

Omalizumab Treatment for Prevention of Anaphylaxis

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Opinion Statement

RCTs utilizing a specific treatment followed by meta-analysis of multiple RCTs for the specific treatment are the cornerstone of evidence-based medicine. This approach provides key insights into the average response of a therapeutic agent in the selected patient population for the target disease. Generally speaking, a developing trend is more investigations of medical therapies aiming to describe individual patient variability; further, such investigations typically aim to discover and subsequently understand this variability based on biomarkers or even disease-specific genetic polymorphisms among patients. This research returns us to the examination room where we treat individual patients. Given the complexity of idiopathic anaphylaxis and the currently available literature, we believe the time is now to initiate treatment trials of omalizumab in patients not well controlled with prior standard therapy. The use of prolonged systemic steroids should be avoided in favor of a trial of omalizumab. We do not intend to minimize the importance of double-blind placebo-controlled trials. However, based on the full spectrum of current evidence, we do not want to be blinded at the present time by the absence of a published RCT specific to idiopathic anaphylaxis.

Introduction

Omalizumab is a humanized IgG1 monoclonal antibody that binds selectively to the heavy chain constant region (Fc) of human IgE. More specifically, omalizumab binds to human IgE within the CH3 region of the Fc portion of IgE. The CH3 portion of human IgE binds physiologically to the high-affinity IgE receptor (FcεRI) on mast cells and basophils; IgE binding to FcεRI receptors along with IgE-IgE crosslinking triggers the

se effector cells to activate and release inflammatory mediators that can lead to anaphylaxis. The binding of omalizumab to the CH3 portion of human IgE essentially blocks the binding of omalizumab-human IgE complexes to FcεRI receptors on mast cells and basophils; thus, omalizumab-human IgE complexes cannot activate mast cells or basophils. Omalizumab therapy leads to a rapid decrease in total free serum IgE as omalizumab-human

IgE complexes are cleared from the circulation through the reticuloendothelial system. In the setting of decreased free total IgE, high affinity IgE receptors on basophils and mast cells are downregulated. This provides a physiologic explanation for the decrease in basophil and mast cell activation that has been documented in patients receiving treatment with omalizumab therapy [1, 2]. Given the key roles of mast cell activation and/or basophil activation in the pathophysiology of IgE-mediated anaphylaxis, including activation-induced release of key mediators such as histamine, leukotrienes and prostaglandins, investigators hypothesized that treating patients with omalizumab had the potential to prevent and/or reduce the severity of anaphylactic reactions in susceptible individuals [3].

Although neither a precise incidence nor lifetime prevalence of anaphylaxis has been definitively established, an expert consensus working group estimated the lifetime prevalence to be 1 %. However, this panel further concluded that the incidence of anaphylaxis was clearly increasing even though many cases are likely not reported [4]. The most commonly identified triggers of antigen-specific IgE-antibody mediated anaphylaxis are foods, medications and hymenoptera insect stings [3]. Subcutaneous allergen immunotherapy is used most commonly for the treatment of medication refractory allergic rhinoconjunctivitis as well as in patients who have experienced anaphylaxis caused by hymenoptera insect stings. Treatment of the latter group of patients decreases the recurrence rate of anaphylaxis related to subsequent hymenoptera stings by 90 % or more in most patients [5]. While relatively uncommon, patients undergoing treatment with subcutaneous allergen immunotherapy for allergic rhinitis or stinging insect allergy do experience systemic allergic reactions. Most such systemic reactions are mild, involving cutaneous manifestations such as urticaria and pruritis with or without a simultaneous flare of rhinitis and/or conjunctivitis. Nevertheless, rare potentially life-threatening and even fatal anaphylaxis can occur [5].

Even after careful evaluation, no external trigger is identified in many patients who experience recurrent episodes of anaphylaxis [6•]. After ruling out other

potential causative or complicating disorders, such as systemic mastocytosis, the diagnosis of idiopathic anaphylaxis can be made as a diagnosis of reasonable exclusion. The critical importance of ongoing questioning and searching for the possibility of previously unidentified trigger(s) is illustrated by the relatively recent description of hypersensitivity reactions including anaphylaxis related to IgE antibodies specific for the oligosaccharide galactose- α -1,3-galactose (alpha-gal) [7]. Ingestion of mammalian meat including but not limited to beef, pork and lamb, which contain the alpha-gal carbohydrate, has been implicated as a causative factor in cases of anaphylaxis with onset of symptoms approximately 3 to 6 h after ingestion of the inciting mammalian meat trigger [7]. This type of delayed IgE-mediated reaction to any food had not previously been described. Given this key discovery, many cases of anaphylaxis that may have been labeled "idiopathic" in the past are now diagnosed as alpha-gal allergy. Alpha-gal is reviewed in detail in a separate review within this series.

