

Stratified medicine in selecting biologics for the treatment of severe asthma

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Purpose of review

Despite optimal treatment, asthma symptoms in about 5–10% of patients remain poorly controlled. Apart from having an impact on their asthma-related quality of life and adverse effects of the medications used (especially corticosteroids), their severe symptoms also impact healthcare resources due to frequent admission and requirement for intensive medications use. The last decade has seen an improved understanding in the pathophysiology of the complex cellular and molecular networks involved in the inflammatory and immunological phenotype of severe asthma. This knowledge may help providing strategies by which these phenotypes operate and pave the way for drug development and individualized treatment.

Recent findings

Here we review the current evidence of biological agents in patients with severe asthma recently assessed for safety and efficacy. Some of these agents have shown to be useful in specifically targeted subpopulations of patients with severe asthma, whereas others have proven to be unsafe and/or unsuccessful. In addition, we discuss recent data on clinical and pharmacokinetic–pharmacodynamic aspects of omalizumab, the only licensed anti-IgE therapy for severe atopic asthma.

Summary

More basic science work is required to improve the current understanding of severe asthma pathophysiology and proof-of-concept clinical studies are required to explore relevant biomolecular targets in this small subset of patients. At present, only one drug is licensed for allergic asthmatic patients with severe disease, omalizumab. Novel therapies in the form of oligonucleotide therapies and other biological agents are also being investigated in the difficult-to-treat asthmatic patient group.

Keywords

biologics, monoclonal antibodies, severe asthma

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Introduction

Asthma may be now considered as a complex syndrome with several clinical phenotypes and inflammatory endotypes [1]. The bulk of asthma patients have mild-to-moderate disease, which can be easily controlled by a combination of inhaled corticosteroids and β_2 -adrenoceptor agonists. However, in about 5–10% of patients, the asthma symptoms remain poorly controlled despite optimal treatment.

Many different terms have been used to describe this group of patients requiring high-intensity treatment for asthma, and clarification of the nomenclature is urgently needed. The terms 'refractory asthma', 'difficult-to-treat asthma' or 'problematic asthma' are increasingly used to

improve clinical characterization of the entire group of patients that remain symptomatic despite prescription of high-intensity asthma treatment [2]. This is clinically relevant because this group may also include patients whose problems are for reasons – such as persistently poor compliance, psychosocial factors or persistent environmental exposure to allergens or toxic substances – requiring complementary therapeutic approaches. It also includes patients who have mild-to-moderate asthma that is aggravated by comorbidities such as chronic rhinosinusitis, reflux disease, or obesity. As noted in recent review articles [3,4,5^{••}], these latter patients require high-intensity asthma treatment because these comorbidities continue to give symptoms in their own right, or have a direct effect on airway inflammation, despite the best available management strategies for these conditions.

An understanding of the complex cellular and molecular networks that characterize the inflammatory and immune phenotype of the most severe forms of chronic asthma may provide a mechanistic rationale for optimal drug development. Induction, maintenance and progression of the inflammatory and remodelling responses of chronic severe asthma are driven by a variety of cells including mast cells, eosinophils, epithelial cells, macrophages, neutrophils, dendritic cells, B cells and activated T cells (Th1, Th2, Th17), which influence airway function through the secretion of preformed and/or newly formed synthesized mediators, immunoglobulin (Ig)E, cytokines and chemokines that can act on airway or indirectly through neural mechanisms [6–10].

The composite nature of asthma, with various phenotypes and pathological mechanisms, suggests that more than one marker may be practical for clinical use and that treatment may need to be tailored to the needs of the asthmatic patients. Consequently, defining and phenotyping of patients with severe asthma are becoming increasingly important for the development of new therapies as some patients who were previously classified as having severe asthma because of poor asthma control despite maximal doses of inhaled corticosteroids and long-acting beta-2-agonist may become well controlled with a targeted phenotype-specific treatment.

