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EDITORIAL

Biologics in severe difficult-to-treat asthma: find the right niche!

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As stated by GAGA *et al*. [1] in this issue of the *European Respiratory Review*, severe asthma still causes substantial mortality and morbidity and has a considerable economic impact worldwide. The burden of asthma is greatest in patients who are inadequately controlled despite therapy combining avoidance measures, inhaled corticosteroids, long-acting β_2-agonists, and other asthma therapy administered according to guidelines [1–4]. These patients are at high risk for developing exacerbations and, possibly, severe consequences of airways remodeling. Therefore, they are candidates for more aggressive management [1].

The mechanisms of asthma are complex and many molecular targets have been proposed [1]. Altogether, there is still no cure for asthma and there have been few new treatment innovations in recent years, despite major research in the field [1, 2]. Since the 1986 regulatory approval of a mouse monoclonal antibody (MAb) directed against the T-cell CD3ε antigen, MAbs have become an increasingly important class of therapeutic compounds in a variety of disease areas, ranging from cancer and autoimmune, infectious and cardiac diseases, as well as asthma [5, 6]. Other biological agents, such as cytokines and fusion proteins, as treatment modalities for a number of immune-mediated and malignant diseases have also yielded great promise, but very few trials in asthma have been conducted [6]. It is very difficult to predict the efficacy of biologics in severe asthma and only one MAb directed to immunoglobulin (Ig)E was found to be effective and approved by both the US Food and Drug Administration and the European Medicines Agency for the treatment of a subset of allergic asthmatics [6, 7]. Other pathways may prove to be of importance for the development of biologics, but it now appears clear that most if not all of these agents will be of interest only in subsets of severe asthmatics [6–8].

IgE is recognised as a key component of atopic asthma pathophysiology [9]. Omalizumab, an IgE MAb which binds free IgE, reduces circulating free IgE and downregulates its high-affinity receptor FcεRI on basophils and mast cells. Thus, it decreases allergen-driven cell degranulation and reduces the release of preformed pro-inflammatory mediators and newly synthesised cytokines and chemokines [6, 9]. In patients with allergic asthma, omalizumab significantly reduces both the early and late phase asthmatic response to allergen challenge [9]. The efficacy of omalizumab has been demonstrated in clinical studies of patients with predominantly severe persistent allergic asthma, including the INNOVATE study, which enrolled patients with severe persistent allergic asthma that was inadequately controlled despite treatment with high-dose inhaled corticosteroids and long-acting β_2-agonists (with additional controller medication if required) [7, 9]. In the INNOVATE study, add-on omalizumab significantly reduced clinically significant exacerbation rate and other secondary end-points, compared with add-on placebo [7]. However, many patients with severe asthma are nonallergic and, even in patients with allergic asthma, there is a proportion of nonresponders to omalizumab [7, 10–12]. This agent is currently the only biologic approved for a subpopulation of difficult asthmatics. Omalizumab was approved in the USA in 2003 for the treatment of patients who had moderate-to-severe persistent allergic asthma despite treatment with inhaled corticosteroids. In the European Union (where it was approved in 2005), omalizumab labelling is more restrictive. It is approved as add-on therapy to improve asthma control in adult and adolescent patients (those aged $\geqslant$12 yrs) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and who, despite receiving daily high-dose inhaled corticosteroids plus a long-acting β_2-agonist, have the following characteristics: reduced lung function (forced expiratory volume in 1 s <80%), frequent daytime symptoms or night-time awakenings, and multiple documented severe asthma exacerbations. Omalizumab treatment should only be considered for patients with convincing IgE-mediated asthma. As analyses have found that it is difficult to predict which patients in the label population will receive greatest benefit based on pre-treatment characteristics [12], eligible patients should

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STATEMENT OF INTEREST
M. Humbert has relationships with drug companies including AB Science, Actelion, Altair, Amgen, AstraZeneca, Chiesi, GlaxoSmithKline, MSD, Novartis and Pfizer. In addition to being investigators in trials involving these companies, relationships include consultancy services and membership of scientific advisory boards.

