

Expert Opinion

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Biologics in asthma: difficulties and drawbacks

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Background: Biologics have become an increasingly important class of therapeutic compounds in a variety of immune and/or inflammatory diseases. Patients with severe uncontrolled asthma represent a significant unmet need. **Methods:** This review gives some examples of the complex use of biologics in asthma. **Results/Conclusions:** It is very difficult to predict the efficacy of biologics in severe asthma and only one monoclonal antibody to date has been found to be effective and approved by both the FDA and European Medicines Agency (EMA) for the treatment of difficult allergic asthma. New pathways may prove to be of importance for the development of biologics. Biologics are not devoid of side effects, which can, although not always, be predicted from their mechanism of action. These include hypersensitivity reactions, which need to be better understood to prevent and control them. Finally, biologics should be cost-effective. This review gives some examples of the complex use of biologics in asthma.

Keywords: asthma, biologics, control, costs, omalizumab, side effects

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1. Introduction

Since the 1986 regulatory approval of muromonab-CD3, a mouse 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/cardiac diseases to asthma. The limitation of murine mAbs due to immunogenicity was overcome by replacement of the murine sequences with their human counterpart leading to the development of chimaeric, humanized and human therapeutic mAbs [1,2]. Remarkable progress has also been made following the development of display technologies, allowing the engineering of antibodies with modified properties such as molecular size, affinity, specificity and valency. Moreover, antibody engineering technologies are constantly advancing to enable further tuning of the effector function and serum half-life. Optimal delivery to the target tissue still remains to be addressed to avoid unwanted side effects as a result of systemic treatment while achieving meaningful therapeutic effects.

Other biological agents like cytokines and fusion proteins used as treatment modalities for a number of immune-mediated and malignant diseases have also yielded great promise but there are very few trials in asthma.

2. Efficacy of biologics: from concept to asthma management

2.1 Anti-IgE mAb

IgE is increasingly recognized as a key component of asthma pathophysiology and contributes to both the early- and late-phase inflammatory cascade of the airways. Omalizumab binds free IgE. By reducing free IgE, omalizumab also downregulates

FcεRI on basophils and mast cells [3-5]. These dual effects of omalizumab are important, since without FcεRI down-regulation, an almost complete removal of free IgE would be necessary to elicit functional consequences on mast cells and basophils. Moreover, unexpectedly, omalizumab considerably decreases the overall airway inflammation in asthma [6].

In patients with allergic asthma, omalizumab significantly reduces both the early- and late-phase asthmatic response to allergen challenge [7]. A large number of randomised trials demonstrated that omalizumab is effective in reducing asthma symptoms and improving quality of life while reducing the need for systemic and inhaled corticosteroids [8]. In patients with severe uncontrolled allergic asthma, omalizumab reduces severe exacerbations and hospitalizations [9-11], and is the only biologic approved by both the FDA and the European Medicines Agency (EMA) for severe asthma.

2.2 Anti-CD4 mAb

CD4⁺ T cells are likely to be involved in asthma as a source of pro-inflammatory cytokines. Keliximab, an anti-CD4 mAb, leads to a transient reduction in the number of CD4⁺ T cells and to a modulation of CD4⁺ receptor expression in severe asthmatics. The effects of keliximab may be mediated through a decrease in CD4⁺ surface expression and T lymphocyte numbers, in addition to a reduction in allergen-induced proliferation [12]. However, the clinical effects were modest [13] and the development of the mAb was stopped.

2.3 Anti-CD25

Airway inflammation in asthma involves T cell activation with increased numbers of activated CD25⁺ T cells and increased levels of IL-2 and soluble IL-2 receptor found in the airways of patients with severe asthma. A randomised, double-blind, placebo-controlled study has evaluated the safety and efficacy of daclizumab, a humanised IgG1 monoclonal antibody against the IL-2 receptor α-chain (CD25) of activated lymphocytes, in adults with moderate-to-severe persistent asthma. Further studies in asthma are needed to more fully define daclizumab's role and contribution to treatment as well as mechanism of action. The mechanism of action most probably involves the inhibition of pro-inflammatory cytokine generation by IL-2 receptor blockade in activated T cells.

