



An Update on Anti-IgE Therapy in Pediatric Respiratory Diseases



Amelia Licari¹, Riccardo Castagnoli¹, Elisa Panfili², Alessia Marseglia¹, Ilaria Brambilla¹ and Gian Luigi Marseglia^{1,*}

¹Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; ²Institute of Paediatrics, Department of Biomedical and Surgical Specialties, University of Perugia, Perugia, Italy

ARTICLE HISTORY

Received: February 08, 2017
Revised: April 24, 2017
Accepted: May 23, 2017

DOI:
10.2174/1573398X13666170616110738

Abstract: Anti-IgE treatment represents a major breakthrough in the therapeutic management of severe allergic asthma. Omalizumab is the unique biologic treatment registered for asthma therapy in children. The clinical efficacy and safety of omalizumab treatment in the pediatric population has been extensively documented in specific trials and consistently expanded from real-life studies. In addition, new experimental evidence suggests that omalizumab may also interfere with the cellular and molecular mechanisms underlying airway remodeling. Novel investigational anti-IgE monoclonal antibodies with improved pharmacodynamic properties are in the pipeline, potentially offering alternative mechanisms of modulating IgE pathway.

The aim of this review is to update current knowledge on anti-IgE therapy in pediatric respiratory diseases.

Keywords: Allergic rhinitis, asthma, IgE, ligelizumab, MEDI4212, omalizumab, quilizumab, rhinosinusitis.

1. INTRODUCTION

The innate immune system, also an integral part of the airways, is interposed between the external environment and the internal acquired immune system [1]. Interaction of allergens with the innate immune system normally results in immune tolerance but, in the case of allergic disease, this interaction induces recurring and/or chronic inflammation, the loss of immunologic tolerance as well as the release of pro-inflammatory cells and related molecules [1-5]. Upon activation by allergens, the innate immune response commits the acquired immune response to a variety of outcomes mediated by distinct T-cell subsets (such as T-helper 2, regulatory T, or T-helper 17 cells) [1, 6]. Immunoglobulin E (IgE) is also an important mediator of allergic reactions and has a central role in allergic respiratory disease pathophysiology, as it is implicated in both the early and late phase of allergic response [7]. IgE has also a number of immunomodulatory functions, including upregulation of IgE receptors, promotion of mast cell survival, enhancement of allergen uptake by B cells for antigen presentation and induction of T-helper 2 (Th2) cytokine expression by mast cell and may collaborate to amplify and perpetuate allergic responses [8]. In addition, recent data suggest that IgE might also be directly and indirectly associated with airway remodelling [9]. Thus, blockade of IgE effects, using novel anti-IgE therapies, is currently expanding the therapeutic perspectives in the field of allergic respiratory diseases such as asthma, with broad benefit for both adults and children.

2. OMALIZUMAB

The flagship of anti-IgE monoclonal antibodies (mAb), omalizumab, is the first biological therapy approved for allergic asthma. Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that targets circulating free IgEs. This IgE-specific IgG1 antibody decreases levels of circulating free IgEs by binding to the constant region (Cε3) of the IgE molecule, which prevents free IgE from interacting with high-affinity and low-affinity IgE receptors (FcεRI and CD23) on mast cells, basophils and other immunologic cells [7]. The reduction of free IgE levels following omalizumab administration leads to downregulation of FcεRI expression on inflammatory cells [7]. In addition, it has been demonstrated that omalizumab also reduces FcεRI expression on dendritic cells, which may lead to a reduction in allergen presentation to T cells and attenuation in the Th2-mediated allergic pathway [10]. In particular, treatment with omalizumab decreases mast-cell activation and sensitivity and reduces eosinophil infiltration and activation [11, 12]. The effects described represent the biological basis for treatment with omalizumab and justify its clinical efficacy.

3. OMALIZUMAB IN ALLERGIC ASTHMA

Asthma, a chronic heterogeneous airway inflammatory disease, is common in children with a reported prevalence ranging from 5 to 15% [13, 14]. About 70% of asthmatic patients have an allergic phenotype characterized by elevated serum levels of allergen-specific IgE [15]. Although most children respond well to safe and evidence-based stepwise pharmacological treatment, about <5% of children show a severe therapy-resistant asthma phenotype [16]. According

*Address correspondence to this author at the Department of Pediatrics, University of Pavia, Pavia, Italy; Tel: +39(0)382502818; E-mail: gl.marseglia@smatteo.pv.it

to the European Respiratory Society/American Thoracic Society guidelines, for children over 6 years of age, when the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (long-acting inhaled β_2 -agonists (LABA) or a leukotriene modifier/theophylline) and/or systemic corticosteroids to prevent it from becoming uncontrolled despite this therapy [17].

To date, omalizumab is the only biological drug currently licensed as add-on therapy in children aged ≥ 6 years with moderate-to-severe and severe allergic asthma uncontrolled after treatment with high dose of ICS plus LABA [13, 17]. In clinical practice, omalizumab is administered by subcutaneous injection every 2 or 4 weeks. Dose and frequency of administration are guided by a nomogram that is derived from total serum IgE level at baseline (eligible between 30-1500 IU/ml) and patients' weight [18].

