



Biologicals for the prevention of anaphylaxis

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Purpose of review

To review the use of biological agents (BA) in the treatment of anaphylaxis in the view of the new knowledge in the field to support the quality of care and prevention.

Recent findings

Some BA, as a single medication or as combined therapy to food or venom immunotherapy, are effectively able to reduce most of the severe anaphylactic reactions.

Summary

Anaphylaxis is a recognized clinical emergency, which requires prompt identification and treatment. Several biologic therapies and new devices are emerging as a potential preventive treatment for anaphylaxis. However, adrenaline (epinephrine) is still the first-line treatment for any type of anaphylaxis. Biological drugs, such as omalizumab, whereas not US Food and Drug Administration (FDA) nor European Medicines Agency (EMA) approved for anaphylaxis, have been used as therapeutic adjuvants in the preventive treatment of anaphylaxis, but cost-effectiveness should be considered individually.

Keywords

anaphylaxis, biological agents, biotherapy, management, omalizumab, treatment

INTRODUCTION

Biological agents

Monoclonal antibodies: the corner stone of modern biotherapeutics

Biological agents (BA) are defined as substances made from living organisms or its products, and used in the prevention, diagnosis or treatment of diseases. Biological drugs include antibodies, interleukins (ILs), and vaccines [1]. Commercial use of new generation of BAs started at the end of the 20th century, contributing dramatically in the management of different conditions so far.

Monoclonal antibodies (mAbs) are BA derived from single clone of antibody-producing plasma cells against aberrant molecules in the body leading to pathology. The commercial use of mAbs began in the early 1980s, and the first therapeutic mAbs targeting the immune system was approved in 1986 [2]. In 2014, 47 mAbs have been 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 an approval rate of four new products per year and predicted the availability of ~70 mAbs on the market by 2020, with a worldwide sale of nearly \$125 billion. Currently, 200 BA are

commercially available. These therapies are responsible for about 30% of all drugs under development [3–6].

Evolution of the biotechnology combined with increasing understanding of underlying mechanisms of diseases allowed remarkable and fast development of new mAbs targeting different conditions and new hopes for resistant or incurable chronic diseases. There are no doubts that BA changed the landscape of how Medicine is practiced by reducing the severity of diseases, promoting long-life expectation and improving the quality of life of patients and their carriers. We here propose to review the use of BA in the treatment of anaphylaxis in the view of the new knowledge in the field to support the quality care and prevention.

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KEY POINTS

- Developments in the field of anaphylaxis have been consistently evolved with the description of phenotypes and endotypes, which contributes for a better understanding of underlying mechanisms and opens the possibility of the application of personalized medicine.
- Adrenaline is still the initial treatment of choice in all cases of anaphylaxis and its administration should not be delayed.
- Biologicals, as the single medications or as combined therapy to food or venom immunotherapy, are effective as preventive treatments to reduce the most severe anaphylactic reactions.
- Cost-effectiveness of the use of biological agents in anaphylaxis should be considered individually.

TEXT REVIEW

Biologicals and allergic and hypersensitivity conditions

There have been major advancements over the past decade in the field of Allergy. New therapeutic options have emerged to optimize the management of patients suffering with allergic and hypersensitivity conditions (A/H) and allowing the clinical application of personalized medicine. Most of BA applied to A/H target respiratory conditions, but new drugs have emerged to cover other A/H conditions, such as atopic dermatitis, chronic spontaneous urticaria, chronic rhinosinusitis with or without nasal polyposis (CRSwNP) or eosinophilic esophagitis. BA has become a key option for the treatment of specific severe A/H [5,6].

Four main classes of BA currently (January 2021) approved by US Food and Drug Administration (FDA) [5] and European Medicines Agency (EMA) [6] for allergic and hypersensitivity diseases are:

Antiimmunoglobulin E (IgE) (Omalizumab) has been approved since 2003 for allergic asthma [7]. It is indicated for patients 6 years or older with moderate to severe persistent asthma with a positive skin test result or in vitro reactivity to a perennial aero-allergen and symptoms that are inadequately controlled with inhaled corticosteroids (GINA 5 asthmatics). It is also indicated for patients 12 years or older with chronic spontaneous urticaria who remain symptomatic despite high-dose H1 antihistaminic treatment. Its efficiency for CRSwNP is being examined. Some trials have reported its effectiveness in controlling idiopathic anaphylaxis and in achieving tolerance in food and Hymenoptera allergies undergoing allergen immunotherapy (AIT) [7–9,10[•],11,12[•]].

