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Omalizumab: an anti-immunoglobulin E antibody for the treatment of allergic respiratory diseases

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ABSTRACT: Immunoglobulin E (IgE) is central to the development of allergic diseases. Cross-linking of cell-bound IgE by the allergen leads to the initiation of the inflammatory cascade. Omalizumab, an anti-IgE antibody, forms complexes with free IgE, thereby inhibiting the allergic reaction before its commencement.

A survey of the clinical trials performed on omalizumab indicated that this anti-IgE antibody is efficacious and well tolerated in the treatment of separate and concomitant asthma and rhinitis. In patients with poorly controlled asthma, omalizumab reduced the asthma exacerbation and emergency visit rate, along with improving the quality of life. The improvement in asthma control was associated with a reduction of inhaled and oral corticosteroids. Improved nasal symptom scores and a reduced need for antihistamines were observed in patients with allergic rhinitis. Omalizumab was also proven to be effective as an add-on therapy for concomitant asthma and rhinitis.

In conclusion, omalizumab provides an integrated approach for the treatment and management of allergic respiratory diseases.

KEYWORDS: Allergic rhinitis, anti-immunoglobulin E antibody, asthma, omalizumab

During the past few decades, there has been a large increase in the prevalence of allergic diseases, such as asthma and rhinitis [1, 2], which has led to a high economic burden on the healthcare systems of the developed nations [3]. In particular, around 300 million people worldwide suffer from asthma and, by 2025, this number is estimated to rise to 400 million. The data on asthma mortality is unreliable in many countries, but it is estimated that the disease accounts for approximately one in every 250 deaths worldwide [2]. Symptoms of asthma lead to limited patient activity, absence from school or work, emergency hospital visits and a reduction in the quality of life (QoL) [4]. In 1998, the total annual cost for asthma to the USA healthcare system alone was projected to be $12.7 billion [5], whereas that of allergic rhinitis (AR) was estimated to be $6 billion per year. Of the total cost for asthma, ~75% is related to improperly controlled disease [3]. Costs of asthma management depend on the severity of the disease, where patients with severe and/or improperly controlled asthma incur disproportionate costs [6].

Studies indicate a strong relationship between asthma and AR [7–9], with ~20–50% patients with AR experiencing concomitant asthma [10]. A 23-yr follow-up study of college students in the USA showed that AR occurred in 86% of asthmatics [11], whereas a French study [12] that assessed the QoL in patients with AR and asthma found that 78% of asthmatics also suffered from AR. GREISNER *et al*. [11] also determined that AR often preceded or occurred at the same time as asthma. Due to the large burden associated with these diseases, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines indicate that improved management of AR could lead to a better management of concomitant asthma [13], and *vice versa*.

Pharmacological treatments of asthma include the use of inhaled corticosteroids (ICSs), leukotriene modifiers, sustained release theophylline, and both short- and long-acting β_2-agonists (LABAs) [14–16]. However, it is well known that many patients with severe asthma are often inadequately controlled by these medications, and remain at a high risk of morbidity and mortality [14].

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STATEMENT OF INTEREST
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ALLERGIC DISEASE AND IMMUNOGLOBULIN E

Asthma and rhinitis are epidemiologically, pathologically and physiologically linked [13]. Immunoglobulin (Ig)E has long been known to play a central role in the pathophysiology of allergic diseases, with ~30–90% of asthma being atopic in nature [17, 18]. Upon entering the body, the allergen is taken up by the dendritic cells. These cells process and present the allergen to the antigen-specific T-cells. A divergence of T-cell response to the T-helper cell type 2 phenotype leads to the development of IgE-producing B-cells. The fragment crystallisable (Fc) part of the released IgE binds to the high-affinity IgE receptors (FcεRI) on basophils and mast cells. Upon subsequent exposure to the allergen, the cell-bound IgE is cross-linked, which initiates degranulation of the cells and the release of mediators, such as histamine, leukotrienes and prostaglandins. During the late allergic phase, eosinophils, one of the primary effector cells in allergic asthma, also enter the airways [19–21]. This whole allergic cascade leads to bronchoconstriction, oedema and airway hyperresponsiveness [22], which in turn results in the manifestation of asthma and/or rhinitis (fig. 1). IgE levels also correlate with the levels of FcεRIs on basophils, whereby increased levels of the antibody in serum can lead to an increased surface expression of its receptors [23]. This can in turn lead to enhanced binding of the antibody to basophils and mast cells. IgE has also been shown to promote survival of mast cells, even under growth factor-limiting conditions [24]. Therefore, it may also be responsible for the elevated number of mast cells during an allergic response.

