



Biologics and anaphylaxis

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Purpose of review

The use of biologicals as therapeutic agents in oncology and other inflammatory diseases has dramatically increased during the last years. Due to their biological nature and inherent immunological activity, they are able to induce important adverse events, such as cytokine release reactions (rapid release of proinflammatory cytokines), serum sickness disease, and immediate or delayed hypersensitivity reactions, including anaphylaxis. The aim of the current article is to review the state of the art of anaphylaxis because of biological agents.

Recent findings

Different phenotypes, and potential underlying endotypes, have been described in anaphylactic reactions to biologicals. There seems to be a spectrum from type 1 reactions (IgE or non-IgE-mediated) to cytokine release reactions, with some reactions falling in between both. Management should be directed according to such phenotypes.

Summary

There is ongoing research to further define immediate adverse reactions to biologicals and to find relevant biomarkers to aid in their diagnosis. Such information will serve in defining their immediate and long term management.

Keywords

anaphylaxis, biologicals, desensitization, hypersensitivity reactions, monoclonal antibodies

INTRODUCTION

Biological agents are becoming true game changers in the current management of numerous medical conditions, but together with their powerful therapeutic actions they are also capable of inducing adverse events. They share two critical traits that distinguish them from chemically derived drugs: they are produced in living systems, and they are relatively large molecules, with an inherently heterogeneous structure that can contain hundreds of amino acids [1]. Biological agents can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities, such as cells and tissues, and may induce humoral and cellular immune responses, and subsequent hypersensitivity and infusion reactions.

The aim of the current article is to review the occurrence of anaphylaxis triggered by the use of biological agents. According to the Food and Drug Administration (FDA) (<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm>), biological agents include a wide range of products, such as vaccines, blood and components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. The present review will focus on monoclonal antibodies.

THERAPEUTIC MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) are antibodies of single specificity, generated from the in-vitro immortalization of plasma B cells. The key events that preceded the discovery of mAbs have been recently reviewed by Alkan [2]. To date, over 80 mAbs have been granted marketing approvals for the treatment of neoplastic, autoimmune, and inflammatory diseases, and their clinical applications are becoming broader.

The WHO established guidelines for the nomenclature of mAbs that have been used since the early 1990s. According to this nomenclature, each International Nonproprietary Name (INN) for a mAb is composed by a random prefix, which contributes to an distinctive name, by a substem A, which

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KEY POINTS

- The use of therapeutical biological agents will rise in the next years; as adverse reactions, including anaphylaxis, are not uncommon, there is a need to optimize their management.
- Adverse reactions during infusion of biologicals may range from type 1 immediate reactions (IgE-mediated or non-IgE-mediated) to cytokine release syndromes, being cytokine storms the most severe of the latter.
- Immediate and long-term management should be undertaken considering the potential underlying mechanisms.

indicates the target (molecule, cell and organ) class of the mAb, by a substem B, which indicates the species on which the immunoglobulin sequence of the mAb is based, and by the stem –mab (Table 1). Chimeric mAb have a human constant region and a murine variable region, whereas humanized mAbs have a human variable region except for the complementary determining regions (mouse) and fully

human mAbs have both constant and variable regions of human origin. The INN Expert Group decided to revise the nomenclature scheme that assigns INN for mAbs in 2017 (https://www.who.int/medicines/services/inn/Revised_mAb_nomenclature_scheme.pdf?ua=1), and recommended to discontinue the substem B (source inflix), except the presubstem -vet- for veterinary use, which would be included in substem A list (Table 1).

Immunogenicity and the induction of antidrug antibodies (ADA), increases according to the 'foreignness' of the mAbs. Fully human mAbs are considered less immunogenic than humanized or chimeric mAbs, which contain variable amounts of sequences of mouse origin. However, even fully human proteins can elicit an unwanted immune response that may reduce their efficacy and/or their safety [3]. Antiidiotypic antibodies are also raised against the antigen-binding site of fully human mAbs because the individual T-cell receptors and immunoglobulins are also immunogenic by virtue of the unique sequence within their variable regions. Despite the fact that most biotechnology-derived therapeutics are derived from recombinant