2.4 Anti-IL5 mAb

Eosinophilia in atopic diseases and hypereosinophilic syndrome is often associated with a high expression of IL-5. IL-5 plays an important role in regulating the production, differentiation, recruitment, activation and survival of eosinophils. Therefore, neutralising IL-5 with an antibody was a promising therapeutic strategy in eosinophilic diseases [14]. A very large number of animal studies proposed that anti-IL-5 mAb could be an effective asthma treatment [15]. A first study using bronchial challenge did not show any efficacy in the late phase reaction and non-specific bronchial hyper-reactivity

following challenge [16]. Mepolizumab treatment does not appear to add significant clinical benefit in patients with asthma with persistent symptoms despite inhaled corticosteroid therapy [17]. These studies may indicate that eosinophil recruitment is not only driven by IL-5 [18] or that eosinophils do not have the major role proposed [19]. However, the effects of IL-5 appear to be mainly in the circulation, inducing peripheral mobilisation of eosinophils to the circulation with less effect on eosinophil mobilisation in the lungs [20].

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 [21]. Moreover, in patients with hypereosinophilic syndrome [22] and eosinophilic oesophagitis, anti-IL-5 mAb resulted in an improvement of symptoms [14]. Some patients with very high eosinophilic inflammation and nasal polyps may also benefit from anti-IL-5 mAb [23]. Further studies are needed to investigate the effect of mepolizumab on exacerbation rates, using protocols specifically tailored to patients with asthma with persistent airway eosinophilia.

2.5 Anti-IL-4 and anti-IL-13

Increases in T helper (Th) 2 cytokine concentrations have been described in atopic asthma, with IL-4 and IL-13 thought to play a role in this condition. Although initial studies targeting IL-4 were disappointing [24,25], novel data with a double inhibition strategy may be more promising. Pitracinra, an IL-4 variant that targets allergic Th2 inflammation by potentially inhibiting the binding of IL-4 and IL-13 to IL-4Rα receptor complexes, was found to have some effect in Phase II trials in asthma [26]. At least three mAbs are under clinical development.

2.6 Anti-TNF-α biologics

It has been suggested that some of the features of severe asthma might be due to upregulation of the TNF-α pathway. 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. Moreover, TNF-α has the ability to induce several of the pro-inflammatory changes associated with severe asthma, including neutrophilic inflammation [27]. Interest in the role of TNF-α in severe asthma has increased following a crossover clinical trial [28] and an open study, which have suggested that etanercept is effective in asthma [29]. However, a large randomised clinical trial using golimumab in patients with severe asthma did not confirm these optimistic results.

2.7 Other research areas

Novel therapeutic approaches include Toll-like receptor 4 and 9 agonists, immunostimulatory oligodeoxynucleotides, oral and parenterally administered cytokine blockers, and specific cytokine receptor antagonists, transcription factor modulators targeting kinase, peroxisome proliferator-activated receptor gamma, and NF-κB [30,31].

3. Safety of biologics

Biological agents, like cytokines, mAb and fusion proteins, can cause a great variety of adverse side effects. Based on the peculiar features of biological agents a new classification of these adverse side effects was proposed – related but clearly distinct from the classification of side effects observed with chemicals and drugs. This classification differentiated five distinct types, namely clinical reactions due to high cytokine levels (type α), hypersensitivity due to an immune reaction against the biological agent (β), immune or cytokine imbalance syndromes (γ), symptoms due to cross-reactivity (δ) and symptoms not directly affecting the immune system (ϵ) (Figure 1 and Table 1) [32]. This classification could help to better deal with the clinical features of these side effects, to identify possible individual and general risk factors and to direct research in this novel area of medicine.

3.1 Hypersensitivity reactions

Monoclonal antibodies can be derived from several sources: murine antibodies (e.g., OKT-3), chimeric (e.g., infliximab), humanised (e.g., omalizumab) or human (e.g., adalimumab). Two forms of reactions have been identified: acute and delayed. They appear to be related to the presence of antibodies to the mAb (against murine [33] or human components) but many reactions do not appear to be anaphylactic (IgE-mediated) [32,34].

TNF- α antagonists (infliximab, etanercept and adalimumab) are widely used in rheumatoid arthritis and several other inflammatory diseases. Both immediate and delayed adverse reactions have been described, suggesting type I and III hypersensitivity mechanisms [35]. These reactions even occur in children [36]. Mild-to-moderate local reactions following injection occur in 29.3% of patients with etanercept [37] and 15.3% of patients with adalimumab [38,39]. In these trials, serious adverse events may occur in over 5% of patients. Some studies describe histological findings of a cell-mediated Th1 reaction, with CD8⁺ T cells composing the majority of the dermal infiltrate [40]. Histological features of eosinophilic cellulitis as a response to etanercept suggest a Th2-mediated phenomenon [41]. Immediate positive skin tests against etanercept have only been demonstrated recently [42]. Adalimumab, a human mAb against TNF- α , was not found to induce anaphylactic reactions and can be used in patients allergic to infliximab [43]. However, delayed-type reactions were observed using intra-dermal skin tests [42].

