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REVIEW

Biologic therapy in asthma: entering the new age of personalized medicine

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Abstract

Objective: Asthma is a common chronic disease with various phenotypes and therapeutic responses. Unlike other diseases, current anti-inflammatory treatment with corticosteroids does not include any reference to biological measures which may vary among different asthma phenotypes. Morbidity from uncontrolled asthma suggests a need for specific targeted treatment approaches such as biologic medications. In half of asthmatics, chronic airway inflammation may be driven by T helper (Th)-2 cells, which release pro-inflammatory cytokines, such as interleukin (IL)-4, IL-5 and IL-13, contributing to eosinophil inflammation and IgE production. Earlier studies of cytokine-targeted biologic therapy on non-phenotyped asthma patients were generally not clinically effective. *Methods*: Literature published from 1958–2013 was identified through PubMed using the search terms which included asthma and therapy. A total of 32 studies were reviewed covering both pediatric and adult asthmatics and included double-blind randomized placebo-controlled trials testing efficacy of biologic agents to treat asthma. *Results*: More recent approaches to personalized medicine with expression profiling studies, genetic analysis and clinical biomarkers of Th2 inflammation have allowed identification of asthma phenotypes including a Th2 "high" phenotype. Studies targeting IgE, IL-5, IL-13 and the IL4 receptor alpha chain have shown some efficacy in phenotyped patients. For those without evidence of Th2 inflammation, no specific therapies have been identified. *Conclusions*: In recent years, the identification of Type-2 cytokine "high" asthma in numerous studies has predicted the clinical response to the Th2 associated therapies. It is not yet clear whether all Type 2 high asthma will respond similarly to IL-4, 5 and 13 approaches.

Keywords

Asthma, biologic therapy, interleukin (IL)-4, IL-5, IL-13, eosinophils, T helper (Th)-2 cells

History

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Objective

Defining asthma

Asthma, affecting 6–8% of the US population [1], is generally defined as a chronic inflammatory airway disorder with reversible airflow limitation or bronchial hyperresponsiveness in association with appropriate clinical symptoms [2]. This definition is similar to those for ''arthritis'' or ''anemia,'' which describe non-specific inflammation in a joint or low red blood cell counts. In fact, the terms asthma, arthritis and anemia are all non-specific descriptors and do little to acknowledge this heterogeneity of the underlying processes that contribute to them. This realization has contributed to the increasing perception that characterizing the heterogeneity of asthma, through identification of its clinical and then molecular phenotypes, is necessary to improve both the understanding and treatment of this heterogeneous syndrome.

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Current asthma treatment predominantly utilizes nonspecific anti-inflammatory drugs such as inhaled and oral corticosteroids (CS) and bronchodilators which are effective in the majority of patients. This ''one size fits all'' approach to asthma treatment has also contributed to a lack of investigation into what now seem like obvious asthma phenotypes. It is now appreciated that 30–40% of asthmatics will have a poor response to traditional treatment approaches, and in 10% this likely contributes to the presence of severe asthma [1,3]. The resulting and continuing morbidity in this population suggests that defining the underlying molecular phenotype could identify effective targeted biologic therapies for these patients (Figure 1).

Biologic therapies in disease treatment

Stedman's medical dictionary defines a biological agent as ''a diagnostic, preventive, or therapeutic preparation derived or obtained from living organisms and their product, e.g. serum, vaccine, antigen, antitoxin; a compound or medicine derived from living products, rather than chemicals'' and therapy as ''the treatment of disease or disorder by any method'' [4]. Since the advent of humanized monoclonal antibodies,

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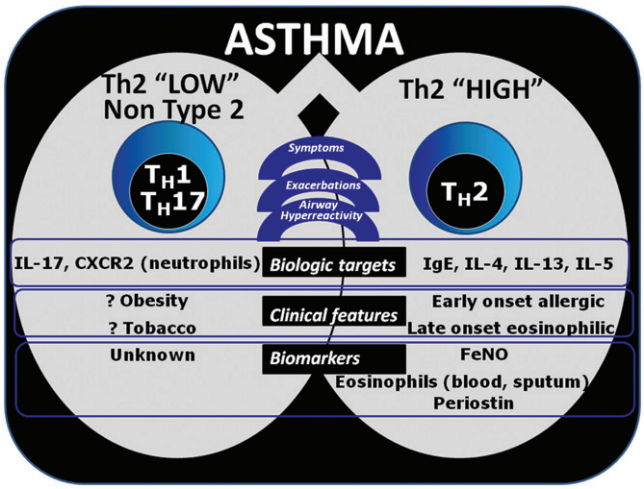