A number of studies have established the efficacy and safety of omalizumab for the treatment of patients with asthma leading to the US Food and Drug Administration's (FDA) approval of omalizumab in 2003 for the treatment of moderate-to-severe persistent allergic asthma uncontrolled with high-dose of ICS plus LABA in patients 12 years or older [8, 19, 20]. In the European Union, omalizumab is approved since 2009 as add-on therapy to improve asthma control in adolescents (aged ≥ 12 years) and children (aged 6 to <12 years) with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity (blood test) to a perennial aeroallergen and who have frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS plus LABA. Patients aged ≥ 12 years must also have reduced lung function (Forced expiratory volume in 1 s (FEV₁) less than 80% of normal) [21]. In July 2016, FDA has approved expanded use of omalizumab to children as young as 6 years of age with uncontrolled moderate-to-severe persistent allergic asthma [22]. This expanded pediatric approval was supported by results of the 3 registrative multicenter, randomized, double-blind, placebo-controlled phase III studies involving children age 6 to 11 years [23-25]. A recent Cochrane meta-analysis, evaluating 25 anti-IgE trials involving a total of 6,382 patients with uncontrolled allergic asthma, concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and was significantly more effective in increasing the number of participants who were able to reduce or withdrawn their ICS [26]. Furthermore, omalizumab was generally well tolerated, with the only exception being transient injection site reactions [26]. To definitively establish the evidence of omalizumab in the pediatric population, Rodrigo *et al.* reviewed the results of pediatric placebo-controlled studies, confirming the efficacy of an add-on omalizumab also in children with moderate-to-severe uncontrolled allergic asthma with an acceptable safety profile [27]. The results of pediatric registrative trials have been consistently expanded from real-life studies (Table 1) [28, 29]. These studies highlighted an extended effectiveness of omalizumab in children <12 years treated continuously for 2 years, resulting in a marked drop in the mean rate of severe exacerbations and hospitalizations and a subsequent improvement of

asthma control and quality of life of affected subjects, together with a consistent steroid-sparing effect, an improvement in lung function tests and a good safety profile [28-30].

Frequently reported adverse events are injection-site reactions and pain, asthenia, nausea, arthralgia, headache, and lower respiratory tract infections [18]. Overall, the pattern of adverse events related to omalizumab treatment and registered in clinical trials is similar to that observed in the placebo group [19]. About adverse events of special interest, hypersensitivity reactions (including anaphylaxis, urticaria and serum sickness) occurred rarely in omalizumab-treated patients with a rate of 0.2%, similar to the incidence of anaphylactic reactions for other drugs, such as oral penicillin, aspirin, and non-steroidal anti-inflammatory drugs, as well as to the incidence of anaphylaxis reported in the general population [31]. Post-marketing data have also highlighted that anaphylaxis may occur not only after first administration of omalizumab, but also after subsequent administrations and sometimes with a delayed time of onset [31]. Health-care providers administering omalizumab should observe patients closely for an appropriate period of time after injection (2 h after the first three injections and for 30 min after all other injections) and should also be prepared to manage anaphylaxis. Isolated cases of Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) in adult patients have been reported during treatment with omalizumab [32, 33]; however, it is questionable if there is a clear relationship between treatment and this disease, or rather if this disease could be pre-existing or unmasked by the progressive reduction and/or suspension of systemic corticosteroids therapy. Moreover, omalizumab has also been recently considered as potential treatment of Churg-Strauss syndrome [34]. Although initial reasonable concerns emerged for the possible association between omalizumab and malignancy risk due to previous analysis from Phase I to III studies of omalizumab, a recent prospective post-marketing safety evaluation requested by FDA, following 7857 patients with moderate-to-severe asthma for up to 5 years, did not suggest any association between omalizumab therapy and risk of malignancy [35, 36]. To date, no cases of malignancy have been reported in clinical trials of omalizumab in children 6 to <12 years of age [19]. Finally, results of Xolair Pregnancy Registry (EXPECT), including data of 188 pregnant women exposed to one or more doses of omalizumab within 8 weeks prior to conception or at any time during pregnancy, showed no increase in the prevalence of major congenital anomalies, prematurity, low birth weight, and small for gestational age in the omalizumab group compared to the control group [37].

New insights on the importance of IgE pathway in the development of airway remodeling have been recently highlighted [9]. The expression of Fc ϵ RI receptors has been detected on the surface of airway smooth muscle cells [38]. In asthmatic patients, IgE-dependent activation of these receptors could be involved in the maintenance of airway allergic inflammation as well as in the production of extracellular matrix proteins (collagen I and III), both remarkably contributing to the remodeling process [39]. To date, a few experimental and clinical studies have investigated the potential interfering role of anti-IgE treatment in the airway remodeling process with promising results [39-41]. In particular, Riccio *et al.* observed a significant reduction in

Table 1. Summary of Omalizumab studies in pediatric patients.

