

Biologic Agents for the Treatment of Anaphylaxis



Luciana Kase Tanno, MD, PhD^{a,b,c,d,*}, Bryan Martin, DO^{e,1}

KEYWORDS

• Anaphylaxis • Biologic agents • Biotherapy • Management • Treatment

KEY POINTS

- Adrenaline is still the initial treatment of choice in all cases of anaphylaxis and its administration should not be delayed.
- Developments in anaphylaxis have consistently followed pharmacologic developments offering possibilities of better management and prevention.
- Avoidance of trigger exposure and adrenaline administration remain the mainstay of long-term control of anaphylaxis; however, inadvertent exposure to allergens always remains a possibility.
- Biological agents as single medications or as combined therapy with food or venom immunotherapy, are effective as preventive treatments to reduce the most severe anaphylactic reactions.
- Cost-effectiveness of the use of biologic agents in anaphylaxis should be considered individually.

ANAPHYLAXIS: A HIGH-PRIORITY PUBLIC HEALTH ISSUE THAT REQUIRES IMMEDIATE TREATMENT AND PREVENTIVE MEASURES

Anaphylaxis: a High-Priority Public Health Issue

Since the term anaphylaxis was first coined in 1902 by Charles Richet and Paul Portier,¹ it has rapidly spread all around the world and its clinical importance as an emergency condition is now well accepted. Anaphylaxis is currently clinically defined as a

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^a Hospital S rio-Liban s; ^b University Hospital of Montpellier, Montpellier, France; ^c Sorbonne Universit , INSERM UMR-S 1136, IPLESP, Equipe EPAR, Paris 75013, France; ^d WHO Collaborating Centre on Scientific Classification Support, Montpellier, France; ^e Department of Medicine, The Ohio State University, 410 West 10th Avenue, Columbus, OH 43210, USA

¹ Present address: 2050 Kenny Road Suite 2200, Columbus, OH 43221.

* Corresponding author. Division of Allergy, Department of Pulmonology, H pital Arnaud de Villeneuve, University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud, Montpellier Cedex 5 34295, France.

E-mail address: luciana.tanno@gmail.com

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severe, life-threatening systemic hypersensitivity reaction characterized by rapid onset and the potential to endanger life through airway, breathing, or circulatory problems^{2–7} that require prompt identification and treatment.

Anaphylaxis is a syndrome with a constellation of features and signs that can manifest at any age, with multiple triggers, and any health professional may face it. Thus, patients with anaphylaxis have a chronic condition with intermittent and potentially fatal acute events. The treatment of anaphylaxis primarily comprises medications at the acute phase (mainly adrenaline) and then long-term avoidance and prevention measures.

The reported rate of occurrence seems to vary widely from one country to another. The lifetime prevalence has been estimated at 0.05% to 2% based on international studies.⁸ In a recent systematic review of the global incidence and prevalence of anaphylaxis in children, the investigators reviewed 59 studies from 20 countries and the range of total anaphylaxis incidence ranged from 1 to 761 per 100,000 person years.⁹ Anaphylaxis is a recognized cause of death in all ages, with the anaphylaxis-related mortality less than 1 per million per year in most high-income countries.^{10–18} There are limited epidemiologic data from middle-income and low-income countries. Deaths from anaphylaxis are difficult to investigate because of misdiagnosis and miscoding, but morbidity and mortality statistics on anaphylaxis may gain new perspectives with the implementation of the eleventh version of the World Health Organization (WHO) International Classification of Diseases, in which anaphylaxis is now better represented.^{19–22}

Because of varied, multidimensional clinical presentations, risk of fatality, and sudden onset in any setting, the allergy community has designated anaphylaxis as a high-priority public health issue.

From Clinical Anaphylaxis to Endotypes

The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been points of controversy among different medical subspecialties and in different countries. Therefore, it became clear that an important goal would be to achieve a true international consensus. For this reason, multinational and multidisciplinary collaboration, led by allergy academies, resulted in the International Consensus on Anaphylaxis.⁷

From the initial description of anaphylaxis as a clinical entity with acute onset of symptoms involving 2 or more organs or association with hypotension or upper respiratory, its definition has evolved in recent publications to a more mechanistic description based on precision medicine classifying phenotypes with underlying endotypes supported by diagnostic biomarkers. At present, anaphylaxis phenotypes are defined by clinical presentation into type I–like reactions, cytokine storm–like reactions, and mixed reactions. The endotypes underlying these phenotypes include immunoglobulin (Ig) E–mediated and non-IgE–mediated mechanisms, cytokine release, mixed reactions, and direct activation of immune cells.^{23,24} Better understanding of underlying mechanisms of anaphylaxis and the stratification of endotypes support precision medicine and may allow the integration of new therapeutic approaches, such as the use of biologic agents.