Figure 1. The schematic representation of phenotyped asthma by Th2/Type 2 cytokines. While all asthma (Th2 high and Th2 low) share certain symptoms and lung function, there are some distinctive features including pathobiology and biomarkers which may guide directed asthma treatment particularly for Th2 high asthmatics.

biologic therapies have generally referred to these compounds, as well as soluble receptors and genetically altered cytokines. These compounds were initially successful in rheumatoid arthritis opening doors to use in other diseases. For years, the inflammation associated with ''asthma'' was assumed to be primarily driven by T helper (Th)-2 cells, which release pro-inflammatory cytokines, such as interleukin (IL)-4, IL-5 and IL-13, contributing to eosinophil inflammation and Immunoglobulin (Ig)E production. Thus, elements of this pathway became natural targets for development of molecularly targeted biologic therapies.

IgE was the first molecule successfully targeted by monoclonal antibodies for the treatment of asthma. Studies using a recombinant humanized monoclonal anti-IgE antibody, rhuMAb-E25, which forms complexes with free IgE and blocks its interaction with mast cells and basophils, have shown moderate efficacy in moderate-to-severe allergic asthma, as defined by the presence of atopy and an IgE >30 IU/ml, primarily reducing asthma exacerbations (Table 1) [5–11]. Anti-IgE therapy has also demonstrated efficacy in allergen challenge models of asthma [12–16]. Widespread use of omalizumab was limited, however, by its expense, its need for 1–2 time per month dosing, involving more than one subcutaneous injection, and perhaps most importantly an inability to predict response to therapy.

IL-5 has also been a target for biologic therapy in asthma. Interestingly, however, unlike anti-IgE therapy, anti-IL5 (mepolizumab) was not effective in decreasing the fall in FEV1 observed during allergen challenge, although it was very effective in reducing blood and sputum eosinophils. In a double-blind randomized placebo-controlled trial, clinical effects of a single intravenous infusion of humanized anti- IL5 were measured at weeks 1 and 4 with monitoring of blood eosinophil counts for up to 16 weeks [17]. While anti-IL5 lowered the mean blood eosinophil count and prevented an increase in blood eosinophils following allergen challenge, there was no significant effect of the drug on the late asthmatic response or on airway hyperresponsiveness to histamine [17]. Mepolizumab, given intravenously over 20 weeks, decreased eosinophils in the airway, bone marrow, and blood, while reportedly having no effect on airway tissue eosinophils or in clinical measures of asthma such as airway hyperresponsiveness and FEV1 [18]. In a follow-up study in moderate persistent non-phenotyped asthmatics despite high dose inhaled CS therapy, treatment with three intravenous infusions of mepolizumab at monthly intervals was associated with a significant reduction in blood and sputum eosinophils, but no significant change in clinical measures including FEV1, symptom scores, daily β-agonist use and quality of life measures and a nonsignificant trend for a decrease in exacerbation rates [19]. In general, these earlier studies of cytokine-targeted biologic therapy on patients with non-phenotyped asthma (i.e. all phenotypes of asthma grouped together) were marginally effective (anti-IgE) or not effective (anti-IL-5). This is, despite efficacy in animal models, which rely primarily on an allergen challenge (allergic phenotype) model system.

In the past decade, there has been a renewed interest in biologic therapy for asthma with the realization that not all patients will respond to standard therapies such an inhaled and even systemic CS. Moreover, there is interest in personalized medicine to improve long-term outcomes in severe asthma, as these patients respond poorly to standard asthma therapy, living day to day with high levels of symptoms, decreased quality of life, frequent and severe exacerbations, all of which contribute to increased health care utilization and expense. However, for these biologic therapies, which are currently all very expensive, to impact the treatment of the various phenotypes of severe asthma, clinicians will need to have molecular and clinical markers available which can help select the asthma patients that would benefit most from these medications.

