



Biologics as treatment options for anaphylaxis

Arianna Cafarotti, Alessandro Fiocchi, and Stefania Arasi

Purpose of review

To provide the most recent insights in the use of biologicals in the treatment of patients with anaphylaxis.

Recent findings

There is evidence that biologics such as omalizumab may be safe and effective in preventing anaphylactic reactions in patients at high risk mainly because of severe food allergy or desensitization procedures to food, airborne allergen, drugs, or hymenoptera venom.

Summary

Further knowledge will guide the adoption and implementation of any new therapy including biologics for anaphylaxis according to the stratification of risk/benefits.

Keywords

allergy severity, anaphylaxis, biologics, omalizumab, precision medicine

INTRODUCTION

Anaphylaxis: from definition and diagnosis to treatment and management

Anaphylaxis events are increasing worldwide [1,2]. According to the definition provided by the recently updated version of the International Classification of Diseases (ICD-11) [3], anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by rapid onset with potentially life-threatening airway, breathing or circulatory problems [4]. ICD-11 represents a great step forward as the previous ICD (ICD-10) did not include proper coding. The diagnosis of anaphylaxis is primarily based on the clinical presentation, as well as an accurate description of acute episode(s), including antecedent activities and events occurring within the preceding minutes to hours (e.g. drugs, alcohol, infections, menses, and asthmatic exacerbations). Typically, exposure to a triggering allergen is followed by rapid development of symptoms and signs over minutes generally up to 2 hours. Different organs/systems may be involved [5]. Data from patients experiencing anaphylaxis revealed that skin and mucosal symptoms occur most frequently followed by symptoms involving the respiratory tract (e.g. loss of voice, dyspnea, wheezing, stridor, and/or cyanosis) and cardiovascular systems (e.g. hypotension, loss of consciousness). The severity degree is variable ranging from mild up to death [6–8] in a minority of cases. In addition, the impact on quality of life and direct, indirect and social costs is high [9].

The most common elicitors of anaphylactic reactions are food, drug, and venom. In some cases, the cause is not obvious (idiopathic anaphylaxis) and investigations for rarer causes or mast cell activation syndromes should be considered. The prevalence of the various causes of anaphylaxis is age dependent and varies in different geographical regions. In Europe, the most frequent causes of food-induced anaphylaxis in children are peanut, hazelnut, milk [10–12]. The main causes of drug-induced anaphylaxis are antibiotics (first, beta-lactam) and nonsteroidal anti-inflammatory drugs [13,14].

The management of anaphylaxis includes prevention measures and the prompt initial pharmacologic treatment. Prevention of anaphylaxis depends primarily on the management of patient-related risk factors, including strict avoidance of confirmed relevant allergens or triggers and, where indicated, immunomodulation (e.g. immunotherapy). Adrenaline (epinephrine) is the first-line treatment for any type of anaphylaxis and is recognized as the only medication documented to reduce hospitalizations,

Translational Research in Pediatric Specialties Area, Division of Allergy, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, Rome, Italy

Correspondence to Stefania Arasi, MD, PhD, Translational Research in Pediatric Specialties Area, Division of Allergy, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy.

Tel: +39 06 68593570; fax: +39 06 68592218;

e-mail: stefania.arasi@opbg.net

Curr Opin Allergy Clin Immunol 2021, 20:000–000

DOI:10.1097/ACI.0000000000000779

KEY POINTS

- Adrenaline (epinephrine) i.m. is currently confirmed to be the first-line treatment for anaphylaxis.
- Glucocorticoids and antihistamines are not part of the initial treatment of anaphylaxis. Epinephrine administration should not be delayed in order to initiate therapy with these agents.
- After treatment of the acute event, anaphylaxis should be treated as a chronic condition. Although avoidance is the mainstay for long-term control of anaphylaxis, inadvertent exposure to allergens is always a possibility.
- The property of biologic drugs, such as omalizumab, to induce not allergen-specific effects on allergic immune responses makes this treatment a potentially attractive candidate for several immunoglobulin E-mediated diseases.
- Further well-designed studies are needed to fill the current gaps in knowledge and guide the adoption and implementation of any new preventive option for anaphylaxis.

hypoxic sequelae, and fatalities [15,16²²,17,18]. Systemic antihistamines have only been demonstrated to alleviate cutaneous symptoms [19,20]. Glucocorticoids are commonly used in anaphylaxis as they are thought to prevent protracted symptoms and possibly biphasic reactions, although there is limited and contradictory evidence of their effectiveness. Their administration could delay adrenaline injection [20,21]. Inhaled β -adrenoreceptor agonists, (e.g. salbutamol) and adrenaline via a nebulizer together with oxygen can be additionally administered respectively in the case of predominant bronchial obstruction or in cases with suspected laryngeal/pharyngeal edema as a supplement to intramuscular administration [16²²]. Over the last years, the approach to the treatment of anaphylaxis has gone from a purely defensive attitude to a proactive one [22]: we no longer wonder mainly how to avoid the allergenic foods, but how to consume them without risk, accidentally or by integrating it into the diet. In this context, the potential use of biologic agents in anaphylaxis has gained interest because it could transform the management of patients suffering from it [20].

This review aims to provide an updated overview on current evidence about the role of biologic agents in anaphylaxis. We will focus on the effects of biologics on preventing and treating anaphylaxis.

