalizumab at a dose between 150–375 mg is administered subcutaneously every 2 or 4 weeks, with a maximum dosage of 750 mg every 4 weeks. The drug is positioned at step 5 of the Global Initiative For Asthma (GINA) guidelines.11

A summary analysis of 12 clinical trials of 6427 patients showed that omalizumab therapy reduces the risk of asthma exacerbations and the need for glucocorticoid therapy.12 Omalizumab also reduced airway mucosal IgE+ cells and improved non-atopic asthma.13 Adverse events (AEs) include injection site reactions (10%), headache (27%), back pain (13%), pruritus (1-10%), nasopharyngitis (1-10%), nausea and abdominal pain (1-10%). However, in patients who have severe asthma requiring daily prednisolone, the effectiveness of omalizumab is still unclear.14 Omalizumab did not suppress sputum eosinophilia in these patients suggesting that atopy

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**Figure 1. Summary of biological treatments for asthma, rhinosinusitis with nasal polyposis, eczema, urticaria and food allergies (Panel A) and the immune targets for the monoclonal antibodies (Panel B).**

**Figure 2**

Dependent on the patient’s weight (40–120 kg) and total serum IgE concentration (30–1500 kU/L) omalizumab at a dose between 150–375 mg is administered subcutaneously every 2 or 4 weeks, with a maximum dosage of 750 mg every 4 weeks. The drug is positioned at step 5 of the Global Initiative For Asthma (GINA) guidelines.11

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Figure 2. Regulation of the cytokine network in allergic inflammation and their pathobiological activities.

IFNγ = gamma interferon; TNF = tumor necrosis factor; CD40L = cluster of differentiation (CD) 40 ligand; CCL11 = C-C motif chemokine 11 or eotaxin.
Figure 3. Alarmins (TSLP, IL-33 and IL-25) and their pathobiological effects on allergic inflammation.

IL = Interleukin, TSLP = Thymic Stromal Lymphopoietin, TSLPR = TSLP receptor, IL7Ra = IL-7 alpha chain, MHC = Major Histocompatibility Complex, OX40 = Cluster of Differentiation (CD) 134, OX40L = CD40 ligand, ST2 = suppression of tumorigenicity 2, ILC2 = type 2 innate lymphoid cells
was not the primary driver of eosinophilia for poor asthma control in this group of individuals.\textsuperscript{15} Omalizumab was approved for use in patients with chronic idiopathic urticaria who remain symptomatic despite H\textsubscript{1}-antihistamine treatment.\textsuperscript{16,17} After 12 weeks of monthly subcutaneous injections of omalizumab, patients’ weekly urticaria count score was reduced by over two-thirds and more than a third were completely itch- and hive-free. A multi-centre, randomised, double blinded, placebo controlled XTEND-CIU (Xolair Treatment Efficacy of Longer Duration in Chronic Idiopathic Urticaria) trial showed that continued treatment with omalizumab prevented symptom recurrence throughout 48 weeks of treatment.\textsuperscript{18}

**Case history 1:** A 53 year old man presented with a one year history of urticaria over the last year. The rashes were troubling him daily and were associated with intermittent swelling of his lips. His symptoms were worse if he drank red wine. He had a history of diabetes mellitus and had been taking Glucophage and Januvia for many years. Total IgE was 118 kU/L but sIgE testing revealed no evidence of sensitisation to conventional allergens so might have been due to alarmin-induced production of IgE autoantibodies to cutaneous antigens, although this was unproven. There was no evidence of autoimmune disease and no history of intolerance of non-steroidal anti-inflammatory drugs. A diagnosis of chronic idiopathic urticaria was made. His symptoms were unresponsive to high doses of antihistamines, so he was started on omalizumab 300 mg at monthly intervals. His urticaria started to improve after the first injection of omalizumab and by 3 months he was virtually asymptomatic. He continued his omalizumab therapy for 9 months after which he was able to stop all medication.

For eczema the ADAPT randomised trial showed that 24 weeks of omalizumab therapy reduced eczema severity, improved quality of life (QoL) and was glucocorticoid-sparing weeks of omalizumab therapy reduced eczema severity, improvement after the first injection of omalizumab and by 3 months he was virtually asymptomatic. He continued his omalizumab therapy for 9 months after which he was able to stop all medication.