In this review we look at some novel biological agents that have been reported over the last 2–3 years in patients with severe/refractory asthma as well as new uses of licensed anti-IgE treatment (omalizumab) in atopic asthmatic patients. This will provide the reader with a current up-to-date overview of the biological therapies in severe asthma. Of note, patients who may have been misdiagnosed and noncompliant need to be excluded prior to labelling a patient with severe asthma and embarking on trying various novel biological treatments.

Methodology of review

For the update of biological therapies full text papers were identified on the basis of a literature search on MEDLINE (September 2008 to August 2010). The terms for the electronic search were severe asthma/or/refractory asthma/or steroid-dependent asthma/and/biological therapy/biological treatments/September 2008 to August 2010. We limited our search to titles and abstracts of human studies published in English, all randomized controlled trials (RCTs) and crossover-controlled trials (CCTs) of biological therapies in severe asthma. For the novel uses of omalizumab, a similar search was conducted to update the use omalizumab in novel findings and populations.

The article retrospectively examines published studies of biological agents in severe asthma by focusing on key

studies to critically appraise effects in terms of key efficacy outcomes and safety.

Omalizumab studies

IgE plays a pivotal pathophysiological role in the development of allergic conditions via enhanced allergen uptake by dendritic cells and activating mast cells and basophils for mediator release [11]. Omalizumab is a humanized IgE-specific nonanaphylactoid antibody that attaches to the receptor-binding region of circulating IgE, leading to marked reduction in high-affinity IgE receptor density and a decrease in mast cell degranulation [12,13]. There have been several randomized, double-blind, placebo-controlled (DBPC) studies that have demonstrated the safety and efficacy of omalizumab in severe atopic asthmatic patients who have symptoms despite being on maximal treatment [14]. In this section we shall update the readers on recent studies in the use and pharmacokinetics–pharmacodynamics of omalizumab.

Ohta *et al.* [15] studied the use of omalizumab in an Asian (Japanese) population in a DBPC study in 315 patients with uncontrolled moderate-to-severe asthmatics for 16 weeks. They reported, similar to other large studies [14], a statistical increase in the morning peak expiratory flow (PEF) and a reduction in the odds of experiencing an asthma exacerbation in the omalizumab group compared with placebo. There were improvements in asthma symptom scores, daily life activity scores, sleep scores and rescue medication usage in favour of omalizumab; however, they were not significant. There were similar nonsevere adverse events in both groups but more injection-site reactions in the omalizumab group.

In another DBPC study in 576 children aged 6 to below 12 years with perennial allergen sensitivity and multiple exacerbations despite medium doses of inhaled corticosteroids (ICS) to assess the efficacy of omalizumab, children were randomized to receive omalizumab or placebo 2:1, respectively, for a 24-week fixed-steroid phase followed by a 28-week adjustable-steroid phase [16]. Over the 24-week period, patients treated with omalizumab had a 31% reduction in clinically significant exacerbations compared with placebo, which increased to 43% over the 52-week study period. These reductions were noted in patients whether they were on long-acting bronchodilator agents (LABAs) or not. Global evaluation of treatment effectiveness (GETE) scores significantly improved in the omalizumab group and there were no major safety issues in the study. There were no significant improvements in any of the other measured objective or subjective parameters; however, the changes were in favour of patients on omalizumab.

In a pooled analysis to examine the efficacy of omalizumab in adolescents (12–17 years) with moderate-to-severe asthma inadequately controlled with ICS and sensitivity to at least one aeroallergen, it was reported that the mean number of systemic corticosteroid treatments for asthma exacerbations was markedly lower in the omalizumab group compared with placebo, relative risk (RR) of 0.47 [17]. Additionally, there were significant improvements in the actual and predicted forced expiratory volume in 1 s (FEV₁), symptom and GETE scores, and reduction in the number of missed school days in favour of omalizumab-treated patients.