Monoclonal agents

The commercial use of monoclonal antibodies (mAbs) began in early 1980s, and the first therapeutic mAb targeting the immune system was approved in 1986 [23]. At present, 200 biologic agents are commercially available for several conditions. The introduction of biologic drugs and their expanding use over the recent years transformed the management of patients suffering from atopic diseases. Several biologic therapies are emerging as potential preventive or adjunctive treatment of anaphylaxis [24]. Unfortunately, their very high cost also creates new challenges in terms of access and sustainability. In Europe, the ten most prescribed biologics accounted for a combined cost of 16.5 billion Euros (14.8 billion USD) [25]. In the USA in 2013, they were found to account for 40% of medication costs while representing only 2% of prescription [26]. Cost-utility analyses have yet to be conducted for anaphylaxis. Since the current relatively low direct healthcare costs in these diseases are not expected to off-set the high cost in medication, cost-effectiveness will likely also be dictated by the extent of utility gain with treatment. Establishing valid and reproducible utility estimates for these indications will be critical to ensure the credibility of future economic analyses [6].

Although biologic agents are still not licensed for the management of anaphylaxis, these drugs, in particular omalizumab, appear to be effective as a preventive measure of the condition (Table 1).

mAbs are exponentially used in clinical practice to treat a wide range of diseases, and represent a novel therapeutic class that is increasingly associated with anaphylaxis, as recently reviewed.

The agent most commonly reported to trigger anaphylaxis is the anti-immunoglobulin E (IgE) mAb omalizumab; however, systematic reporting and analysis of cofactors related to mAb-related anaphylaxis are currently lacking [27]. Typically, medications are avoided after hypersensitivity reactions unless there is no alternative treatment and there is an excellent clinical response to omalizumab previously. There are some prior reports of omalizumab administration by desensitization protocol after acute or delayed reactions using a desensitization protocol with a pathway for possible return to standard injection [28].

Omalizumab

Omalizumab (Xolair) is an anti-IgE humanized monoclonal antibody developed by recombinant DNA techniques (anti-IgE mAb). In particular, Omalizumab is an immunoglobulin G1, which

Table 1. Summary of findings from the main studies on off-label use of biologics in preventing anaphylaxis due to different allergenic triggers

Biological treatment	Study (first author, year of publication)	Design and population	Main findings
FOOD			
OMALIZUMAB	Fiocchi <i>et al.</i> , 2019 [48]	Single-center, single arm, real-life, retrospective observational study in 15 pediatric patients (median, range: 144, 96–276 months) undergoing Omalizumab as monotherapy for 4 months	After 4 months of omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested. Overall, the median (interquartile range) eliciting threshold in milligrams of protein was 460.8 (31–1740) at baseline, which improved to 8,192 (5568–10,400) after treatment, representing a statistically significant improvement for egg, milk, baked milk, and wheat. Nine of the 15 were able to tolerate without symptoms a full serving size amount of all the foods tested, two others were able to do so to at least one of the foods tested, and four partially improved. In the 11 patients who asymptotically consumed the full challenge amount, the previously allergenic food was added to the diet. Furthermore, patients improved their health-related quality of life (PedsQL instrument), and reduced symptomatic accidental food allergen exposures
	Sampson <i>et al.</i> , 2011 [47]	4-week- long, double-blind, placebo-controlled, multicenter study in peanut allergic adolescents and adults testing Omalizumab as monotherapy	14 participants (9 omalizumab and 5 placebo) completed the trial. Omalizumab-treated participants experienced an 80.9 fold improvement in the tolerated dose of peanut proteins at the week 24 peanut oral food challenge (OFC) compared with the baseline peanut OFC, whereas only a 4.1-fold improvement was observed in the placebo group.
	Wood <i>et al.</i> , 2016 [42]	A randomized, double-blind, placebo-controlled study (DBPRCT) with subjects randomized to omalizumab or placebo. Open-label milk OIT was initiated after 4 months of omalizumab/placebo with escalation to maintenance over 22 to 40 weeks, followed by daily maintenance dosing through month 28. At month 28, omalizumab was discontinued, and subjects passing an OFC continued OIT for 8 weeks, after which OIT was discontinued with rechallenge at month 32 to assess sustained unresponsiveness (SU).	57 subjects (7–32 years) were enrolled. At month 28, 24 (88.9%) omalizumab-treated subjects and 20 (71.4%) placebo-treated subjects passed the 10g “desensitization” OFC ($P = .18$). At month 32, SU was demonstrated in 48.1% in the omalizumab group and 35.7% in the placebo group ($P = .42$). Adverse reactions were markedly reduced during OIT escalation in omalizumab-treated subjects for percentages of doses per subject provoking symptoms (2.1% vs. 16.1%, $P = .0005$), dose-related reactions requiring treatment (0.0% vs. 3.8%, $P = .0008$), and doses required to achieve maintenance (198 vs. 225, $P = .008$). Therefore, authors found significant improvements in measurements of safety but not in outcomes of efficacy (desensitization and SU).
DUPILUMAB	Rial <i>et al.</i> , 2018 [81]	Case report of a 30-year-old woman with severe atopic dermatitis (AD) and food allergy (corn and pistachio) began treatment with dupilumab due to severe AD (SCORAD score, 88) and a previous poor response to ciclosporin.	The patient received an initial dose of 600 mg, followed by 300 mg every 2 weeks. After 3 months of treatment with dupilumab, improvement in dermatitis was seen (SCORAD 50) and she acquired tolerance to the culprit foods.
QUILIZUMAB	Harris <i>et al.</i> , 2016 [87]	Double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut. Patients received either TNX-901 (150, 300, or 450 mg) or placebo subcutaneously every four weeks for four doses.	450-mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg). This effect should translate into protection against most unintended ingestions of trace of peanuts.