Study and Duration	Participants	Main Outcomes
<p>Milgrom <i>et al.</i> [23] RDBPCT - 28 wk <u>Study Design</u></p> <p>1) 4- to 6-wk run-in phase: all children switched to equivalent BDP dose, adjusted to maintain asthma control achieved with previous ICS, before randomization to omalizumab or placebo; 2) 16-wk stable-steroid phase: constant ICS dose; 3) 12-wk steroid-reduction phase: 8-wk steroid-reduction phase to minimum effective dose and then maintained for the final 4 wk.</p>	<p>6-12 y of age with moderate-to-severe allergic asthma, well controlled for ≥ 3 months with ICS + reliever as needed, FEV₁ (pred) $\geq 60\%$, total serum IgE level of 30-1300 UI/L</p> <p>Randomized patients (no.) - Total: 334; omalizumab: 225; Placebo: 109</p> <p>Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 wk</p>	<p>Median percentage reduction of ICS dose: omalizumab, 100%; placebo, 66.7%, $P = .001$</p> <p>Proportion of patients in whom ICS use was withdrawn completely: omalizumab, 55%; placebo, 39%; $P = .004$</p> <p>Exacerbation rate during steroid-reduction phase: omalizumab, 18.2%; placebo, 38.5%; $P < .001$</p>
<p>Lanier <i>et al.</i> [24] RDBPCT - 52 wk <u>Study design</u></p> <p>1) 8-wk run-in phase: asthma control optimized. ICS/controller medication dose adjustment during first 4 wk only. Patients who remained symptomatic during the last 4 wk were randomized to omalizumab or placebo; 2) 24-wk stable-steroid phase: constant ICS dose; 3) 28-wk steroid-adjustable phase: ICS dose reduced only if patients met strict predefined criteria</p>	<p>6-12 y of age with moderate-to-severe allergic asthma, uncontrolled with ICS and history of severe exacerbation within prior 2 y + reliever as needed, total serum IgE level of 30-1300 UI/L</p> <p>Randomized patients (no.) - Total: 627; omalizumab: 421; Placebo: 206</p> <p>Treatment dose frequency: 75-375 mg according to dosing table every 2-4 wk</p>	<p>Exacerbation rate reduction (omalizumab vs placebo): Baseline to week 24: 31% (RR, 0.69 [95% CI, 0.53-0.90]; $P = .007$); Baseline to week 52: 43% (RR, 0.57 [95% CI, 0.45-0.73]; $P < .001$)</p> <p>Severe exacerbation rate reduction (omalizumab vs placebo): Baseline to week 24: 44% (RR, 0.55 [95% CI, 0.32-0.95]; $P = .031$); Baseline to week 52: 50% (RR, 0.49 [95% CI, 0.30-0.80]; $P = .004$)</p>
<p>Busse <i>et al.</i> [25] RDBPCT - 60 wk <u>Study design</u></p> <p>1) 4-wk run-in phase: asthma control optimized before randomization to omalizumab or placebo; 2) 60-wk treatment period</p>	<p>6-20 y of age with persistent allergic asthma, uncontrolled asthma indicated by persistent symptoms or hospitalization/unscheduled urgent care in prior 6-12 months, total serum IgE level 30-1300 IU/mL</p> <p>Randomized patients (no.) - Total: 419; omalizumab: 208; Placebo: 211</p> <p>Treatment dose frequency: 0.016 mg/kg/IgE (IU/mL) per 4 wk</p>	<p>Number of days with asthma symptoms (omalizumab vs placebo): 24.5% reduction; mean number of days: 1.48 (0.10) vs 1.96 (0.10); $P < .001$</p> <p>Reduction in ICS - Mean ICS (mg/d): omalizumab, 663 (23.3); placebo, 771 (23.5); difference, 2109 (95% CI, 2172 to 245); $P < .001$</p> <p>Reduction in seasonal exacerbations after omalizumab treatment (post hoc analysis): Placebo: fall 9.0%, spring 8.1%, vs summer 4.6%; Omalizumab: fall 4.3%, spring 4.2%, vs summer 3.3%. $P < .001$ for interaction vs placebo</p>
<p>Deschildre <i>et al.</i> [28, 29] Real-life observational study - 52 and 104 wk <u>Study design</u></p> <p>Multicenter survey conducted in pediatric pulmonology and allergy tertiary care centers (France)</p>	<p>6-18 y of age, with severe allergic asthma, partially/poorly controlled asthma (18/82%)</p> <p>Randomized patients (no.) - Omalizumab: 104</p> <p>Treatment dose frequency: 75-375 mg according to dosing table every 2-4 wk</p>	<p>Week 52 vs baseline: Control improvement: good control, 67% vs 0%; Rate of exacerbation: 72% reduction (mean, 1.25 [95% CI, 0.55-1.95] vs 4.4 [95% CI, 3.7-5.2]; $P < .0001$); Proportion of patients requiring hospitalization: 6.7% vs 44%, $P < .001$; Mean improvement in FEV₁(pred): 4.9% (95% CI, 0.69-9.19); $P = .023$; Mean ICS dose (mg/d): 30% reduction; 481 (95% CI, 412-551) vs 703 (95% CI, 642-764), $P < .0001$</p> <p>At week 104 vs week 52: Control improvement: good control, 80% vs 67%, respectively; Rate of exacerbation: 83% reduction (mean, 0.22 [95% CI, 0.03-0.41]; $P = .0001$)</p>

BDP:beclomethasone dipropionate; ICS: inhaled corticosteroids; RDBPCT: Randomized double-blind, placebo-controlled trial; wk: weeks; y: year.

reticular basement membrane (RBM) thickness on bronchial biopsy samples obtained from 11 adult patients with severe persistent allergic asthma before and after 1 year of treatment with omalizumab [41]. Moreover, a proteomic analysis of

the airway tissues of responders highlighted an overexpression of galectin-3, an extracellular matrix protein expected to be a future reliable biomarker of response to omalizumab [42]. The effects of omalizumab on airway

inflammation and remodeling open new perspectives in pediatric asthma management; in addition of being an effective anti-inflammatory drug, omalizumab may possibly represent as a disease-modifying agent in selected children, interfering with the natural history of asthma.

