Anti-IgE Therapy: Clinical Utility and Mechanistic Insights

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Abstract As the major trigger of acute allergic reactions, IgE has long been considered an ideal target for anti-allergy treatments. Omalizumab, first approved by the USA in 2003 and now in use in many other countries is a humanized monoclonal antibody that binds serum IgE. Anti-IgE therapy using omalizumab reduces circulating free IgE levels and blocks both early and late-phase reactions to allergen challenge. It has proven effective for allergic asthma and is currently being evaluated for use in a number of other atopic conditions including allergic rhinitis and chronic idiopathic urticaria. Clinical observations and mechanistic studies with omalizumab have shed new light on the multifaceted roles of IgE in immune homeostasis and in allergic disease.

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1 IgE Functions in Immune Homeostasis and Pathology

1.1 IgE, IgE Receptor, and Effector Cells

Atopic diseases are characterized by production of allergen-specific IgE antibodies. These arise when IgM^+ or IgG^+ B cells of committed antigenic specificity are driven into the process of class switch recombination (CSR) by T helper-2 (Th2) cells. As with CSR to other isotypes, the IgE switch can occur in germinal centers of secondary lymphoid tissues. This may be where some or all IgE memory resides and where affinity maturation occurs during the stage of pre-IgE-switched IgG^+ B cell intermediates (Xiong et al. 2012). However, CSR to IgE is not restricted to lymphoid tissues; it also occurs directly in mucosal tissue sites of allergen exposure (Cameron et al. 2003).

Several unique features of the IgE antibodies bear on the design and implementation of effective strategies of IgE blockade. IgE is the least prevalent antibody in circulation, with concentrations of 50–100 ng/ml in normal individuals, logs lower than the normal level of IgG (5–10 mg/ml). IgE also has a short circulating half-life of only 2–3 days, but it is stable in tissues for many weeks where is it tightly bound to FcεRI on mast cells and not readily accessible to inhibitors designed to target-free IgE. This latter aspect of IgE physiology poses one of the major challenges to the designers of novel anti-IgE strategies (Kubo et al. 2003; Gould et al. 2003). The creation of an agent which would displace tightly bound IgE antibodies from FcεRI would be the ultimate aspiration for a designer of anti-IgE therapeutics.

IgE shares a similar molecular structure with other immunoglobulin isotypes, with two pairs of identical heavy and light chains. However, the constant regions of the ε-heavy chains are comprised of four Cε domains, Cε1–Cε4, in contrast to three Cγ domains in IgG proteins. The constant regions determine the isotype-specific functions of IgE, including binding to its high- and low-affinity receptors. Membrane-bound IgE expressed on the surface of IgE^+ B cells is the product of a splice

isoform containing hydrophobic sequences encoded by M1 and M2 exons (Gould et al. 2003). Monoclonal antibodies targeting the unique M1 domain of transmembrane IgE are under development as potential inhibitors of IgE production (Brightbill et al. 2010).

IgE antibodies exert their biological effects via several receptors. The two major ones are commonly referred to as the "high-affinity receptor," FcεRI, and the "low-affinity receptor," CD23, the latter having a more respectable affinity for IgE than its name would imply. FcεRI is expressed on mast cells and basophils as a $\alpha\beta\gamma_2$ tetramer (Fig. 1). A trimeric $\alpha\gamma_2$ form of FcεRI exists on the surface of dendritic cells, Langerhans cells, and eosinophils in humans. In rodents, FcεRI expression is generally restricted to mast cells and basophils, and trimeric FcεRI expression is observed only under limited circumstances such as viral infection (Dombrowicz et al. 2000; Grayson et al. 2007; Kraft and Kinet 2007; Lin et al. 1996). The α subunit is a type I integral membrane protein which binds the Fc region of IgE. It is comprised of two extracellular immunoglobulin domains, which

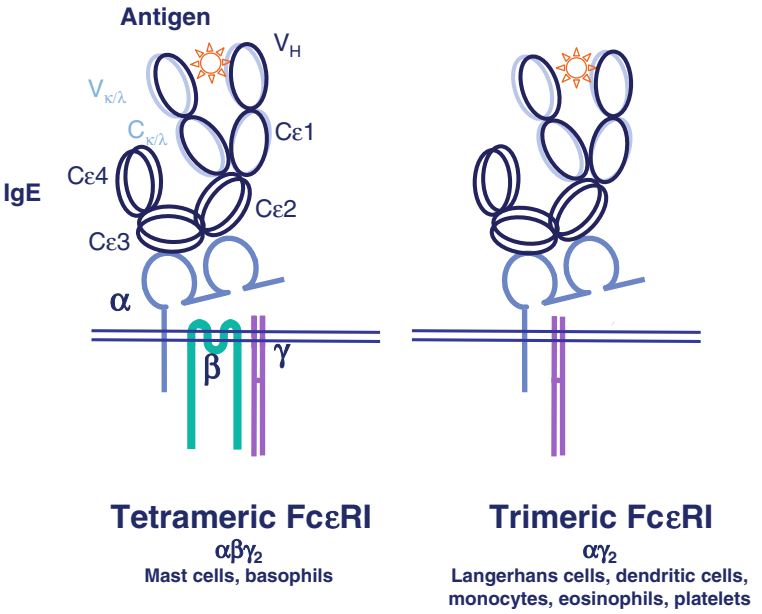

Fig. 1 Structure of the high-affinity IgE receptor, FcεRI. FcεRI is assembled in a tetrameric $\alpha\beta\gamma_2$ form on mast cells and basophils and a trimeric $\alpha\gamma_2$ form on numerous other cell types. The α subunit is a type I integral membrane protein which binds the $C\varepsilon_{2-3}$ domains of the Fc region of IgE. It is comprised of two extracellular immunoglobulin domains, a transmembrane domain and a short intracellular tail. The β-chain, a member of the tetraspanin family of proteins that cross the plasma membrane four times, serves to amplify receptor signal transduction. A pair of disulfide-linked γ-chains, also shared with FcγRIII, contains several intracellular ITAM motifs and is primarily responsible for docking of the signaling protein tyrosine kinase, SYK, in the initiation of IgE-triggered signaling

bind the $C\varepsilon_{2-3}$ regions, a transmembrane domain and a short intracellular tail. In comparison with FcγRs, FcεRI is typically completely saturated at normal physiological concentrations of IgE due to the exceedingly low K_d ($\sim$1 nm) for IgE binding. This underlies the persistence of allergen-specific IgE in tissues for many weeks even in individuals being treated with anti-IgE.

Neither the β subunit nor γ subunits assist in ligand binding. The β chain provides accessory signaling and amplification, while the γ chain, which is shared with FcγRIII, is the main activator of key signaling pathways (Kraft and Kinet 2007). Cross-linking of FcεRI causes signal transduction by phosphorylation of tyrosine-based activation motifs (ITAM) in the γ subunit through activation of constitutively receptor-associated tyrosine kinases.

The low-affinity IgE receptor, CD23, is completely distinct from FcεRI. It is a type II transmembrane glycoprotein with a c-terminal extracellular globular domain containing a calcium-dependent lectin domain. This is followed by an alpha-helical coiled-coil stalk region with a short n-terminal cytoplasmic domain (Acharya et al. 2010). The stalk region contains leucine zipper motifs that mediate oligomerization of CD23. Trimeric CD23 exhibits an avidity for IgE of 10–100 nM which approaches the affinity of FcεRI for IgE (Gould and Sutton 2008). The membrane-bound form of CD23 is susceptible to proteolysis, generating a free receptor known as soluble CD23 that retains the capacity to bind IgE.