Table 1 (Continued)

Biological treatment	Study (first author, year of publication)	Design and population	Main findings
ETOKIMAB	Chinthrajah <i>et al.</i> , 2019 [75]	6-week, placebo-controlled phase 2a study. Participants received either etokimab ($n = 15$ adults) or blinded placebo ($n = 5$ adults)	At the day 15 and 45, food challenge (tolerating a cumulative 275 mg of peanut protein) demonstrated, respectively, 73% vs. 0% ($P = 0.008$) to 57% vs. 0% (ns). The etokimab group had fewer adverse events compared with placebo. Peanut-specific IgE was reduced in active vs. placebo ($P = 0.014$ at day 15). The phase 2a results suggest etokimab is safe and well tolerated and that a single dose of etokimab could have the potential to desensitize peanut-allergic participants and possibly reduce atopy-related adverse events.
AIRBORNE IMMUNOTHERAPY			
OMALIZUMAB	Kamin <i>et al.</i> , 2010 [50]	DBPCRT, multicentre trial; 221 children were randomly assigned to four different groups and treated with allergen specific immunotherapy (AIT), starting at least 14 weeks before the local birch pollen season. After the 12-wk AIT titration phase, omalizumab or placebo therapy was added.	Tolerability of AIT and omalizumab treatment was good (82% of patients). Only some adverse events with possible causal relationship to treatment occurred slightly more often in the verum groups, i.e. local reactions (16.8 vs. 12.3%) and gastrointestinal (2.7 vs. 0.9%) and ear symptoms (1.8 vs. 0%). Systemic adverse events were restricted to four patients with asthma in the placebo group, two subjects with headache in the verum group and three patients with infections (two in verum and one in placebo group). Further, redness and swelling at the AIT injection site appeared significantly more often in the placebo group which suggests a positive effect of omalizumab on local reaction induced by AIT.
DRUG IMMUNOTHERAPY			
OMALIZUMAB	Arroabarren <i>et al.</i> , 2019 [55]	Case report of a 5-year-old child, affected by Type IV A mucopolysaccharidosis who developed two allergic reactions during Enzyme replacement therapy (ERT) administration: the first time urticaria and later anaphylaxis despite pretreatment with desloratadine during elosulfase infusion with dexchlorpheniramine, desloratadine, methylprednisolone and acetaminophen	Omalizumab allowed to control breakthrough reactions and to continue ERT administration. In long term, it allowed to cease the desensitization itself and to continue treatment under normal conditions
	Oude Elberink <i>et al.</i> , 2020 [57]	Case report of a 57-year-old woman diagnosed with stage III ovarian cancer with allergic reactions to carboplatin despite an optimized desensitisation schedule and the conventional antiallergic pretreatment	The addition of single dose of omalizumab to the conventional antiallergic medication was successful in the patient with severe breakthrough allergic reactions to carboplatin. A positive skin test and basophil activation test (BAT) suggest IgE-mediated anaphylaxis
VENOM IMMUNOTHERAPY (VIT)			
OMALIZUMAB	Palgan <i>et al.</i> , 2014 [59]	Case report of a 30-year-old woman, suffering from mild persistent asthma, who had a history of severe anaphylactic reactions after yellow jacket sting, and after eating peanuts, contact with guinea pig hair, and i.v. administration of dexamethasone sodium phosphate. Initial specific immunotherapy had to be stopped due to severe anaphylaxis (hypotension, dyspnea, and angioedema) and it was reintroduced accompanied by the omalizumab	Subcutaneous omalizumab 150 mg was initiated 1 day before the resumption of VIT. Rush treatment was uneventful, and the usual cumulative dose of 111.1 microg was successfully reached. The combination of omalizumab and VIT could be a valid option of therapy

Table 1 (Continued)

Biological treatment	Study (first author, year of publication)	Design and population	Main findings
IDIOPATHIC ANAPHYLAXIS	Ricciardi <i>et al.</i> , 2016 [66]	Case report of two cousins aged 12 years and 17 years with anaphylaxis after bee sting. In both patients ltra-rush beeVIT after a cumulative dose of 25 mcg had to be stopped due to anaphylaxis.	Two months after starting omalizumab treatment, bee ultra-rush VIT was re-administered and a cumulative dose of 100 mcg was tolerated with the occurrence of only facial edema in the build-up phase, which resolved spontaneously in both patients.
	OMALIZUMAB Demirtürk <i>et al.</i> , 2012 [71]	Case report of a 46-year-old female patient with severe uncontrolled allergic asthma and idiopathic anaphylaxis.	Omalizumab at a dose of 375 mg once every 2 weeks was administered and after sixth month the injection intervals were extended to 4 weeks. At the end of 3 months anaphylactic attacks had ceased.
MASTOCYTOSIS	OMALIZUMAB Pitt <i>et al.</i> , 2010 [68]	Case report of a 15-year-old girl with 5 episodes of unprovoked anaphylaxis.	Omalizumab therapy was initiated at 300 mg every 4 weeks and has now been continued for 14 months. She had no episodes of anaphylaxis since the initiation of treatment, and the omalizumab has been tolerated with minimal local swelling.
	Broesby-Olsen <i>et al.</i> , 2019 [73]	Single-center, single arm, real-life, retrospective observational study; 13 adults with systemic mastocytosis received omalizumab with a median duration of 17 months.	A significant reduction in symptoms, with complete symptom control in five (38.5%), major response in three (23.1%), and a partial response in three (23.1%) patients, whereas two patients (15.4%) withdrew due to subjective side-effects at first dose. The treatment was most effective for recurrent anaphylaxis and skin symptoms, less for gastrointestinal, musculoskeletal, and neuropsychiatric symptoms. Patient-reported quality of life showed significant improvement.