Table 1. Monoclonal antibody nomenclature scheme

Previous mAb nomenclature scheme			
Prefix	Substem A: target class		Substem B: species
Random	-b(a)-	bacterial	-a- rat
	-am(i)-	serum amyloid protein (SAP)/amyloidosis (presubstem)	-axo- rat-mouse (presubstem)
	-c(i)-	cardiovascular	-e- hamster
	-f(u)-	fungal	-i- primate
	-gr(o)-	skeletal muscle mass related growth factors and receptors (presubstem)	-o- mouse
	-k(i)-	interleukin	-u- human
	-l(i)-	immunomodulating	-vet- veterinary use (presubstem)
	-n(e)-	neural	-xi- chimeric
	-s(o)-	bone	-xizu- chimeric-humanized
	-tox(a)-	toxin	-zu- humanized
	-t(u)-	tumour	
	-v(i)-	viral	
New mAb nomenclature scheme			
Prefix	Substem A: target class		Stem
Random	-b(a)-	bacterial	-mab
	-am(i)-	serum amyloid protein (SAP)/amyloidosis (presubstem)	
	-c(i)-	cardiovascular	
	-fung-	fungal	
	-gros-	skeletal muscle mass related growth factors and receptors (presubstem)	
	-ki-	interleukin	
	-li-	immunomodulating	
	-ne-	neural	
	-os-	bone	
	-toxa-	toxin	
	-ta- -vet-	tumour	
	-v(i)-	veterinary use (prestem)	
		viral	

human protein libraries, immunogenicity continues to occur confirming that multiple factors other than 'nonhumanness' influence immunogenicity [4].

ADVERSE REACTIONS TO MONOCLONAL ANTIBODIES

The major safety concerns related to immunogenicity of mAbs are the induction of severe adverse reactions, such as cytokine release reactions (CRRs, rapid release of high amounts of proinflammatory cytokines), serum sickness disease, immediate and delayed hypersensitivity reactions [5]. However, the current article will focus on anaphylactic reactions [6].

Excellent reviews on adverse reactions to biological agents and specifically to mAbs have been published over the last 18 months [7,8,9[■]–12[■]]. The particularities of each one are cited in the references, but in general terms they cover all types of hypersensitivity reactions, from type I to type IV and CRRs, and do not focus specifically in anaphylactic reactions. Nevertheless, anaphylaxis has been reported with a large number of biological agents. Some excipients, such as polysorbate, present in the formulations of mAbs have also been identified as elicitors of hypersensitivity [13]. Table 2 lists anaphylactic reactions reported to date with the most commonly used mAbs. As the diagnosis of anaphylaxis is based on clinical symptoms, and not all reports include an allergy workup, the specific mechanism underlying each reaction is not always evident.

HYPERSENSITIVITY REACTIONS TO BIOLOGICAL AGENTS

Although the Gell and Coombs classification has been useful to understand the mechanism involved in drug hypersensitivity reactions (HSRs) [111], in the case of HSRs to biological agents, clinical presentation (phenotype) and underlying mechanisms (endotype) frequently overlap hampering a straightforward classification and management indications [112[■]].

Anaphylaxis is a rapid and severe systemic reaction resulting from release of cell mediators [113], and may be classified as immunologic (IgE-mediated or non-IgE-mediated) or nonimmunologic [114]. When elicited by biological agents, phenotypes of anaphylaxis are classified depending on clinical presentation in a spectrum ranging from type I reactions to CRRs, with mixed reactions in between, as shown in Fig. 1.

The corresponding endotypes underlying these phenotypes include IgE and other immunologic-mediated mechanism (such as IgG), where the main

Table 2. Cases reported in PubMed of anaphylaxis because of biological drugs

Drug	Number of cases	References
Abatacept	1	[14]
Abciximab	3	[15–17]
Adalimumab	1	[18]
Agalsidase beta	2	[19,20]
Alemtuzumab	1	[21]
Alglucosidase alfa	1	[22]
Anakinra	2	[23,24]
Asparaginase (l-asparaginase, PEG-asparaginase, erwinia-asparaginase)	36, 13, 10	[25–32]
Basiliximab	4	[33–35]
Brentuximab vedotin	3	[36–38]
Certolizumab pegol	1	[39]
Cetuximab	81	[40–49]
Ecallantide	21	[50–54]
Eculizumab	1	[55]
Elosulfase alfa	20	[56–58]
Etanercept	6	[59–61]
Filgrastim	2	[62,63]
Galsulfase	1	[64]
Ibritumomab tiuxetan	1	[65]
Idarucizumab	1	[66]
Idursulfase	3	[67]
Infliximab	30	[68–83]
Interferón	4	[84–87]
Laronidase	1	[88]
Natalizumab	13	[89–91]
Omalizumab	96	[92]
Onabotulinumtoxin A	1	[93]
Palifermin	1	[94]
Palivizumab	1	[95]
Pegfilgrastim	1	[96]
Pegloticase	>11	[97,98]
Pertuzumab	1	[99]
Rasburicase	6	[100]
Reteplase	1	[101]
Rituximab	>15	[102–107]
Sebelipase alfa	3	[108]
Tocilizumab	1	[109]
Vedolizumab	1	[110]
Total	>402	

mediators involved are released from basophil and mast cell, such as tryptase, histamine, leukotrienes and prostaglandins. IgE reactions typically occur after at least one previous administration (sensitization phase). An elevated serum tryptase level