IgE antibodies are best known for their role in inducing immediate hypersensitivity reactions, in which exposure to an allergen results in rapid development of allergic symptoms. These reactions are initiated by activation of the high-affinity receptor FcεRI on effector cells including mast cells and basophils. FcεRI aggregation induced by polyvalent antigen-induced IgE cross-linking incites the rapid release of preformed mediators along with de novo synthesis of lipid mediators, which act on target tissues to trigger the early phase allergic response within minutes of allergen exposure. Hours later FcεRI-activated cells produce proinflammatory and immunomodulating cytokines and chemokines that promote recruitment of cells including eosinophils, monocytes, and T cells (Sutton and Gould 1993). These events can elicit “late-phase” symptoms of allergy, in which a second wave of allergic symptoms is experienced 8–12 h after the acute reaction. These proinflammatory mediators, when produced chronically in the course of recurrent IgE-triggered reactions also drive the chronic allergic inflammation characteristic of a number of atopic diseases. In the setting of asthma, mediators released by degranulation of mast cells and basophils act on endothelial cells to increase vascular permeability leading to edema of the airway wall. Mucus production and constriction of airway smooth muscles, induced by the same mediators, lead to further airflow airway narrowing. In an individual with aeroallergen sensitivity, these events manifest as acute airflow obstruction, measured in the clinical laboratory as a drop in forced expiratory volume of air in 1 s (FEV_1). Asthmatic individuals exhibit acute drops in FEV_1 immediately after allergen challenge and late phase decreases 8–12 h later. In some chronic asthmatics, cellular infiltration of the airway wall and chronic fibrotic changes cause stable airflow obstruction with a fixed decrease in FEV_1.

The major rationale underlying the development of anti-IgE therapies has been that blockade of acute and late-phase reactions precipitated by allergen exposure would reduce symptoms. There have additionally been expectations that interference with chronic recurrent acute reactions to allergen would diminish the pool of mast cell and basophil-derived mediators that might drive cellular recruitment and chronic allergic inflammation. However, recent findings regarding functions of IgE in the regulation of its own receptors and in mast cell homeostasis suggest additional mechanisms whereby IgE blockade might be beneficial.

1.2 IgE and Regulation of IgE Receptors

IgE plays an important role in the regulation and expression of both its high- and low-affinity receptors. Our studies with IgE-deficient mice revealed reduced expression of both FcεRI on their mast cells and basophils and CD23 on their B cells (Kisselgof and Oettgen 1998; Yamaguchi et al. 1997). Reconstitution of normal circulating IgE levels via *i.v.* infusion restored surface expression of both receptors to normal levels. In human studies, Saini et al. (2000) showed a direct correlation between total serum IgE levels and FcεRI cell surface expression, across a range of atopic and nonatopic conditions. IgE binding to CD23 inhibits cleavage of the receptor by proteases, thus allowing the IgE-CD23 complex to remain on the effector cell surface (MacGlashan 2008). Similarly, binding of IgE to cell surface FcεRI stabilizes the receptor and prevents both removal of the receptor from the surface of the effector cell, and degradation by proteases. Empty FcεRI receptors are rapidly internalized, and the presence of IgE in the milieu of effector cells supports accumulation of FcεRI at the cell membrane (Borkowski et al. 2001; Saini et al. 2000). It is very likely that some of these effects of IgE on the stability and expression of its receptors underlie the benefits of anti-IgE therapy.

1.3 Mast Cell Homeostasis

Up until recently, the accepted paradigm of FcεRI-mediated IgE signaling held that cross-linking of receptor-bound IgE by polyvalent allergen and consequent aggregation of FcεRI in the membrane were critical for signaling. A mast cell or basophil bearing FcεRI-bound IgE was considered a loaded gun, ready for allergen-driven triggering but unaffected by the mere presence of IgE. A number of studies now reveal that IgE itself, in the absence of exogenous allergen, can exert significant effects. These findings have significance with respect to consideration of potential mechanisms of action of IgE blockade. Initial findings supporting the antigen-independent effects of IgE on FcεRI signaling and on the survival and proliferation of cultured mast cells were presented as back-to-back reports in 2001 (Asai et al. 2001; Kalesnikoff et al. 2001). A role for IgE antibodies in mast cell

expansion in vivo is supported by our observation that the appearance of mast cells in the airways of mice subjected to repeated inhalation of *Aspergillus funigatus* was markedly impaired in animals lacking IgE antibodies (Mathias et al. 2009).

Studies of antigen-independent effects of IgE antibodies on mast cells have been performed using monoclonal IgE antibodies of varying specificity. Kawakami and colleagues observed that there is considerable variability among individual antibodies with respect to the potency of their antigen-independent effects on mast cells, and they have designated clones capable of inducing high-level antigen-independent cytokine secretion, including SPE-7, as "Highly Cytokinergic" (HC) (Kashiwakura et al. 2012). They have demonstrated that HC IgE clones exhibit reactivity to autoantigens (dsDNA, ssDNA, and thyroglobulin) an observation that provides a potential mechanism whereby cross-linking of receptor-bound IgE is induced by ubiquitous autoantigens in the absence of nominal antigen. James and colleagues published a very interesting finding in 2003 that both anticipated this autoreactivity of HC IgE antibodies and provided a structural basis (James et al. 2003). Using X-ray crystallography, they observed that the antigen-binding site of HC IgE, SPE-7, exists in equilibrium of alternative isoforms, at least one of which could bind to an autoantigen (thioredoxin) identified by peptide screening. Taken together, these observations indicate that the pro-allergic effects of IgE antibodies may be observed in the absence of allergen exposure and that IgE blockade could exert effects even in allergen-independent contexts.

1.4 Antiviral Responses

Consideration of potential impacts of IgE on antiviral responses is intriguing, as viral infections are the most common triggers of asthma. Multiple studies have demonstrated reduced production of type I interferons in atopic patients. Cells recovered from bronchoalveolar lavage, dendritic cells, and peripheral blood mononuclear cells from asthmatic patients were evaluated after treatment with viruses including influenza and rhinovirus (Gill et al. 2010; Sykes et al. 2012; Durrani et al. 2012). Dendritic cells from atopic patients produced significantly less IFN-α when exposed to influenza, and the amount produced was inversely proportional to total serum IgE (Gill et al. 2010). Supportive data were shown from BAL cells from allergic patients exposed to rhinovirus. Production of type I interferons was again deficient, and this reduced production was associated with worsening airway hyperresponsiveness (Sykes et al. 2012). In addition, cross-linking FcεRI on PBMCs prior to exposure to human rhinovirus also triggered a significant decrease in IFN-α production (Durrani et al. 2012). Such observations suggest that reductions in free IgE may help improve immune responses to viral infections and attenuate asthma exacerbations in patients exposed to respiratory viruses.

2 Omalizumab: Structure and Pharmacology

2.1 Structure: Humanized MAb Against IgE

Omalizumab (initially designated rhuMAb-E25) is a humanized $IgG_1\kappa$ monoclonal anti-IgE antibody that binds with high affinity to IgE at the Cε3 domain and has a molecular weight of approximately 149 kD (Fig. 2). The antibody is derived from the murine monoclonal antibody, MAE11. MAE11 was humanized by incorporating the mouse-derived complementarity-determining region into a human IgG1 framework (Presta et al. 1993; Boushey 2001). The IgG1 human framework comprises approximately 95 % of the omalizumab molecule, leaving 5 % murine sequences. Importantly, omalizumab binds circulating IgE regardless of its antigen specificity. It effectively blocks the binding site of IgE for both FcεRI and CD23, and its high affinity for IgE allows it to compete with FcεRI. Preclinical studies demonstrated reduction in serum levels of free IgE in murine models (Haak-Frendscho et al. 1994), while subsequent clinical studies established this capacity to reduce IgE in asthmatic patients. Omalizumab was approved for use in the USA in 2003 and was later approved as adjunctive therapy in 2005 by the European Medicines Agency. While omalizumab remains licensed only for patients aged 12 or older in the USA, the medication was recently approved by the European Medicines Agency for use in children aged 6 years and older (Pelaia et al. 2011).