AD, atopic dermatitis; BAT, basophil activation test; DBPCRT, double-blind, placebo-controlled randomized, trial; ERT, Enzyme replacement therapy; OFC, oral food challenge; VIT, venom immunotherapy.

selectively binds to the two Cε3 constant domains of free circulating IgE, thus forming trimeric or hexameric IgE/anti-IgE immune complexes.

Because omalizumab specifically interacts with the Cε3 domain, that includes the IgE-binding sites for both FcεR1s and FcεR2s/CD23, this humanized antibody impedes IgE-linkage to high-affinity and low-affinity receptors on effector cells (primarily basophils and mast cells), interfering with degranulation and release of pro-inflammatory mediators [29]. Moreover, by reducing free circulating IgE, omalizumab decreases FcεR1 expression on these cells, and, therefore, decreases their degranulation. In general, omalizumab is not able to induce degranulation by effector cells because it does not bind to FcεR1-bound IgE or IgE receptors. Additionally, the IgE/omalizumab immune complexes are characterized by a strong stability and very limited dimension that make them soluble and unable to precipitate [29]. Notwithstanding, in rare cases (0.09%), omalizumab induces an anaphylaxis-like reaction through unknown mechanism(s) [30].

Furthermore, by preventing IgE linkage to FcεR1s present on the cell membrane of dendritic cells, omalizumab neutralizes IgE-dependent facilitation of antigen presentation to T-cells. Consequently, it decreases the T helper two -mediated allergic pathway activity, including decreased IgE production, anergy of B cells, induction of regulatory T cells, and eosinophil apoptosis [31]. In addition to high-affinity FcεR1 receptor, IgE can bind to low-affinity FcεR2 receptors (CD23), which can modulate (toward either upregulation or downregulation) the IgE synthesis. There is evidence that omalizumab may downregulate FcεR2, making effector cells insensitive to incoming allergen [31].

Omalizumab targets the constant IgE region and thus induces specific nonallergenic effects on allergic immune responses. This property makes this biological treatment a potentially attractive candidate for various IgE-mediated diseases even outside the indications currently approved by the European Medicines Agency [32] and the US Food and Drug Administration [33] (i.e. allergic asthma, chronic idiopathic urticarial, and nasal polyps).

Omalizumab in anaphylaxis: current evidence

Besides the formal indications, omalizumab has also been shown to have a potential therapeutic effect for several allergic diseases which may present with severe anaphylaxis [34–36,37].

In particular, in the field of food allergy, oral immunotherapy (OIT) is a promising treatment but has some limitations, including safety issues [38–41]. The adjunctive treatment with omalizumab has shown to

accelerate milk OIT with increased safety by reducing the number of adverse events and their severity [42]. Similar data are available for OIT to several foods, including peanut [43] and multiple-food allergens [44]. The PRROTECT study (Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial) evaluated in a prospective, controlled manner about 40 high-risk subjects with peanut allergy between 7 and 18 years of age. Those treated with omalizumab were able to undergo a rapid OIT and to tolerate doses of peanut 10 times higher than those treated with placebo [45]. An ongoing clinical trial called OutMATCHT (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults), is testing Omalizumab monotherapy and as an adjunct to multifoed OIT, in a randomized, double-blind, placebo-controlled fashion [46]. The results are expected to shed light on different aspects of Omalizumab as adjunctive treatment to OIT and as monotherapy in the therapy of food allergy and thus in the prevention of anaphylaxis episode triggered by a food allergen.

Preliminary data suggest that omalizumab would be capable to reduce anaphylaxis episodes by shifting eliciting allergen thresholds and inducing clinically meaningful levels of desensitization when used by itself [6,34,47]. In 2019, a single-center, real-life, retrospective observational study has provided uncontrolled data in support of omalizumab as effective monotherapy for food allergy [48]. A total of 15 out of the 115 patients with severe atopic asthma received omalizumab for their asthma per standard-care guidelines, had allergy to at least two foods, and underwent paired OFCs before, and 4 months into, omalizumab treatment. The 15 patients selected for the analysis had clinical histories of immediate reactions to foods. After 4 months of omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested and reduced symptomatic accidental food allergen exposures [48]. More recently, these data have been confirmed by the same research group in an oral communication in a larger independent, retrospective cohort of patients with food allergy and concomitant asthma [49]. Therefore, omalizumab has been proposed for controlling adverse reactions during desensitization to different allergens, including airborne ones [37,50–51], also in asthmatic patients [37,52], venom [53] and drug [36]. Omalizumab has been successfully used prior to drug desensitization: to insulin [54]; to the enzyme Elosulfase α [55] and to chemotherapeutics agents [carboplatin [56,57] oxaliplatin [58]].