ANTI-IMMUNOGLOBULIN E THERAPY

Omalizumab is a humanised monoclonal anti-IgE antibody that binds to FcεRI (high-affinity IgE receptor) and FcεRII (low-affinity receptor) areas of the IgE heavy chain (CHε3 region), thus preventing the interaction of free IgE with its receptors on mast cells and basophils [25]. As a result, the omalizumab–IgE complex does not bind to the FcεRI-bound IgE on the mast cells and basophils, thereby avoiding sensitisation of mast cells and basophils (fig. 1), and minimising the potential for an anaphylactic reaction [26].

Omalizumab was the first anti-IgE antibody developed for the treatment of allergic respiratory disease, and is currently the only anti-IgE agent approved for the treatment of allergic asthma [27]. Its mode of action is different from other anti-allergic drugs as this antibody inhibits the inflammatory cascade before its initiation. Although the efficacy of omalizumab has been assessed for allergic respiratory diseases [28, 29], the current article focus on studies conducted in patients with both asthma and AR.

Several studies [30, 31] have shown that omalizumab significantly reduces serum IgE levels by >96%. Omalizumab also results in a reduction of mast cell function and a marked downregulation of FcεRI IgE receptors on basophils [30–32]. These effects are very important because, without the down-regulation of IgE receptors, almost all IgE molecules must be removed from the circulation to prevent it from inducing the inflammatory cascade.

In a small study of 35 patients suffering from asthma, NOGA *et al.* [33] observed a decline in the peripheral eosinophil count and histamine release in subjects treated with omalizumab. The same group further demonstrated the anti-allergic and anti-inflammatory properties of omalizumab in a study where a significant increase in eosinophil apoptosis and a decline in interleukin (IL)-2+ and IL-13+ T-lymphocytes was observed [19]. These findings were mirrored for patients with seasonal allergic rhinitis (SAR), where PLEWAKO *et al.* [34] observed an increase in blood eosinophil levels in the placebo group but not in the omalizumab group. They also detected a decline in IgE+ cells in the omalizumab group. The anti-inflammatory effects of the anti-IgE antibody were further corroborated in a study by DJUKANOVIĆ *et al.* [35], where a significant decline in bronchial and sputum eosinophils was observed in asthmatic patients on omalizumab. Omalizumab has been shown to reduce airway hyperresponsiveness to bronchoconstrictors, such as adenosine 5′-monophosphate [36], and also to decrease both early- and late-phase asthmatic responses to allergen inhalation [37].

These studies demonstrate that IgE plays a key role in asthma inflammation and that omalizumab decreases the overall airways inflammation, making it possible to reduce exacerbations due to allergen exposure or other inciters.

OMALIZUMAB IN TREATMENT FOR ALLERGIC ASTHMA

Patients with severe persistent asthma, who are poorly controlled by LABAs and ICS despite optimal compliance to treatment, are at a risk of frequent exacerbations and hospitalisations. In the European Union, omalizumab is indicated as an add-on therapy to improve asthma control in adult and adolescent patients (aged ⩾12 yrs) with severe persistent allergic asthma and in those receiving a daily high-dose ICS or LABA, with reduced lung function (forced expiratory volume in one second (FEV_1) <80%), frequent daytime symptoms or night-time awakenings, and multiple documented severe asthma exacerbations. Omalizumab is indicated for patients with baseline total IgE levels of 30–700 $IU \cdot mL^{-1}$ [38]. This anti-IgE antibody has been evaluated for efficacy and safety in a large number of studies. It was tested in adults and adolescents of variable severity to find out whether this biological agent could reduce asthma severity and medication needs (oral or ICSs). SOLÈR *et al.* [39] reported >52% fewer exacerbations in patients treated with omalizumab as compared with the placebo group, along with reducing the need for the ICS beclomethasone dipropionate. In an extension study by the same group (n=483), fewer patients on omalizumab required concomitant medication and more patients completed the study without the need for ICS [40]. To predict the efficacy of omalizumab, a *post hoc* analysis of the two studies attempted to define the baseline characteristics of the patients. It was found that the more severe the patient at baseline (according to FEV_1 level and ICS dose), the more significant the difference with placebo [41].