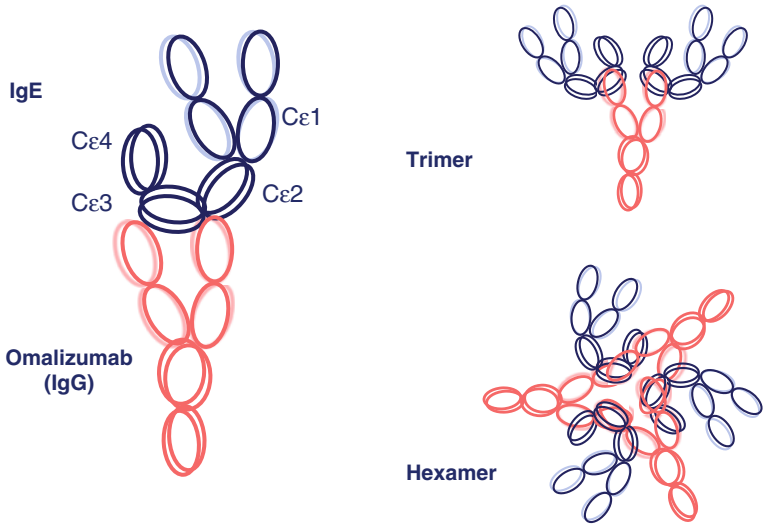

Fig. 2 Omalizumab. Omalizumab is a humanized $IgG_1\kappa$ monoclonal anti-IgE antibody that binds to IgE at the Cε3 domain. Omalizumab forms trimeric and hexameric complexes with IgE, which circulate. IgE in these complexes is detected in standard clinical IgE assays so that total IgE levels appear to rise following institution of omalizumab therapy

2.2 IgE–Omalizumab Interaction

Omalizumab specifically binds circulating free IgE at the high-affinity receptor-binding site, thus inhibiting binding of the antibody to effector cells. Once bound to free IgE, small complexes are formed. Typically, omalizumab:IgE complexes are trimers of approximately 490–530 kD or hexamers of approximately 1,000 kD. The size of complexes depends on the relative concentrations of both serum-free IgE and omalizumab. A study of anti-IgE in cynomolgus monkeys found the largest complex formed in vivo was a hexamer (Liu et al. 1995; Fox et al. 1996). Omalizumab does not cause cross-linking of the IgE receptor or subsequent effector cell degranulation, a property that has been referred to as its being "nonanaphylactogenic" (Chang 2000).

2.3 Pharmacokinetics

Omalizumab is administered subcutaneously, with a bioavailability of 62 %. Peak serum concentrations are reached after an average of 7–8 days, and the half-life is approximately 26 days. This is in contrast to the much shorter 2-day half-life of free IgE. Omalizumab dosing utilizes important data gleaned from a phase II clinical trial of anti-IgE for the treatment of allergic rhinitis triggered by ragweed allergen (Pelaia et al. 2011). The study concluded that significant symptomatic benefit was reached only when free IgE levels were completely suppressed and that the magnitude of suppression was associated with both pretreatment serum IgE level and anti-IgE dosing. Therefore, omalizumab is administered every 2–4 weeks at a dose of 150–375 mg subcutaneously, with the dose and frequency determined based on patient body weight and IgE level. Due to the requirement of near-total suppression of IgE levels for clinical efficacy, the drug is only FDA approved for pretreatment IgE levels of 30–700 IU/mL (XOLAIR PACKAGE INSERT).

Following administration of omalizumab, serum-free IgE concentrations decrease rapidly in clinical studies, with a mean drop of over 96 % from baseline using standard dosing. However, total serum IgE including both bound and unbound fractions increased subsequent to omalizumab dosing. The clearance of omalizumab:IgE complexes is slower than that of free IgE, and standard clinical lab assays detect IgE in both free and complexed forms. Thus, an apparently paradoxical *increase* in total IgE is observed in omalizumab-treated patients. After discontinuation of omalizumab dosing, serum total IgE decreases, while free IgE increases. However, this reversal occurs slowly and does not reach pretreatment levels even one year after discontinuation of therapy.

3 Early Clinical Studies in Asthma

3.1 Inhalation Challenge

Early clinical studies demonstrated that anti-IgE treatment in asthmatic patients led to significantly decreased free IgE levels and reduced both immediate symptoms and late-phase responses to inhaled aeroallergen challenge (Fahy et al. 1997; Boulet et al. 1997).

3.2 Early and Late-phase Suppression, Further Analyses

Attenuation of the early allergen response in the above studies was demonstrated both by a decrease in the degree of the fall of FEV_1 after exposure to fixed doses of allergen and by an increase in the threshold dose of allergen necessary to elicit bronchoconstriction. Fahy et al. (1997) showed that late-phase responses in the airway were also reduced in the treatment groups, as evidenced by protection from late drops in FEV_1 and by a reduction in the percentage of airway eosinophils in sputum 24 h after challenge. These early studies set the stage for future evaluations of the safety and efficacy of anti-IgE in asthma and other atopic diseases. The demonstration that anti-IgE could counteract both early and late-phase allergic responses confirmed the importance of IgE antibody function both in immediate hypersensitivity and in cellular recruitment and the initiation of inflammation, providing a strong rationale for clinical trials of IgE blockade in chronic allergic diseases such as asthma.

4 Asthma Studies

Subsequent studies evaluating the efficacy of anti-IgE therapy for allergic asthma in adolescent and adult patients further underscored the ability of anti-IgE to attenuate early and late-phase asthma symptoms. Milgrom and colleagues completed a large randomized, placebo-controlled phase II study evaluating patients with moderate to severe allergic asthma (Milgrom et al. 1999). In treatment groups, serum-free IgE levels dropped precipitously, and asthma symptoms were significantly improved as evidenced by reduced use of rescue β-agonist inhalers, decreased oral and inhaled corticosteroid (ICS) requirement, and improved pulmonary function testing.

Two critical phase III clinical trials of anti-IgE therapy in patients with severe chronic asthma, performed in the USA and Europe, provided the evidence that led to FDA approval of omalizumab (Soler et al. 2001; Busse et al. 2001). Both groups studied ICS-dependent asthmatics and utilized a study design that included initial continuation of daily ICS, with a subsequent steroid reduction phase during

anti-IgE treatment. In both trials, treatment group patients suffered fewer asthma exacerbations during both the steroid stable and reduction phases. Other primary end points in the treatment groups included a significant reduction in ICS dose, decreased frequency of rescue inhaler use, improved pulmonary function parameters including mean FEV_1, and improved asthma symptoms scores. The frequency of adverse events was not increased in the anti-IgE treatment groups.

A veritable flood of trials followed on the heels of these initial studies. The results of twenty-five of these anti-IgE studies comprising a total of 6,382 participants with mild to severe allergic asthma were analyzed in a recent Cochrane review (Normansell et al. 2014). Most of the included studies evaluated anti-IgE as adjunctive therapy to inhaled corticosteroids and/or long acting beta agonists (LABAs). Overall, the pooled data indicated that clinical benefit from anti-IgE therapy was improved from placebo, including reduced asthma exacerbation frequency, reduced hospitalizations, and reduction in daily ICS and rescue inhaler use. Also, anti-IgE therapy significantly increased the number of participants who were able to completely withdraw from daily ICS use as compared to placebo. Participants in 7 of 11 studies also noted modest but significant improvements in asthma scores and quality of life assessments. However, changes in pulmonary function parameters were inconsistent. Overall, the message of both the initial pivotal studies and the large number of follow-up trials has been that anti-IgE reduces the frequency of acute flares and hospitalizations while only modestly affecting the chronic day-to-day indicators of disease activity such as quality of life scores and physiologic measures of small airway obstruction. These findings suggest that anti-IgE attenuates disease flares precipitated by aeroallergen exposure or respiratory infection but that it does not interfere with the chronic Th2-driven allergic inflammatory process that leads to the infiltration of the airways with inflammatory cells, edema of the airway mucosa, hyper-responsiveness of bronchial smooth muscle, and hyper-production of mucus all of which can likely arise in the absence of IgE signals.