Thus, over the last 15 years there have been intensive efforts to better understand both the presence of asthma phenotypes, as well as the underlying pathobiology which drives them. This connection of clinical and molecular phenotypes is required before the biomarkers to identify the correct group of patients for specific biologic therapies are understood. This process took a major step forward in 2007 when Woodruff et al. found increased airway epithelial expression of 3 genes [chloride channel, calcium activated, family member 1 (CLCA1), periostin, and serine peptidase inhibitor, clade B (ovalbumin), member 2 (serpinB2)] in asthma, down-regulated by corticosteroid treatment, and upregulated in vitro in airway epithelial cells in response to IL-13, suggesting that their ex vivo expression was likely due to Th2 (IL-4 or -13) stimulation of the epithelial cells [20]. Subsequent studies found these 3 genes to be upregulated only in a subgroup of mild, CS naïve asthmatics [21]. Using these 3 signature genes, a ''cluster'' of mild asthmatics with more atopy, eosinophils and bronchial hyperresponsivness and more expression of canonical Type 2 cytokines IL-4, 5 and 13 was found and suggested to be a group of Th2 ''high'' asthmatics, suggesting these as Th2 signature genes in the asthmatic epithelium [21].

This concept of Th2-high asthma (probably more correctly Th2-like or Type-2 cytokine ''high'' asthma given the ability of non-Th2 cell to express these cytokines) has quickly

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Table 1. Features of Biologic therapy studies in Th2-like high versus low asthma.

Parameter	Clinical features	Mediator involved	Biologic therapy target	Benefits
Asthma Phenotype				
	Chronic asthma, symptoms despite bronchodilators, ↑ sputum eosinophilia		Prednisolone	↓ Asthma bronchospasm [22]
Th2-like high	*General:* Early-onset, atopic			
	Moderate–severe allergic asthma on ICS or OCS (ages 11–50 years)	IgE	Monoclonal anti-IgE antibody (rhuMAb-E25)	↓ Asthma symptoms, ↓ oral CS use, ↓ free IgE in serum [5]
	Moderate–severe allergic asthma on ICS (ages 6–12 years)		Monoclonal anti-IgE antibody (Omalizumab)	↓ ICS requirement, ↓ asthma exacerbations [6]
	Persistent, inner-city asthma, +perennial allergy testing, total serum IgE ≥30 to ≤ 1300 IU/mL ages 6–20 years		Monoclonal anti-IgE antibody (Omalizumab)	↓ Asthma exacerbations, ↓ days with asthma symptoms [8]
	Moderate-severe allergic asthma, + perennial allergy testing, total serum IgE ≥30 to ≤ 700 IU/mL		Monoclonal anti-IgE antibody (Omalizumab)	↓ ICS use, ↓ asthma exacerbations [7,9,11] ↓ rescue β agonist use [7]
	Moderate-severe allergic asthma, +allergy testing to indoor allergen, total serum IgE ≥30 to ≤1300 IU/mL, persistent allergic rhinitis		Monoclonal anti-IgE antibody (Omalizumab)	↓ Asthma exacerbations, ↑ asthma and rhinitis quality of life [10]
More recent phenotyped study	Severe persistent allergic asthma inadequate controlled on ICS/LABA, Th2 high biomarker subgroups:↑ FeNO, ↑ blood eosinophils or ↑ serum periostin		Monoclonal anti-IgE antibody (Omalizumab)	↓ asthma exacerbations in all 3 Th2 high biomarker subgroups [45]
	Mild, stable, atopic asthma undergoing allergen challenge		Mutant IL-4 molecule (pitrakinra)	Less ↓ in FEV1 and β agonist use after allergen challenge [28]
	Moderate, CS treated asthma, otherwise non-phenotyped	IL-4 & IL-13	Humanized monoclonal antibody to IL4R α (AMG 317)	↓ serum IgE, no improvement in asthma outcomes, modest benefit in worst asthma control subgroup [16]
	+SNPs of IL-4R α gene in moderate-severe asthma		Mutant IL-4 molecule (pitrakinra)	↓ asthma exacerbations [32]
More recent phenotyped study	Moderate-severe asthma, mid-high dose ICS/LABA; Blood eosinophils ≥300cells/ul or sputum eosinophils ≥3%		Humanized monoclonal antibody to IL4R α (dupilumab)	↓ asthma exacerbations, ↓ β agonist use, ↓ upper airway symptoms, ↓ FeNO (@ week 12),↑ FEV1, ↑ asthma control [35]
	Mild, stable atopic asthma, no ICS undergoing allergen challenge		Humanized IL13 antibody (IMA-638)	↓ early and late asthma response [29]
More recent phenotyped study	Th2 ''high'' status determined by: Total serum IgE >100 IU/mL and blood eosinophils >140cells/ul or high serum periostin or high FeNO	IL-13	Monoclonal IL13 antibody (lebrikizumab)	↑ FEV1, ↓ FeNO, trend to ↓ exacerbation [16]
	Moderate-severe uncontrolled asthma, measureable IL-13 in sputum		Monoclonal IL13 antibody (tralokinumab)	↓ β-agonist use, trend to ↑ FEV1 [33]
	General: Later onset asthma, severe, inhaled CS refractory disease, sinus disease, less atopy			
	Mild, allergic asthmatic males, no ICS use undergoing inhaled allergen challenge		Anti-IL5 (SB-240563)	↓ eosinophils in blood and sputum, no effect on late asthmatic response or airway hyperreactivity [17]
	Mild, stable, atopic asthma, no ICS (otherwise non-phenotyped)	IL-5	Anti-IL5 (mepolizumab)	↓ eosinophils in airway, bone marrow, and blood, no effect on FEV1 or other clinical measures of asthma [18]
	Moderate, persistent asthma (otherwise non-phenotyped)		Anti-IL5 (mepolizumab)	