The efficacy of omalizumab in asthma treatment was further supported by the INNOVATE (INvestigatioN of Omalizumab in seVere Asthma TrEatment) [42] and SOLAR (Study of OmaLizumab in co-morbid Asthma and Rhinitis) [9] studies. The INNOVATE study specifically enrolled patients with severe persistent asthma who were suboptimally controlled even with Global Initiative for Asthma (GINA) 2002 step 4 therapy. Omalizumab, which was used as an add-on therapy to ICS and LABAs, significantly reduced the rate of asthma exacerbations (following correction for baseline exacerbation

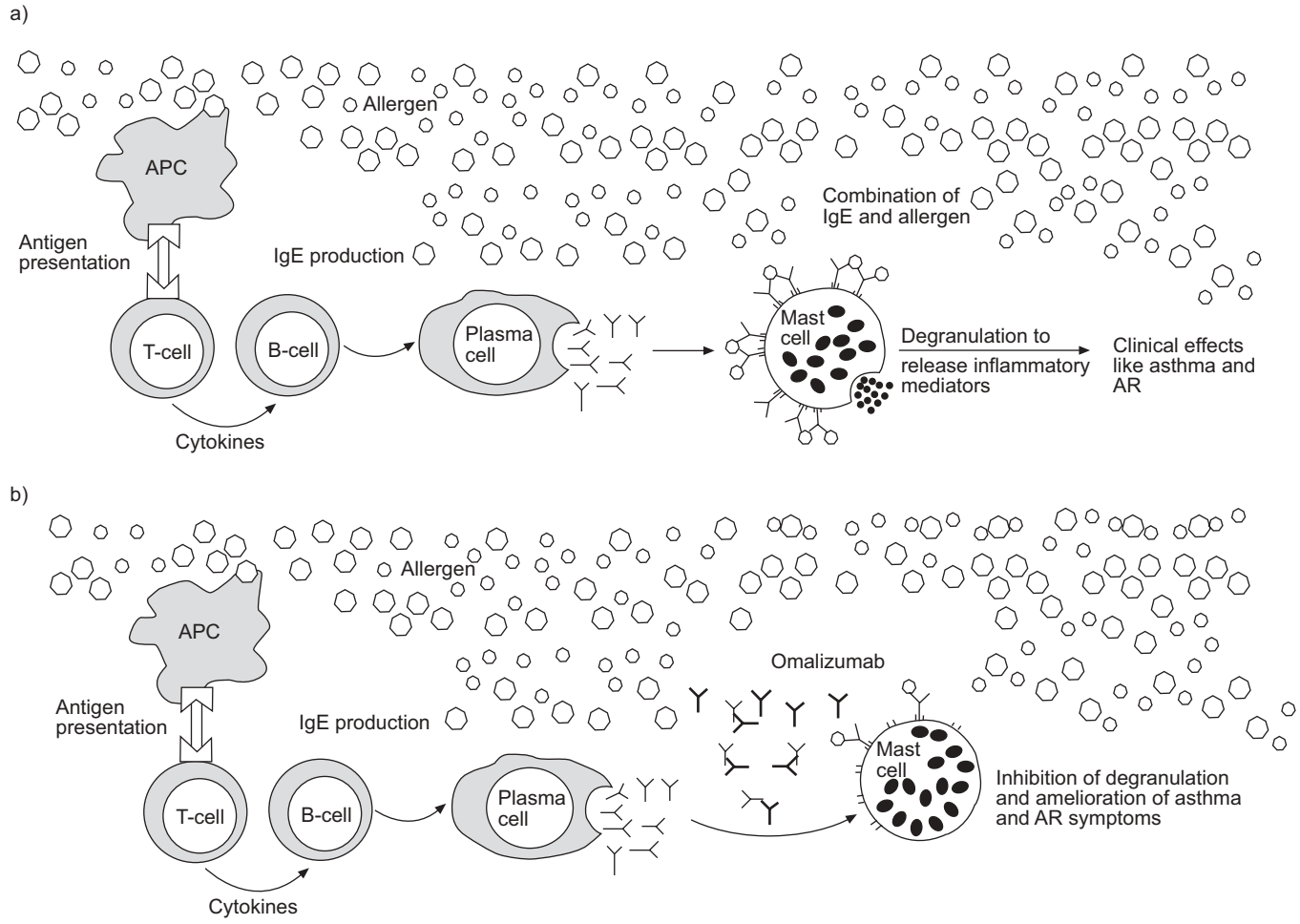

FIGURE 1. a) Demonstrates the exposure, sensitisation and re-exposure to the allergen, which results in initiation of the allergic cascade. Release of inflammatory mediators upon cross-linking of cell-bound immunoglobulin (Ig)E by allergens leads to an allergic response, which translates into asthma and allergic rhinitis (AR) symptoms. b) Shows the effect of omalizumab on the allergic cascade. Inability of the omalizumab–IgE complex to bind to mast cells and basophils inhibits degranulation and alleviation of asthma and AR symptoms. APC: antigen-presenting cell.

history). Omalizumab add-on therapy decreased the clinically significant asthma exacerbation rate by 26% compared with placebo after adjustment for baseline exacerbation. This halved the severe exacerbation rate (FEV1 reduced to <60% of personal best). Consequently, the emergency visit rate was reduced by 44% when compared with placebo. Also, the hospital admission rate was halved [42]. These results were reflected in the SOLAR study and an open-label study [43], which compared the effects of omalizumab with best standard care ($p<0.001$ for asthma exacerbations). The open-label study also showed a significant improvement in FEV1.