5 Pediatric Asthma

Most of the initial anti-IgE studies focused on adult participants, but in recent years more emphasis has been placed on childhood asthma, a disease that appears to be more consistently allergen driven. Milgrom and colleagues performed a large, double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of anti-IgE in the treatment of children aged 6–12 years with moderate to severe asthma (Milgrom et al. 2001). This study design echoed adult studies, with the 334 enrolled children treated with anti-IgE as adjunctive therapy to stable ICS regimens. Inclusion criteria for pediatric participants included moderate to persistent asthma well controlled on ICS, positive skin prick testing to at least one common aeroallergen, and total IgE levels between 30 and 1,300 IU/mL. These criteria differ from the previously discussed adolescent and adult studies, where the majority of trials included patients with poorly controlled asthma despite ICS use

and a more restricted pretreatment IgE level. Results were encouraging in the treatment group, with significant reductions in ICS dosage and more frequent complete withdrawal of ICS use. During the steroid reduction phase in the treatment group, use of rescue albuterol was reduced, and asthma exacerbations requiring additional treatment declined in both frequency and severity. No significant change between the groups was seen in asthma symptom scores or pulmonary function parameters. Anti-IgE was well tolerated, with no serious adverse effects. Following completion of the above trial, further information regarding quality of life evaluations was published (Lemanske et al. 2002). No change in quality of life was found during the steroid-stable phase of the trial, but at the end of the study treatment group participants reported improved asthma scores and a statistically significant increase in overall asthma-related quality of life. This was likely affected by the reduction in exacerbations, decrease in ICS use, and lack of hospitalizations in the treatment group.

A more recent pediatric anti-IgE trial performed by Lanier et al. (2009) had similar results. This study more closely resembled the adult trials, as enrolled pediatric subjects included children aged 6 to <12 years old with moderate to severe persistent asthma incompletely controlled with ICSs. Over the course of the trial, the overall exacerbation frequency was reduced by 43 % versus the placebo group. Additionally, in contrast to the previous pediatric study, treatment group subjects experienced a significant attenuation in exacerbation frequency during the fixed-steroid phase. Further support of the effectiveness of omalizumab in adjunctive treatment of pediatric asthma was exhibited by a recent retrospective analysis of pooled data extracted from five adolescent and adult anti-IgE trials (Massanari et al. 2009). This analysis included patients aged 12–17 years old and also demonstrated a reduction in frequency of asthma exacerbations, improved pulmonary function parameters, and improvement in asthma scores. In all studies, regardless of participant age, anti-IgE therapy significantly reduced asthma exacerbations, thus highlighting the importance of IgE during times of asthma exacerbation. However, as was evident in the meta-analyses of the adult trials, improvements in pulmonary function parameters and quality of life were inconsistent across studies. This again reveals the key role of IgE in acute flares while suggesting a dominant role for IgE-independent mechanisms in the pathogenesis of the chronic inflammation and impairments in airway physiology seen in asthma.

6 Omalizumab in Other Atopic Diseases

Alongside the successes of omalizumab in asthma trials, anti-IgE was evaluated early on for its effectiveness in allergic rhinitis (AR), another disease characterized by high-titer IgE responses to inhaled aeroallergens and by seasonal flares of

symptoms driven by allergen inhalation (Casale et al. 1997). Subsequently, other disorders became candidates for anti-IgE trials, including atopic dermatitis, urticaria, and food allergy (Chang et al. 2007; Incorvaia et al. 2014).

6.1 Allergic Rhinitis

Allergic rhinitis is a prevalent problem in both adult and pediatric patient populations. A number of trials have evaluated use of anti-IgE in patients with allergic rhinitis triggered by a variety of environmental allergens, most commonly birch pollen or ragweed. Their results established that anti-IgE decreased nasal and ocular symptoms, reduced antihistamine use, and improved quality of life scores (Adelroth et al. 2000; Casale et al. 1997, 2001; Chervinsky et al. 2003). Anti-IgE also improved symptom scores and decreased sensitivity to nasal allergen challenge (Hanf et al. 2004). Nasal biopsy specimens in patients receiving anti-IgE showed none of the mucosal tissue eosinophilia evident in the placebo group (Plewako et al. 2002). Further evidence for improvement in allergic rhinitis was demonstrated by a trial of anti-IgE administered in combination with traditional subcutaneous immunotherapy in children and adolescents with moderate to severe allergic rhinitis. Study participants receiving anti-IgE in addition to standard allergen immunotherapy showed significant clinical improvement in symptoms as compared to immunotherapy alone (Kuehr et al. 2002). Thus, removal of IgE seems to ameliorate both early and late-phase hypersensitivity responses in allergic rhinitis.

6.2 Rush Immunotherapy

Rush immunotherapy is an accelerated subcutaneous immunotherapy regimen that allows patients to reach maintenance dosing much more quickly than with traditional protocols. However, these faster protocols are associated with an increased incidence of serious adverse reactions including anaphylaxis. Casale et al. (2006) established that adult patients treated with anti-IgE prior to induction of rush immunotherapy had fewer reactions. Another study showed addition of anti-IgE prior to cluster immunotherapy in patients with persistent asthma reduced the risk of adverse events during immunotherapy. More patients in the anti-IgE treatment group reached goal maintenance dosing and had fewer adverse events, including those requiring epinephrine, throughout the cluster protocol (Massanari et al. 2010).

6.3 Food-induced Anaphylaxis and Oral Immunotherapy

Food allergy has emerged as another attractive option for anti-IgE therapy. Immediate hypersensitivity reactions to allergenic food ingestion depend on the presence of food-specific IgE antibodies and can be quite severe, progressing to potentially fatal systemic anaphylaxis. As current therapeutic options are limited to strict avoidance of the allergenic food for safety reasons, patients are paradoxically deprived of their only hope for achieving tolerance, namely oral ingestion of the allergenic food. Anti-IgE has been considered an attractive treatment option in this setting both because it might reduce dangerous reactions following inadvertent food ingestions and as an adjunct to oral immunotherapy.

The first study evaluating use of anti-IgE in food allergy was conducted by Leung et al. (2003) who showed that administration of an anti-IgE monoclonal antibody, TNX-901, led to significant increases in the threshold dose of peanut required to trigger hypersensitivity reactions in oral peanut food challenges. This result established the efficacy of anti-IgE in blunting IgE-mediated food reactions and provided the basis for the more recent application of anti-IgE treatment during oral immunotherapy (OIT) in children with food allergies. While OIT, in which allergic subjects are fed incrementally increasing doses of allergenic food under very controlled conditions, has shown promise in terms of reducing food sensitivity, its broad application has been impeded by the frequency of undesirable and potentially dangerous reactions experienced by patients in the course of dose escalation. Nadeau et al. reasoned that anti-IgE might mitigate these reactions and conducted a pilot study in children with cow's milk allergy undergoing rapid oral milk desensitization under cover of anti-IgE. Nine of 10 patients reached the goal dose of 2,000 mg milk after desensitization over 7–11 weeks. Anti-IgE therapy was then discontinued, and daily milk ingestion continued. All 9 patients subsequently passed a double-blind, placebo-controlled food challenge (DBPCFC) 8 weeks after discontinuation of anti-IgE (Nadeau et al. 2011).