(*continued*)

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Table 1. Continued

Parameter	Clinical features	Mediator involved	Biologic therapy target	Benefits
				↓ eosinophils in blood and sputum, trend to ↓ exacerbations, otherwise no effect on clinical measures of asthma [19]
	Asthmatics with ↑ sputum eosinophilia		Anti-IL5 (mepolizumab)	↓ asthma exacerbations, ↓ blood and sputum eosinophils, improved quality of life, ↓ airway wall thickening [39]
	Severe, late-onset asthma, ↑ blood eosinophils		Anti-IL5 (mepolizumab)	↓ asthma exacerbations [40]
	Poorly controlled asthma on high dose ICS + additional controller and sputum eosinophils ≥3%		Anti-IL5 (reslizumab)	↓ sputum eosinophils, trended to ↑ FEV1 and asthma control [41]
	Mild, atopic stable asthma undergoing allergen challenge	CCR3, common β subunit of IL3, IL-5	Antisense oligonucleotide for CCR3 (TPI ASM8)	↓ Early asthmatic response, ↓sputum eosinophil influx after allergen challenge [42]
				↓ Early and late asthmatic response, ↓sputum eosinophil influx after allergen challenge, ↓ airway responsivenss to methacholine [43,44]
Th2-like low	Severe asthma, ↑sputum neutrophilia	Neutrophils	CXCR2 receptor antagonist (SCH527123)	↓ sputum neutrophils, no other clinical effect [46]
	Moderate-severe asthma with ≥20% bronchodilator response	IL17	Anti-IL17 receptor antibody (brodalumab)	Marginal efficacy [47]

ICS = inhaled corticosteroids; LABA = long-acting β-agonists; IgE = immunoglobulin E, FeNO = fraction of exhaled Nitric oxide, SNP = single nucleotide polymorphism.

evolved and now includes many further biomarkers. Current potential biomarkers for Th2-like asthma include exhaled nitric oxide (FeNO) and the presence of blood and lung eosinophils. Interestingly, although atopy and IgE have been traditional markers of ''an allergic phenotype,'' many atopic individuals do not demonstrate Th2-like inflammation and many individuals with evidence for increases in Type-2 cytokines and eosinophils are not atopic. However, the presence of this Th2-like process does appear to identify a CS responsive phenotype, especially in milder asthma. Interestingly, this concept has existed for years. In 1958, Dr. H. Morrow Brown published that an asthmatic group with elevated sputum eosinophils responded better to systemic CSs than those without eosinophils [22]. However, with the advent of inhaled CS, and their excellent safety profile, much of this concept was forgotten for many years.