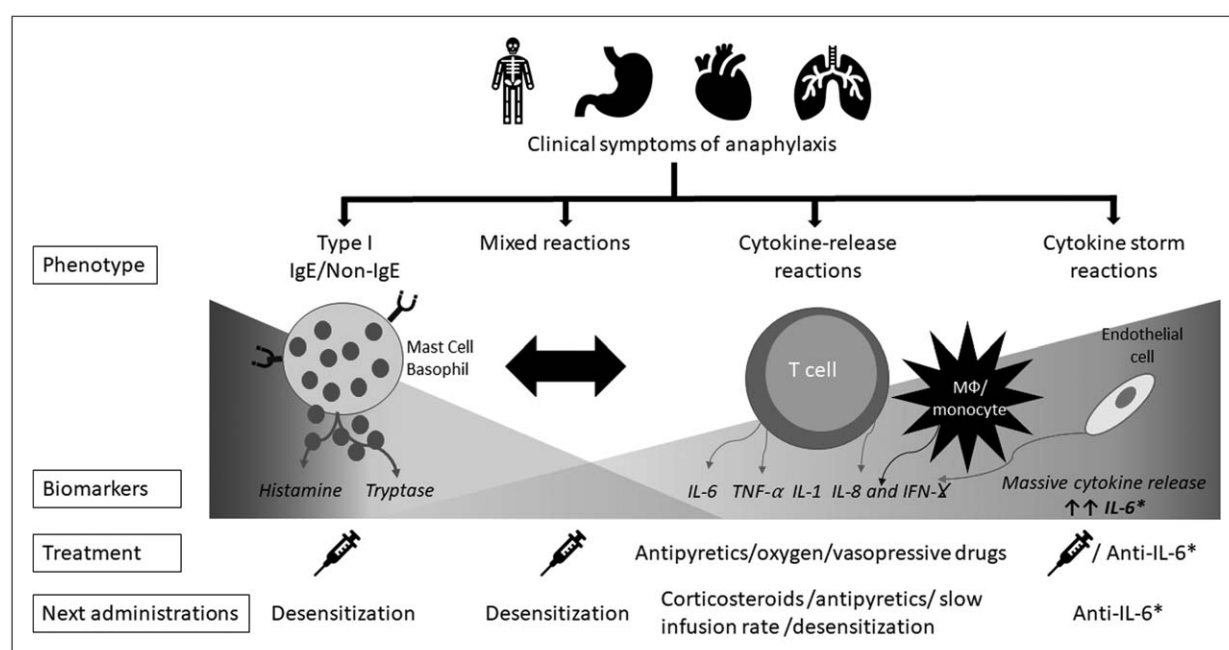


FIGURE 1. Overview of immediate adverse reactions to biological agents, phenotype, endotype and management. Adrenaline/epinephrine. MΦ, macrophages. *High concentrations of IL-6, consider using anti-IL-6 (tocilizumab).

measured at the time of the reaction indicates mast cell/basophil degranulation and suggests the possibility of an IgE reaction [115]. On the other hand, IgG-mediated reactions to biological agents have not been clearly demonstrated in humans. However, it is hypothesized that the biological agents could stimulate antiAb IgGs bound to Fc-gamma-receptors on macrophages, basophils, mast cell and neutrophils triggering the release of mediators, as shown in the mouse model of IgG-dependent anaphylaxis [116]. Symptoms of IgG-mediated reactions would be quite similar to IgE-mediated reactions as both involve mainly mast cell/basophil activation. Also, they should typically occur after at least one infusion as sensitization would also be required. Skin testing is typically negative in these cases, whereas in IgE-mediated reactions, skin tests or specific IgE may be positive.

CRRs may occur at first infusion, and can present with a variety of symptoms [117^{***}]. Mild symptoms constitute fever, chills, rash, arthralgia, myalgia, cough, tachypnea and headache. Severe cases include intense respiratory symptoms that can progress to acute respiratory distress, hypotension, high fever, vascular leakage, disseminated intravascular coagulation and multiorgan system failure. In such cases, common laboratory abnormalities are cytopenias, elevated liver enzymes, creatinine or coagulation disorders with high c-reactive protein. Main cell types involved in these reactions are macrophages/monocytes, T cells (mainly cytotoxic CD8⁺ lymphocytes) and endothelial cells.

Symptoms are caused by the release of proinflammatory mediators, such as IL-6, TNF- α , IFN- γ , IL-8 IL-10 and IL-1. The most serious CRRs is known as 'cytokine storm'. It is an acute, severe and potentially lethal reaction because of the release of large amounts of cytokines and chemokines, which will produce catastrophic systemic symptoms [117^{***},118].