Recently, BOUSQUET *et al.* [29] performed a pooled analysis of six published phase III clinical trials [9, 27, 39, 40, 42–46] and an unpublished trial [47] to assess the efficacy of omalizumab as add-on therapy in adults and adolescents with allergic asthma (table 1). Across all seven studies, 93% of patients met the GINA 2002 criteria for severe persistent asthma. They observed that the annual rate of asthma exacerbations was reduced by 38% in the omalizumab group as compared with the control group ($p<0.0001$). Similarly, the rate of total emergency visits declined by 47% (treatment group *versus* control group, $p<0.0001$). All seven studies showed that omalizumab was associated with a good safety and tolerability profile in patients with asthma. The incidence of adverse events (AEs) was similar to best standard care or placebo and there were few treatment-related AEs in all the studies.

Asthma impairs the physical and psychological well being of affected individuals. QoL is a significant health measure for asthma as it underlines the impact of the disease on the patient's daily life [48, 49]. The Juniper Asthma Quality of Life Questionnaires (AQLQ) are designed to be sensitive to small but effective changes in the asthma QoL [4]. The AQLQ scores (≥ 0.5) showed that omalizumab improves the asthma-related QoL in patients with moderate-to-severe asthma, severe asthma and concomitant asthma and rhinitis [9, 27, 42].

OMALIZUMAB TREATMENT FOR AR

Although omalizumab was only approved for the treatment of asthma, several studies revealed the efficacy of omalizumab in patients with SAR and perennial AR (PAR; table 2). HANF *et al.* [50] found that it significantly reduces nasal responses to allergens in patients with AR. Omalizumab significantly decreased the daily