As noted earlier, studies of targeted therapy in non-phenotyped asthma did not show profound or even any efficacy. However, it was postulated that specific Type 2 cytokine blockers could be effective in phenotyped patients (i.e. those showing evidence for activation of Type-2 cytokine associated pathways). Lastly, while the identification of Type 2 ''high'' asthmatics has begun to identify a specific phenotype or phenotypes of asthma, there are no surrogate markers proposed for identifying Type 2 ''low'' asthma. Considerable work is needed to better understand the molecular pathobiology of this group of patients.

Data sources

Data reviewed in this manuscript included selected human asthma clinical research studies published from 1958 to 2013. Studies were identified through a PubMed literature search using the terms which included asthma and therapy with a focus on more recent biologic therapies in asthma targeting the Th2 cytokine associated pathways. Based on these selection criteria, a total of 32 studies were reviewed covering both pediatric and adult asthmatics.

Study selections

Subjects studied in these research trials were male and females, aged ≥6 years with a range of asthma severity from mild intermittent to very severe. The majority of trials were adult subjects (aged ≥12 years). In each study a specific medication was administered to the asthmatics and treatment response was assessed. The majority of these studies reviewed were double-blind randomized placebo-controlled trials targeting the Th2 cytokine associated pathways including IL-4, 13 and 5 as well as IgE in non-phenotyped (earlier studies) and phenotyped (later studies) asthmatics. A summary of studies reviewed based on the asthma phenotype and the mediator targeted is listed in Table 1.

Results

Studies targeting IL-4/13 pathways

There are two overlapping receptors for IL-4 and IL-13 each of which contains the α-subunit of the IL-4 receptor (IL4Rα) [23–26]. Type 1 receptors, found on B and T lymphocytes, monocytes, eosinophils and fibroblasts, controls

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differentiation of Th2 cells and are activated by IL4 alone. The type II receptors, found on epithelial cells, smooth muscle cells, fibroblasts, monocytes, and activated B cells, are activated by both IL4 and IL13 [27]. Because of this overlap, antibodies that target the IL4Rα chain should inhibit both cytokine pathways.

Mouse ova-allergen challenge models consistently confirmed the critical importance of the ligands for these receptors, IL-4 and IL-13 in allergic models. Therefore it is not surprising that targeting an allergic model in humans with antibodies to IL-13 or mutant/blocking IL-4 molecules are also effective in human allergic models [28,29]. In mild, atopic asthma, the humanized IL-13 antibody, IMA-638, attenuated the early and late asthmatic response following allergen challenge at Day 14, but had no effect on allergen-induced airway hyper-responsiveness or sputum eosinophils [29].

Published studies in chronic asthma patients have focused on antibodies to IL-13, the IL-4Rα and mutant versions of IL-4. Studies using these approaches in non-phenotyped asthmatic patients have all been negative [30–33]. In a study of an antibody to IL-4Rα in moderate, CS treated, but otherwise non-phenotyped asthma, there were no improvements in any reported asthma outcome, although serum IgE levels were reduced, while modest benefit was seen in those with the worst asthma control [30]. In a randomized, double-blind, placebo-controlled study of 219 adults with moderate to severe asthma inadequately controlled despite mid to high dose ICS and long acting β-agonists, the use of lebrikizumab, a monoclonal antibody to IL-13, was evaluated as add-on therapy compared to placebo [31]. Patients were subgrouped according to baseline Th2 status based on a combined index using both total IgE level and blood eosinophil count, by serum periostin, or by FeNO. Anti-IL-13 was only modestly effective in improving FEV1 in all comers and had no effects on exacerbations. However, when dividing the patients into Th2 ''high'' and ''low'' groups on the basis of median splits in periostin or FeNO (but not the IgE/blood eosinophil index), significant improvements in FEV1 were observed with anti-IL13 treatment, with some trend towards improvement in exacerbations, but without effects on any other asthma outcomes [31]. While periostin levels did not change in response to lebrikizumab, there were significant reductions in FeNO in those treated with active drug, confirming its biologic impact on an IL-13 associated pathway [34].