Omalizumab posology is based on pretreatment total serum IgE levels and body weight, and calculated using a dosing table. Omalizumab binds to IgE to reversibly form IgG–IgE complexes, which when it occurs pushes the reaction towards the IgG–IgE complex, rendering the IgE receptors incapable of binding any more, hence suppressing free IgE and reducing the clinical symptoms of asthma. Such pharmacokinetics–pharmacodynamics models exist [18,19]; Slavin *et al.* [20] used a pharmacokinetics–pharmacodynamics model to examine the relationship between omalizumab, free IgE, and clinical outcomes in patients with severe persistent allergic asthma from a DBPC (INNOVATE [21]) study and a bioequivalence study (single-dose, parallel-group study of omalizumab in healthy atopic individuals with IgE levels 30–300 IU/ml). The model accurately fitted omalizumab and free (and total) IgE, correlating well with changes in clinical measures of asthma (symptom scores, PEF and rescue medication usage), that is on administration of omalizumab free IgE fell rapidly below the target of 50 ng/ml, but the clinical improvement was following a notable period and *vice versa* on treatment cessation; demonstrating both a time-dependent and concentration-dependent relationship between IgE and clinical outcomes especially in omalizumab-treated responders. This relationship displayed characteristic hysteresis loops indicating delays between IgE and downstream physiological events that manifest as clinical asthma symptoms. Thus, to answer the question of should we cease treatment or reduce the dose of omalizumab once patients have clinical improvement, either of these would result in re-emergence of asthma symptoms.

Another pharmacokinetics–pharmacodynamics omalizumab study conducted by Lowe *et al.* [22] examined 1781 patients with moderate-to-severe asthma from four sparsely sampled DBPC studies [21,23–25] and 152 in a richly sampled single-dose study. Similar to the Slavin *et al.* study [20], the model accurately predicted observed omalizumab, free and total IgE levels, and free IgE levels correlated well with clinical asthma symptoms. However, in this study a target level of 14 ng/ml of free IgE at the midpoint of the 4-week clinical observation period was

considered to be the marker for determining the dose and regimen for omalizumab. Given the clear clinical end-point-linked biomarker criterion, this model aids to deduce doses and regimens for narrow subsets of patients, thus potentially improving on currently available dosing tables.

Other biological therapies

Here we discuss the various studies evaluating biological therapies in severe asthmatics to date. These include antitumour necrosis alpha (etanercept and golimumab), anti-IL-5 (mepolizumab), anti-CD25 (daclizumab), stem cell factor receptor (c-kit)/platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor (Masitinib) and IL-4 receptor alpha antagonist (AMG 317).

Anti-tumour necrosis factor alpha

Tumour necrosis factor alpha (TNF- α) is a multifunctional pro-inflammatory cytokine. As asthma severity increases there is predilection towards a TH1 inflammatory profile. Furthermore, various studies have shown the presence of TNF- α in the pathophysiology of severe asthma [26–29]. One proof-of-concept study [30], one CCT [31] and one DBPC [32] study have been conducted using the soluble TNF receptor (TNFR), etanercept, although the former two showed marked improvements in the subjective and objective asthma measures, the latter only showed some subjective improvements. More recently, in another large DBPC study [33**] using the monoclonal antibody, golimumab, of 309 patients with severe persistent asthma randomized to placebo and three doses of golimumab (50, 100 and 200 mg) [33**] no significant improvement in any of the efficacy measurements has been reported. In fact the study was terminated prematurely due to the number of severe infections and solid malignancies in the golimumab groups compared with placebo. Of note, post-hoc analysis of the study reported that patients on golimumab (100 and 200 mg) with an at least 12% prestudy reversibility of FEV₁ with ICS and a history of sinusitis were less likely to experience severe asthma exacerbations compared with placebo. In view of findings of the two DBPC studies of the lack of efficacy and safety, there are no further trials of anti-TNF- α agents in severe asthma planned.

Anti-IL-5 (Mepolizumab)

Eosinophil infiltration and degranulation in bronchial airways has been implicated in the pathology of asthma [34–36]. IL-5, which is most specific to eosinophils, is responsible for eosinophilic growth, differentiation, mobilization, recruitment, activation and survival [37–40]; hence antagonizing IL-5 may be a beneficial therapy in eosinophilic predominant asthma. However, prior studies in mild-to-moderate asthma patients have not shown

significant clinical improvements in functional airways outcomes [35,41–46].