Anaphylaxis Treatment and Prevention: Current Status

In order to decrease the risk of death and optimize the treatment of anaphylaxis, all the guidelines^{2–7} convey the need for a standardized protocol in which the removal of the trigger, the prompt initial pharmacologic treatment (epinephrine mainly), the appropriate positioning of the patient, and call for help should be started simultaneously.

Because anaphylaxis mimics common conditions, such as asthma and urticaria, and because it can present without hypotension, its diagnosis is often missed or delayed. As a consequence, this may lead to the delay of appropriate treatment, increasing the risk of death.

Adrenaline (epinephrine) is still the first-line treatment of any type of anaphylaxis and is recognized as the only medication documented to prevent hospitalizations, hypoxic sequelae, and fatalities. Glucocorticoids and antihistamines should be used only as third-line treatment in anaphylaxis treatment. Their administration should never delay adrenaline injection in anaphylaxis.^{2-7,24,25} Delay in the use of adrenaline (recognized as a factor that may increase the risk of death in anaphylaxis) and the global availability of adrenaline autoinjectors are still key issues in the management of anaphylaxis.²⁶

Because public health's core mission is prevention of injury or disease, there are many potential strategic interventions. Tertiary prevention strategies are the most familiar for physicians worldwide who are involved in clinical medicine. When applied to anaphylaxis, it is intended to reduce the risk of another reaction and/or manage it appropriately to avoid negative outcomes. Prevention of anaphylaxis depends primarily on optimal management of patient-related risk factors; strict avoidance of confirmed relevant allergens or triggers; and, where indicated, immunomodulation (eg, Hymenoptera venom immunotherapy). The use of biologic agents in anaphylaxis has been gaining interest over the last years.²⁵

This article reviews the use of biologic agents used in the treatment of anaphylaxis with the view that new knowledge can support high-quality practice and empower allergists and health professionals with new tools that can be used to treat symptoms and prevent anaphylaxis.

IS THERE A PLACE FOR BIOLOGIC AGENTS IN ANAPHYLAXIS TREATMENT?

Monoclonal Agents: Current Status

The recent description of phenotypes provides new insight and understanding into the mechanisms and causes of anaphylaxis through a better understanding of endotypes and application of precision medicine. Several biologic therapies are emerging as potential preventive or adjuvant treatment of anaphylaxis.

The commercial use of monoclonal antibodies (mAbs) began in early 1980s, and the first therapeutic mAb targeting the immune system was approved in 1986.²⁷ In 2014, 47 mAbs were approved in the United States or Europe for the treatment of a variety of diseases, and many of these products have also been approved for the global market. It was estimated that there would be an approval rate of 4 new products per year and the availability of ~70 mAbs on the market by 2020, with worldwide sales of nearly \$125 billion. At present, 200 biologic agents are commercially available for all conditions. These therapies are responsible for about 30% of all drugs under development.²⁷⁻³¹

Overall Evidence Base for Anaphylaxis Treatment with Biologic Agents

Most biologic agents target respiratory conditions, but new drugs have emerged to cover other allergic and hypersensitivity conditions such as atopic dermatitis, and eosinophilic conditions such as eosinophilic esophagitis. Although biologic agents are still not licensed for the treatment of anaphylaxis, in recent years these drugs, in particular omalizumab (anti-IgE mAb), have been used as therapeutic adjuvants as a preventive treatment of anaphylaxis. At present, there are 63 clinical trials registered for anaphylaxis; only 3 involve omalizumab.³²

Omalizumab is 95% humanized mAb that recognizes and binds to the Fc portion of the IgE molecule in order to block IgE binding to mast cells and basophils. It prevents IgE expression on allergic effector cells and subsequent allergen-induced cross-linking of IgE.³² This treatment is now formally indicated for moderate to severe persistent allergic asthma with proven sensitization to perennial aeroallergen in patients refractory to usual treatment and for chronic idiopathic urticaria in patients who remain symptomatic despite H1 antihistamine treatment. Therapeutic strategies based on omalizumab administration in other disorders are currently only based on limited clinical trials, observations, case series, and expert opinions.³³