The key studies on mepolizumab in asthma are summarised in Table 1.\textsuperscript{25-33} The drug is positioned at step 5 of the GINA guidelines. It is recommended as an add-on maintenance treatment in patients with severe asthma who have an eosinophilic phenotype (> 150 peripheral blood eosinophils/μL).

### Table 1. Pivotal Trials for mepolizumab on asthma.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
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<tbody>
<tr>
<td>DREAM\textsuperscript{25}</td>
<td>Design: Phase 2 PBO vs mepo 75 mg IV; 48% reduction at week 52 (p &lt; 0.0001) in clinically significant exacerbations; 60% reduction at week 52 in hospitalizations or emergency room visits.</td>
</tr>
<tr>
<td>MENSA\textsuperscript{26}</td>
<td>Design: Phase 3 PBO vs mepo 100 mg IV; 53% reduction at week 32 (p &lt; 0.001) in clinically significant exacerbations; 61% reduction at week 32 (p = 0.02) in hospitalizations or emergency room visits; 0.44-point improvement at week 32 (p &lt; 0.001) in asthma control; 7.0-point improvement in SGRQ total score at week 32 (p &lt; 0.001); 98 ml improvement in pre-bronchodilator FEV1 at week 32 (p = 0.03).</td>
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<tr>
<td>SIRIUS\textsuperscript{27}</td>
<td>Design: Phase 3 PBO vs mepo 100 mg SC; 32% reduction at week 24 (p = 0.04) in clinically significant exacerbations; 50% reduction of median OCS dose at week 24 (p = 0.007); 0.52-point improvement at week 24 (p = 0.004) in asthma control; 5.8-point improvement in SGRQ total score at week 24 (p = 0.02).</td>
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<tr>
<td>COSMOS\textsuperscript{28}</td>
<td>Design: Phase 3b mepo 100 mg SC; PMG OCS remained low at 2.5 mg/day; PPG OCS reduction from 10.0 mg/day in SIRIUS to 5.0 mg/day in COSMOS; PMG: improvement in asthma control maintained at 52 week; PPG: 0.20-point improvement in asthma control at week 52 (comparing MENSA/SIRIUS and COSMOS); PMG: improvement in pre-bronchodilator FEV1 maintained at week 52; PPG: 100 ml improvement in pre-bronchodilator FEV1 at week 52 (comparing MENSA/SIRIUS and COSMOS).</td>
</tr>
<tr>
<td>COLUMBA\textsuperscript{29}</td>
<td>Design: Phase 3 mepo 100 mg SC; 61% reduction in clinically significant exacerbations (all patients; comparing off-treatment between DREAM and COLUMBA vs on-treatment in COLUMBA); 0.47-point mean improvement in asthma control (0.40-point improvement at week 188 to 0.66-point improvement at week 124) (comparing off-treatment between DREAM and COLUMBA vs on-treatment in COLUMBA) 144 ml improvement in pre-bronchodilator FEV1 at week 24 but no clinically significant difference from baseline at week 20.</td>
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**Table 1. (Continued)**