Recent key investigations shed light on the mechanisms of severe asthma exacerbations [25, 43]. In children and adolescents, asthma exacerbations are more likely to occur during the fall, probably because of rhinovirus infections and underlying allergic sensitization. Considering that certain viruses, such as rhinovirus and respiratory syncytial virus, may induce Th₂-type immunity by upregulating FcεRI expression on plasmacytoid dendritic cells [15], it has been postulated a possible antiviral role of omalizumab. This assumption has been already reflected in clinical outcomes of Inner-City Anti-IgE Therapy for Asthma (ICATA) study [25]. Furthermore, the most recent Preventive Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study clinically demonstrated a preventive effect of omalizumab on respiratory virus-associated exacerbations: the addition of 4-month treatment with omalizumab to guideline-based therapy before the fall season resulted in a significant reduction in asthma exacerbations in inner-city children and adolescents with asthma [43]. Results of PROSE study highlighted a possible antiviral role by which omalizumab exerts its beneficial effect: reduction of IgE by omalizumab restores the innate antiviral immunity in plasmacytoid dendritic cells and increases the release of interferon-α on rhinovirus exposure, which is deficient in presence of high IgE.

The possibility of modulation of innate immunity by anti-IgE treatment may partially also explain the positive effect of omalizumab in a subset of uncontrolled severe nonatopic asthma adult patients [44]. These preliminary results need to be further investigated, especially in the pediatric population.

Although the consolidated effectiveness and safety profile of omalizumab in asthma population, there are several issues needing additional investigations. First of all, the optimal duration of treatment with omalizumab has not yet been clearly determined. Based on results of available studies, the optimal treatment duration is longer than 1 year; to date, experience with real-life studies in children is of around 2 years [29]. However, further long-term studies are needed to assess the optimal duration treatment, the eventual sustained efficacy after the end of treatment and the comprehensive impact of omalizumab therapy on the natural history of asthma in children. Adherence to prolonged treatment is also a relevant open issue: data from studies conducted in adults and adolescents revealed a larger number of missed doses per year in patients with younger age, great lung function, and more frequent dosing (*i.e.* 2-week vs 4-week interval) [45]. Similar data in the pediatric population are still lacking, highlighting the need to identify subjects with poor adherence in this group of age. Although expensive, omalizumab treatment costs may theoretically be compensated by reduction in health-care resource use for patients with severe asthma. To date, cost-effectiveness studies on omalizumab therapy still lack in children; available data on adults showed mixed results depending on the country in which the economic analysis was conducted [46]. Furthermore, outcomes of cost-effectiveness studies are

directly influenced by certain subgroup of patients. Due to the heterogeneity of severe asthma phenotypes, the identification of responders to omalizumab treatment is an urgent need in order to improve both cost-effectiveness and safety. To date, only few data on biomarkers in adolescent patients can be extrapolated from the EXTRA study conducted in adults [47]. Elevated fractional exhaled nitric oxide (FeNO), blood eosinophilia and elevated serum periostin have been proposed as promising biomarkers of better response to omalizumab treatment [48, 49]. Finally, a significant proportion of pediatric potential candidates for omalizumab are currently excluded because of high IgE levels. The development of new anti-IgE antibodies may potentially fill this gap.

4. OMALIZUMAB IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease resulting from a hypersensitivity reaction to *Aspergillus fumigatus*. This condition is more frequent in patients with cystic fibrosis (CF), with a prevalence of 2 to 15% [50]. ABPA is a disease differentiated by recurrent infiltrates on chest x-ray, markedly elevated IgE, eosinophilia and underlying asthma and clinically characterized by afebrile episodes of cough, sputum production and dyspnea and wheezing. Timely diagnosis of ABPA is important because untreated ABPA results in progressive and irreversible lung damage [50]. Systemic corticosteroids are considered first-line treatment for ABPA, while adjunctive antifungal oral therapy may be cautiously considered in steroid-dependent patients or in case of steroid-related adverse effects [51]. Considering that ABPA is due to hypersensitivity to specific allergens with high IgE production, omalizumab has been proposed as an off-label therapeutic option. A review of “real-life” evidence on the use of omalizumab for ABPA in children with cystic fibrosis was published by Tanou *et al.* [52]. In the eight case reports analyzed, treatment with omalizumab was associated with improved expiratory flow function, reduced frequency of respiratory symptoms and decreased use of systemically administered corticosteroids [52]. However, all available data were obtained from case reports. As assessed by The Cochrane Collaboration, there is a need for large prospective randomized controlled trials of anti-IgE therapy in people with CF and ABPA with both clinical and laboratory outcome measures such as steroid requirement, ABPA exacerbations and lung function [53]. A recent case series by Nové-Josserand *et al.* demonstrated that omalizumab therapy was associated with a steroid-sparing effect in CF patients with ABPA. However, a randomized-controlled trial is required to provide higher level of evidence regarding the efficacy and cost-effectiveness of omalizumab in patients with ABPA [51].