Recently, two DBPC trials have assessed the role of the anti-IL-5 antagonist, mepolizumab, on exacerbations in subgroups of patients with persistent airway eosinophilia despite corticosteroid therapy [47*,48*]. In the study by Nair *et al.* [47*], they recruited 20 patients (9 on mepolizumab, 11 placebo) with prednisolone-dependent asthma with sputum eosinophilia (>3%) to receive five intravenous (i.v.) treatments on a monthly basis, prednisolone tapering after the second infusion, followed by an 8-week follow-up. They reported a significant reduction in the number of patients with asthma exacerbations during the prednisolone tapering and a reduction in the median time to exacerbation; prednisolone dose reduction, without a clinical exacerbation; improvement in the FEV₁ and Juniper's Asthma Control Questionnaire (ACQ) from baseline; and reduction in the blood and sputum eosinophil counts from baseline in favour of mepolizumab.

In the study by Haldar *et al.* [48*], patients with refractory eosinophilic asthma and recurrent severe exacerbations of their asthma were recruited to receive 12 doses of i.v. mepolizumab (*n* = 29) or placebo (*n* = 32) on a monthly basis. They reported a significant mean 12-month reduction in asthma exacerbations and Juniper's Asthma-related Quality of Life Questionnaire in favour of mepolizumab. There were no improvements in any of the other clinical parameters assessed. Akin to the Nair *et al.* study [47*], they demonstrated a significant reduction in the blood and sputum eosinophil count in the patients receiving mepolizumab compared with placebo.

Moreover, in both studies there were no serious risks or adverse events associated with the administration of mepolizumab and the drug was well tolerated. Larger studies to evaluate the role of mepolizumab in this small but difficult-to-treat subgroup of patients are planned.

Anti-CD25 (Daclizumab)

T-cell activation has been implicated in airway inflammation in asthma, with elevated CD25⁺ T cells, IL-2 and soluble (s) IL-2 receptor alpha chains (sCD25) noted in the airways of patients with severe asthma [49–52]. With this in mind, Busse *et al.* [53] conducted a study to evaluate the efficacy and safety of a humanized monoclonal antibody to the alpha (CD25) subunit of the high-affinity IL-2 receptor, daclizumab, in patients with moderate-to-severe asthma. A total of 115 patients dependent on ICS were switched to an equivalent dose of inhaled triamcinolone and then randomized to receive (3:1) daclizumab i.v. (*n* = 88) or placebo (*n* = 27) every 2 weeks for 12 weeks. Over the ensuing 8 weeks tapering of the ICS was tried while on the study drug, and thereafter a follow-up for 16 weeks off the study drug. They reported

small significant improvements in favour of daclizumab in FEV₁, daytime asthma symptoms, increased time to exacerbation and short-acting β_2 -agonist use compared with placebo. Although there were no mild-to-moderate adverse events between the two study groups, there were no more patients with serious adverse events in the daclizumab group compared with placebo. This small study shows that there may be a small subset of severe asthmatic patients in whom there may be a role for daclizumab as add-on therapy.

Stem cell factor receptor (c-kit)/platelet-derived growth factor receptor tyrosine kinase inhibitor (Masitinib)

Dendritic and mast cells have been implicated in severe asthma; they are activated via the binding of stem cell factor (SCF) receptor c-kit [1,54,55]. Antagonism of the SCF/c-kit pathway leads to a reduction in mast cells, histamine levels, eosinophil infiltration, IL-4 synthesis and BHR [55]. Furthermore, growth factors like PDGF have been reported to contribute in airway remodelling [56,57]. Masitinib is tyrosine kinase inhibitor which effectively and specifically inhibits c-kit and PDGF receptors [58].