TABLE 1 Studies of omalizumab in patients with asthma

First author [Ref.]	Population	Patients n	Treatment groups	Rhinitis at baseline n (%)	Treatment duration weeks	Outcome
HUMBERT [42]	Severe allergic asthma	419	Omalizumab + ICS	Not available	28	Clinically significant exacerbation rate/patient: omalizumab 0.68, placebo 0.91, p=0.042
			Placebo + ICS			Severe exacerbation rate/patient: omalizumab 0.24, placebo 0.48, p=0.002
AYRES [43]	Moderate/severe allergic asthma	312	Omalizumab + CAT	205 (66)#	52	Asthma deterioration incident rate·yr^{-1}: omalizumab 4.92, control 9.76, p<0.001
			CAT			Exacerbations·patient·yr^{-1}: omalizumab 1.12, control 2.86, p<0.001
VIGNOLA [9]	Moderate/severe asthma and persistent allergic rhinitis	405	Omalizumab + ICS	405 (100)¶	28	Patients with exacerbations: omalizumab 21%, placebo 30%, p=0.02
			Placebo + ICS			
BUSSE [44]	Moderate/severe allergic asthma	525	Omalizumab + ICS	518 (99)#	28	Exacerbations/patient in stable steroid phase (16 weeks): omalizumab 0.28, placebo 0.54, p=0.006
			Placebo + ICS			Exacerbations/patient in steroid reduction phase (12 weeks): omalizumab 0.39, placebo 0.66, p=0.003
LANIER [45]	Moderate/severe allergic asthma	460	Omalizumab + ICS	Not available	24-week extension	Exacerbations/patient: omalizumab 0.60, placebo 0.83, p=0.023
			Placebo + ICS			
SOLÈR [39]	Moderate/severe allergic asthma	546	Omalizumab + ICS	478 (88)#	28	Exacerbations/patient in stable steroid phase (16 weeks): omalizumab 0.28, placebo 0.66, p<0.001
			Placebo + ICS			Exacerbations/patient in steroid reduction phase (12 weeks): omalizumab 0.36, placebo 0.75, p<0.001
BUHL [40]	Moderate/severe allergic asthma	483	Omalizumab + ICS	Not available	24-week extension	Exacerbations/patient: omalizumab 0.48, placebo 1.14, p<0.001
			Placebo + ICS			
HOLGATE [46]	Severe allergic asthma	246	Omalizumab + ICS	203 (83)#	32	Reduction in fluticasone dose: omalizumab 57%, placebo 43.3%, p=0.003
			Placebo + ICS			
ALTO [47]	Severe asthma	1760	Omalizumab + CAT	1561 (89)#	24	Exacerbation rate·yr·patient^{-1}: omalizumab 1.02, control 1.20, p=0.08
			CAT			

Additional data on numbers of patients with rhinitis not included in published references were obtained from Novartis Pharma AG (data on file at Novartis Pharma AG, Basel, Switzerland). ICS: inhaled corticosteroids; CAT: current asthma therapy. #: seasonal or persistent allergic rhinitis; ¶: persistent allergic rhinitis.

nasal symptom scores to birch [28] and ragweed pollen [51], and reduced the need for rescue antihistamines in patients with SAR compared with patients who were administered placebo. Both studies showed an improvement in the QoL, assessed by the Rhinoconjunctivitis Quality of Life Questionnaire that included sleep impairment, non-nasal symptoms and emotional function scores. CASALE *et al.* [51] also observed an improvement in the ocular symptom scores in patients receiving omalizumab. Analogous results were obtained from a study on patients with PAR [52], where treatment with omalizumab significantly lowered nasal symptom severity scores when compared with placebo.

Further support is provided by the improved outcomes for rhinitis, and concomitant rhinitis and asthma, in omalizumab-treated patients [9, 43]. These studies demonstrated significant

TABLE 2 Studies of omalizumab in patients with rhinitis

First author [Ref.]	Population	Patients n	Treatment groups	History of asthma n (%)	Treatment duration	Outcome
ÄDELROTH [28]	SAR (birch pollen)	251	Omalizumab Placebo	85 (34)	Birch pollen season	Daily nasal symptom severity score: omalizumab 0.70, placebo 0.98, p<0.01
CASALE [51]	SAR (ragweed pollen)	536	Omalizumab 300, 150 or 50 mg Placebo	137 (26)	Ragweed pollen season	Daily nasal symptom severity score: omalizumab 300 mg 0.75, 150 mg 0.86, 50 mg 0.88, placebo 0.98, p=0.02 for 300 mg dose *versus* placebo
CHERVINSKY [52]	PAR	289	Placebo Omalizumab	76 (26)	16 weeks	Daily nasal symptom severity score: omalizumab 0.99, placebo 1.3, p<0.001
HANF [50]	AR	23	Placebo Omalizumab Placebo	Not available	16 weeks	Allergen-challenge nasal symptom score: omalizumab reduced nasal symptom score compared with baseline and placebo (p<0.01).
VIGNOLA [9]	Moderate/severe asthma and persistent allergic rhinitis	405	Omalizumab Placebo	405 (100)	28 weeks	Omalizumab reduced Wasserfallen rhinitis score by 3.5 compared with placebo (p<0.001)

SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; AR: allergic rhinitis.