Like nearly all systemic cancer therapies, mAbs are associated with hypersensitivity reactions [44]. Severe hypersensitivity reactions are rare, with an incidence of $\leq 5\%$. Reactions to taxanes and monoclonal antibodies are generally immediate, occurring during the first few minutes of the first or second infusion. However, 10 – 30% of reactions to mAbs are delayed, and may occur in later infusions, indicating the importance of close observation of the patient following all

administrations of the biologic. Immediate-type reactions should lead to the interruption of treatment and an allergy workup. Rechallenge should be considered after complete resolution of all symptoms, and in cases of mild – moderate reactions, the continuation of treatment may be envisaged with care.

Cetuximab, a chimeric antiepidermal growth factor receptor mAb, currently used to treat metastatic colorectal cancer, is often associated with hypersensitivity reactions [45]. Although cutaneous manifestations are the most common toxicities associated with cetuximab, they are rarely life-threatening. In a small controlled study, the reaction rate was 22% and significantly higher than the rate noted in any large published trial. In this study, all reactions occurred during the first dose and there was a strong relationship between prior allergy history and risk of reaction [46]. It appears that patients living in some areas of the US present more frequent anaphylactic reactions to this mAb. Unlike most mAbs, cetuximab is produced by the mouse cell line SP2/0 which expresses the gene for α -1,3-galactosyltransferase, and IgE antibodies specific for the post-translational modification of the molecule have been found both in patients with anaphylaxis to the mAb and other patients with anaphylaxis [47]. It is likely that these IgE antibodies existed prior to the treatment.

The risk of anaphylaxis was included in the US and EU prescribing information for omalizumab (anti-IgE mAb) but the nature of these reactions needed further elaboration. A review of spontaneous postmarketing adverse event reports submitted to the FDA's Adverse Event Reporting System database and to the manufacturers of omalizumab as well as cases published in the literature was carried out in December 2006 [48]. Diagnostic criteria for anaphylaxis outlined by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network were used to screen cases. 124 cases of anaphylaxis associated with omalizumab administration in 57,300 patients with asthma were identified (0.2%). Many cases had a delayed onset of symptoms beyond 2 h after dose administration. Many cases were also characterised by a protracted progression, with individual signs and symptoms of anaphylaxis staggered over hours. Review of the case reports did not reveal any predictive risk factors for the delayed onset or protracted progression of anaphylaxis.

The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees formed the Omalizumab Joint Task Force with the purpose of reviewing the omalizumab clinical trials and postmarketing surveillance data on anaphylaxis and anaphylactoid reactions [49]. Using the definition of anaphylaxis proposed at a 2005 multidisciplinary symposium [50], the Omalizumab Joint Task Force concluded that 35 patients had 41 episodes of anaphylaxis associated with omalizumab administration between June 1 2003 and December 31 2005. With 39,510 patients receiving omalizumab during the same

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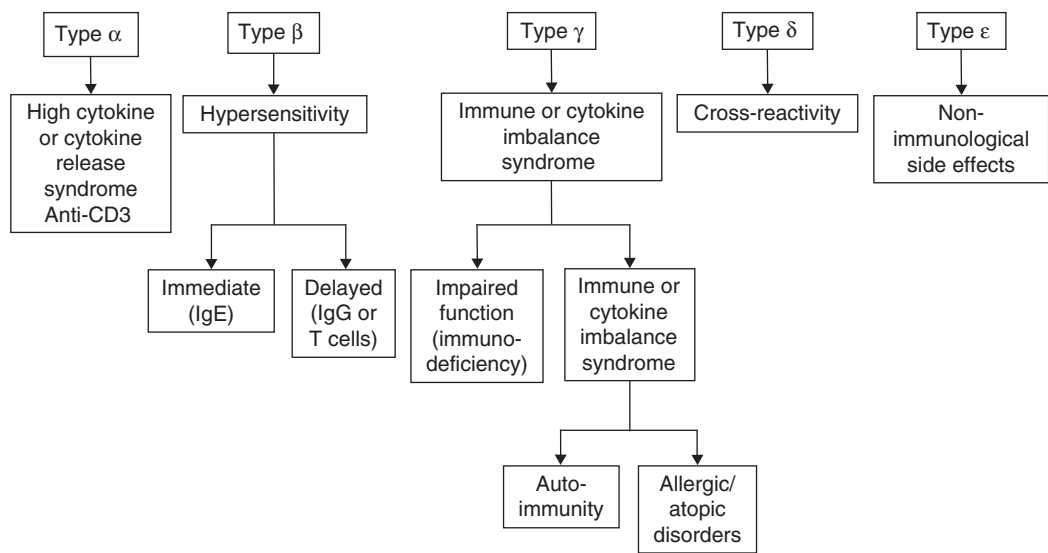


Figure 1. Classification of adverse side effects of biological agents.