Antiinterleukin 5 (IL5) (Mepolizumab, Reslizumab) are indicated for severe eosinophilic asthma. Mepolizumab is approved for patients aged 6 years or older with a blood eosinophilic count ≥ 150 cells/ μ L or ≥ 300 cells/ μ L within the previous year. It is under investigation for eosinophilic esophagitis and CRSwNP. It is also approved for eosinophilic granulomatosis with polyangiitis. Reslizumab is authorized for adults with a blood eosinophilic count ≥ 400 cells/ μ L. It is also being studied for eosinophilic esophagitis and nasal polyposis [13–17,18[•],19[•]].

Anti-IL4/13 (Dupilumab) was initially approved for patients aged 12 years and above with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The indication has been extended to patients aged 12 years and above with severe asthma associated with elevated blood eosinophilia (≥ 300 cells/ μ L) and/or an elevated fraction of exhaled nitric oxide (FeNO). It has also been approved for CRSwNP insufficiently controlled with systemic corticosteroids and/or surgery. Dupilumab is being investigated for use in eosinophilic esophagitis [20–22,23,24,25[•],26[•]].

Anti-IL5 R (Benralizumab) is indicated for adults with severe eosinophilic asthma (blood eosinophilia ≥ 300 cells/ μ L). More studies need to be realized to prove its efficacy in CRSwNP [27,28].

Anti-thymic stromal lymphopoietin (TSLP) mAb (Tezepelumab, AMG 157/MEDI9929), a human mAb specific for the epithelial-cell-derived cytokine TSLP, in patients whose asthma remained uncontrolled despite treatment with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids [29] and in severe to moderate atopic dermatitis [30].

Biological and anaphylaxis

Anaphylaxis management: current status

Anaphylaxis is a recognized clinical emergency, which requires prompt identification and treatment [31–36,37^{••}]. Adrenaline (epinephrine) is still the first-line treatment for any type of anaphylaxis and is recognized as the only medication documented to prevent hospitalizations, hypoxic sequellae, and fatalities [31–36,37^{••}]. Therapy should begin at 0.01 mg/kg up to a dose of 0.5 mg, and repeated if needed. Delay in the use of adrenaline is recognized as a factor that may increase the risk of death in anaphylaxis and the global availability of adrenaline auto-injectors are still key issues in the management of anaphylaxis [37^{••}]. Glucocorticoids and antihistamines should be used only as third-line treatment in anaphylaxis treatment [31–36,37^{••}].

After treatment of the acute event, anaphylaxis should be treated as a chronic condition with the potential for life-threatening relapses/exacerbations. Although avoidance is the mainstay for long-term control of anaphylaxis, inadvertent exposure to allergens is always a possibility [38^{***}].

From the initial description of anaphylaxis as a clinical entity with acute onset of symptoms involving two or more organs or with the association with hypotension or upper respiratory commitment, its definition has evolved to a more mechanistic description based on precision medicine into phenotypes with underlying endotypes supported by diagnostic biomarkers [39^{***}]. Clinical and basic research have been evolved since the first description of anaphylaxis 118 years ago, which has advanced the field and provided insight into its pathogenesis and management. For example, IL-33 has been described as a key cytokine involved in anaphylaxis [40], neutrophils as potential cellular actors in defined types of anaphylaxis [41] and PAF as a new mediator of anaphylaxis among many other basic discoveries [40] and the fact that chemotherapy and monoclonals have been described as the new most important drugs inducing anaphylaxis [42]. Also, mastocytosis, hereditary alpha tryptasemia and non-clonal mast cell activation syndrome have been described as the essential clinical causes of nonallergic anaphylaxis [43].

Biologicals in 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 are emerging as potential preventive or adjuvant treatment for anaphylaxis.

Although BA are still not licensed for the treatment of anaphylaxis, over the last years these drugs, in particular omalizumab (anti-IgE mab), have been used as therapeutic adjuvants as a preventive treatment of anaphylaxis. Currently, there are 63 clinical trials registered for anaphylaxis; only 3 involve omalizumab [38^{***},43]. Nowadays this treatment is formally indicated for moderate-to-severe persistent allergic asthma with proven sensitization to perennial aeroallergen in patients refractory to usual treatment and for chronic spontaneous 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 [44].

Biologicals in food-induced anaphylaxis

Omalizumab is a potential adjuvant in food oral immunotherapy. A phase 2 randomized, double-blind, placebo-controlled trial of 37 peanut-allergic children undergoing oral immunotherapy showed that omalizumab administration (12 weeks) allowed for tolerance of 2000 mg of peanut upon discontinuation of immunotherapy more often than placebo (74% versus 13%, $P < 0.01$) [45^{***}]. Participants assigned to omalizumab were also less likely to experience adverse reactions to peanut immunotherapy. Omalizumab, administered solely or in combination for 28 months, has also been shown to improve safety but not efficacy, in 57 subjects (7–32 years) with a cow's milk allergy undergoing oral immunotherapy [46]. A phase 1 randomized trial performed with children with proven multiple food allergies suggested that omalizumab in combination with oral immunotherapy with multiples food allergens was able to reduce the time to reach the target dose and to minimize the severe symptoms during the procedure [47,48].