Using this principle, Humbert *et al.* [59] conducted a phase IIa, 16-week DBPC multicentre study in 44 patients with severe persistent asthma to assess the efficacy and safety of masitinib in this population. The patients were randomized to receive oral masitinib, at doses of 3 (*n* = 12), 4.5 (*n* = 11) or 6 (*n* = 10) mg/kg/day or placebo (*n* = 11) in three phases of a 4-week stable corticosteroid dose, 8-week OCS-reduction phase and 4-week stabilization period for observation. They reported no significant difference with respect to OCS weaning, which was the primary endpoint, or airway function parameters (secondary endpoints). However, there was a significant improvement in the ACQ score in favour of masitinib. Due to the small sample size no intra-dose comparisons were possible, but in patients on high dose OCS (>15 mg of prednisolone equivalent) who received masitinib six patients were able to be weaned off OCS compared with none in the placebo group. Moreover, patients receiving masitinib had more minor and serious (nonrespiratory) adverse events compared with those on placebo. Although the authors have suggested that larger studies need to be conducted to evaluate the role of masitinib in severe asthma, this pilot study only showed an improvement in asthma control despite OCS withdrawal. It was small, had many dropouts due to drug-related causes and poor outcomes on objective markers assessed.

IL-4 receptor alpha (IL-4R α) antagonist

IL-4 and IL-13 have been reported to mediate IgE production, mucous hypersecretion, BHR and inflammatory cell influx in asthma [60–62]. The IL-4 receptor α

chain (IL-4R α) is used by IL-4 and IL-13 for binding to manifest their activity [63]. Using this concept, Corren *et al.* [64^{*}] conducted a phase II, DBPC study in moderate-to-severe asthmatics to evaluate the efficacy and safety of AMG 317, a fully human monoclonal IgG2 antibody that binds with high affinity to IL-4R α . Two hundred and ninety-four patients on ICS of at least 200–1000 μ g or less were randomized to receive subcutaneous AMG 317 at doses of 75 mg ($n=73$), 150 mg ($n=73$) and 300 mg ($n=74$) or placebo ($n=74$) for 12 weeks. Overall, there were no significant differences in either the primary endpoint (ACQ scores) or any of the secondary clinical endpoints between any of the doses of AMG 317 and placebo. However, they did report that patients on AMG 317 experienced numerically fewer asthma exacerbations, and that those on the higher dose of AMG317 (300 mg) and in the top tertile of ACQ scores had a constant trend of a more clinically meaningful effect in change in ACQ, FEV₁, morning peak flows and asthma exacerbations. Hence, suggesting that AMG 317 is largely useful in patients with the most symptoms. Although there were minor and serious adverse events ($n=3$) in patients on AMG 317, the latter were unrelated to the study agent. Neutralizing antibodies to AMG 317 were noted in one patient in the placebo group, and six, nine and two in the patients receiving 75, 150 and 300 mg of AMG 317, respectively. Overall, AMG 317 is well tolerated; however, its efficacy in severe asthma is questionable. It may be more useful in patients with significant symptoms.

Conclusion

By and large findings with current biologics for the treatment of severe asthma have not been very exciting. However, with careful phenotypic stratification and meticulous monitoring for adverse effects, these therapeutic options could be still considered as a beneficial add-on alternative in a few selected patients. Yet, the true significance of phenotyping severe asthma can be firmly established only when detailed characterization of hundreds of patients will be completed and analysed, as proposed in the newly established pan-European consortium Unbiased BIOMarkers for the PREdiction of Respiratory Disease Outcome (U-Biopred) funded by the Innovative Medicines Initiative in its programme Understanding Severe Asthma (<http://www.fp7-consulting.be/en/ubiopred/>). Whatever the outcomes of these research programmes, stakeholders of the national healthcare systems around the globe will always raise the obvious pharmacoeconomic concerns in view of the high acquisition cost of biologics and of the diagnostic screening procedures for the identification of responders and nonresponders. Therefore a careful and comprehensive evaluation of their cost-effectiveness will be warranted.

References and recommended reading

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

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 67–68).

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