Hymenoptera venom immunotherapy is indicated in patients with sting anaphylaxis. Patients with mast cell activation disorders or mastocytosis who developed sting anaphylaxis can also receive

venom immunotherapy. However, in these patients, the venom immunotherapy is likely to provide incomplete protection and the patient may have increased adverse reactions. Pretreatment with omalizumab has been shown effective as an adjunctive treatment in patients with mastocytosis, for both symptom improvement and to dampen adverse effects caused by venom immunotherapy [37,50–66]. In this highly sensitized and reactive patient population, the benefit of rapid desensitization is important because future stings may be fatal. Giannetti *et al.*, reported a successful implementation of a ultrarush 1-day venom desensitization protocol coupled to an option for omalizumab that enables successful venom immunotherapy in patients with life-threatening anaphylaxis after Hymenoptera sting, mast cell activation disorders, and/or recurrent systemic reactions during conventional venom immunotherapy [67].

Omalizumab has been shown to be a promising treatment of idiopathic anaphylaxis, successfully reducing the number of episodes and improving the quality of life. Patients with idiopathic anaphylaxis who were not controlled despite continuous use of oral corticosteroids and/or antihistamines were treated with omalizumab (300–375 mg every 2–4 weeks) for 10–14 months [68–71]. In these four patients, no anaphylaxis episode was recorded after onset of omalizumab injection. Omalizumab may be a preventive therapeutic option in patients with idiopathic anaphylaxis depending on the severity and frequency of episodes, but the cost/benefit ratio should be assessed individually.

Mastocytosis and mast cell activation disorders may be identified as a cause of idiopathic anaphylaxis [65]. Effectively omalizumab has been shown to prevent recurrent anaphylaxis, reduce skin symptoms and increase quality of life in a cohort of 13 adults with systemic mastocytosis who received this treatment with a median duration of 17 months (range 1–73 months) [72,73]. Controlled studies are needed to corroborate this finding.

Moreover, omalizumab has been shown to reduce anaphylaxis in patients with hereditary alpha-tryptasemia (HaT) who reported severe symptoms of mast cell activation [74].

Further monoclonal antibodies alongside omalizumab

Other mAbs are being studied and may be possible measures in the management and prevention of anaphylaxis in the future.

ETOKIMAB - An exploratory study evaluated the effect of a single administration of Etokimab, an antagonist of interleukin (IL)-33, on IgE-mediated

peanut allergy. In this protocol, a single administration of etokimab was performed in patients with a positive DBPCFC to peanut at baseline. A DBPCFC to peanut 14 and 45 days postadministration was programmed to explore changes in tolerance threshold, together with skin prick tests and immunologic evaluations. The drug induced an increase of the proportion of peanut-tolerating patients. This clinical result was paralleled by a reduction in IL-4, IL-5, IL-9, and IL-13 in CD4+ T cells [75].

DUPILUMAB - Dupilumab is a monoclonal antibody, available in the USA and in Europe for the indications of atopic dermatitis [76], asthma [77], and nasal polyposis [78]. It targets the α -chain of the IL-4 receptor (IL-4R α), which is also common to IL-13. This binding results in a blockade of the downstream signaling initiated by both IL-4 and IL-13. As these cytokines are key players in the Th2 cell differentiation, Dupilumab inhibits several Th2-dependent immune ways, including the signaling pathway of IgE class switching, the macrophage polarization into the pro-inflammatory (M2) phenotype, and peripheral eosinophilia [79]. The molecule exerts effects on B lymphocytes, eosinophils, dendritic cells, monocytes/macrophages, basophils, keratinocytes, bronchial epithelial cells, endothelial cells, fibroblasts, and airway smooth muscle cell [80]. In anecdotal observations, dupilumab used for severe atopic dermatitis shown efficacy in getting tolerance to concomitant food allergy eliciting anaphylactic shock [81]. Two studies are underway to evaluate the effectiveness of this biological associated or not with oral immunotherapy treatment in food allergy [82,83].

Another study assessing the possible synergy with omalizumab in food allergy is the 44-weeks NCT03679676 trial. [84] Omalizumab is compared to placebo and dupilumab in their ability to get tolerance to two or more food allergens at Week 38. Taken together, the evidence suggests that omalizumab is close to entering the clinic with an indication of food allergy, though we eagerly anticipate the availability of further data from trials that are ongoing. For this threatening pathology, orphan of effective and safe treatments, it is our opinion that obtaining an indication for this biological would be a robust step forward in patient management [85].

LIGELIZUMAB - Ligelizumab is an IgG1 khhigh-affinity humanized monoclonal anti-IgE antibody that binds with higher affinity to the C ϵ 3 domain of IgE than omalizumab, with a sixfold to ninefold greater suppression of allergen-induced skin prick tests in vivo. The dissociation constant (Kd) of omalizumab is 6–8 nM, whereas for ligelizumab it is 139 pM [81]. A recent study evaluated the efficacy and

safety of this drug in patients with moderate/severe urticaria, with positive outcomes [86], but there is still no study involving anaphylactic patients.

QUILIZUMAB- Quilizumab is a humanized mAb that targets the main segment M1 (M1 prime segment) of IgE expressed on the membrane of B cells and plasmablasts with an IgE switch. In clinical studies in healthy volunteers and patients with asthma and rhinitis, quilizumab reduced the levels of total and specific IgE and sustained them for at least 6 weeks [87]. Although targeting IgE expression, there are still no registered studies in anaphylaxis.