improvements in the Wasserfallen asthma symptom scores in omalizumab-treated patients when compared with placebo. The SOLAR study also revealed a significant improvement in rhinitis symptom score (treatment difference -3.53, p<0.001) and total asthma/rhinitis composite score (treatment difference -5.36, p=0.0002) for the omalizumab group (fig. 2). Omalizumab was shown to improve symptom control in patients with poorly controlled asthma and concomitant rhinitis [53]. As an add-on to the current asthma therapy (CAT) [54], omalizumab significantly improved the asthma, rhinitis and total (asthma + rhinitis) symptom scores at all post-treatment visits (p<0.001). At the end of the study, patients on CAT did not experience a change in the total symptom score (+1.7), whereas those on CAT plus omalizumab therapy showed a decline (-11.5) in this score (fig. 3; J. Bousquet, Service des Maladies Respiratories, Montpellier, France; personal communication).

NAYAK *et al.* [55] showed that re-treatment with omalizumab during a second pollen season did not give rise to anti-omalizumab antibodies and did not cause any serious or severe AEs; therefore, omalizumab is safe to use in repeated pollen seasons.

Omalizumab has also been studied in combination with specific immunotherapy (SIT). The use of SIT is a complementary approach to omalizumab, where an allergen-specific IgG ''blocking antibody'' is used to alleviate the symptoms of allergic diseases like rhinitis [56]. Combined SIT and omalizumab therapy reduced symptom load and the need for rescue medication in children with SAR as compared with either therapy alone [57, 58]. KOPP *et al.* [59] demonstrated a decline in the release of inflammatory mediators, sulphidoleukotrienes, when children suffering from SAR were provided SIT and omalizumab combination therapy. These initial findings suggest that omalizumab in combination with SIT may be effective in treating SAR; however, further studies need to be conducted to confirm the utility of such an intervention.

Evidence of the efficacy and safety of omalizumab comes from a study conducted on the combined effects of rush immunotherapy (RIT) and omalizumab. The shorter time period required for treatment makes RIT an attractive alternative to SIT. However, a risk of acute allergic reactions remains due to the accelerated dosing schedule. CASALE *et al.* [60] found that RIT plus omalizumab therapy led to fewer AEs as compared with patients receiving RIT alone.

SAFETY PROFILE OF OMALIZUMAB

Omalizumab-related adverse reactions included injection site reactions, viral infections, upper respiratory tract infections, sinusitis, headache and pharyngitis [10]. Patients on omalizumab also experienced increased incidence of rash, a broad range of gastrointestinal events, bleeding and female genitourinary adverse events. Moreover, the potential effect of omalizumab on