Biologicals and drug-induced anaphylaxis

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 [49].

BA are generally safe, but severe hypersensitivity reactions (HSR) can occur requiring guided allergy workup and management. HSR due to BA can occur with different severity degrees, which hamper their use in these rare cases. A recent international survey conducted through the allergy community regarding the HSR due to BA used for A/H, demonstrated that the majority of allergists observed local mild reactions treated symptomatically without change of the BA. Anaphylaxis has been reported by 6.8% of participants and required acute anaphylaxis treatment and switching for an alternative BA or desensitization [50^{***}].

Recent reports of anaphylaxis-induced by SARS-CoV-2 vaccination have raised the importance of allergic hypersensitivity due to polyethylene glycol (PEG), used as adjuvant in mRNA-based SARS-CoV-2 vaccine. PEG is also used as adjuvant in many drugs, including BA. All cases of anaphylaxis induced by BA containing PEG or PEG derivatives (e.g., polysorbates) should undergo PEG skin tests to tailor

specific decision of the type of SARS-CoV-2 vaccine to be indicated and decision of the continuation of the BA [51[¶]].

Biologicals and allergen immunotherapy

Besides the formal indication of omalizumab for allergic asthma, this drug has also been demonstrated to reduce the frequency and intensity of side effects when combined with sub-cutaneous AIT to allergic rhinitis induced by grass pollen. A multicenter study demonstrated that patients who received omalizumab had lower frequency of adverse events than the group receiving AIT alone. Post hoc analysis demonstrated that the association of omalizumab resulted in a fivefold decrease in the risk of AIT-induced anaphylaxis [52].

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 demonstrated 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 [53–57].

Biologicals in idiopathic anaphylaxis and mast cell disorders

Omalizumab has been shown to be a successful treatment for idiopathic anaphylaxis, effectively reducing the number of episodes and improving the quality of life [58–64,65[¶],66[¶]]. Idiopathic anaphylaxis patients 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. In these four patients, no anaphylaxis episode was recorded after onset of omalizumab injection. Omalizumab may be a preventive therapeutic option in cases of idiopathic anaphylaxis depending on the severity and frequency of episodes, but the cost-benefit ratio should be taken individually.

Mastocytosis and mast cell activation disorders may be identified as a cause of idiopathic anaphylaxis [59]. 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) [61–64,65[¶],66[¶]].

Biological agents: costs and prescription

Cost of BA remains a problematic issue for Public Health. Costing on average between \$10,000 and

\$30,000 per year and per patient [65[¶]], BA represented in 2017, 2% of all United States prescriptions but 37% of net drug spending [67]. Biosimilars drugs, or highly similar copies of biologics, can help reduce costs. Although Europe has at least 40 biosimilars approved in 2018, United States has only had five commercially available. This could be explained by Europe's 10-year head start in establishing a biosimilar approval pathway, but also by rulings in the United States making barriers to competition, therefore to lower prices of biologics.

In several countries, the prescription of BA is restricted to certain authorized specialties, such as dermatologists, pediatricians, and pneumologists. The prescription rights of BA may be related to the recognition of allergy as a full specialty nationally and the region/country specialty developments. In our recent international survey, right to prescribe BA was restricted to 68% of all allergists. Almost all allergists in EU did not have the right to issue first prescription BA (96.5%), remarkably in France (91%). Allergy has been recognized as a full specialty in France only in 2017 and the rights to prescribe BA may follow this process, but it is still not a reality as demonstrated in our survey. [50[¶]].

CONCLUSION

Knowledge in the field of anaphylaxis and the description of specific phenotypes and endotypes have contributed for a better understanding of underlying mechanisms and optimization of personalized medicine. Although not registered to anaphylaxis, new BA have emerged and are under early stages of clinical trials (such as next generation anti-IgE Ligelizumab or Quilizumab), which can be possible therapeutic options for anaphylactic patients in the future.

Adrenaline remains the first-choice treatment of anaphylaxis. However, BA, as a single medication or as combined therapy to food or venom immunotherapy, are effectively able to reduce most of the severe anaphylactic reactions. Cost-effectiveness of the use of BA in anaphylaxis should be considered individually.

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Conflicts of interest

There are no conflicts of interest.

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

- of special interest
- of outstanding interest

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