Idiopathic anaphylaxis is not rare, but similar to all cause anaphylaxis, the exact incidence is not known. A practical "real world" perspective involving adults reviewed 601 patients who were evaluated for anaphylaxis of unknown cause at a single allergy practice with special interest and expertise in the diagnosis and management of anaphylaxis. Patients who were diagnosed with stinging insect anaphylaxis as well as those who experienced systemic reactions caused by subcutaneous allergen immunotherapy were excluded. A total of 356 of the 601 patients (59 %) were reported to have idiopathic anaphylaxis [8]. In children, the estimated incidence of idiopathic anaphylaxis is much lower at approximately 10 % [9, 10]. Fortunately, even though the syndrome of idiopathic anaphylaxis in adults is relatively common, fatal anaphylaxis related to this condition remains a rare occurrence with only three fatalities reported in the literature to our knowledge [11, 12]. Nevertheless, the negative impact on an individual patient's quality of life can be profound.

Treatment

Peanut allergy

- In 2003, Leung and colleagues published the first randomized double-blind placebo controlled trial (RCT) of "omalizumab-like" therapy

targeted at preventing or decreasing allergic reactions in patients with confirmed peanut allergy [13]. They used the monoclonal antibody, TNX-901. Patients received the study drug or placebo every 4 weeks for a total of four doses. Peanut allergy was confirmed by double-blind placebo-controlled graded oral peanut challenge (DBPCPC) prior to the study. Following the fourth dose of TNX-901 or placebo, the patients (total of 84 randomized to placebo or anti-IgE therapy) repeated the double-blind graded oral peanut protein challenge. Compared to baseline oral challenge, patients who received the highest of the three doses, 450 mg, showed a significantly increased ability to tolerate peanut compared to placebo. The baseline threshold dose of peanut protein causing mild to moderate anaphylaxis was approximately half a peanut (178 mg). Following treatment, the threshold dose in the high dose arm approached the equivalent of nine peanuts (2,805 mg). However, 25 % of the patients in the high dose group did not show an increase in threshold peanut dose. Thus, while the results were overall positive, the individual variability in response was an important finding that was unexplained. This early study was not designed to include physiologic markers that could have potentially provided some insight in this regard. Overall, the study suggested that anti-IgE therapy had the potential to protect most peanut allergic patients from potentially fatal reactions related to accidental peanut ingestion.

- In a subsequent study using omalizumab, the same group of investigators aimed to confirm the positive findings of the prior peanut allergy study utilizing a similar study design but in a larger patient population. The investigators performed graded oral peanut challenge utilizing essentially the same (DBPCPC) as in the prior 2003 study. The target number for randomization was 150 participants. Unfortunately, two participants experienced severe anaphylactic reactions during the baseline peanut challenge portion of the study prior to the randomization phase. These two serious adverse events led to the study being stopped early based on the recommendation of the Data Safety Monitoring Committee. At the time of study termination, only 14 patients had completed repeat blinded graded peanut challenge following 24 weeks of omalizumab therapy at a total dose of 0.016 mg/kg/IgE (IU/ml) monthly. Among the 14 patients who had completed the study, nine had been receiving treatment with omalizumab and five had been receiving placebo. While trends in increased threshold doses for peanut-induced allergic reactions were seen, the study was not able to confirm findings from the previous study [14].
- In 2012, the results of an open-label trial of omalizumab in adult peanut allergic patients looked again for a protective effect as measured by response to DBPCPC. The investigators also measured the effects of treatment on effector cells, principally basophils. Of the 14 participants, 10 were able to complete all three blinded peanut challenges. The ten patients who completed the study showed a median 56-fold increase in peanut oral tolerance (baseline peanut

protein threshold dose=80 mg, omalizumab treatment phase median peanut protein threshold dose=6,500 mg; one peanut \approx 300 mg protein). Peanut-induced basophil histamine release was completely suppressed in five patients, while in the nine others a ten-fold increase in peanut dose was required to induce the prior maximal histamine release response. The first food challenge while receiving omalizumab treatment took place 2-8 weeks after treatment initiation based on the study design, which called for this challenge to occur prior to week 8 if basophil histamine response had decreased to less than 20 % of baseline ($n=5$). The final peanut oral challenge was given at week 24.