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Table 1. Example of side effects of biologics: anti-TNF-α mAbs.

Type β hypersensitivity	Local and systemic urticaria, erythema Serum sickness Loss of efficiency Acute and delayed reactions after infusion	
Type γ	Immunodeficiency Auto immunity-inflammatory Atopic/Allergic	Tuberculosis, listeriosis Other granulomatous infectious diseases Neoplasia Cellulosis and acute infections Interstitial pneumopathy Acute fibrosis Systemic sclerosis SLE Demyelinating diseases Pancytopenia Lichenoid skin reactions, psoriasis Atopic dermatitis
Type ε: Non-immunological effects		Heart insufficiency

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period of time, this would correspond to an anaphylaxis-reporting rate of 0.09% of patients. Thus, omalizumab induces very few anaphylactic reactions in comparison with other biologics. Of those 36 events for which the time of reaction was known, 22 (61%) reactions occurred in the first 2 h after one of the first three doses. Five (14%) of the events after the fourth or later doses occurred within 30 min. Considering the timing of these 36 events, an observation period of 2 h for the first three injections and 30 min for subsequent injections would have captured 75% of the anaphylactic reactions.

These reactions have led to a proposed modification of the administration of omalizumab [49]. The Omalizumab Joint Task Force report provides recommendations for physicians who prescribe Xolair (omalizumab) on the suggested wait periods after administration as well as patient education regarding anaphylaxis (Box 1).

3.2 Serum sickness

Monoclonal antibodies that induce the formation of IgG antibodies can activate complement and lead to serum sickness [51]. Omalizumab does not usually activate

Box 1. Summary of AAAAI/ACAAI Omalizumab Joint Task Force (OJTF) recommendations concerning omalizumab use [49].

Informed consent should be obtained from the patients after discussing the risks, benefits and alternatives to Xolair (omalizumab)

The patients should be educated regarding the signs, symptoms and treatment of anaphylaxis

Patients should be prescribed, and educated on the proper use of the adrenaline autoinjector. They should be advised to carry this with them before Xolair (omalizumab) administration as well as for the 24 h following administration

An assessment of the patient's current health status should be made before each injection to determine whether recent health changes might require withholding treatment. This assessment should include vital signs and some measure of lung function (e.g., peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV1))

The OJTF recommends that patients be kept under observation for 30 min after each injection. This time should be extended to 2 h for the first 3 injections based on data reviewed by the OJTF, and as suggested in the 2007 National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 guidelines for the diagnosis and management of asthma. However, this could be modified based on a physician's judgement after discussing risks with the patient

complement and only one reaction of serum sickness has been described [52].

3.3 Toxic effects of biologics

Biologics that suppress the immune system such as TNF- α blocking drugs are associated with minor infections of the urinary tract, respiratory tract and sinuses, and with serious infections such as tuberculosis, sepsis (bacteria in the blood) and fungal infections. Individuals with active infections should not be treated with TNF- α -blocking biologics. Some patients who used TNF- α -blocking biologics developed cancer. In a study in severe asthma, golimumab-treated patients experienced serious adverse events, infections were the most common adverse events. One patient died from sepsis and some malignancies occurred.

3.4 Parasitic infections

Although the role of IgE in immunity against helminth parasites is unclear, there is concern that omalizumab may be unsafe in subjects at risk of helminth infection. An exploratory study was conducted in Brazil to investigate the safety of omalizumab in subjects with allergic asthma and/or allergic rhinitis at high risk of intestinal helminth infection [53]. 137 subjects (12 – 30 years of age) at high risk of geohelminth infection received prestudy anthelmintic treatment, followed by 52 weeks' treatment with omalizumab or placebo. Of the omalizumab subjects 50% experienced at least one intestinal geohelminth infection compared with 41% of placebo subjects, providing some evidence for an increased incidence of geohelminth infection in subjects receiving omalizumab. Omalizumab therapy was well tolerated, and did not appear to be associated with increased morbidity attributable to intestinal helminths as assessed by clinical and laboratory adverse events, maximal helminth infection intensities and additional anthelmintic requirements. Time to first infection was similar between treatment groups. Infection severity and response to anthelmintics appeared to be unaffected by omalizumab therapy.

