

Monoclonal antibodies in pediatric allergy

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From the womb to the adult

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Abstract

Production of monoclonal antibodies (mAbs) involving human-mouse hybrid cells was first described in 1970s, but these biologics are now used for a variety of diseases including cancers, autoimmune disorders and allergic diseases. The aim of this article is to review current and future applications of mAbs, in particular focusing on anti-IgE therapy, in the field of pediatric allergy.

Keywords

Monoclonal antibodies (mAbs), severe asthma, chronic spontaneous urticaria, anti-IgE mAbs, omalizumab.

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Introduction

Monoclonal antibodies (mAbs), obtained by cellular clones derived from animals that have been immunized with a specific antigen, are in-service of medicine for the diagnosis and treatment of diseases since 1970s [1]. A major concern of using rodent mAbs is the potential for triggering reactions after repeated usage, with loss of efficacy due to antibodies to the species part of the therapeutic antibody, particularly if effectiveness depends on multiple uses. Production of human mAbs, by transforming B cells with EBV or fusing antibody-producing cells with human cell lines, has overcome this problem. An alternative approach has been to “humanize” mouse mAbs genetically by transposing their antigen-binding sites (hypervariable regions) onto a human antibody framework; this retains the full range of effector properties of human Fc regions while minimizing the immunogenicity of the mouse component [2].

Biologic therapies provide the advantage of targeting specific cells or pathways, theoretically increasing efficacy and limiting complications related to nonspecific effects of more traditional therapies [3]. The therapeutic application of mAbs in children is a developing field, though a number of promising results have already been obtained, such as the mAbs used in cancer therapy, for the treatment of autoimmune disorders, allergic diseases and graft rejection in transplant-receiving patients. Mention is also made of mAbs use in the prevention of respiratory syncytial virus (RSV) infection (**Tab. 1**).

Table 1. Applications of monoclonal antibodies (mAbs).

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| <ul style="list-style-type: none"> • Cell identification • Cell functional status • Diagnosis: infectious diseases, systemic diseases • Treatment: neoplasms, transplants, autoimmune diseases, allergic diseases • Prevention: infectious diseases |
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The aim of this article is to review current and future applications of mAbs, in particular focusing on anti-IgE therapy, in the field of pediatric allergy.

Anti-IgE therapy and its applications in pediatric allergy

The use of biologics in pediatric allergy has been established with the approval of the

humanized monoclonal immunoglobulin E targeted antibody omalizumab as an add on treatment for inadequately controlled asthma.

Omalizumab, a humanized anti-IgE monoclonal antibody, acts specifically binding serum-free IgE and interrupting the allergic cascade by preventing binding of IgE with its high-affinity FcεRI receptors on mast cells, basophils, antigen presenting cells and other inflammatory cells [4].

By reducing serum free IgE levels, omalizumab induces a downregulation of FcεRI expression on inflammatory cells [4]. Moreover, it has been demonstrated that omalizumab reduces the expression of the high-affinity receptors for IgE on dendritic cells, which may lead to a reduction in allergen presentation to T cells and attenuation in the Th2-mediated allergic pathway [5].

Thanks to these mechanisms of action, omalizumab limits the release of proinflammatory mediators, thus reducing allergic inflammation [6]. In particular, treatment with omalizumab decreases the activation of mast-cells and eosinophils [6, 7]. All the effects described represent the biological background for treatment with omalizumab and justify its clinical efficacy.

Omalizumab is administered as a subcutaneous injection. The dose and frequency of dosing are guided by a nomogram that is derived from the total serum IgE level and the body mass index.

A number of clinical trials involving adults, adolescents and children with moderate-to-severe and severe allergic asthma demonstrated the efficacy of omalizumab [8, 9]. In a recent Cochrane review, 25 anti-IgE trials involving a total of 6,382 patients with moderate-to-severe allergic asthma have been analyzed [10]. Most of the included studies evaluated subcutaneous administration of omalizumab as adjunctive therapy to inhaled corticosteroids (ICS) and/or long-acting β₂-adrenoceptor agonists (LABA). Overall, the pooled data showed the efficacy of omalizumab in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and during steroid tapering phases of clinical trials. Participants in 7 of 11 studies also noted modest but significant improvements in asthma symptom scores and quality-of-life (QoL) assessments. Furthermore, omalizumab was generally well tolerated, with the only side effect being transient injection site reactions [10]. It is important to highlight that only three of these studies enrolled exclusively a pediatric or adolescent population, and, in adult studies, the adolescent population was represented

by a small percentage (6-8%) [9]. However, the results of clinical trials with omalizumab in children (6 to < 12 years) were consistent with those in the adult and the adolescent populations [11-13]. To date, several multicenter, observational studies support results of randomized trials, demonstrating the efficacy of omalizumab as adjunctive therapy in adults, adolescents and children with severe persistent allergic asthma in the real-world setting [14, 15].