Even with the limitation of an open-label design, this investigation provided details that contributed valuable mechanistic insights and again demonstrated individual patient variability in treatment response; this variability was not explained by differences in basophil histamine response alone. At the time of the second oral peanut challenge, two patients showed little to no change in peanut threshold dose; these two patients did show an increased threshold dose approaching 2,000 mg during the oral peanut challenge at week 24. Three other individuals reacted at the threshold dose of approximately 2,000 mg at week 24. In contrast, six patients had an increased threshold dose of peanut protein of approximately 10,000 mg or greater during the second oral peanut challenge. Two of these patients did not complete the final oral peanut challenge. The four of these six patients who did complete the study maintained this robust increase in peanut protein threshold dose at week 24 challenge. With open-label treatment, all peanut allergic patients in this study tolerated at least the equivalent of \approx six peanuts during at least one of the double-blind oral peanut challenges [15].

Subcutaneous allergen immunotherapy

- Casale and colleagues investigated the use of omalizumab for prevention of anticipated systemic allergic reactions observed in prior reports with the use of a rapid desensitization (RUSH) protocol for subcutaneous ragweed immunotherapy in adults. A total of 159 patients with ragweed allergic rhinitis in this RCT received either two total monthly doses of omalizumab [0.016 mg/kg/IgE (IU/ml)] or placebo. This treatment was followed by single-day RUSH ragweed subcutaneous immunotherapy (to a dose of 1.2-4.0 μ g of the major short ragweed protein allergen, Amb a 1) or placebo subcutaneous injections. Subsequently, patients continued every 2- or 4-week treatment with omalizumab versus placebo along with ragweed immunotherapy versus placebo immunotherapy for an additional 12 weeks. Among patients receiving active ragweed immunotherapy, those who were also receiving omalizumab demonstrated a significantly decreased risk of anaphylaxis caused by ragweed RUSH immunotherapy (2.6 % versus 15 % of patients). The

- authors concluded that omalizumab pretreatment significantly improved the safety of ragweed RUSH immunotherapy [16].
- A RCT performed by Massanari and colleagues [17••] investigated the utility of adjunctive omalizumab therapy in patients with persistent allergic asthma with allergy triggers identified to cat, dog and/or dust mite. The inclusion criteria required the patients to have ongoing asthma symptoms that were not well controlled with standard inhaled corticosteroid therapy. The patients continued inhaled corticosteroid therapy, and a total of 275 such patients were randomized to receive omalizumab or placebo for 16 weeks. At week 13, all patients initiated subcutaneous allergen immunotherapy, which included standard target allergen doses of at least one of the above allergens (two or all three based on individual skin test results) given using a cluster dose escalation protocol. The cluster portion of immunotherapy essentially overlapped the double-blind omalizumab or placebo-dosing period. Patients continued stable maintenance doses of immunotherapy for an additional 7 weeks. Omalizumab-treated patients had significantly decreased systemic allergic reactions to allergen immunotherapy compared to placebo-treated patients (13.5 % versus 26.2 %). Further, patients receiving omalizumab treatment demonstrated improved asthma symptoms and were more likely to achieve the target allergen immunotherapy dose compared to placebo.
 - Several case reports have suggested omalizumab therapy may prevent subsequent episodes of anaphylaxis caused by stinging insect immunotherapy injections. These reports include patients with and without underlying systemic mastocytosis. Several of these case reports suggest variability in effective dose as well as time to treatment response [18–22]. No RCT data have been published to date, but the case reports taken together are certainly suggestive of “real” benefit. In light of the efficacy demonstrated in the RCTs discussed above with RUSH IT using ragweed allergen mixtures and cluster IT using dust mite, cat and/or dog allergen mixtures, a trial of omalizumab therapy aiming to prevent or reduce reactions caused by stinging insect IT therapy should be attempted in select at-risk patients in our opinion. As mentioned in the introduction, stinging insect IT has proven efficacy in protecting patients from potentially fatal future insect sting reactions [5].

Idiopathic anaphylaxis

- No RCT has been published evaluating omalizumab treatment for the prevention of anaphylaxis in patients diagnosed with idiopathic anaphylaxis. However, investigators at the National Institute of Health (NIH) are actively recruiting patients for a single-center RCT of omalizumab therapy in this patient population (ClinicalTrials.gov

Identifier: NCT00890162). At the time of preparation of this review, a total of 14 patients had been randomized to omalizumab or placebo. Twelve patients have completed the trial (personal communication with principal investigator, Melody Carter, M.D., at the National Institute of Allergy and Infectious Disease).