5. OMALIZUMAB IN UPPER AIRWAYS DISEASES

5.1. Omalizumab in Allergic Rhinitis

Epidemiologic, pathophysiological and clinical evidence have recently revealed the link between upper and lower airways (the so-called concept of united airway disease), changing the global pathogenic view of respiratory allergy

[54, 55]. In particular, allergic rhinitis (AR) and asthma are both manifestations of a single inflammatory process and require an integrated diagnostic and therapeutic approach in order to get global disease control [56-59]. Immunological and clinical effects of anti-IgE therapy in AR have been recently investigated, highlighting a therapeutic benefit that disclose future perspectives in the management of patients with AR [60]. Several randomized controlled trials evaluated the effectiveness of omalizumab in AR (both seasonal and perennial), alone or in combination with allergen immunotherapy (AIT) [61-71]. The generated results from these studies differ in clinical outcomes, for the presence of comorbidities (*i.e.*, allergic asthma), as well as for the association of omalizumab with AIT [60]. However, omalizumab has been generally reported to be effective in improving symptoms, quality of life and rescue medications needed in patients with AR [65-68]. In a meta-analysis of randomized clinical trials, Tsabouri *et al.* assessed the efficacy and safety of omalizumab in patients with poorly controlled AR. A statistically significant reduction in the daily nasal symptom severity score and in daily nasal rescue medication score was observed [72]. According to this evidence, omalizumab may provide a new treatment strategy for AR. In particular, omalizumab may benefit patients with moderate-severe AR with proven allergen-specific antibodies who have no sufficient response to recommended medications. Moreover, treatment with omalizumab would be beneficial in patients with comorbid AR and asthma [73]. The recently published position paper on pediatric rhinitis by the European Academy of Allergy and Clinical Immunology considers omalizumab as a possible treatment for patients with AR and moderate-to-severe asthma, when other recommended therapies are ineffective [74]. However, the use of omalizumab for the treatment of AR has not been approved by the FDA and the high cost limits its chronic application for AR [59, 75].

5.2. Omalizumab in Chronic Rhinosinusitis and Nasal Polyposis

The association of chronic rhinosinusitis with nasal polyposis (CRSwNP) and asthma has been extensively studied: more specifically, CRSwNP is estimated to occur in 7% of all those with asthma, whereas asthma is reported to occur in 26% to 48% of patients with CRSwNP [55, 76-79]. Increased asthma severity has also been shown to be associated with sinonasal inflammation [80]. Although the cellular and molecular mechanisms underlying CRSwNP are not fully understood, CRSwNP and asthma share common pathophysiologic characteristics as local eosinophilic inflammation, with high production of IL-5, local IgE production and a Th2-type cytokine profile [81, 82]. The involvement of IgE in the pathogenesis of CRSwNP associated with asthma suggests that anti-IgE treatment might be beneficial in these patients. A pilot study by Penn *et al.* examined the possible application of anti-IgE therapy for the treatment of CRSwNP. Patients with allergic asthma and CRSwNP who underwent endoscopic sinus surgery were allocated into a control group or a treatment group, who received omalizumab, postoperatively. Despite the small number of patients, the nasal polyp scores significantly improved in the anti-IgE group [83]. In a recent randomized,

double-blind, placebo-controlled phase II trial, Gevaert *et al.* reported a reduction of nasal polyp size and an improvement of symptoms when compared with placebo in patients with CRSwNP independent of atopic status [84]. Despite these promising results, further studies are needed in order to confirm them and the use of omalizumab, as well as of other biologics, is currently off-label in CRSwNP [73]. It is important to highlight that all these studies were conducted in patients 18 years and above. In children, the endoscopic finding of nasal polyposis should always raise suspicion for other underlying clinical conditions, as cystic fibrosis, immunodeficiency, or primary ciliary dyskinesia [85].

6. NOVEL ANTI-IGE THERAPIES

The therapeutic success of omalizumab has prompted the development of a generation of the new anti-IgE antibodies, potentially providing a further step forward in the future treatment of allergic diseases. QGE031 (Iigelizumab) is a novel humanized IgG₁ mAb against human IgE, which binds to the Cε3 domain of IgE with higher affinity (50 fold-higher *in vitro* and 6- to 9-fold greater potency *in vivo*) than omalizumab [86]. Two phase I randomized, double-blind, placebo-controlled clinical trials investigating the pharmacological properties and the safety of QGE031 have been conducted in atopic but healthy subjects: in comparison with omalizumab, QGE031 showed greater suppression of free IgE, basophil FcεRI, and surface IgE and skin prick test responses to allergen [86]. The results of a phase II randomized, double-blind, placebo-controlled parallel-group multicenter trial comparing the effects of QGE031 with those of omalizumab in adult patients with mild allergic asthma have also demonstrated an enhanced suppression of allergen-induced responses in the airways [87]. With regards to safety and tolerability, mild-to-moderate urticaria was reported in 4 of 60 subjects who completed the phase I study; other mild-to-moderate adverse events, including headache and upper respiratory infections, were reported, as well as local reactions occurring at injection sites [86, 87]. More recently, a new investigational high affinity anti-IgE antibody (MEDI4212) was generated with the potential to both neutralize soluble IgE and eliminate IgE-expressing B-cells through antibody-dependent cell-mediated cytotoxicity [88]. In addition to neutralizing free IgE, the effect of long-term reduction of IgE synthesis confers to MEDI4212 the potential to exceed the current limits of omalizumab and to widen the treatable population of severe asthmatics, even with very high IgE levels. However, the results of the phase I study of MEDI4212 in atopic subjects highlighted a limited potential for dosing schedule advantage over omalizumab, due mainly to a rapid recovery of free IgE to baseline in MEDI4212-dosed subjects when compared with the slow and gradual recovery seen in omalizumab-dosed individuals [89]. Finally, the approach of upstream targeting the IgE pathway has led to the conception of an anti-CεmX domain antibody, which targets IgE-expressing B lymphocytes by binding to membrane-bound IgE (mIgE) on IgE-switched cells, lysing mIgE-expressing B lymphoblasts thus preventing the allergen-induced generation of IgE-producing plasma cells [90]. The safety, tolerability, and activity of anti-CεmX has been demonstrated in phase I and II clinical trials of quilizumab [91, 92]. Quilizumab is a humanized, monoclo-

nal IgG1 that binds to the M1-prime segment present only on membrane IgE, but not on soluble IgE in serum [93]. The efficacy, safety, and pharmacokinetics of quilizumab was recently evaluated in adults with allergic asthma inadequately controlled despite high-dose ICS and a second controller [94]. After 36 weeks of treatment, quilizumab was well tolerated, with a safety profile consistent with previous clinical studies; however, quilizumab treatment did not result in a clinically significant impact on exacerbation rate, lung function, or quality of life [94].