Similarly, studies of the humanized monoclonal antibody to IL-13, tralokinumab, in 194 adult asthmatics with moderate-to severe uncontrolled asthma despite controller medications showed only a trend toward a greater FEV1 and a significant reduction in β-agonist use at 12 weeks compared to placebo [33]. However, the greatest improvement in FEV1 was seen in those asthmatic subjects with measureable IL-13 in the sputum [33]. Finally, pitrakinra, a mutant IL-4 molecule, was also not effective when added to combination therapy or when the therapy was withdrawn in all comers [32]. While it appeared to be more effective in those with blood eosinophilia >350 cells/mm^3, genetics may also play a role in targeting therapy. When dividing patients in the pitrakinra study on the basis of the presence or absence of certain alleles in single nucleotide polymorphisms (SNPs) of the IL-4Rα gene, marked efficacy in reducing protocol defined exacerbations was observed, with both genetic and drug dose responses apparent [32]. This suggests that genetics may help define molecular phenotypes of asthma and help to target therapy.

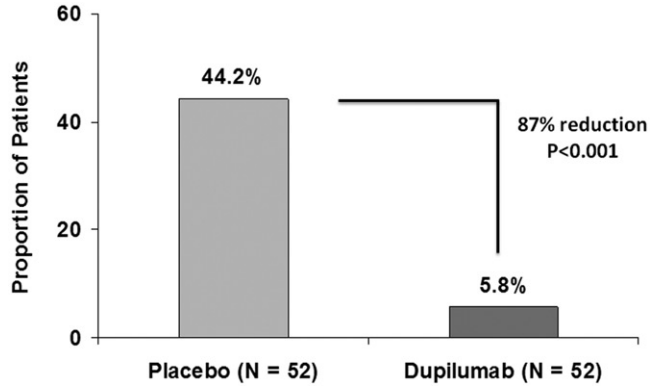

Figure 2. As compared with placebo, dupilumab therapy was associated with an 87% relative reduction in the proportion of patients with an asthma exacerbation during the 12-week intervention period (odds ratio, 0.08; 95% confidence interval [CI], 0.02–0.28; $p < 0.001$). (From Figure 2A, Wenzel, NEJM, 2013, ref. [35]).

These studies posed the question of whether designing an asthma trial of a Type-2 cytokine focused therapy based on a prespecified phenotype would lead to improved outcomes. A recent study did just that, targeting a Th2-like phenotype of asthma as identified by blood eosinophils ≥300 cells/μl. Dupilumab, a humanized monoclonal antibody to the α subunit of the IL4 receptor, was specifically evaluated in eosinophilic moderate-to severe asthmatics, on mid to high dose combination therapy (blood eosinophil count (≥300 cells/uL) or sputum eosinophil level (≥3% at screening) [35]. Despite medium to high dose ICS and long acting β-agonists (LABA), baseline symptoms were not well controlled in this Th2 ''high'' asthma phenotype. When ICS and LABAs were withdrawn, dupilumab therapy was associated with fewer asthma exacerbations (87% reduction in induced asthma exacerbations) (Figure 2). In addition, dupilumab significantly improved asthma control and FEV1, both on top of combination ICS/LABA therapy, as well as when background therapy was withdrawn [35]. In addition, there were significant improvements in upper airway symptoms and β-agonist use. Proof of biologic efficacy was also apparent as dupilumab reduced biomarkers associated with Type-2 cytokine driven inflammation including FeNO, Thymus and activation-regulated chemokine (TARC/CCL17), eoxtaxin-3 and IgE at week 12 compared to baseline values despite discontinuation of ICS [35]. To further emphasize the relationship of the biologic blockade of Type 2 cytokine associated pathways to clinical improvements, the change in FeNO correlated with change in FEV1 [35].