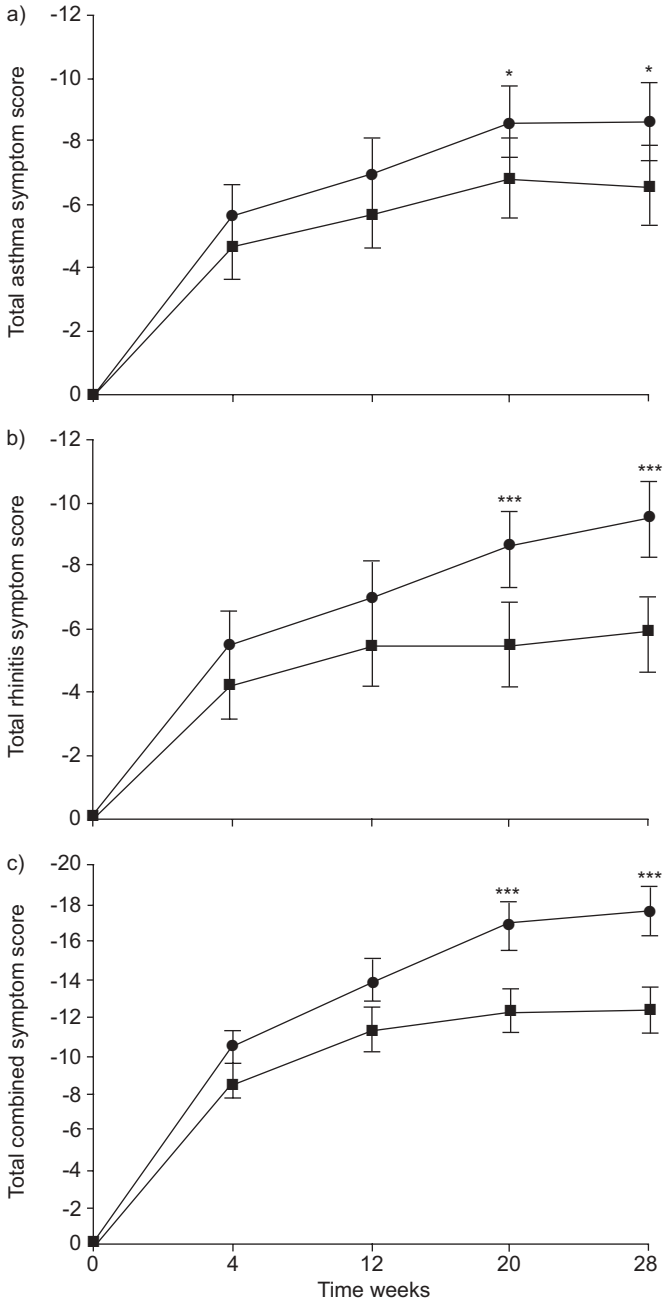

FIGURE 2. Effect of omalizumab on change from baseline in a) total asthma symptom score, b) total rhinitis symptom score, and c) combined asthma and rhinitis symptom score (least square mean±SEM). ●: omalizumab; ■: placebo. *: $p<0.05$; ***: $p<0.001$. Adapted from VIGNOLA *et al.* [9], with permission from the publisher.

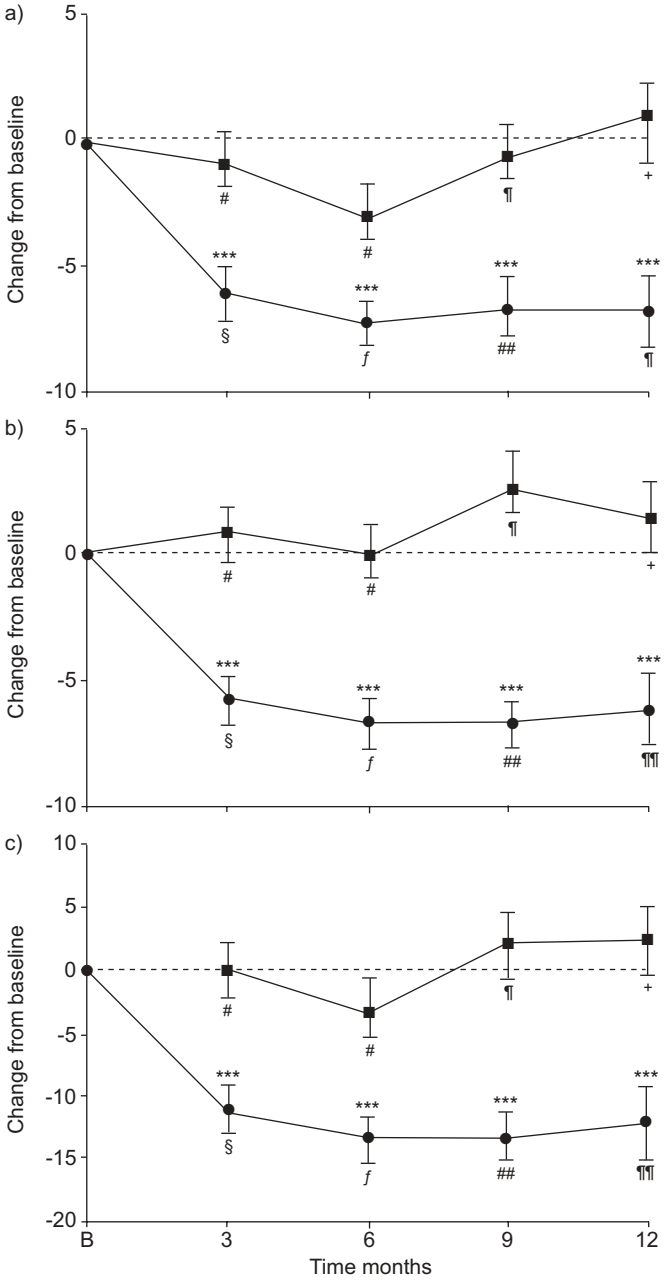

FIGURE 3. Effect of omalizumab on change from baseline (B) in a) total asthma symptom score, b) total rhinitis symptom score, and c) combined asthma and rhinitis symptom score (least square mean±SEM). ●: omalizumab (n=135); ■: current asthma therapy alone (n=70). #: n=54; ¶: n=51; +: n=46; §: n=126; ƒ: n=124; ##: n=120; ¶¶: n=117. ***: $p<0.001$. (J. Bousquet, Service des Maladies Respiratories, Montpellier, France; personal communication).