CONCLUSION

Omalizumab is the first and, to date, the unique biologic treatment registered for asthma therapy in children. In addition to its established efficacy and safety, new experimental evidence suggests that omalizumab may also interfere with the cellular and molecular mechanisms underlying airway remodeling, a potential benefit of great impact in pediatric age. To date, novel investigational anti-IgE monoclonal antibodies with improved pharmacodynamic properties are in the pipeline, potentially offering alternative mechanisms of modulating IgE pathway.

LIST OF ABBREVIATIONS

ABPA	=	Allergic Bronchopulmonary Aspergillosis
AIT	=	Allergen Immunotherapy
AR	=	Allergic Rhinitis
CD23	=	Low-affinity IgE Receptor
CF	=	Cystic Fibrosis
CRSwNP	=	Chronic Rhinosinusitis with Nasal Polyps
FcεRI	=	High-affinity IgE Receptor
FDA	=	Food and Drug Administration
FeNO	=	Fractional Exhaled Nitric Oxide
FEV ₁	=	Forced Expiratory Volume in 1 s
ICS	=	Inhaled Corticosteroids
IgE	=	Immunoglobulin IgE
LABA	=	Long-acting Inhaled β ₂ -agonists
mAb	=	Monoclonal Antibody
mIgE	=	Membrane-bound IgE
RBM	=	Reticular Basement Membrane
Th ₂	=	T-helper Type 2

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

AL, RC, EP, IB and AM made substantial contribution to conception and design of the review and drafted the article; GLM made substantial contribution to conception and design of the review and revised it critically for important intellectual content; all authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors thank Novartis Farma S.p.A. for the payment of open access publication fee.

REFERENCES

- [1] Minnicozzi M, Sawyer RT, Fenton MJ. Innate immunity in allergic disease. *Immunol Rev* 2011; 242(1): 106-27.
- [2] Miraglia Del Giudice M, Marseglia GL, Leonardi S, *et al.* Fractional exhaled nitric oxide measurements in rhinitis and asthma in children. *Int J Immunopathol Pharmacol* 2011; 24(4 Suppl): 29-32L.
- [3] Leonardi S, Cuppari C, Lanzafame A, *et al.* Exhaled breath temperature in asthmatic children. *J Biol Regul Homeost Agents* 2015; 29(2 Suppl 1): 47-5.
- [4] Cavone L, Cuppari C, Manti S, *et al.* Increase in the level of proinflammatory cytokine HMGB1 in nasal fluids of patients with rhinitis and its sequestration by glycyrrhizin induces eosinophil cell death. *Clin Exp Otorhinolaryngol* 2015; 8(2): 123-8.
- [5] Cuppari C, Manti S, Chirico V, *et al.* Sputum high mobility group box-1 in asthmatic children: a noninvasive sensitive biomarker reflecting disease status. *Ann Allergy Asthma Immunol* 2015; 115(2): 103-7.
- [6] Miraglia Del Giudice M, Pedullà M, Brunese FP, *et al.* Neutrophilic cells in sputum of allergic asthmatic children. *European J Inflamm* 2010; 8(3): 151-6.
- [7] Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005; 115(3): 459-65.
- [8] Licari A, Marseglia G, Castagnoli R, Marseglia A, Ciprandi G. The discovery and development of omalizumab for the treatment of asthma. *Expert Opin Drug Discov* 2015; 10(9): 1033-42.
- [9] Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev* 2015; 24(138): 594-601.
- [10] Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεpsilonRI expression. *J Allergy Clin Immunol* 2003; 112(6): 1147-54.
- [11] Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy* 2009; 64(12): 1728-36.
- [12] Djukanović R, Wilson SJ, Kraft M, *et al.* Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004; 170(6): 583-93.
- [13] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Update 2016 [cited: 14th Dec 2016]. Available from: www.ginasthma.com
- [14] Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65: 152-67.
- [15] Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. *Eur Respir J* 2016; 47(1): 304-19.
- [16] Bozzetto S, Carraro S, Zanconato S, Baraldi E. Severe asthma in childhood: diagnostic and management challenges. *Curr Opin Pulm Med* 2015; 21(1): 16-21.