4. Development of tolerance against the biologic

Infliximab, a human-murine chimeric monoclonal IgG antibody against TNF- α , is effective in rheumatoid arthritis and other inflammatory diseases. With repeated infusions, however, the formation of neutralising anti-infliximab antibodies becomes a problem, necessitating increased doses or more frequent drug administration and sometimes discontinuation of therapy due to secondary response failure and/or infusion-related side effects. This has been observed both in rheumatoid arthritis patients and in patients with other immunoinflammatory diseases. In clinical practice, however, patients with rheumatoid arthritis or any other chronic inflammatory disease treated with infliximab may differ considerably from the average patient in randomised clinical trials [54,55]. Trough serum infliximab levels after the first two intravenous infusions of infliximab at 3 mg/kg varied considerably between patients (range 0 – 22 g/ml). At this stage, only 13% of the patients were anti-infliximab-antibody-positive. With subsequent infusions, the frequency of antibody positivity rose to 30 and 44% (at 3 and 6 months, respectively), accompanied by diminished trough levels of infliximab. Indeed, low infliximab levels at 1.5 months predicted antibody development and later treatment failure. There were highly significant correlations between high levels of antibodies and later dose increases, side effects and cessation of therapy. Adalimumab is well tolerated and appears to be effective in maintaining clinical remission in patients with inflammatory bowel disease and lost response to infliximab [56,57].

Certolizumab pegol is a pegylated humanised Fab' fragment with a high binding affinity for TNF- α used to treat Crohn's disease. Antinuclear antibodies developed in 8% of the patients in the certolizumab group; antibodies against certolizumab pegol developed in 9% of treated patients [58].

Such a tolerance has not yet been reported for omalizumab.

4.1 Costs

All biologics are very expensive treatments and many are not devoid of side effects. Thus, the patients treated should be perfectly characterised and biologics only administered if they can reduce severe symptoms and hospitalisations. This is the case for omalizumab which is indicated in severe uncontrolled asthmatics despite the use of optimal therapy. However, even in these patients, the costs of treatment need to be scrutinised. It has been shown that omalizumab is cost-effective in some but not all studies [59-62]. In one study assessing costs in the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE) randomised controlled trial [11], omalizumab yearly costs were over 75,000 € per patient [60]. In another study, using data from the Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma (ETOPA) real life trial, yearly costs ranged from 30,000 to 50,000 € per patient [59]. Finally, in unselected patients, omalizumab was found to be less cost-effective [62]. However, since this treatment can reduce severe exacerbations and improve quality of life, it is indicated in patients with severe uncontrolled asthma despite optimal pharmacotherapy who should be treated according to the labelling.

5. Expert opinion

Biologics have become an increasingly important class of therapeutic compounds in a variety of disease areas including cancer, autoimmune, infectious and cardiac diseases as well as asthma. Remarkable progress has been made in the development and production of a wide range of biologics, but, to date, only one has been approved by both FDA and EMEA for the treatment of difficult allergic asthma. A small percentage of asthmatics present uncontrolled asthma despite optimal strategies combining avoidance measures and treatment using inhaled corticosteroids, long-acting β_2 agonists, and other

asthma therapy administered according to international or US guidelines. These patients are at high risk of developing severe exacerbations, and possibly severe consequences of airways remodelling and are thus candidates for a more aggressive management. The mechanisms of asthma are complex and many targets have been proposed. Among the numerous studies, omalizumab, an anti-IgE humanised monoclonal antibody, was found to be effective in severe allergic asthma that was uncontrolled despite best standard of care according to international guidelines. Other approaches such as anti-CD4 or anti-IL-5 monoclonal antibodies were not successful, although some agents need to be evaluated in subcategories of patients (such as hypereosinophilic asthma). TNF- α inhibitors are still under investigation. Many new candidates are in early stage clinical development but they need to be at least as effective as omalizumab although they may be used in a broader range of patients (so-called intrinsic nonatopic asthma, patients with very high or low serum IgE concentrations). Biological agents, like cytokines, monoclonal antibodies and fusion proteins, can cause a great variety of adverse side effects. Based on the peculiar features of biological agents a new classification of these adverse side effects of biological agents was proposed. It is related to, but clearly distinct from, the classification of side effects observed with chemicals and drugs. Biologics can cause expected side effects depending on their mechanisms but hypersensitivity reactions are not exceptional and should be known by physicians and patients in order to manage them. Finally, biologics need to be cost-effective, and only patients with severe uncontrolled asthma are candidates for treatment with biologics.

Declaration of interest

The authors declare no conflicts of interest and have received no payment for the production of this manuscript.

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