CONCLUSION

Allergen avoidance and prompt reaction strategies (epinephrine) remain the mainstay of the treatment of any type of anaphylaxis. However, several biologic therapies are emerging as potential preventive treatment of anaphylaxis. Better understanding of the underlying mechanisms of anaphylaxis, and the stratification of endotypes support precision medicine, may allow the integration of new therapeutic approaches, such as the use of biologic agents. There are no ideal biomarkers to stratify anaphylaxis and guide therapy in clinical practice. Nevertheless, some biomarkers may be helpful to select subsets of atopic patients that might benefit from biologic agents.

Biologic drugs, such as omalizumab, have been used as therapeutic adjuvants as a preventive measure of anaphylaxis. However, additional research on the effects of omalizumab not only is likely to shed light on its mechanism of action, but also will help health policy makers in considering further integrative options for anaphylaxis management tailored on the single patient. Cost-effectiveness should be considered individually. The cost of such medications and knowledge gaps about long-term benefit/risk require further research and expertise.

Adequately powered and rigorously conducted randomized controlled clinical trials are needed to minimize bias and provide high-quality data to guide the adoption and implementation of any new therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Salter SM, Marriott RJ, Murray K, *et al.* Increasing anaphylaxis events in Western Australia identified using four linked administrative datasets. *World Allergy Organ J* 2020; 13:100480.
 2. Yao TC, Wu AC, Huang YW, *et al.* Increasing trends of anaphylaxis-related events: an analysis of anaphylaxis using nationwide data in Taiwan, 2001–2013. *World Allergy Organ J* 2018; 11:23.
 3. 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11); World Health Organization, 2020. Available at: <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1868068711>. [Accessed 24 April 2021]
 4. Cardona V, Ansotegui IJ, Ebisawa M, *et al.* World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J* 2020; 13:100472.
 5. Francis A, Fatovich DM, Arendts G, *et al.* Serum mast cell tryptase measurements: sensitivity and specificity for a diagnosis of anaphylaxis in emergency department patients with shock or hypoxaemia. *Emerg Med Australas* 2018; 30:366–374.
 6. Arasi S, Nurmatov U, Dunn-Galvin A, *et al.* Consensus on Definition of Food Allergy SEverity (DEFASE) an integrated mixed methods systematic review. *World Allergy Organ J* 2021; 14:100503.
 7. Dribin TE, Schnadower D, Spergel JM, *et al.* Severity grading system for acute allergic reactions: A multidisciplinary Delphi study. *J Allergy Clin Immunol* 2021; 148:173–181.
 8. Muraro A, Fernandez-Rivas M, Beyer K, *et al.* The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy* 2018; 73:1792–1800.
 9. Azzano P, Dufresne É, Poder T, Bégin P. Economic considerations on the usage of biologics in the allergy clinic. *Allergy* 2021; 76:191–209.
 10. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, *et al.* Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol* 2016; 137:1128–1137.
 11. Worm M, Eckermann O, Dolle S, *et al.* Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. *Dtsch Arztebl Int* 2014; 111:367–375.
 12. Worm M, Moneret-Vautrin A, Scherer K, *et al.* First European data from the network of severe allergic reactions (NORA). *Allergy* 2014; 69:1397–1404.
 13. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309–316.
 14. Joint Task Force on Practice P, American Academy of Allergy A, Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; 105:259–273.
 15. Gilfoyle E, Koot DA, Annear JC, *et al.* Improved clinical performance and teamwork of pediatric interprofessional resuscitation teams with a simulation-based educational intervention. *Pediatr Crit Care Med* 2017; 18:e62–e69.
 16. Muraro A, Roberts G, Worm M, *et al.* EAACI Food Allergy and Anaphylaxis ■ Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014; 69:1026–1045.
- Updated international guidelines on the diagnosis, treatment and management of anaphylaxis.
17. Tanno LK, Alvarez-Perea A, Pouessel G. Therapeutic approach in anaphylaxis. *Curr Opin Allergy Clin Immunol* 2019; 19:393–401.
 18. Tanno LK, Simons FER, Sanchez-Borges M, *et al.* Joint Allergy Academies. Applying prevention concepts to anaphylaxis: A call for worldwide availability of adrenaline auto-injectors. *Clin Exp Allergy* 2017; 47:1108–1114.
 19. Nurmatov UB, Rhatigan E, Simons FE, Sheikh A. H2-antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014; 112:126–131.
 20. Shaker MS, Wallace DV, Golden DBK, *et al.* Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol* 2020; 145:1082–1123.
 21. Gabrielli S, Clarke A, Morris J, *et al.* Evaluation of prehospital management in a Canadian emergency department anaphylaxis cohort. *J Allergy Clin Immunol Pract* 2019; 7:2232–2238. e2233.
 22. Fiocchi A, Ebisawa M. Food allergy: from defense to attack. *Curr Opin Allergy Clin Immunol* 2021; 21:261–262.
 23. Ecker DM, Jones SD, Levine HL. The therapeutic monoclonal antibody market. *MAbs* 2015; 7:9–14.
 24. Menzella F, Galeone C, Bertolini F, *et al.* Innovative treatments for severe refractory asthma: how to choose the right option for the right patient? *J Asthma Allergy* 2017; 10:237–247.
 25. Dutta B, Huys I, Vulto AG, Simoens S. Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs* 2020; 34:159–170.
 26. Mehr SR, Brook RA, Brook. Factors influencing the economics of biosimilars in the US. *J Med Econ* 2017; 20:12. 1268-1271.