- [17] Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43(2): 343-73.
- [18] http://ec.europa.eu/health/documents/communityregister/2016/20160909135675/anx_135675_it.pdf [cited: 14th Dec 2016]
- [19] Licari A, Marseglia A, Caimmi S, *et al.* Omalizumab in children. *Paediatr Drugs* 2014; 16(6): 491-502.
- [20] Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103976s5211bl.pdf. [cited: 14th Dec 2016]
- [21] European public assessment report (EPAR) for Xolair. EMA http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000606/WC500057293.pdf [cited: 14th Dec 2016]
- [22] <https://www.genentechaccess.com/content/dam/gene/accesssolution/s/brands/xolair/Appeals%20Tips/XOLAIR-FDA-Approval-Letter-Allergic-Asthma.pdf> [cited: 14th Dec 2016]
- [23] Milgrom H, Berger W, Nayak A, *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001; 108(2): E36.
- [24] Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009; 124(6): 1210-6.
- [25] Busse WW, Morgan WJ, Gergen PJ, *et al.* Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364(11): 1005-15.
- [26] Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014; (1): CD003559.
- [27] Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol* 2015; 26(6): 551-6.
- [28] Deschildre A, Marguet C, Salleron J, *et al.* Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013; 42(5): 1224-33.
- [29] Deschildre A, Marguet C, Langlois C, *et al.* Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J* 2015; 46(3): 856-9.
- [30] Lemanske RF, Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics* 2002; 110: e55.
- [31] Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009; 39(6): 788-97.
- [32] Puéchal X, Rivereau P, Vinchon F. Churg-Strauss syndrome associated with omalizumab. *Eur J Intern Med* 2008; 19(5): 364-6.
- [33] Bargagli E, Madioni C, Olivieri C, Penza F, Rottoli P. Churg-Strauss vasculitis in a patient treated with omalizumab. *J Asthma* 2008; 45(2): 115-6.
- [34] Jachiet M, Samson M, Cottin V, *et al.* Anti-IgE monoclonal antibody (omalizumab) in refractory and relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Data on seventeen patients. *Arthritis Rheumatol* 2016; 68(9): 2274-82.
- [35] Busse W, Buhl R, Fernandez Vidaurre C, *et al.* Omalizumab and the risk of malignancy: Results from a pooled analysis. *J Allergy Clin Immunol* 2012; 129(4): 983-9.e6.
- [36] Long A, Rahmaoui A, Rothman KJ, *et al.* Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol* 2014; 134(3): 560-567.e4.
- [37] Namazy J, Cabana MD, Scheuerle AE, *et al.* The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol* 2015; 135(2): 407-12.
- [38] Redhu NS, Saleh A, Shan L, *et al.* Proinflammatory and Th2 cytokines regulate the high affinity IgE receptor (FcεpsilonRI) and IgE-dependant activation of human airway smooth muscle cells. *PLoS One* 2009; 4(7): e6153.
- [39] Roth M, Zhong J, Zumkeller C, S'ng CT, Goulet S, Tamm M. The role of IgE-receptors in IgE-dependent airway smooth muscle cell remodelling. *PLoS One* 2013; 8(2): e56015.
- [40] Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration* 2012; 83(6): 520-8.
- [41] Riccio AM, Dal Negro RW, Micheletto C, *et al.* Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients. *Int J Immunopathol Pharmacol* 2012; 25(2): 475-84.
- [42] Mauri P, Riccio AM, Rossi R, *et al.* Proteomics of bronchial biopsies: galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients. *Immunol Lett* 2014; 162(1 Pt A): 2-10.
- [43] Teach SJ, Gill MA, Togias A, *et al.* Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015; 136: 1476-85.
- [44] Lommatzsch M, Korn S, Buhl R, Virchow JC. Against all odds: anti-IgE for intrinsic asthma? *Thorax* 2014; 69: 94-6.
- [45] Janson SL, Solari PG, Trzaskoma B, Chen H, Haselkorn T, Zazzali JL. Omalizumab adherence in an observational study of patients with moderate to severe allergic asthma. *Ann Allergy Asthma Immunol* 2015; 114: 516-21.
- [46] Romano C. Omalizumab therapy for children and adolescents with severe allergic asthma. *Expert Rev Clin Immunol* 2015; 11: 1309-19.
- [47] Hanania NA, Wenzel S, Rosén K, *et al.* Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013; 187: 804-11.
- [48] Hanania NA, Alpan O, Hamilos DL, *et al.* Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; 154: 573-82.
- [49] Tajiri T, Matsumoto H, Gon Y, *et al.* Utility of serum periostin and free IgE levels in evaluating responsiveness to omalizumab in patients with severe asthma. *Allergy* 2016; 71: 1472-9.
- [50] Zhou Y, Xu D, Zhang Y, Sheng Y, Chen X, Chen Z. Allergic bronchopulmonary aspergillosis in children. *Pediatr Int* 2015; 57: e73-6.
- [51] Nové-Josserand R, Grard S, Auzou L, *et al.* Case series of omalizumab for allergic bronchopulmonary aspergillosis in cystic fibrosis patients. *Pediatr Pulmonol* 2017; 52(2): 190-7.
- [52] Tanou K, Zintzaras E, Kaditis AG. Omalizumab therapy for allergic bronchopulmonary aspergillosis in children with cystic fibrosis: a synthesis of published evidence. *Pediatr Pulmonol* 2014; 49: 503-7.
- [53] Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. *Cochrane Database Syst Rev* 2015; 11: CD010288.
- [54] Ciprandi G, Caimmi D, Miraglia Del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in United airways disease. *Allergy Asthma Immunol Res* 2012; 4: 171-7.
- [55] Marseglia GL, Merli P, Caimmi D, *et al.* Nasal disease and asthma. *Int J Immunopathol Pharmacol* 2011; 24: 7-12.
- [56] Brozek JL, Bousquet J, Baena-Cagnani CE, *et al.* Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126: 466-76.
- [57] Licari A, Castagnoli R, Bottino C, Marseglia A, Marseglia G, Ciprandi G. Emerging drugs for the treatment of perennial allergic rhinitis. *Expert Opin Emerg Drugs* 2016; 21: 57-67.
- [58] Zicari AM, Nebbioso M, Lollobrigida V, *et al.* Vernal keratoconjunctivitis: atopy and autoimmunity. *Eur Rev Med Pharmacol Sci* 2013; 17: 1419-23.
- [59] Licari A, Ciprandi G, Marseglia A, *et al.* Current recommendations and emerging options for the treatment of allergic rhinitis. *Expert Rev Clin Immunol* 2014; 10(10): 1337-47.
- [60] Ciprandi G, Marseglia GL, Castagnoli R, *et al.* From IgE to clinical trials of allergic rhinitis. *Expert Rev Clin Immunol* 2015; 11: 1321-33.
- [61] Kuehr J, Brauburger J, Zielen S, *et al.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109: 274-80.
- [62] Casale TB, Busse WW, Kline JN, *et al.* Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; 117: 134-40.
- [63] Kopp MV, Hamelmann E, Zielen S, *et al.* Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and comorbid seasonal allergic asthma. *Clin Exp Allergy* 2009; 39: 271-9.
- [64] Kamin W, Kopp MV, Erdnuss F. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010; 21: e160-5.