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<tr>
<th>Trial</th>
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<tr>
<td>MUSCA36</td>
<td>Design: Phase 3 PBO vs mepo 100 mg SC; 58% reduction at week 24 (p &lt; 0.0001) in clinically significant exacerbations; 68% reduction in hospitalizations and emergency room visits at week 24 (p = 0.0031); 0.4-point improvement in asthma control at week 24 (p &lt; 0.0001); Treatment improvement of 7.7 points in SGRQQ total score from baseline at week 24 (p &lt; 0.0001); 120 ml improvement in pre-bronchodilator FEV1 at week 24 (p = 0.001)</td>
</tr>
<tr>
<td>COSMEX31</td>
<td>Design: Phase 3b mepo 100 mg SC; Annual exacerbation rate maintained from COSMOS (0.93) to COSMEX (0.93). Sustained reduction in daily OCS usage from SIRIUS (median OCS dose at weeks 124-128 is 1.3 mg/day; sustained improvement at week 168.</td>
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<tr>
<td>OSMO32</td>
<td>Design: Phase 4 mepo 100 mg SC; 64% reduction in clinically significant exacerbations at week 32; 69% reduction in hospitalizations and emergency room visits at week 32; 1.45-point improvement in asthma control at week 32; 19.0-point improvement in SGRQ total score at week 32; 26.2-point improvement in SGRQ symptom domain at week 32; 159 ml improvement in pre-bronchodilator FEV1 at week 32.</td>
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<tr>
<td>REALITI-A33</td>
<td>Design: Phase 4 open label, single arm, real world; mepo 100 mg SC; 77% reduction of hospitalizations and emergency room visits at week 52; 50% reduction of median OCS dose at week 52; 34% of patients stopped maintenance OCS at week 52.</td>
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Comparison done between mepolizumab dosing arm and placebo or baseline unless otherwise specified. Only statistical significance reported in respective published literature is included. Mepolizumab 75 mg IV dose is equivalent in terms of bioavailability to 100 mg SC dose. The expected completion of the REALITI-A study is 2021 and the data currently published contains the interim-analysis of the 1-year duration of the study. ACQ: Asthma control questionnaire; FEV1: forced expiratory volume in 1 second; mepo: mepolizumab; PMG: previous mepolizumab group; PPG: previous placebo group; PBO: placebo; SC: subcutaneous; SGRQ: St George’s Respiratory Questionnaire.

**Case history 2:** An 83 year old Chinese lady had longstanding chronic asthma with 2 monthly exacerbations associated with mucopurulent sputum and intermittent rhinosinusitis. Her forced expiratory volume in one second (FEV1) was 82% predicted, forced expired ratio (FER) 65% and FENO 213 ppb (normal range < 25 ppb). Skin prick testing showed a small 5×5 mm weal to Dermatophagoides farinae (DF) and Dermatophagoides pteronyssinus (DP) only. Her peripheral blood eosinophil count was 1600 /μL (22.3%).

She had been treated for many years with all the classes of anti-asthma medications recommended for steps 4 and 5 of the GINA guidelines, but none of them reduced the frequency of her asthma exacerbations. As she exhibited an eosinophilic asthma phenotype, she was started on monthly mepolizumab 100 mg SC. Within 2 weeks of starting treatment her FEV1 was 111% predicted, FER 72%, FENO 44 ppb and her peripheral blood eosinophil count was undetectable. She continues her monthly injections and she has been well for 6 months. The cause of her IL-5 induced eosinophilia is unknown, but alarmin-driven production of IL-5 from respiratory mucosal ILC2 cells, which are resistant to glucocorticoid inhibition, is a strong though unproven possibility.

**Reslizumab** (Cinqair) also binds specifically to IL-5. It is an IgG4 mAb. It is given intravenously 3 mg/kg IV over 20 to 50 minutes every 4 weeks. Intravenous reslizumab or placebo administered every 4 weeks for 1 year was compared in 2 multicentre, double-blind, parallel-group, randomised, placebo-controlled phase 3 trials. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations.34-36 Post-hoc analysis of this data suggests that the drug is also of benefit for those patients taking daily prednisolone,35 and also those who may not adequately respond to the fixed-dosage regimen of mepolizumab.36 AEs include oropharyngeal pain (1-10%), elevated CPK (14%) and anaphylaxis (0.1-1%).

**ANTI IL-5 RECEPTOR**

**Benralizumab** (Fasenra) is an IgG1 mAb directed against the alpha-chain of the IL-5 receptor, thereby blocking the binding of IL-5. In addition, it binds simultaneously to FcγRIIa on natural killer cells triggering antibody-dependent cell-mediated cytotoxicity. This leads to amplified eosinophil apoptosis and reduced eosinophilic inflammation. This unique action of benralizumab is not observed with mepolizumab and reslizumab.

Benralizumab 30mg is injected SC 4-weekly for 8 weeks followed by 30 mg every 8 weeks thereafter. AEs are mild and include headache (8.6%), pharyngitis (4%), arthralgia (3.9%), cough (3.3%) and injection site reactions (2.2%).

The key studies on benralizumab in asthma are summarised in Table 2.39-42 The drug is also positioned at step 5 of the GINA guidelines and, identical to mepolizumab and reslizumab, is recommended as an add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype (> 150 peripheral blood eosinophils/μL).