Anti-IgE therapy has also been applied to OIT for the extremely allergenic food, peanut. A phase II trial performed by Sampson et al. (2011) to evaluate the effectiveness of anti-IgE in reducing the frequency of peanut-induced allergic reactions during OIT was discontinued early due to anaphylactic episodes that occurred during initial pre-enrollment peanut food challenges. However, data obtained prior to discontinuation revealed that participants receiving anti-IgE therapy were able to tolerate higher peanut doses than placebo-treated participants. Another study evaluating peanut oral immunotherapy under cover of anti-IgE has been performed (Schneider et al. 2013). High-risk peanut allergic children were treated with anti-IgE, and then underwent oral desensitization. Patients reached a cumulative dose of 992 mg without symptoms of hypersensitivity, and subsequently tolerated a peanut food challenge of 8,000 mg peanut flour. These studies illuminate the possibilities of future successful, safe oral desensitization to foods. It will be of great interest to determine whether IgE blockade during OIT, in addition

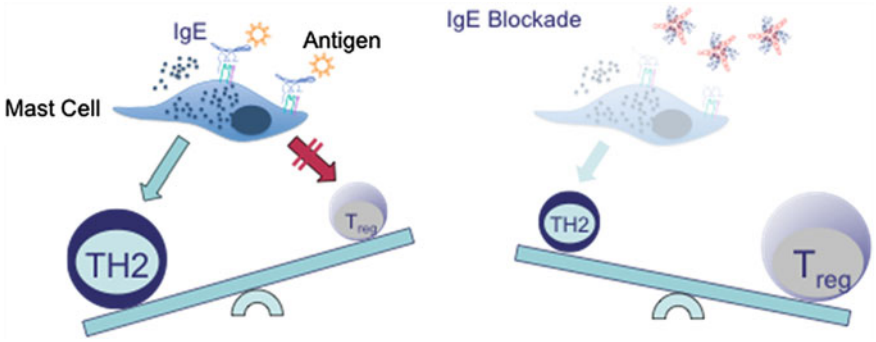

Fig. 3 Hypothetical model for IgE-mediated regulation of T cell responses to allergen and effects of omalizumab in this model. Mast cells produce significant levels of the Th2-skewing cytokine IL-4. We speculate that IgE-mediated mast cell activation drives IL-4-mediated Th2 expansion and concomitant Treg suppression and that inhibition of this effect in the setting of omalizumab therapy would favor Treg responses over Th2

to enhancing safety by reducing anaphylactic reactions, might also modulate immune responses to food allergens, suppressing allergen-driven Th2 expansion, and favoring Treg induction (Fig. 3).

6.4 Chronic Idiopathic Urticaria

Chronic idiopathic urticaria (CIU) is a condition characterized by hives that last for a minimum of 6 weeks, without obvious trigger. Therapeutic options currently include antihistamines, leukotriene receptor antagonists, systemic steroids, and other immunosuppressive medications. However, the condition is often refractory to these therapies and the side effects of systemic steroids are undesirable. An early proof of concept study using anti-IgE demonstrated improvement in the Urticaria Activity Score (UAS), which includes pruritus severity, number of hives, and size of largest hive, as well as a reduction in rescue antihistamine use and improvement in overall quality of life (Kaplan et al. 2008). Subsequent phase II and III trials evaluating the efficacy of anti-IgE compared to placebo in treating CIU unresponsive to traditional therapies substantiated the findings of previous proof of concept trials. The first phase III trial performed by Maurer et al. (2013) included 323 patients with treatment-resistant moderate to severe CIU and evaluated efficacy of increasing doses of omalizumab.

Since CIU is not generally considered an atopic disease and allergen triggers are not usually identified in these patients, the efficacy of omalizumab was a surprise to some. The average IgE level of the study population was only 168.2 ± 231.9 IU/ml, which is only very modestly elevated and much lower than the levels observed in the other atopic conditions responsive to anti-IgE. The study found significant dose

responsive diminution of symptoms as compared to placebo, with the greatest clinical effects generated by the highest anti-IgE dose (300 mg). A subsequent phase III trial performed by Kaplan et al. (2013) substantiated these results. Omalizumab was recently approved by the FDA for the treatment of CIU refractory to antihistamine therapy in patients aged 12 years and older.

The mechanisms by which anti-IgE reduces symptoms in patients with CIU remain to be elucidated, but a rapid reduction in free IgE levels has been consistently demonstrated in omalizumab-treated patients with CIU and this reduction in IgE correlates closely with clinical improvement. Several mechanistic studies of omalizumab have demonstrated downregulation of FcεRI on peripheral blood basophils and on skin and nasal mast cells (Saini et al. 1999; Beck et al. 2004; Eckman et al. 2010). There is some evidence that a subset of patients with CIU has autoantibodies directed against FcεRI (Grattan et al. 1991; Hide et al. 1993; Kikuchi and Kaplan 2001), and it has been speculated that the reduction in FcεRI density induced by omalizumab therapy reduces the susceptibility of $FcεRI^+$ cells to activation by such antibodies. An alternative possibility is that these patients have HC IgE antibodies (see Sect. 1.3) that interact with autoantigens and omalizumab decreases the titers of these antibodies. While both the results of the CIU trials and these proposed mechanisms are thought provoking, further studies are required before firm conclusions can be made.

6.5 Atopic Dermatitis

Atopic dermatitis (AD) typically presents in childhood and can persist throughout the lifetime of an affected patient. Patients typically have dramatically elevated serum IgE levels and are often affected by other concurrent allergic diseases suggesting a potential pathogenic role of IgE in AD. Treatment of recalcitrant AD can be difficult and may include immunosuppressive medications. Clinical studies of anti-IgE therapy for AD have resulted in variable conclusions. Case reports and an early pilot study using omalizumab suggested improvement in clinical atopic dermatitis symptoms (Sheinkopf et al. 2008). A larger explorative study also found treatment with anti-IgE significantly reduced free serum IgE, decreased FcεRI expression on basophil cell surfaces, and also decreased IgE saturation of FcεRI. However, treatment group patients had no improvement in clinical symptoms (Heil et al. 2010). These findings, like those of the asthma studies, suggest that the chronic inflammatory component of AD is likely driven in large part by IgE-independent mechanisms and that the utility of IgE blockade may be limited in this setting.

6.6 Eosinophilic Gastrointestinal Disorders

Eosinophilic gastrointestinal disorders include eosinophilic esophagitis, eosinophilic colitis, and eosinophilic gastroenteritis. Affected patients experience a range of chronic gastrointestinal symptoms including difficulty swallowing, pain, and diarrhea but, unlike typical food allergy patients, they do not generally experience immediate hypersensitivity reactions, such as systemic anaphylaxis. In this way, the disease process seems more analogous to that involved in AD. However, eosinophilic gastrointestinal disorders can be associated with atopy, and some patients have positive skin prick testing to foods. A clinical trial evaluating the effects of anti-IgE therapy in patients with eosinophilic gastroenteritis gave results consistent with those for anti-IgE therapy for other atopic conditions (Foroughi et al. 2007). As expected, serum-free IgE and food allergen skin prick test reactions were decreased in the treatment group along with reductions in FcεRI surface expression on basophils and dendritic cells. A downward trend in tissue eosinophilia was observed in biopsies of the duodenum, gastric antrum, and gastric body but this did not reach significance. Symptom scores improved both midstudy and at the conclusion of the trial, but did not correlate with reduction in tissue eosinophilia.

7 Mechanisms

Many of the clinical trials of IgE blockade described above have been accompanied by immunologic analyses, which have provided valuable insights both into the pathogenesis of allergic diseases and the mechanisms of action of anti-IgE.