- [65] Adelroth E, Rak S, Haahtela T, *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 106: 253-9.
- [66] Casale TB, Condemi J, LaForce C, *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; 286: 2956-7.
- [67] Casale TB, Bernstein IL, Busse WW, *et al.* Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997; 100: 110-21.
- [68] Chervinsky P, Casale T, Townley R, *et al.* Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 91: 160-7.
- [69] Vignola AM, Humbert M, Bousquet J, *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59: 709-17.
- [70] Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int* 2006; 55: 379-86.
- [71] Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M, Ishikawa T. Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Clin Exp Allergy* 2008; 38: 329-37.
- [72] Tsubouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract* 2014; 2: 332-40.e1.
- [73] Verbruggen K, Van Cauwenberge P, Bachert C. Anti-IgE for the treatment of allergic rhinitis--and eventually nasal polyps? *Int Arch Allergy Immunol* 2009; 148: 87-98.
- [74] Roberts G, Xatzipsalti M, Borrego LM, *et al.* Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013; 68: 1102-16.
- [75] Vashisht P, Casale T. Omalizumab for treatment of allergic rhinitis. *Expert Opin Biol Ther* 2013; 13: 933-45.
- [76] Fokkens WJ, Lund VJ, Mullol J, *et al.* European position paper on rhinosinusitis and nasal polyps. *Rhinol* 2012; 23: 3 p preceding table of contents, 1-298.
- [77] Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract* 2016; 4: 565-72.
- [78] Licari A, Caimmi S, Bosa L, Marseglia A, Marseglia GL, Caimmi D. Rhinosinusitis and asthma: A very long engagement. *Int J Immunopathol Pharmacol* 2014; 27: 499-508.
- [79] Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *Int Forum Allergy Rhinol* 2016; 6: 373-7.
- [80] Lin DC, Chandra RK, Tan BK, *et al.* Association between severity of asthma and degree of chronic rhinosinusitis. *Am J Rhinol Allergy* 2011; 25: 205-8.
- [81] Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 2001; 107: 607-14.
- [82] Duse M, Caminiti S, Zicari AM. Rhinosinusitis: Prevention strategies. *Pediatr Allergy Immunol* 2007; 18: 71-4.
- [83] Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: A pilot study. *Am J Rhinol* 2007; 21: 428-32.
- [84] Gevaert P, Calus L, Van Zele T, *et al.* Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013; 131: 110-6.e1.
- [85] Caimmi D, Matti E, Pelizzo G, *et al.* Nasal polyposis in children. *J Biol Regul Homeost Agents* 2012; 26: S77-83.
- [86] Arm JP, Bottoli I, Skerjanec A, *et al.* Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy* 2014; 44: 1371-85.
- [87] Gauvreau GM, Arm JP, Boulet LP, *et al.* Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. *J Allergy Clin Immunol* 2016; 138: 1051-59.
- [88] Nyborg AC, Zacco A, Ettinger R, *et al.* Development of an antibody that neutralizes soluble IgE and eliminates IgE expressing B cells. *Cell Mol Immunol* 2016; 13: 391-400.
- [89] Sheldon E, Schwickart M, Li J, *et al.* Pharmacokinetics, pharmacodynamics, and safety of medi4212, an anti-IgE monoclonal antibody, in subjects with atopy: A phase I study. *Adv Ther* 2016; 33: 225-51.
- [90] Liour SS, Tom A, Chan YH, Chang TW. Treating IgE-mediated diseases *via* targeting IgE-expressing B cells using an anti-CemX antibody. *Pediatr Allergy Immunol* 2016; 27: 446-51.
- [91] Gauvreau GM, Harris JM, Boulet LP, *et al.* Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med* 2014; 6: 243ra85.
- [92] Harris JM, Maciuga R, Bradley S, *et al.* Efficacy and safety of quilizumab in adults with allergic asthma inadequately controlled on inhaled corticosteroids and a second controller (COSTA Study). *Am J Respir Crit Care Med* 2015; 191: A5168.
- [93] Brightbill HD, Lin YL, Lin Z, *et al.* Quilizumab is an afucosylated humanized anti-M1 prime therapeutic antibody. *Clin Anti-Inflamm & Anti-Allergy Drugs* 2014; 1: 24-31.
- [94] Harris JM, Maciuga R, Bradley MS, *et al.* A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. *Respir Res* 2016; 17: 29.