Even though no RCTs have been published specifically addressing idiopathic anaphylaxis, important insight into this potential therapeutic use comes from studies in patients with chronic idiopathic urticaria. A pivotal phase III RCT published in 2013 included 323 patients with chronic idiopathic urticaria refractory to at least "high dose" antihistamine therapy (typically four times the approved H1 antihistamine dose for the treatment of allergic rhinitis). Omalizumab doses of 150 mg every 4 weeks and 300 mg every 4 weeks demonstrated statistically significant improvement in both the primary and secondary endpoints, which included patient-reported standard symptom scores of pruritus severity and the total number/maximum size of urticarial lesions [23]. Given that mast cell and basophil activation are important in the pathogenesis of both disease processes and approximately 90 % of patients who experience an anaphylactic reaction have skin manifestations including urticaria, this study in our opinion suggests that many patients with idiopathic anaphylaxis are likely to benefit from omalizumab treatment.

- Presently, publications of omalizumab therapy in the setting of idiopathic anaphylaxis are limited to case reports and small case series. In 2008, Jones and colleagues were the first to publish a case report of omalizumab therapy in a 48-year-old male who reported more than a decade of recurrent idiopathic anaphylaxis despite prophylactic treatment including antihistamines, antileukotrienes and systemic corticosteroids [24]. The frequency of his anaphylactic episodes without daily corticosteroid therapy occurred at a rate of at least six episodes yearly. With daily systemic corticosteroid therapy, the frequency and severity of episodes decreased but continued to occur at least four times in the year prior to initiation of omalizumab. His specific anaphylactic symptoms involved the skin with urticaria and flush; respiratory with wheezing and chest tightness; gastrointestinal with cramping pain and diarrhea; cardiovascular with hypotension. Urinary histamine metabolite elevation was documented during multiple anaphylactic episodes but remained normal at baseline. Bone marrow biopsy, which had been performed "multiple" times, was reported as normal; specifically, the bone marrow specimen obtained at our institution did not reveal abnormal numbers or morphology of mast cells and was negative for C-KIT D816V mutation. After initiation of omalizumab at a dose of 375 mg every 2 weeks, he had no further episodes of anaphylaxis during the course of a year and was able to discontinue oral corticosteroids within this time frame as well. The authors' most recent

contact with this patient was in 2013; he remained on omalizumab therapy and reported sustained control with no anaphylactic reactions requiring epinephrine and/or acute emergency care. He continued to take oral H1 and H2 blocking antihistamines; he reported periodic mild symptom flares involving central flush with or without urticaria (personal communication). Since that time multiple case reports have appeared in the world literature describing complete or partial control of idiopathic anaphylaxis previously refractory to standard therapies [25–27]. Many reports, particularly in patients with underlying systemic mastocytosis or monoclonal mast cell activation syndrome, have reported a longer period of time before onset of symptomatic improvement. Further, select patients have required more frequent dosing and/or a need for higher doses of therapy [28, 29]. In a case series of four patients with monoclonal mast cell activation or systemic mastocytosis, three experienced significant improvement, but in two of the patients (a male with aggressive systemic mastocytosis and a female with monoclonal mast cell activation syndrome), improvement was not clearly evident until they had been receiving omalizumab therapy for 6 months. One of the patients did not tolerate omalizumab related to adverse effects including headache, nausea and dizziness, which were more severe following a second dose of omalizumab. These symptoms were attributed to mast cell mediator release presumably based on her clinical history; objective measures of mediator release were not reported in this individual. However, in two of the patients who responded to therapy, serum tryptase levels and/or urine histamine metabolite decreased along with the need for oral corticosteroids [30]. The findings of decreasing serum tryptase and/or decreasing levels of histamine urinary metabolite in association with clinical improvement with omalizumab therapy were not observed in the previously cited case reports in other patients with systemic mastocytosis [28, 29].

Class of drugs (monoclonal antibody)

Omalizumab

Standard dosage	150 mg or 300 mg subcutaneous injection every 4 weeks for chronic idiopathic urticaria
Contraindications	prior hypersensitivity reaction
Main side effects	local injection site reactions; anaphylaxis 0.2 %
Special points	Further study needed to determine optimal dosing in chronic idiopathic urticaria; initial randomized controlled trial underway in patients with idiopathic anaphylaxis
Cost/cost-effectiveness	Wholesale acquisition cost in 2014, \$820/150 mg vial; expensive

Pediatric considerations

- Multiple clinical investigations have evaluated the efficacy and safety of omalizumab use in children for a variety of allergic conditions. RCTs of omalizumab performed in children with persistent asthma ages 6 through 11 have demonstrated efficacy and relative safety (not FDA approved) [31•]. FDA approved for allergic asthma ages 12 years and older. FDA approved for chronic idiopathic urticaria ages 12 years and older [32].

Compliance with Ethics Guidelines

Conflict of Interest

Hector Rodriguez and John Fahrenholz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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