It is important to distinguish CRRs from other inflammatory disorders that present with similar clinical signs and symptoms but require different treatment. Tumour lysis syndrome (TLS) can mimic CRRs with symptoms, such as fever, acute renal failure, cardiac arrhythmia and seizures. TLS presents characteristic laboratory abnormalities including hyperphosphatemia, hyperuricemia, hyperkalemia, and hypocalcaemia and may occur simultaneously to CRRs [119]. Also, serum sickness (Gell and Coombs type III) may present similar symptoms (pruritus, arthralgia/arthritis, lymphadenopathy, fever, alteration in renal function). This reaction is presumed to result from the deposition of immune complexes [120].

In some cases, simultaneous CRRs and IgE-mediated reactions occur, resulting in 'mixed reactions' [112^{***}].

MANAGEMENT OF ANAPHYLACTIC REACTIONS TO BIOLOGIC AGENTS

When facing an acute immediate reaction to biological agents, quick recognition of the most likely

mechanism of the reaction will be the base for further actions. In anaphylaxis, where the suspected mechanism is a type I reaction, rapid intramuscular epinephrine is the treatment of choice followed by standard therapy recommended in guidelines [113]. An increase of serum tryptase supports the diagnosis [114]. After the reaction (2–4 weeks), a positive skin test to a nonirritating concentration of the mAb strongly suggests an IgE-mediated mechanism and warrants re-exposure only through desensitization [7,121]. For non-IgE-mediated type I reactions, after initial treatment including epinephrine, the subsequent approach for future exposures should be based on the severity. Desensitization is recommended in severe cases. In mild–moderate reactions, a decision between a diagnostic challenge or a desensitization should be considered individually for each patient (risk stratification and necessity of the treatment) [114].

In immediate reactions suggesting a CRR, initial treatment consists of antipyretics for fever, vasopressors as epinephrine and intravenous fluids for hypotension, and supportive care with oxygen or mechanical ventilation for respiratory distress. High-dose corticosteroids have been used to decrease the toxicity in some cases, although in chimeric antigen receptor (CAR) T-cell therapy corticosteroids may reduce clinical effectiveness [117²²]. In nonsevere CRRs, premedication with paracetamol (acetaminophen), nonsteroidal anti-inflammatory agents and corticosteroids, together with a slow infusion rate, generally can prevent the reaction. In very mild CRRs, slow infusion alone may be sufficient [122]. In severe CRRs, such as cytokine storms, in which IL-6 is a central driver of the reaction, the use of tocilizumab (a recombinant humanized monoclonal antibody directed against the interleukin-6 receptor) has been approved for treatment, as in severe CAR T-cell-induced CRRs [123].

In cases of ‘mixed’ reactions, the patient has to be managed with a combined strategy for both reactions.

MONOCLONAL ANTIBODIES FOR THE TREATMENT OF ANAPHYLAXIS

mAbs have also been used out of label to treat or prevent anaphylactic reactions. Omalizumab has been used in anaphylaxis associated with allergen immunotherapy, difficult food allergy, idiopathic anaphylaxis and mast cell disorders. There is a moderate evidence, based on small clinical trials on its effects facilitating peanut oral immunotherapy and improving the safety of rush immunotherapy to ragweed and venom immunotherapy [124,125].

Omalizumab effectively prevented recurrent anaphylaxis in a cohort of 14 adults with systemic mastocytosis [126], but controlled studies are needed to corroborate this finding. There are no well designed trials of omalizumab for idiopathic anaphylaxis, but recent case reports suggest a beneficial effect in the treatment of complicated cases of recurrent anaphylaxis, such as ethylene oxide intra-operative anaphylaxis [127], progesterone-induced anaphylaxis [128] and in seminal plasma hypersensitivity [129], insulin hypersensitivity in patients with diabetes [130] or in a challenge confirmed exercise-induced anaphylaxis [131]. The mechanism by which omalizumab may prevent recurrent anaphylaxis is not fully understood but may be related to its effect on reducing IgE high-affinity receptor (FcεRI) expression on effector cells and by suppressing the basophil response to allergens [132]. Another approach has been the use of rituximab, a chimeric anti-CD20 monoclonal antibody that depletes circulating B cell, in a case of refractory idiopathic anaphylaxis [133].

CONCLUSION

Health-care professionals prescribing and administering biological agents will be facing numerous immediate adverse reactions, including anaphylaxis, in which they will have to make a quick management choice. Long-term management will require an accurate diagnosis and risk assessment on which future treatment decisions should be based. Further profiling such reactions and determining relevant biomarkers will help to establish the best approach in such cases.

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Conflicts of interest

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