Besides the formal indication of omalizumab for allergic asthma, this drug has also been shown to reduce the frequency and intensity of side effects when combined with allergen immunotherapy (AIT) to allergic rhinitis induced by grass pollen. A multicenter study showed that patients who received omalizumab had lower frequency of adverse events than the group receiving AIT alone. Post hoc analysis showed that the association of omalizumab resulted in a 5-fold decrease in the risk of AIT-induced anaphylaxis.³⁴

mAbs can also induce hypersensitivity conditions, ranging from mild cutaneous reactions to life-threatening presentations. Recent data have provided evidence of successful desensitization to an increased number of mAbs, including rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab.²⁴ However, mAbs can also be used as adjuvants in the desensitization to other drugs in order to reduce the severity of side effects during these procedures. Desensitization to antibiotics in combination with omalizumab has been successfully done in targeted populations, such as patients with cystic fibrosis, with a similar protocol as for chemotherapy drugs. Desensitization to aspirin combined with omalizumab for aspirin-exacerbated respiratory disease has provided increased sense of smell, prevented the regrowth of polyps, and helped stabilize asthma symptoms.

Omalizumab is a potential adjuvant in food oral immunotherapy. A recent phase 2 randomized, double-blind, placebo-controlled trial of 37 peanut-allergic children undergoing oral immunotherapy showed that omalizumab administration (12 weeks) allowed tolerance of 2000 mg of peanut on discontinuation of immunotherapy more often than placebo (74% vs 13%, $P < .01$).³⁵ Participants assigned to omalizumab were also less likely to experience adverse reactions to peanut immunotherapy. Omalizumab, administered solely or in combination for 28 months, was also shown to improve safety but not efficacy in 57 subjects (7–32 years old) with a cow's milk allergy undergoing oral immunotherapy.³⁶ A phase 1 randomized trial performed with children with proven multiple food allergies suggested that omalizumab in combination with oral immunotherapy with multiple food allergens was able to reduce the time to reach the target dose and to minimize the severe symptoms during the procedure.³⁷

Omalizumab has been shown to be a successful treatment of idiopathic anaphylaxis, effectively reducing the number of episodes and improving the quality of life.^{38–41} 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 to 14 months.^{38–41} In these 4 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.⁴⁰ Omalizumab has been shown also to reduce anaphylaxis

episodes and skin symptoms and increase quality of life in 13 adult patients with systemic mastocytosis who received this treatment with a median duration of 17 months (range, 1–73 months).^{42,43}

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 to be effective as an adjunctive treatment in patients with mastocytosis, used for both symptom improvement and to dampen adverse effects caused by venom immunotherapy.^{44–51}

New Monoclonal Antibodies, New Perspectives?

Although anaphylaxis is not only IgE mediated, new mAbs targeting IgE are being studied and may be possible adjuvants in the management and prevention of anaphylaxis in the future.

Ligelizumab is a humanized IgG1 mAb that binds to the Ce3 domain of IgE193.⁵² A recent phase 2b study evaluated the efficacy and safety of this drug in patients with moderate/severe urticaria, with positive outcomes.⁵³ Phase 3 studies are ongoing, but there is still no study involving anaphylactic patients.⁵⁴

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.⁵⁴ 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.⁵⁵ In a small study with patients with refractory urticaria, quilizumab showed no significant benefits in changing the pruritus score. The investigators speculate that higher doses or longer treatment could have provided a more efficient response.⁵⁶ Although targeting IgE expression, there are still no registered studies in anaphylaxis.

BIOLOGIC AGENTS AND ANAPHYLAXIS

The recent description of phenotypes provides new insight and understanding into the mechanisms and causes of anaphylaxis through a better understanding of endotypes and application of precision medicine. Several biologic therapies and new devices are emerging as potential preventive treatment of anaphylaxis. However, adrenaline (epinephrine) is still the first-line treatment of any type of anaphylaxis.

Biologic drugs, such as omalizumab, have been used as therapeutic adjuvants as a preventive treatment of anaphylaxis, but cost-effectiveness should be considered individually. Real-world questions about safety and effectiveness of such novel approaches remain unclear. The cost of such medications and knowledge gaps about long-term benefit/risk, adherence, and comparative effectiveness require further research and expertise.

CLINICAL CARE POINTS

- Acute anaphylaxis is often underdiagnosed and undertreated.
- Adrenaline (epinephrine) is the treatment of choice for anaphylaxis; therapy should begin at 0.01 mg/kg up to a dose of 0.5 mg.
- Glucocorticoids and antihistamines are not part of the initial treatment of acute 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 with the potential for life-threatening exacerbations. Although avoidance is the mainstay for long-term control of anaphylaxis, inadvertent exposure to allergens is always a possibility.
- Understanding the underlying endotypes of anaphylaxis may lead to new therapeutic options.

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