**Table 2. Pivotal trials on benralizumab for asthma.**

<table>
<thead>
<tr>
<th>Trial</th>
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<tbody>
<tr>
<td>Sirocco36</td>
<td>Benralizumab significantly decreased the annual asthma exacerbation rate compared with placebo at week 48, for the Q8W cohort, the rate ratio versus placebo was 0.49 (0.37-0.64; p &lt; 0.0001)</td>
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<tr>
<td>SIROCCO36</td>
<td>Reduced asthma exacerbations leading to emergency department visits or hospital admissions compared with placebo treatment (rate ratio 0.37, 95% CI 0.20-0.67; p = 0.0010). Significantly improved pre-bronchodilator FEV1 in patients at week 48 compared with placebo. Reductions in asthma symptoms (Total Asthma Score) at week 56 and 48 compared to patients receiving placebo. Similar improvement was observed for the Asthma Control Questionnaire-6 (ACQ-and Standardized Asthma Quality of Life Questionnaire for 12 Years and older (AQLQ(6) +12).</td>
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A 55 year old lady with asthma, chronic rhinosinusitis and nasal polyposis had been receiving frequent courses of prednisone 4-5 times a year. Her skin prick tests to ragweed pollen and house dust mites (HDM) were positive and her total serum IgE was 500 kU/L. Her asthma control had been maintained on daily 20 mg prednisone, budesonide 2400 µg/fomoterol 24 µg and nasal budesonide saline rinses. Her blood eosinophil count was 900/µL and sputum eosinophil count was 60% with many free eosinophil granules. Her Asthma Control Questionnaire-5 (ACQ-5) score was 3.4.

She had previously failed to show any clinical improvement following one year of treatment with omalizumab. In the context of a clinical trial, she received mepolizumab 100 mg SC for a year and her blood eosinophil counts were normalised. However, on reducing her prednisone to 12.5 mg daily, she had an exacerbation of asthma that was associated with a sputum eosinophil count of 20% with many free granules. Her sinus CT showed bilateral ethmoid, maxillary and sphenoid mucosal thickening without polyposis.

She then participated in a clinical trial of reslizumab 3 mg/kg IV monthly for 4 months. At the end of the treatment, her sputum eosinophil count had reduced to 8% but still with many free granules. Her blood eosinophils remained undetectable. On gradual reduction of prednisone to 7.5 mg daily, she developed an exacerbation of asthma which was associated with both blood and sputum eosinophilia, and her prednisone dosage had to be increased up to 12.5 mg daily.

She was switched to receive benralizumab 30 mg SC monthly for 3 months and then every alternate month. Her prednisone dosage was slowly tapered in a controlled manner after 1 month and then every alternate month. Her prednisone dosage had been maintained throughout the entire treatment period.

Table 2. (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
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<tr>
<td>CALIMA</td>
<td>56 weeks of treatment with benralizumab Q8W resulted in approximately 28% lower in annual exacerbation rate compared with placebo for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥ 300 cells per µL. Significant increase in pre-bronchodilator FEV1, compared with placebo for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥ 300 cells per µL. Improvements in pre-bronchodilator FEV1 were present within 4 weeks of treatment start and were maintained throughout the entire treatment period.</td>
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<tr>
<td>ZONDA</td>
<td>Benralizumab treatment (28 week) significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group (P &lt; 0.0001 for both comparisons).</td>
</tr>
<tr>
<td>BORA</td>
<td>753 (72%) of 1046 patients with blood eosinophil counts of 300 cells per µL or greater at baseline did not have asthma exacerbations during benralizumab treatment. The pre-bronchodilator FEV1 values, ACQ-6 and AQOL(s) +12 scores for patients who had received benralizumab in SIROCCO or CALIMA were maintained into the second year of treatment.</td>
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**Case History 3**: A 55 year old lady with asthma, chronic rhinosinusitis and nasal polyposis had been receiving frequent courses of prednisone 4-5 times a year. Her skin prick tests to ragweed pollen and house dust mites (HDM) were positive and her total serum IgE was 500 kU/L. Her asthma control had been maintained on daily 20 mg prednisone, budesonide 2400 µg/fomoterol 24 µg and nasal budesonide saline rinses. Her blood eosinophil count was 900/µL and sputum eosinophil count was 60% with many free eosinophil granules. Her Asthma Control Questionnaire-5 (ACQ-5) score was 3.4.