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receive an initial 16-week course of omalizumab and the decision to continue therapy should be based on whether a marked improvement in overall asthma control has been achieved, as specified in European Union labelling. These statements emphasise the increasing understanding that some asthma patients may benefit from a given targeted therapy, while others do not.

It has been suggested that some of the features of severe asthma might be due to upregulation of the tumour necrosis factor (TNF)-α pathway [13, 14]. In support of this, studies have shown that severe asthma is associated with an increased presence of TNF-α within the airways and an increase in TNF-α expression on peripheral blood mononuclear cells [13–15]. Moreover, TNF-α has the ability to induce several of the pro-inflammatory changes associated with severe asthma, including neutrophilic inflammation [13, 14]. Interest in the role of TNF-α in severe asthma has increased following a small crossover clinical trial [15] and an open study that suggested that etanercept (an IgG1-TNF p75 receptor fusion protein) is effective in asthma [16]. However, recent large randomised clinical trials in patients with severe asthma have not confirmed these results [17, 18]. For instance, an unfavourable risk/benefit profile led to early discontinuation of therapy with golimumab, a human MAb against TNF-α, in severe persistent asthma [17], while etanercept therapy over 12 weeks demonstrated only a small improvement in asthma control and systemic inflammation, as measured by serum albumin and C-reactive protein [18]. Ongoing research is attempting to clarify whether a subpopulation of patients may benefit from this class of drugs, but this remains uncertain.

Interleukin (IL)-5 plays an important role in regulating the production, differentiation, recruitment, activation and survival of eosinophils [6, 8]. Eosinophilia in atopic diseases and hypereosinophilic syndrome are classically associated with a high expression of IL-5 [8]. Therefore, neutralising IL-5 with an antibody is regarded as a promising therapeutic strategy in eosinophilic diseases [19]. Several animal studies have indicated that anti-IL-5 MAb could be an effective asthma treatment [20]. A first study in humans using bronchial allergen challenge did not show any efficacy in the late phase reaction and nonspecific bronchial hyperreactivity following challenge [21]. Anti-IL-5 (mepolizumab) treatment did not appear to add significant clinical benefit in patients with asthma with persistent symptoms, despite inhaled corticosteroid therapy [22]. These studies may indicate that eosinophil recruitment is not only driven by IL-5 [23], or that eosinophils do not play a major role in the studied patients [24]. Notably, the effects of IL-5 appeared to occur mainly in the circulation, with less effect on eosinophil mobilisation in the lungs [25]. Moreover, the role of anti-IL-5 MAb may not be totally ruled out since it was found that remodelling may be reduced by anti-IL-5 MAb [26]. Moreover, in patients with hypereosinophilic syndrome [27], anti-IL-5 MAb resulted in an improvement of symptoms. Some patients with very high eosinophilic inflammation and nasal polyps may also benefit from anti-IL-5 MAb [28]. Recent studies have investigated the effect of mepolizumab on exacerbation rates, using protocols specifically tailored to patients with asthma who have persistent airway eosinophilia [29, 30]. These recently published studies confirm that, in a subgroup of patients with severe difficult eosinophilic asthma, eosinophils play a role in exacerbations and may be successfully targeted with mepolizumab [29, 30]. Once again, it appears that targeted therapy has some clinical benefit in a small subgroup of patients. However, many patients with asthma do not have eosinophilia and even in patients with eosinophilic asthma, mepolizumab had no effect on other physiological and clinical factors [8].

Severe asthmatics may present with uncontrolled disease, despite optimal strategies administered according to guidelines [1, 31]. These patients are candidates for innovative therapies [1, 32]. Remarkable progress has been made for the development and production of a wide range of biologics in asthma but, to date, only one has been approved for the treatment of difficult allergic asthma [6, 7]. Therefore, it appears likely that biologics may be helpful in subsets of well-phenotyped patients with difficult asthma. Future studies will have to define precisely the target population of these novel asthma therapies [1, 32, 33].

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