27. Sala-Cunill A, Luengo O, Cardona V. Biologics and anaphylaxis. *Curr Opin Allergy Clin Immunol* 2019; 19:439–446.
28. Bernalola M, Hamadi SA, Lynch DM, *et al.* Successful administration of omalizumab by desensitization protocol following systemic reactions in 12 patients. *J Allergy Clin Immunol Pract* 2021; 9:2505–2508.
29. Cardet JC, Casale TB. New insights into the utility of omalizumab. *J Allergy Clin Immunol* 2019; 143:923–926. e1.
30. Cox L, Platts-Mills TA, Finegold I, *et al.* American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; 120:1373–1377.
31. Prussin C, Griffith DT, Boesel KM, *et al.* Omalizumab treatment downregulates dendritic cell FcεpsilonRI expression. *J Allergy Clin Immunol* 2003; 112:1147–1154.
32. Xolair (Omalizumab) [Online], European Medicines Agency. Available from <https://www.ema.europa.eu/en/medicines/human/EPAR/xolair#product-information-section>. [Accessed 3 January 2021]
33. Xolair Prescribing Information [Online], Food and Drug Administration.: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103976s5235lbl.pdf#page=40. [Accessed 3 January 2021]
34. Arasi S, Mennini M, Cafarotti A, Fiocchi A. Omalizumab as monotherapy for food allergy. *Curr Opin Allergy Clin Immunol* 2021; 21:286–291.
Recent update on the use of omalizumab as monotherapy for preventing severe anaphylactic reactions to food allergy.
35. Dantzer JA, Wood RA. Omalizumab as an adjuvant in food allergen immunotherapy. *Curr Opin Allergy Clin Immunol* 2021; 21:278–285.
Recent update on the use of omalizumab as an adjuvant in food allergen immunotherapy for preventing severe anaphylactic reactions to food allergy.
36. Fernandez J, Ruano-Zaragoza M, Blanca-Lopez N. Omalizumab and other biologics in drug desensitization. *Curr Opin Allergy Clin Immunol* 2020; 20:333–337.
Recent update on the use of omalizumab as an adjuvant in drug desensitization.
37. Kopp MV, Hamelmann E, Zielen S, *et al.* Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy* 2009; 39:271–279.
38. Pajno GB, Castagnoli R, Muraro A, *et al.* Allergen immunotherapy for IgE-mediated food allergy: there is a measure in everything to a proper proportion of therapy. *Pediatr Allergy Immunol* 2019; 30:415–422.
39. Arasi S, Caminiti L, Crisafulli G, Pajno GB. A general strategy for de novo immunotherapy design: the active treatment of food allergy. *Expert Rev Clin Immunol* 2018; 14:665–671.
40. Pajno GB, Fernandez-Rivas M, Arasi S, *et al.* EAACI Allergen Immunotherapy Guidelines Group. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018; 73:799–815.
41. Chu DK, Wood RA, French S, *et al.* Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019; 393:2222–2232.
42. Wood RA, Kim JS, Lindblad R, *et al.* A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 2016; 137:1103–1110.
43. Schneider LC, Rachid R, LeBovidge J, *et al.* A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013; 132:1368–1374.
44. Bégin P, Dominguez T, Wilson SP, *et al.* Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 2014; 10:7.
45. Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial (PRROTECT). Available at <https://clinicaltrials.gov/ct2/show/NCT01781637> [Accessed 8 April 2021].
46. Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants (OUTMATCH). Available at <https://clinicaltrials.gov/ct2/show/NCT03881696> [Accessed 8 April 2021].
47. Sampson HA, Leung DY, Burks AW, *et al.* A phase II, randomized, double blind, parallel group, placebo controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011; 127:1309–1310.
48. Fiocchi A, Artesani MC, Riccardi C, *et al.* Impact of omalizumab on food allergy in patients treated for asthma: a real-life study. *J Allergy Clin Immunol Pract* 2019; 7:1901–1909.
49. Arasi S, Colucci C, Cafarotti A, *et al.* Impact of omalizumab on severe food allergy in 54 Italian patients with concomitant asthma: 6-year-long experience Allergy: Special Issue: Abstracts from the European Academy of Allergy and Clinical Immunology Digital Congress, 06–08 June 2020. *LB-OAS1650*; 75 (S109): 106 (oral communication).
50. Kamin W, Kopp MV, Erdnuss F, *et al.* Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010; 21(1 Pt 2):e160–e165.
51. Bayar Muluk N, Bafaqeh SA, Cingi C. Anti-IgE treatment in allergic rhinitis. *Int J Pediatr Otorhinolaryngol* 2019; 127:109674.
52. Study to evaluate the effect of omalizumab on improving the tolerability of specific immunotherapy in patients with persistent allergic asthma. Available at <https://clinicaltrials.gov/ct2/show/NCT00267202>. [Accessed 8 April 2021]
53. Golden DBK. Venom immunotherapy: questions and controversies. *Immunol Allergy Clin North Am* 2020; 40:59–68.
54. Matheu V, Franco A, Perez E, *et al.* Omalizumab for drug allergy. *J Allergy Clin Immunol* 2007; 120:1471–1472.
55. Arroabarren E, Aznal E, Anda M, Sanchez-Valverde F. Anaphylaxis after elosulfase A infusion: omalizumab as coadjuvant for enzyme replacement therapy desensitization. *Pediatr Allergy Immunol* 2019; 31:491–494.