However, on reducing her prednisone to 12.5 mg daily, she had an exacerbation of her asthma which was associated with both blood and sputum eosinophilia, and her prednisone dosage had to be increased up to 12.5 mg daily. She then participated in a clinical trial of reslizumab 3 mg/kg IV monthly for 4 months. At the end of the treatment, her sputum eosinophil count had reduced to 8% but still with many free granules. Her blood eosinophils remained undetectable. On gradual reduction of prednisone to 7.5 mg daily, she developed an exacerbation of asthma which was associated with both blood and sputum eosinophilia, and her prednisone dosage had to be increased up to 12.5 mg daily. She was switched to receive benralizumab 30 mg SC monthly for 3 months and then every alternate month. Her prednisone dosage was slowly tapered in a controlled manner after her 2nd dose of benralizumab. Following one year of treatment, she was completely weaned off prednisone and was maintained on 400 µg of budesonide and 12 µg of formoterol daily. Her spirometry was normal and FENO was 15 ppb. Blood and sputum eosinophils were undetectable and her ACQ-5 score was zero. However, her sinuses were still not optimally controlled.

This case suggests that for adequate asthma control and a prednisone-sparing effect, an intervention needs to control both peripheral blood and airway eosinophilia. Mepolizumab and reslizumab bind to IL-5 while benralizumab is an IL-5 receptor antagonist as well as promoting eosinophil apoptosis, so while the drugs are related and are all anti IL-5 biologicals, they are not identical in their modes of action. Thus it may still benefit patients to have a trial of another related mAb with a different mode of action even when a previous course of therapy with other anti IL-5 biologicals was ineffective, provided the reason for inadequate asthma control is ongoing eosinophilia. It is important to assess this as exacerbations on anti-eosinophilic biologicals do not necessarily have to be eosinophilic. Some of them, particularly on benralizumab, for currently unknown reasons, may be neutrophilic due to infective bronchitis.

**ANTI IL-4/13 RECEPTOR**

*Dupilumab (Dupixent)* is a receptor antagonist and binds to the alpha subunit of the IL-4 receptor (IL-4Ra). As both IL-4 and IL-13 signal through IL-4Ra, dupilumab modulates both pathways. The pivotal clinical trials on eczema are shown in Table 3. It is indicated for the treatment of patients with moderate-to-severe eczema whose disease is not adequately controlled. The most frequent AEs of about 10% are injection site reactions and conjunctivitis.

Table 3. Pivotal trials on dupilumab for eczema.

<table>
<thead>
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<tr>
<td>SOLO 1 and SOLO 2</td>
<td>671 patients &gt; 18 years old with moderate-to-severe eczema that was inadequately controlled by or medically inadvisable for treatment with topical therapy were enrolled in SOLO 1 and 708 in SOLO 2. In SOLO 1, the primary outcome occurred in 38% who received dupilumab every other week and in 37% who received dupilumab weekly, as compared with 10% who received placebo (P &lt; 0.001). The results were similar in SOLO 2. Improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in more patients who received dupilumab (P &lt; 0.001). Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups.</td>
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Case history 4: A 25 year old Chinese student had long-standing severe asthma since the age of 2 years old. He had been treated intensively with emollients, topical steroids, calcineurin inhibitors, topical and oral antibiotics and antihistamines on many occasions but without sustained improvement. His SCORAD (SCORing Atopic Dermatitis) score was 69.35. He was sleeping poorly and could not concentrate on his studies because of the constant itchiness and discomfort. His total IgE was 1515 kU/L and he was allergic to DF, DP and Blomia tropicalis (BT). He was commenced on dupilumab 600 mg SC stat and then 300 mg SC every two weeks thereafter. His eczema improved after his first injection of dupilumab. His SCORAD score was 18.25 at 4 months after starting his treatment. He could sleep better and was able to concentrate on his studies achieving a distinction grade in one of his final examinations.

The key studies on dupilumab in asthma and chronic rhinitis with nasal polyposis are shown in Table 4. It is recommended for use as an add-on maintenance treatment for patients with moderate-to-severe asthma with an eosinophilic phenotype, or with glucocorticoid-dependent asthma regardless of phenotype (step 5 of GINA guidelines).