Recently, omalizumab was licensed also as add-on therapy for the treatment of chronic spontaneous urticaria (CSU) in adults and adolescents (12 years of age and above) with inadequate response to H1 antihistamine treatment [9]. To date, the mechanism of action of omalizumab in CSU has not been completely clarified. The reduction of serum free IgE by omalizumab, with subsequent downregulation of IgE high- and low-affinity receptors, as well as possible sequestration of allergen molecules by omalizumab-IgE immune complexes, may block the ability of IgE to potentiate mast cell activity [9]. Interestingly, the mechanism of omalizumab seems to be different in CSU and allergic asthma. In urticaria, dosage is not dependent on serum IgE levels, and response is seen very often after only 12 h [9].

Besides these two approved applications, treatment with omalizumab has been explored in other allergic diseases. Omalizumab has been reported to be effective for the treatment of patients with allergic rhinitis (AR), both seasonal and perennial. Recent studies demonstrated that, in adults and adolescents (> 12 years and above) with AR, omalizumab improved symptoms, quality of life, and necessity of rescue [9]. In a meta-analysis of randomized clinical trials, Tsabouri et al. evaluated the efficacy and safety of omalizumab in patients with poorly controlled AR [16]. Of the 352 citations retrieved, 11 studies of 2,870 patients were finally included in the analysis. The results showed that, in seasonal and perennial AR, treatment with omalizumab provides a significant improvement of daily nasal symptom severity score and a reduction of anti allergic medication use compared with placebo [16]. The QoL also appears to be improved in the limited evidence available. The reported treatment-related overall adverse events occurred in comparable rates for patients on omalizumab and patients treated with placebo, confirming that anti-IgE treatment is a safe and well tolerated procedure with limited, mostly mild, adverse events [16, 17].

According to this evidence, omalizumab may represent a new therapy for AR. In particular, omalizumab may benefit patients with moderate-to-severe AR with proven allergen-specific antibodies who have no sufficient response to conventional pharmacotherapy or allergen immunotherapy. Moreover, treatment with omalizumab would be beneficial in patients with comorbid AR and asthma. The European Academy of Allergy and Clinical Immunology position paper on pediatric rhinitis considers omalizumab as a possible treatment for patients with AR and moderate-to-severe asthma, when other recommended therapies are ineffective [18]. However, the use of omalizumab for the treatment of AR has not been approved and the costs are claimed to be major barrier without mentioning the prize/prize estimate.

Severe atopic dermatitis (AD) is a chronic debilitating disease that is associated with elevated serum IgE levels. Several reports and a pilot study in adults and adolescents investigating anti-IgE therapy in patients with severe refractory AD showed symptomatic improvement with omalizumab [9]. No clinical trials are available for the pediatric population.

Food allergy is a major public health problem affecting nearly 10% of children in most industrialized countries. Unfortunately, there are no effective therapies, relegating patients to simply avoid the offending foods and treat reactions that occur on accidental exposure. Interestingly, recent studies suggest that food immunotherapy may provide a promising new approach to food allergy, particularly using the oral form of immunotherapy (OIT). However, enthusiasm for this approach must be tempered because of the significant allergic reactions that often occur with OIT and tend to limit its use to patients with less severe disease. On the other hand, novel studies suggest that concomitant treatment of patients with omalizumab (anti-IgE monoclonal antibody) during the up dosing phase of OIT may greatly reduce the allergic reactions associated with OIT, even in high-risk patients [18, 19]. This combined method may provide a new approach to successfully and rapidly treat a large fraction of patients with high-risk food allergy.

Conclusions

The field of mAbs is constantly changing and developing as new and continuous evidence emerges on how this strategy is a powerful tool to

target different inflammatory processes connected with allergic diseases.

Omalizumab is the first and, at present, the only mAb available for the treatment of moderate-to-severe and severe allergic asthma and CSU. Any other prescription can only be off label. Moreover, case reports and/or case series suggest that omalizumab is a promising therapeutic option for various allergic conditions, such as AR, severe refractory AD and food allergy. Clinical trials are needed to confirm these results. In addition, evidence is accumulating in support of the efficacy of other promising mAbs, such as interleukin 5 (IL 5)-and IL 13 specific drugs. Other targets are still under evaluation.

Declaration of interest

The Authors declare that there is no conflict of interest.

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