7.1 Blockade of Early and Late-phase Hypersensitivity

The seminal studies of anti-IgE therapy have demonstrated sharp reductions in circulating levels of free IgE antibodies along with strong evidence that anti-IgE blockade impairs both early and late-phase hypersensitivity reactions. Anti-IgE therapy reduces early and late-phase allergic asthma responses after inhalational allergen challenge (Fahy et al. 1997), diminishes late-phase skin responses to intradermal allergen exposure (Ong et al. 2005), and decreases sputum eosinophilia (Fahy et al. 1997; Djukanovic et al. 2004) and airway submucosal eosinophil, T cell, and B cell numbers in asthmatic subjects (Djukanovic et al. 2004). A study performed on adult subjects with allergic rhinitis secondary to dust mites showed a rapid reduction in serum-free IgE levels and a 97 % decrease of basophil cell surface expression of FcεRI (MacGlashan et al. 1997). Basophil histamine release was also decreased by approximately 90 %, and basophil response was completely eradicated in 50 % of subjects. Mast cell involvement was implicated by

requirement of antigen doses of 100 times the original dose in order to generate similar pre-anti-IgE skin prick wheals. Peripheral eosinophilia and serum levels of Th2-inducing cytokines including IL-13 are also decreased in asthmatic patients treated with anti-IgE (Noga et al. 2003). The latter observation is consistent with a role for IgE antibodies in the maintenance of Th2-driven allergic responses and highlights the importance of anti-IgE therapy in combating these responses (Fig. 3).

7.2 Regulation of IgE Receptors

Prior to the application of anti-IgE therapy, it was known that IgE levels regulate expression and stability of FcεRI receptors on the surface of basophils, mast cells, and dendritic cells. Treatment with anti-IgE depletes the concentration of free IgE in serum, and therefore, as predicted, results in decreased cell surface density of FcεRI (MacGlashan et al. 1997; Beck et al. 2004; Prussin et al. 2003). Beck and colleagues evaluated the effects of omalizumab treatment on mast cell FcεRI expression. After 1 week of therapy, minimal reduction in mast cell surface FcεRI was noted, and later in therapy FcεRI receptor density was significantly decreased, along with a reduction in skin prick allergen-stimulated wheal size (Beck et al. 2004). While these studies have been interpreted to imply discordance in rate of FcεRI reduction between mast cells and basophils, there are technical differences in the approach to FcεRI measurement that limit this extrapolation. Basophil FcεRI density has typically been quantitated by flow cytometry, a method that reliably detects only cell surface receptor while the measurements of FcεRI on skin mast cells have been performed using immunohistochemical staining which does not discriminate surface from internalized FcεRI. In analyses of cultured rodent mast cells, surface FcεRI levels modulate very rapidly in response to changes in ambient IgE. It will be important in future studies to determine the kinetics of reduction of surface levels of FcεRI on mast cells of omalizumab-treated subjects.

Dendritic cells, which also express FcεRI, are key inducers and regulators of immune responses. Omalizumab therapy results in reduction of FcεRI expression on circulating plasmacytoid dendritic cells (pDCs) as demonstrated by Prussin et al. (2003). The reduction of pDC surface FcεRI receptor density was evident within 7 days of anti-IgE therapy and correlated well with reduced serum-free IgE levels. Schroeder et al. (2010) have reported that the reduction in DC FcεRI following omalizumab therapy is associated with a reduction in IgE-facilitated antigen presentation in the induction of Th2 responses in a cell culture system. These results are of great interest and suggest that anti-IgE therapy may interfere with IgE-facilitated antigen presentation by dendritic cells. This ultimately could cause a blockade of early sensitization to antigens. This in turn acts in concert with reduction of effector cell mediation of immediate hypersensitivity responses to further reduce hypersensitivity reactions.

7.3 Effects on Viral Immunity

Upper respiratory viral infections are probably the most important trigger of asthma exacerbations across age groups. While anti-IgE therapy has proven to be effective in decreasing the frequency of asthma exacerbations overall, it has been unclear whether this is exclusively because of interference with immediate hypersensitivity reactions in patients exposed to inhaled aeroallergens or whether omalizumab might also alter the onset of asthma flares after viral infection. In the "Inner City Asthma Study," (Busse et al. 2011) made the intriguing observation that anti-IgE treatment is associated a significant reduction of the frequency of asthma flares associated with seasonal virus exposure. In a substudy of this cohort, the investigators found that rates of viral infection as measured in nasal swabs were the same in treatment and placebo groups, suggesting a benefit of anti-IgE treatment in attenuating virus-induced asthma flares. We speculate that this resistance to flares might be due either to an elevated threshold for bronchial obstruction because of reduced allergic inflammation of the airway mucosa in omalizumab-treated subjects or to interference with the negative effects of IgE:FcεRI signaling on innate immune responses (Type I interferon production) to viruses by dendritic cells (see Sect. 1.4).

8 Future Directions

The success of omalizumab in the treatment of allergic asthma has generated new insights into the roles of IgE in allergic pathophysiology and has opened doors for novel strategies. The generation of higher affinity anti-IgE reagents is in progress (Cohen et al. 2014) as is the design of therapeutics, which uniquely bind to IgE^+ B cells and could selectively target IgE production at the source (Brightbill et al. 2010). There is considerable interest in the development of inhibitors of the very high-affinity interaction of IgE with FcεRI. Jardetzky and colleagues have presented encouraging data regarding designed ankyrin repeat inhibitors (DARPins), which have the potential to dislodge IgE bound to FcεRI (Eggel et al. 2014). Other promising studies have focused on blocking critical activators of key IgE-mediated signaling pathways. Spleen Tyrosine Kinase (SYK) is the critical proximal protein tyrosine kinase in FcεRI signaling. Early studies have shown inhibition of SYK leads to mitigation of airway inflammation and mast cell degranulation (Matsubara et al. 2006; Penton et al. 2013; Yamamoto et al. 2003). Moy et al. utilized a small molecule and very highly selective inhibitor of SYK (SYKi) to achieve blockade of allergen-induced bronchoconstriction in murine models (Moy et al. 2013). Meanwhile, ongoing analyses of omalizumab efficacy and mechanisms of action in a range of allergic diseases promise to further illuminate the role of IgE in sensitization and pathogenesis of allergy.

References

Acharya M, Borland G, Edkins AL, Maclellan LM, Matheson J, Ozanne BW, Cushley W (2010) CD23/Fc epsilon RII: molecular multi-tasking. Clin Exp Immunol 162(1):12–23. doi:10.1111/j.1365-2249.2010.04210.x

Adelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, Byrne A, Champain K, Thirlwell J, Cioppa GD, Sandstrom T (2000) Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 106(2):253–259. doi:10.1067/mai.2000.108310

Asai K, Kitaura J, Kawakami Y, Yamagata N, Tsai M, Carbone DP, Liu FT, Galli SJ, Kawakami T (2001) Regulation of mast cell survival by IgE. Immunity 14(6):791–800

Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S (2004) Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. J Allergy Clin Immunol 114 (3):527–530

Borkowski TA, Jouvin MH, Lin SY, Kinet JP (2001) Minimal requirements for IgE-mediated regulation of surface Fc epsilon RI. J Immunol 167(3):1290–1296

Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun VA, Laviolette M, Cleland LD, Deschesnes F, Su JQ, DeVault A, Fick RB Jr, Cockcroft DW (1997) Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 155(6):1835–1840. doi:10.1164/ajrccm.155.6.9196083

Boushey HA Jr (2001) Experiences with monoclonal antibody therapy for allergic asthma. J Allergy Clin Immunol 108(2 Suppl):S77–83

Brightbill HD, Jeet S, Lin Z, Yan D, Zhou M, Tan M, Nguyen A, Yeh S, Delarosa D, Leong SR, Wong T, Chen Y, Ultsch M, Luis E, Ramani SR, Jackman J, Gonzalez L, Dennis MS, Chuntharapai A, DeForge L, Meng YG, Xu M, Eigenbrot C, Lee WP, Refino CJ, Balazs M, Wu LC (2010) Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice. J Clin Investig 120(6):2218–2229. doi:10.1172/JCI40141

Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N (2001) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 108(2):184–190

Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szefler SJ, Sorkness CA (2011) Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 364(11):1005–1015. doi:10.1056/NEJMoa1009705