breastfed infants and in patients aged <12 yrs need to be addressed. A Cochrane database systemic review of 14 clinical trials involving 3,143 patients concluded that omalizumab was well tolerated, but the safety profile required long-term assessment [61].

Anaphylaxis occurred as early as the first dose of omalizumab and even 1 yr after the scheduled treatment, with 39% occurring with the first dose, 19% with the second dose, 10% with the third dose and rest after subsequent doses. In 35% of patients, the time-to-onset of anaphylaxis was within 30 min of injection, but 5% had a delayed onset of reaction of >24 h. Out of 23 patients, 18 (78%) had a recurrence of anaphylaxis when re-challenged with omalizumab [62]. Therefore, omalizumab should be administered (according to a recent medication guide released by the Food and Drug Administration) in healthcare settings where anaphylaxis can be managed, and patients should be observed for an appropriate time following

each injection [63–65]. Although omalizumab is well tolerated, its potential long-term side-effects need careful monitoring.

COSTS ASSOCIATED WITH OMALIZUMAB

Cost-effectiveness analyses are very important because they provide the payers with information on parameters such as death and hospitalisation rates, cost of the medication, needs for emergency or unscheduled visits, and QoL associated with the drug/biologically active agent. DEWILDE *et al.* [66] performed an economic evaluation of omalizumab, which was based on the data from the INNOVATE trial [41]. They found the incremental cost-effectiveness ratio (ICER), which is the difference in total costs between two treatment arms per quality-adjusted life year, for omalizumab as an add-on therapy to be €56,091. However, as randomised controlled trials are performed under ideal experimental conditions, results from cost-effectiveness analyses from such trials can be questionable [67]. A second study was performed using data from a real-life, 1-yr, randomised, open-label trial [68]. The authors found that the ICER for omalizumab ranged between €27,739 and €40,840. This range was considerably lower than the ICER calculated by DEWILDE *et al.* [66] and would suggest that omalizumab is cost-effective as an add-on therapy in patients with severe persistent asthma.

Further work is needed to explore the cost-effectiveness of omalizumab. Recently, the National Institute for Health and Clinical Excellence (UK) considered an economic analysis of omalizumab and concluded that the treatment is cost-effective in the high-risk hospitalised subgroup of patients with severe persistent allergic (IgE-mediated) asthma [69].

CONCLUSION

The prevalence of asthma and AR has increased over the last few decades. There is a high degree of concomitance between the two diseases, which points to common pathogenic pathways. These pathways engage the allergen-specific IgE antibodies that in turn lead to the inflammatory cascade.

The common pathogenic origin has led to the concept of ''one airway disease'' [13]. This in turn provides a strong rationale for development and evaluation of novel therapies that control both diseases. Although leukotriene inhibitors and glucocorticosteroids can be effective in both diseases, an inability to completely control symptoms of severe asthma has been observed. IgE plays a primary role in initiation of allergic processes. This evidence led to the development of omalizumab (a humanised monoclonal anti-IgE antibody). Omalizumab acts by significantly reducing the circulating IgE levels and downregulating IgE receptors on basophils and mast cells. Various clinical trials demonstrated its efficacy in controlling separate and concomitant asthma and rhinitis. Furthermore, there are relatively few AEs related to omalizumab [70], making it a safe option for the treatment of allergic diseases. The efficacy and safety of omalizumab have also been highlighted in the combined studies with immunotherapy where it enhanced the efficacy of SIT and improved the safety of RIT.

In conclusion, omalizumab provides an integrated approach for the treatment and management of allergic respiratory diseases, such as severe allergic asthma and allergic rhinitis. Future studies need to evaluate whether omalizumab may also benefit patients with other immunoglobulin E-mediated diseases, such as allergic bronchopulmonary aspergillosis, chronic urticaria and chronic rhinosinusitis.

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