56. Ojaimi S, Harnett PR, Fulcher DA. Successful carboplatin desensitization by using omalizumab and paradoxical diminution of total IgE levels. *J Allergy Clin Immunol Pract* 2014; 2:105–106.
57. Oude Elberink H, Jalving M, Hilda Dijkstra H, van de Ven A. Modified protocol of omalizumab treatment to prevent carboplatin-induced drug hypersensitivity reactions: a case study. *Clin Transl Allergy* 2020; 10:5.
58. Prieto-García A, Noguera B, Rojas P, *et al.* Unexpected anaphylaxis after completing a desensitization protocol to oxaliplatin: successful adjuvant use of omalizumab. *J Investig Allergol Clin Immunol* 2019; 29:53–55.
59. Palgan K, Bartuzi Z, Gotz-Zbikowska M. Treatment with a combination of omalizumab and specific immunotherapy for severe anaphylaxis after a wasp sting. *Int J Immunopathol Pharmacol* 2014; 27:109–112.
60. Da Silva EN, Randall KL. Omalizumab mitigates anaphylaxis during ultrarush honey bee venom immunotherapy in monoclonal mast cell activation syndrome. *J Allergy Clin Immunol Pract* 2013; 1:687–688.
61. Slaughter EM, Boyer N, Bennett S. The bee sting that was not: an unusual case of hymenoptera anaphylaxis averted in a patient treated with omalizumab for asthma. *Case Rep Med* 2014; 2014:138963.
62. Galera C, Soohun N, Zankar N, *et al.* Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. *J Investig Allergol Clin Immunol* 2009; 19:225–229.
63. Castells MC, Hornick JL, Akin C. Anaphylaxis after hymenoptera sting: is it venom allergy, a clonal disorder, or both? *J Allergy Clin Immunol Pract* 2015; 3:350–355.
64. Sokol KC, Ghazi A, Kelly BC, *et al.* Omalizumab as a desensitizing agent and treatment in mastocytosis: a review of the literature and case report. *J Allergy Clin Immunol Pract* 2014; 2:266–270.
65. Carter MC, Robyn JA, Bressler PB, *et al.* Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. *J Allergy Clin Immunol* 2007; 119:1550–1551.
66. Ricciardi L. Omalizumab: a useful tool for inducing tolerance to bee venom immunotherapy. *Int J Immunopathol Pharmacol* 2016; 29:726–728.
67. Giannetti M, Silver J, Hufdhi R, Castells M. One-day ultrarush desensitization for hymenoptera venom anaphylaxis in patients with and without mast cell disorders with adjuvant omalizumab. *J Allergy and Clin Immunol Pract* 2020; 8:1431–1435.
68. Pitt TJ, Cisneros N, Kalicinsky C, *et al.* Successful treatment of idiopathic anaphylaxis in an adolescent. *J Allergy Clin Immunol* 2010; 126:415–416.
69. Warrier P, Casale TB. Omalizumab in idiopathic anaphylaxis. *Ann Allergy Asthma Immunol* 2009; 102:257–258.
70. Jones JD, Marney SR Jr, Fahrenholz JM. Idiopathic anaphylaxis successfully treated with omalizumab. *Ann Allergy Asthma Immunol* 2008; 101:550–551.
71. Demirtürk M, Gelincik A, Colakoglu B, *et al.* Promising option in the prevention of idiopathic anaphylaxis: omalizumab. *J Dermatol* 2012; 39:552–554.
72. Lieberman PL, Umetsu DT, Carrigan GJ, *et al.* Anaphylactic reactions associated with omalizumab administration: analysis of a case-control study. *J Allergy Clin Immunol* 2016; 138:913–915.
73. Broesby-Olsen S, Vestergaard H, Mortz CG, *et al.* Mastocytosis Centre Odense University Hospital (MastOUH). Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: efficacy and safety observations. *Allergy* 2018; 73:230–238.
74. Giannetti MP, Weller E, Bormans C, *et al.* Hereditary alpha-tryptasemia in 101 patients with mast cell activation-related symptomatology including anaphylaxis. *Ann Allergy Asthma Immunol* 2021; 126:665–660.
75. Chinthrajah S, Cao S, Liu C, *et al.* Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. *JCI Insight* 2019; 4:e131347.
76. Simpson EL, Paller AS, Siegfried EC, *et al.* Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol* 2020; 156:44–56.
77. Castro M, Corren J, Pavord ID, Maspero J, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378:2486–2496.
78. Bachert C, Han JK, Desrosiers M, *et al.* Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019; 394:1638–1650.
79. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol* 2017; 13:425–437.
80. Harb H, Chatila TA. Mechanisms of Dupilumab. *Clin Exp Allergy* 2020; 50:5–14.
81. Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. *J Allergy Clin Immunol Pract* 2019; 7:673–674.

82. Study in Pediatric Subjects With Peanut Allergy to Evaluate Efficacy and Safety of Dupilumab as Adjunct to AR101 (Peanut Oral Immunotherapy) <https://clinicaltrials.gov/ct2/show/NCT03682770>. [Accessed 10 March 2021]
83. Study to Evaluate Dupilumab Monotherapy in Pediatric Patients With Peanut Allergy <https://clinicaltrials.gov/ct2/show/NCT03793608>. [Accessed 11 March 2021]
84. Clinical Study Using Biologics to Improve Multi OIT Outcomes <https://clinicaltrials.gov/ct2/show/NCT03679676>. [Accessed 3 March 2021]
85. Leung DY, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
86. Arm JP, Bottoli I, Skerjanec A, *et al.* Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy* 2014; 44:1371–1385.
87. Harris JM, Maciucă R, Bradley MS, *et al.* A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. *Respir Res* 2016; 17:29.