IL-5 targeted therapy in ''Eosinophilic'' asthma

IL-5, also a Type 2 cytokine, is the most potent eosinophilic cytokine known. However, its effects are rather selective on the eosinophil and not on other aspects of ''Th2-like'' inflammation. Interestingly, several studies have shown that eosinophilia is more common in a later onset asthma phenotype, often associated with a severe, inhaled CS

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refractory disease [36–38]. These patients usually have sinus disease, often associated with polyps but are less likely to be atopic than patients with early onset asthma. In a recent study of 176 adult-onset asthmatics with high symptom scores and exacerbation rates, poor quality of life, low lung function and the need for high-intensity treatment, late onset asthmatics were more often non-atopic with more nasal symptoms and nasal polyposis, higher exhaled nitric oxide levels, blood neutrophil counts and sputum eosinophilia [38]. The lesser degree of atopy has caused the relation to Type 2 immunity to be questioned. However, the very high FeNO levels and persistent eosinophilia suggest some relationship to this adaptive immune system. Given the pro-eosinophilic effects of IL-5, directing anti-IL-5 therapy to patients with persistent blood and/or lung eosinophilia was eventually pursued, despite the earlier negative studies in non-phenotyped asthma. A small study targeting anti-IL-5 in patients with a history of ''eosinophilic asthma'' (based on sputum eosinophilia) led to 40% reduction in asthma exacerbations [39]. As in earlier studies, blood and sputum eosinophils were markedly decreased by mepolizumab, but effects on tissue eosinophils were less [17–19]. There were modest effects on asthma quality of life and airway wall thickening but the remainder of asthma-associated outcomes were not impacted by this therapy. Intriguingly, and in contrast to the studies of IL-4/-13 blockers, there was no effect on FeNO [39]. In a follow-up and much larger study, anti-IL5 treatment with mepolizumab significantly reduced the risk of asthma exacerbations in patients with severe eosinophilic asthma, as identified primarily on the basis of blood eosinophils [40]. Blood eosinophils predicted the likelihood of exacerbations and responses to anti-IL5 therapy in these asthmatics, the majority of whom were a late onset phenotype of eosinophilic asthma [40]. Blood eosinophils were found to be as good of a biomarker for an anti-IL5 responsive asthma phenotype as sputum eosinophils, and the effect on exacerbations was proportional to the level of blood eosinophils, as blood eosinophilia itself was a predictor of more frequent exacerbations [40]. Clinically, this is important because blood testing is more readily available than induced sputum.

Reslizumab, another monoclonal antibody to IL-5, has also been studied in 106 poorly controlled eosinophilic asthmatics, despite high dose ICS. Infusions of reslizumab significantly reduced sputum eosinophils and trended to improve lung function and asthma control compared to those receiving placebo [41]. These patients were highly eosinophilic with $\geq$3% eosinophilia on 2 separate occasions, perhaps explaining the broader improvements in outcomes as compared to mepolizumab [41]. The study was not of long enough duration to address exacerbations. While these approaches to anti-IL5 confirm this Th2 cytokine as a pathologic feature in eosinophilic asthma, they also raise the question of whether there is also a role for IL-4/IL-13 in adult onset, eosinophilic asthma, or conversely whether anti-IL-5 approaches will be successful in early onset, allergic (but less eosinophilic) asthma. Further studies on this topic are necessary.

As a broader therapeutic approach, antisense oligonucleotides which target the chemokine receptor CCR3 and the common β subunit of the IL-3, IL-5, and GM-CSF receptors (TPI ASM8) have also been used in two small studies. In 17 mild atopic asthmatics who inhaled 1500*u*g of TPI ASM8 or placebo for 4 days, with allergen challenge on day 3, the drug inhibited sputum eosinophil influx by 46%, blunted the increase in total cells after allergen challenge, significantly reduced the early asthmatic response and had a tendency to reduce the late asthmatic response without changing FEV1 on Day 2 [42]. In a follow up study, 14 stable, mild allergic asthmatics received TPI ASM8 and were similarly allergen challenged. In that 2nd study, sputum eosinophils were again reduced and the early and late airway responses were attenuated. There was also decreased airway responsiveness to methacholine [43,44].