Case history 5: A 66 year old Chinese man had rhinitis since childhood. Ingestion of aspirin caused wheezing and eye swelling when he was 60 years old and asthma started to trouble him 2 years later. The patient's most disturbing symptom was a loss of his sense of smell and taste because he was a food and wine connoisseur. His sense of smell would return briefly if he took prednisolone 25 mg daily for 2 weeks but it would be lost again when the drug was stopped. His total IgE was 859 kU/L and his skin prick test was only barely positive.
Recent evidence suggested that the use of dupilumab was associated with a reduced risk of discontinuation due to AEs. The rates of discontinuation in the 52 week trial by 61%, 71% and 66% at 280 mg injected SC every two weeks, 210 mg every 4 weeks and 70 mg every 2 weeks for 12 weeks with concomitant inhaled asthma medications, theophyllines, montelukast, nasal washes, nasal steroids, intermittent courses of oral steroids and even mepolizumab, but none of them provided any sustained improvement. His ENT specialist advised against surgery because of the high likelihood of recurrence of the polyps following surgical removal.

His aspirin exacerbated respiratory disease (AERD) was treated with dupilumab 600 mg SC stat followed by 300 mg SC at 2 weekly intervals. Within 2 weeks of his first injection of dupilumab his sense of smell was normal. Nasendoscopic examination performed at 4 months showed that the nasal polyps had disappeared. His recent FEV1 was 85% predicted, FER 67% and FENO 36 ppb.

**ANTI IL-13**

*Tralokinumab* neutralises IL-13. In a phase 2b study, 204 adults with eczema were treated with increasing doses of the mAb or placebo every 2 weeks for 12 weeks with concomitant topical glucocorticoids. Subjects injected with tralokinumab 300 mg SC showed improvements in SCORAD, Dermatology Life Quality Index and pruritus. Upper respiratory infections were the most frequent AE (3.9%).

*Lebrikizumab* binds to free IL-13 with very high affinity and inhibits the formation of the IL-13Ra/IL-4Ra heterodimer complex and downstream signalling. The mAb was tested in a multi-centre, randomised, double blind, placebo controlled, phase 2b trial over 16 weeks in 280 adult patients with moderate to severe eczema. The drug effected significant and dose-dependent improvements at 125 mg injected SC every 4 weeks (p = 0.017), 250 mg injected SC every 2 weeks (p = 0.002) and 250 mg administered SC every 4 weeks (p = 0.0005). It is now in phase 3 trials. The most common AEs reported ranged from 3.1–7.5% and included upper respiratory tract infection, nasopharyngitis, headache and injection site pain. Early phase 2 studies showed it to be effective in asthma, but it did not meet pre-specified outcomes in late phase 3 trials, so is not being developed any further to treat asthma.

**ANTI TSLP**

*Tezepelumab* is a human mAb that competes with the receptor binding site on TSLP. In 550 adult patients with moderate-to-severe asthma, the drug reduced asthma exacerbations in the 52 week trial by 61%, 71% and 66% at 280 mg injected SC every two weeks, 210 mg every 4 weeks and 70 mg every 4 weeks respectively. It appeared to be efficacious irrespective of asthma phenotype and is currently in phase 3 trials. Three serious adverse events were recorded: two (pneumonia and stroke) occurred in the same patient and one subject developed the Guillain–Barré syndrome. The rates of discontinuation due to AEs were 1.2% among patients and 0.7% in the placebo group.

**ANTI IL-22**

Serum IL-22 levels are increased in patients with eczema and expression in the skin of mice caused an atopic dermatitis-like phenotype. *Fzezakinumab*, which is an anti IL-22 mAb, was tested in a randomised, double-blind, placebo-controlled phase 2a trial in eczema patients as intravenous monotherapy every 2 weeks for 10 weeks with follow-up assessments until 20 weeks. In the severe subset the improvement in SCORAD was significantly stronger in the drug-treated patients at 12 weeks and 20 weeks (P = 0.010). Improvements in body surface area involvement were significantly stronger in the drug-treated patients (P = 0.009). Commonest AE was upper respiratory tract infections (10%).