Cameron L, Gounni AS, Frenkiel S, Lavigne F, Vercelli D, Hamid Q (2003) S epsilon S mu and S epsilon S gamma switch circles in human nasal mucosa following ex vivo allergen challenge: evidence for direct as well as sequential class switch recombination. J Immunol 171(7):3816–3822

Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, Dockhorn RJ, Reimann J, Su JQ, Fick RB Jr, Adelman DC (1997) Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 100(1):110–121

Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, McAlary M, Fowler-Taylor A, Racine A, Gupta N, Fick R, Della Cioppa G (2001) Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 286(23):2956–2967

Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, Mokhtarani M, Seyfert-Margolis V, Asare A, Bateman K, Deniz Y (2006) Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 117(1):134–140. doi:10.1016/j.jaci.2005.09.036

Chang TW (2000) The pharmacological basis of anti-IgE therapy. Nat Biotechnol 18(2):157–162

Chang TW, Wu PC, Hsu CL, Hung AF (2007) Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. Adv Immunol 93:63–119. doi:10.1016/S0065-2776(06)93002-8

Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, Shen H, Fox H (2003) Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 91(2):160–167. doi:10.1016/S1081-1206(10)62171-0

Cohen ES, Dobson CL, Kack H, Wang B, Sims DA, Lloyd CO, England E, Rees DG, Guo H, Karagiannis SN, O'Brien S, Persdotter S, Ekdahl H, Butler R, Keyes F, Oakley S, Carlsson M, Briend E, Wilkinson T, Anderson IK, Monk PD, von Wachenfeldt K, Eriksson PO, Gould HJ, Vaughan TJ, May RD (2014) A novel IgE-neutralizing antibody for the treatment of severe uncontrolled asthma. MAbs 6(3):1

Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, Bao W, Fowler-Taylor A, Matthews J, Busse WW, Holgate ST, Fahy JV (2004) Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 170(6):583–593. doi:10.1164/rccm.200312-1651OC

Dombrowicz D, Quatannens B, Papin JP, Capron A, Capron M (2000) Expression of a functional Fc epsilon RI on rat eosinophils and macrophages. J Immunol 165(3):1266–1271

Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, Gangnon RE, Gill MA, Gern JE, Lemanske RF Jr, Jackson DJ (2012) Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol 130(2):489–495. doi:10.1016/j.jaci.2012.05.023

Eckman JA, Sterba PM, Kelly D, Alexander V, Liu MC, Bochner BS, Macglashan DW Jr, Saini SS (2010) Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. J Allergy Clin Immunol 125(4):889–895. doi:10.1016/j.jaci.2009.09.012 e887

Eggel A, Baravalle G, Hobi G, Kim B, Buschor P, Forrer P, Shin JS, Vogel M, Stadler BM, Dahinden CA, Jardetzky TS (2014) Accelerated dissociation of IgE-Fc epsilon RI complexes by disruptive inhibitors actively desensitizes allergic effector cells. J Allergy Clin Immunol 133 (6):1709–1719. doi:10.1016/j.jaci.2014.02.005

Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB Jr, Boushey HA (1997) The effect of an anti-IgE monoclonal antibody on the early-and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 155(6):1828–1834. doi:10.1164/ajrccm.155.6.9196082

Foroughi S, Foster B, Kim N, Bernardino LB, Scott LM, Hamilton RG, Metcalfe DD, Mannon PJ, Prussin C (2007) Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. J Allergy Clin Immunol 120(3):594–601. doi:10.1016/j.jaci.2007.06.015

Fox JA, Hotaling TE, Struble C, Ruppel J, Bates DJ, Schoenhoff MB (1996) Tissue distribution and complex formation with IgE of an anti-IgE antibody after intravenous administration in cynomolgus monkeys. J Pharmacol Exp Ther 279(2):1000–1008

Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, Jiang N, Gan VN, Gruchalla RS (2010) Counterregulation between the Fc epsilon RI pathway and antiviral responses in human plasmacytoid dendritic cells. J Immunol 184(11):5999–6006. doi:10.4049/jimmunol.0901194

Gould HJ, Sutton BJ (2008) IgE in allergy and asthma today. Nat Rev Immunol 8(3):205–217. doi:10.1038/nri2273

Gould HJ, Sutton BJ, Beavil AJ, Beavil RL, McCloskey N, Coker HA, Fear D, Smurthwaite L (2003) The biology of IGE and the basis of allergic disease. Annu Rev Immunol 21:579–628

Grattan CE, Francis DM, Hide M, Greaves MW (1991) Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 21(6):695–704

Grayson MH, Cheung D, Rohlfing MM, Kitchens R, Spiegel DE, Tucker J, Battaile JT, Alevy Y, Yan L, Agapov E, Kim EY, Holtzman MJ (2007) Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia. J Exp Med 204 (11):2759–2769

Haak-Frendscho M, Robbins K, Lyon R, Shields R, Hooley J, Schoenhoff M, Jardieu P (1994) Administration of an anti-IgE antibody inhibits CD23 expression and IgE production in vivo. Immunol 82(2):306–313

Hanf G, Noga O, O'Connor A, Kunkel G (2004) Omalizumab inhibits allergen challenge-induced nasal response. Eur Respir J 23(3):414–418

Heil PM, Maurer D, Klein B, Hultsch T, Stingl G (2010) Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course—a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges 8(12):990–998. doi:10.1111/j.1610-0387.2010.07497.x

Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW (1993) Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 328(22):1599–1604. doi:10.1056/NEJM199306033282204

Incorvaia C, Mauro M, Russello M, Formigoni C, Riario-Sforza GG, Ridolo E (2014) Omalizumab, an anti-immunoglobulin E antibody: state of the art. Drug Des Devel Ther 8:197–207. doi:10.2147/DDDT.S49409

James LC, Roversi P, Tawfik DS (2003) Antibody multispecificity mediated by conformational diversity. Science 299(5611):1362–1367. doi:10.1126/science.1079731

Kalesnikoff J, Huber M, Lam V, Damen JE, Zhang J, Siraganian RP, Krystal G (2001) Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. Immunity 14(6):801–811

Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK (2008) Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 122(3):569–573. doi:10.1016/j.jaci.2008.07.006

Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, Veith J, Kamath N, Staubach P, Jakob T, Stirling RG, Kuna P, Berger W, Maurer M, Rosen K (2013) Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 132(1):101–109. doi:10.1016/j.jaci.2013.05.013

Kashiwakura J, Okayama Y, Furue M, Kabashima K, Shimada S, Ra C, Siraganian RP, Kawakami Y, Kawakami T (2012) Most highly cytokinergic IgEs have polyreactivity to autoantigens. Allergy Asthma Immunol Res 4(6):332–340. doi:10.4168/aair.2012.4.6.332

Kikuchi Y, Kaplan AP (2001) Mechanisms of autoimmune activation of basophils in chronic urticaria. J Allergy Clin Immunol 107(6):1056–1062. doi:10.1067/mai.2001.115484

Kisselgof AB, Oettgen HC (1998) The expression of murine B cell CD23, in vivo, is regulated by its ligand, IgE. Int Immunol 10(9):1377–1384

Kraft S, Kinet JP (2007) New developments in Fc epsilon RI regulation, function and inhibition. Nat Rev Immunol 7(5):365–378. doi:10.1038/nri2072

Kubo S, Nakayama T, Matsuoka K, Yonekawa H, Karasuyama H (2003) Long term maintenance of IgE-mediated memory in mast cells in the absence of detectable serum IgE. J Immunol 170(2):775–780

Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, Leupold W, Bergmann KC, Rolinck-Werninghaus C, Grave M, Hultsch T, Wahn U (2002) Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 109(2):274–280

Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF (2009) Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol 124(6):1210–1216. doi:10.1016/j.jaci.2009.09.021

Lemanske RF Jr, Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N (2002) Omalizumab improves asthma-related quality of life in children with allergic asthma. Pediatrics 110(5):e55

Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr (2003) Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 348(11):986–993

Lin S, Cicala C, Scharenberg AM, Kinet JP (1996) The Fc(epsilon)RI beta subunit functions as an amplifier of Fc(epsilon)RI gamma-mediated cell activation signals. Cell 85(7):985–995

Liu J, Lester P, Builder S, Shire SJ (1995) Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. Biochemistry 34(33):10474–10482

MacGlashan D Jr (2008) IgE receptor and signal transduction in mast cells and basophils. Curr Opin Immunol 20(6):717–723. doi:10.1016/j.coi.2008.08.004

MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, Sterbinsky SA, Hamilton RG, Lichtenstein LM (1997) Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 158(3):1438–1445

Massanari M, Milgrom H, Pollard S, Maykut RJ, Kianifard F, Fowler-Taylor A, Geba GP, Zeldin RK (2009) Adding omalizumab to the therapy of adolescents with persistent uncontrolled moderate–severe allergic asthma. Clin Pediatr (Phila) 48(8):859–865. doi:10.1177/0009922809339054

Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, Zeldin RK (2010) Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol 125(2):383–389. doi:10.1016/j.jaci.2009.11.022

Mathias CB, Freyschmidt EJ, Caplan B, Jones T, Poddighe D, Xing W, Harrison KL, Gurish MF, Oettgen HC (2009) IgE influences the number and function of mature mast cells, but not progenitor recruitment in allergic pulmonary inflammation. J Immunol 182(4):2416–2424. doi:10.4049/jimmunol.0801569 [pii] 182/4/2416

Matsubara S, Li G, Takeda K, Loader JE, Pine P, Masuda ES, Miyahara N, Miyahara S, Lucas JJ, Dakhama A, Gelfand EW (2006) Inhibition of spleen tyrosine kinase prevents mast cell activation and airway hyperresponsiveness. Am J Respir Crit Care Med 173(1):56–63. doi:10.1164/rccm.200503-361OC

Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T (2013) Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 368(10):924–935. doi:10.1056/NEJMoa1215372

Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, Metzger WJ (1999) Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 study group. N Engl J Med 341(26):1966–1973

Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P (2001) Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 108(2):E36

Moy LY, Jia Y, Caniga M, Lieber G, Gil M, Fernandez X, Sirkowski E, Miller R, Alexander JP, Lee HH, Shin JD, Ellis JM, Chen H, Wilhelm A, Yu H, Vincent S, Chapman RW, Kelly N, Hickey E, Abraham WM, Northrup A, Miller T, Houshyar H, Crackower MA (2013) Inhibition of spleen tyrosine kinase attenuates allergen-mediated airway constriction. Am J Respir Cell Mol Biol 49(6):1085–1092. doi:10.1165/rcmb.2013-0200OC

Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT (2011) Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol 127(6):1622–1624. doi:10.1016/j.jaci.2011.04.009

Noga O, Hanf G, Kunkel G (2003) Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. Int Arch Allergy Immunol 131(1):46–52 doi: 70434

Normansell R, Walker S, Milan SJ, Walters EH, Nair P (2014) Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 1:CD003559. doi:10.1002/14651858.CD003559.pub4

Ong YE, Menzies-Gow A, Barkans J, Benyahia F, Ou TT, Ying S, Kay AB (2005) Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. J Allergy Clin Immunol 116(3):558–564. doi:10.1016/j.jaci.2005.05.035

Pelaia G, Gallelli L, Renda T, Romeo P, Busceti MT, Grembiale RD, Maselli R, Marsico SA, Vatrella A (2011) Update on optimal use of omalizumab in management of asthma. J Asthma Allergy 4:49–59. doi:10.2147/JAA.S14520

Penton PC, Wang X, Amatullah H, Cooper J, Godri K, North ML, Khanna N, Scott JA, Chow CW (2013) Spleen tyrosine kinase inhibition attenuates airway hyperresponsiveness and pollution-induced enhanced airway response in a chronic mouse model of asthma. J Allergy Clin Immunol 131(2):512–520. doi:10.1016/j.jaci.2012.07.039 e511-510

Plewako H, Arvidsson M, Petruson K, Oancea I, Holmberg K, Adelroth E, Gustafsson H, Sandstrom T, Rak S (2002) The effect of omalizumab on nasal allergic inflammation. J Allergy Clin Immunol 110(1):68–71

Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, Jardieu PM (1993) Humanization of an antibody directed against IgE. J Immunol 151(5):2623–2632

Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB (2003) Omalizumab treatment downregulates dendritic cell Fc epsilon RI expression. J Allergy Clin Immunol 112(6):1147–1154

Saini SS, MacGlashan DW Jr, Sterbinsky SA, Togias A, Adelman DC, Lichtenstein LM, Bochner BS (1999) Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. J Immunol 162 (9):5624–5630

Saini SS, Klion AD, Holland SM, Hamilton RG, Bochner BS, Macglashan DW Jr (2000) The relationship between serum IgE and surface levels of Fc epsilon R on human leukocytes in various diseases: correlation of expression with Fc epsilon RI on basophils but not on monocytes or eosinophils. J Allergy Clin Immunol 106(3):514–520

Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA (2011) A phase II, randomized, doubleblind, parallelgroup, placebocontrolled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 127(5):1309–1310. doi:10.1016/j.jaci.2011.01.051 e1301

Schneider LC, Rachid R, Lebovidge J, Blood E, Mittal M, Umetsu DT (2013) A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol 132(6):1368–1374. doi:10.1016/j.jaci.2013.09.046

Schroeder JT, Bieneman AP, Chichester KL, Hamilton RG, Xiao H, Saini SS, Liu MC (2010) Decreases in human dendritic cell-dependent T(H)2-like responses after acute in vivo IgE neutralization. J Allergy Clin Immunol 125(4):896–901. doi:10.1016/j.jaci.2009.10.021 e896

Sheinkopf LE, Rafi AW, Do LT, Katz RM, Klaustermeyer WB (2008) Efficacy of omalizumab in the treatment of atopic dermatitis: a pilot study. Allergy Asthma Proc 29(5):530–537. doi:10.2500/aap.2008.29.3160

Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G (2001) The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 18(2):254–261

Sutton BJ, Gould HJ (1993) The human IgE network. Nature 366(6454):421–428. doi:10.1038/366421a0

Sykes A, Edwards MR, Macintyre J, del Rosario A, Bakhsoliani E, Trujillo-Torralbo MB, Kon OM, Mallia P, McHale M, Johnston SL (2012) Rhinovirus 16-induced IFN-alpha and IFN-beta are deficient in bronchoalveolar lavage cells in asthmatic patients. J Allergy Clin Immunol 129 (6):1506–1514. doi:10.1016/j.jaci.2012.03.044 e1506

Xiong H, Curotto de Lafaille MA, Lafaille JJ (2012) What is unique about the IgE response? Adv Immunol 116:113–141. doi:10.1016/B978-0-12-394300-2.00004-1

Yamaguchi M, Lantz CS, Oettgen HC, Katona IM, Fleming T, Miyajima I, Kinet JP, Galli SJ (1997) IgE enhances mouse mast cell Fc(epsilon)RI expression in vitro and in vivo: evidence for a novel amplification mechanism in IgE-dependent reactions. J Exp Med 185(4):663–672

Yamamoto N, Takeshita K, Shichijo M, Kokubo T, Sato M, Nakashima K, Ishimori M, Nagai H, Li YF, Yura T, Bacon KB (2003) The orally available spleen tyrosine kinase inhibitor 2-[7-(3, 4-dimethoxyphenyl)-imidazo[1, 2-c]pyrimidin-5-ylamino]nicotinamide dihydrochloride (BAY 61-3606) blocks antigen-induced airway inflammation in rodents. J Pharmacol Exp Ther 306 (3):1174–1181. doi:10.1124/jpet.103.052316