Targeted approaches with Anti-IgE

Omalizumab is a recombinant human monoclonal antibody that binds to free human IgE and was the first biologic treatment used for targeting moderate to severe allergic asthma, defined as a positive allergen skin test or *in vitro* reactivity to a perennial aeroallergen and pre-treatment serum IgE level of 30–700 IU/ml. However, despite this early attempt at phenotyping asthma, it was almost impossible to predict who would respond to omalizumab. A recent study has suggested that identification of the Type-2 biomarkers periostin, FeNO and blood eosinophils may allow improved prediction of the responder phenotype for this therapy. Building on information learned from studies of novel biologic therapies, it may now be possible to better identify responders to the 1st biologic therapy used for asthma, anti-IgE. In a post-hoc analysis of the EXTRA study of omalizumab, 850 poorly controlled severe, persistent asthmatic patients aged 12–75 years were assigned a Th2-like phenotype on the basis of three biomarkers: FeNO, peripheral blood eosinophil count, and serum periostin [45]. After 48 weeks of omalizumab, only those patients with evidence for elevations in Th2-like ''high'' biomarkers had reductions in exacerbations, while no efficacy was seen in those without elevations in these biomarkers [45]. While a prospective study randomizing patients by their ''Th-2-like'' characteristics is still needed, these data suggest that measuring these Th2-like biomarkers prior to initiating this biologic therapy may better predict responders than IgE/atopic status alone.

Biologic approaches to non-type-2 asthma.

Directed therapies for non/low Type-2 like asthma are not yet available as no definite markers have been associated with this phenotype of asthma. However, there are some suggestions that oxidative stress, IL-17 and its associated pathways, as well as other neutrophilic related pathways could be playing a role. In that regard, a selective CXCR2 receptor antagonist, SCH527123, was studied in patients with severe asthma and increased sputum neutrophilia. CXCR2, the receptor for CXCL2, a potent pro-neutrophilic chemokine, reduced sputum neutrophils, but had no clinical effect, including no effects on FEV1 compared to placebo [46]. Similarly, a recent study was performed in patients with moderate to severe asthma using an anti-IL17 receptor antibody, brodalumab. This antibody blocks the activities of all the known IL-17 family members, including the type-2 cytokine associated IL-25. This antibody was not effective in

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non-phenotyped asthmatics but did show marginal efficacy in a subgroup of patients with a marked (>20%) bronchodilator response, while having no effect in asthmatics with low bronchodilator reversibility [47]. Interestingly, subphenotyping by presence of blood neutrophils (or eosinophils) did not define a responder group.

Conclusions

In recent years, the use of molecular phenotyping in asthma has allowed the identification of Type-2 cytokine ''high'' asthma phenotype which is associated with significant clinical responses to the Type-2 cytokine associated therapies. It is not yet clear whether all Type 2 high asthma will respond similarly to IL-4/-13 or IL-5 approaches. It is likely that efficacy of these Type 2 cytokine approaches will vary by underlying molecular mechanisms in association with different clinical phenotypes. While IL-4, 5 and 13 are all canonical Type 2 cytokines, their sources may differ. IL-4 is more likely to be produced by all Th2 lymphocytes while more mature Th2 cells may produce IL-5 [48]. Additionally, IL-5/-13 can be produced by innate lymphoid type 2 cells (ILC2 cells) [48]. Thus, one could hypothesize that there will be phenotypic differences in IL4/13 vs. IL5 responders. IL-4/13 approaches may be better in early onset allergic asthmatics while IL-5 directed therapies may be more effective in late onset, eosinophilic asthma. Clinically, the ability to identify a Th2/Type 2 high asthma phenotype on the basis of blood testing (eosinophils) may facilitate the use of effective biologically targeted approaches in our asthma patients. Non-Type 2 asthma is not yet ready for biologic approaches but further studies will likely teach us more about the immunology of human asthma.

Declaration of interest

Dr Wenzel has received research support paid to her institution from GSK, MedImmune, Merck, Sanofi-Aventis. She has received consulting fees from GSK, Amgen, Novartis and Sterna. Dr. Fajt reports no conflicts of interest.

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