**ANTI IL-31**

IL-31 is released from Th2 cells and mast cells following cutaneous penetration by antigens. It stimulates sensory neurons and contributes to itching in eczema. *Nemolizumab* is directed against the IL-31Ra subunit so blocks IL-31 signalling. A 24-week, randomised, double-blind, multicentre study of nemolizumab (10 mg, 30 mg and 90 mg) SC improved the Eczema Area and Severity Index, the peak pruritus numeric rating scale, and the Investigator’s Global Assessment, with the 30-mg dose being most effective. It is now in phase 3 studies. AEs included nasopharyngitis, eczema exacerbation, increased CPK, upper respiratory infection, headache, peripheral oedema and impetigo.

**ANTI IL-33**

IL-33, an alarmin, is expressed in epithelial cells, endothelial cells and lymphoid organs. It is rapidly released by pollutants, allergens or infection. It binds to the receptors ST2, also known as IL-1RL1 (interleukin 1 receptor-like 1) and IL-1RacP (IL-1 receptor accessory protein), both of which are expressed by innate immune cells (ILC2) and Th2 cells. It stimulates production of IL-5 and IL-13. Recent evidence suggests that TSLP and IL-33 may reciprocally promote each other’s lung protein expression and ILC2 receptor expression to enhance innate type-2 airways inflammation.

*Etokimab* is an anti–IL-33 mAb in phase 2b development and its half-life is 15.5 days. A single dose, 6-week, placebo-controlled phase 2a study in 15 adults with severe peanut allergy showed efficacy. On days 15 and 45 after dosing with etokimab 300 mg IV, 73% and 57% respectively of the patients tolerated ingestion of 275 mg of peanut protein. No subject in the placebo group passed the peanut challenge. Peanut-specific IgE was significantly reduced in the active group compared with the placebo group on day 15 (P = 0.014). Thus a single dose of etokimab desensitised many peanut-allergic patients for at least 6 weeks. No patients reported AEs. The mechanism of efficacy is being investigated but could reflect, at least in part, attenuation of those downstream allergic pathways dependent upon IL-33 (IL-5, IL-9, IL-13, IL-4) in CD4+ T cells. It has also been proposed that the effect on IgE synthesis could be due to the blockade of IL-33 stimulating ST2 on B cells.
Proposed pragmatic scheme for selecting a mAb to treat severe asthma

The majority of asthmatic patients will respond to the traditional guidelines–based therapies but 5-10% will fail to improve despite optimisation of compliance and management of co-morbidities. These patients comprise up to 95% of health care costs and economic burden. The advent of biologicals introduces a new paradigm of targeted medicine which could potentially help these patients with severe asthma.

Some indirect comparative studies between the effectiveness of different mAbs have been published for asthma, in contrast to biologicals for other allergic diseases which have not been similarly compared. Even in asthma more independent research employing direct head-to-head comparisons is urgently needed. In addition while some biomarkers have been identified that define different disease endotypes in asthma, or at least endotypes likely to respond to anti-IL-5 strategies, there are few or no biomarkers used in clinical practice that will predict responsiveness to targeted biologicals for the other diseases discussed in this review.

Until more data are forthcoming, a pragmatic framework for targeted therapy is proposed based on a patient’s biomarkers, namely peripheral blood eosinophil count, FENO, induced sputum analysis, total IgE, the physiological measurement of airway hyperresponsiveness and prednisolone usage, to aid selection of the mAb to use in severe uncontrolled asthma. (Figures 4A and 4B) Apart from quantitative sputum cytometry, the other biomarkers are readily available in virtually all Centres.

It is suggested that in the presence of a high peripheral blood and sputum eosinophilia that may or may not be associated with raised FENO, an anti IL-5 approach could be an appropriate choice. (Figure 4A) It is worth noting that elevated FENO is not a predictor of response to anti IL5 mAbs and that FENO is not reliably reduced with anti IL5 therapies.

In general with anti IL-5 strategies the higher the blood eosinophil counts, the better the clinical response. It appears that eosinophil counts of > 300 cells/µL in the context of asthma and not some other external causes are more likely to be truly indicative of the eosinophil being a key effector cell in the patient’s asthma pathobiology.

![Figure 4. Proposed framework for selecting a biological treatment for asthma based on (A) peripheral eosinophil count, FENO, induced sputum cytometry and total IgE concentrations. If patient remains symptomatic despite normalizing blood and sputum eosinophil counts, symptoms may be driven by airway hyperresponsiveness. (B) blood eosinophils, FENO and prednisolone dosage. There are no head to head comparisons or cross-over studies of patients who had failed on one therapy. Panel B is modified from reference 69.](image-url)
With respect to the selection of which anti IL-5 mAb, all molecules are equally effective in reducing exacerbations by 50-60% in most patients with severe asthma who are on high dose of inhaled corticosteroids. Three doses of benralizumab are injected in the first 2 months then one dose is given every 2 months, whereas mepolizumab is given monthly, and reslizumab is given monthly intravenously, so the final decision on which mAb to use may depend on patient preferences. The magnitude of the treatment effects on reductions in exacerbations and prednisolone-sparing, at least with the current recommended dosing regimens in the prednisolone-dependent patients may be greater with benralizumab and dupilumab than with mepolizumab but more research is required to substantiate this clinical observation. As the action of benralizumab involves NK cells, it may not be the first choice if the patient has reduced NK cell counts or has a predisposition to airway infections, but this hypothesis also requires further prospective examination.

The presence of recurrent respiratory viral infections with or without high IgE and severe allergies could encourage the use of omalizumab. (Figure 4B) In the absence of an eosinophilia, especially if there is accompanying eczema, chronic rhinosinusitis and nasal polyposis with or without NSAID sensitivity, and particularly when associated with raised FENO,46 airway mucus47,48 and airway hyperresponsiveness, dupilumab may be the best option. Novel imaging techniques such as noble gas functional MRI and dual-source airway CT scans may enable a determination of intraluminal mucus plugging but these are not readily available in most Centres. In patients requiring < 10 mg/day of prednisolone, mepolizumab, benralizumab or reslizumab could be the drugs of choice, whereas for those taking > 10 mg/day prednisolone with accompanying persistent sputum eosinophilia, benralizumab or reslizumab may be better options.50 (Figure 4B)

Persistent sputum eosinophilia despite normalising blood eosinophilia in a symptomatic patient may reflect inadequate dosing, neutralising antibodies, or other causes of eosinophil recruitment. On-going symptoms and poor asthma control may also reflect recurrent respiratory tract infection (reflected by neutrophilic bronchitis) rather than lack of efficacy of the anti IL-5 mAb. Mepolizumab, benralizumab and dupilumab are untested for the management of acute asthma exacerbations.

Depletion of eosinophils inevitably raises concerns about the safety of long term usage of anti IL-5 drugs. Clinical and experimental evidence from eosinopenic human subjects and murine strains devoid of eosinophils have not, however, suggested any increased susceptibility to infections, cancer or other abnormalities of global health.70 Nonetheless helminthic infections should be treated prior to commencing anti IL-5 therapies and some clinicians, especially in endemic regions, advocate screening of patients for pre-existing helminthic infections, for example with a blood test for Strongyloides IgG. If a helminthic infection is contracted during anti IL-5 therapy, the drug should be stopped if anti helminthic treatment is not effective. In a small proportion of severe prednisolone-dependent patients, inadequate dosing with anti IL5 mAb may exacerbate asthma secondary to the effects of IL5 anti IL5 mAb immune complexes activating complement.

Conclusions

This is an exciting time for asthma and allergy. Omalizumab, mepolizumab, benralizumab and reslizumab are already licensed for the treatment of severe uncontrolled asthma. Omalizumab is used for urticaria and its efficacy in paediatric eczema looks promising. Dupilumab is licensed for treating eczema, asthma and chronic rhinosinusitis with nasal polyposis. In addition there are many other biologicals in the pipeline, so the demand for effective and targeted mAbs to treat allergic diseases will surely grow. The introduction of potent and specific non-allergen directed biological treatments with or without new allergen-specific desensitisation strategies, which are also in the advanced stages of development, could herald an unprecedented era of personalised medicine for allergic diseases. The on-going challenge is to identify biomarkers that define disease endotypes which can then be used to exploit these specific and potent biologicals for targeted therapy in the context of precision medicine.

Conflict of interest

The authors have no potential conflicts of interests to declare.

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