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Anaphylaxis (M Sanchez-Borges, Section Editor)

Anaphylaxis Induced by Biologics

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Abstract

Purpose of review Biologic agents are increasingly utilized in the medical management of many conditions. Their safety has become an important topic as a myriad of reactions can occur due to the immune-modulating properties of these agents. Of these, anaphylaxis remains a substantial concern, but its incidence and pathophysiology have not been comprehensively reviewed.
Recent findings Over the past two decades, a multitude of case reports and series have been published describing anaphylactic reactions to biologic agents, although the true incidence and prevalence remains unknown for the vast majority of them. Based on cytokine and mediator profiles, three mechanisms have been proposed: IgE-mediated, non-IgE-mediated, and cytokine release.
Summary The clinical presentation of anaphylaxis is highly variable between biologic agents. The degree of humanization, excipient involvement, and development process of each biologic agent all likely play an important role in determining its level of allergenicity. As biologic agents become even more commonplace in healthcare, more thorough evaluations of the incidence of anaphylaxis induced by BAs as well as the underlying mechanisms may provide clinically useful data when determining the most appropriate management option.

Introduction

Since the 1990s, biologic therapies have become increasingly used in the medical management of a multitude of conditions, including chronic inflammatory diseases, autoimmune diseases, and

malignancies. Over 150 biologic agents (BAs) have been approved by the United States Food and Drug Administration (FDA) since the 1970s [1]. BAs are defined as large molecules which are structurally comparable to autologous proteins which promote their ability to modulate the immune system (Table 1). BAs are unique in that they are able to directly alter the immune system allowing them to modify the pathophysiology and change the clinical course of many diseases. The development of these agents has transformed the management of various inflammatory diseases including psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma, and atopic dermatitis.

The safety of BAs is of particular importance due to their increasing use in clinical practice. Multiple types of adverse reactions (AEs) have been well documented including cytokine release syndrome, infusion reactions, autoimmunity, secondary immunodeficiencies, and hypersensitivity reactions. The focus of this article will be on the current literature of anaphylactic reactions to some of the more notable BAs including discussing diagnostic strategies and management considerations.

Types of biologic agents

BAs can be categorized into three main subsets: monoclonal antibodies (mAbs), cytokines, and fusion proteins. Monoclonal antibodies have been developed against various soluble proteins such as cell surface molecules, cytokines, and tumor antigens. They were originally created as murine analogs but have been generally replaced by chimeric, humanized, and fully human antibodies to improve efficacy and decrease allergenicity. Cytokines, such as interferons and interleukins, have been designed as BAs by altering their natural structure to provide increased potency and durability. They have been FDA-approved for the management of multiple malignancies, infectious diseases, and immunodeficiencies. Fusion proteins are developed by fusing a soluble protein with the Fc portion of immunoglobulin (IgG1). The fused protein is a ligand or receptor that is specially selected to have a high affinity towards its target protein. Interaction between the Fc portion of the fusion protein and Fc-receptors on immunologic cells can lead to immune activation and mediator release.

Adverse events to biologic agents

AEs are not uncommon for both traditional drugs and BAs. BAs differ from traditional, chemically derived drugs in numerous ways including larger size, common need for parenteral administration, and similarity to natural compounds. These unique characteristics likely play an important role in their risk of AEs. Unlike typical drugs, as BAs have been developed to mimic and alter the immune system, it is not surprising that new types of AEs have been noted. These are often due to overstimulation or suppression of the immune system leading to conditions such as cytokine release syndrome, infusion reactions, immunodeficiency, and autoimmunity. A unique classification system for biologics was originally proposed by Pichler with revisions by Haussman et al. [2, 3]. While non-hypersensitivity reactions are more commonly seen, hypersensitivity remains an important concern due to its high rate of morbidity and mortality.

Table 1. Common biologic agents with their categorization, degree of humanization, proposed anaphylaxis mechanism, and special consideration

Biologic Agent	Target	Proposed Anaphylaxis Type	Special Considerations
Malignancy and Organ Transplant			
Muromumab	Murine mAb – CD3 receptor	IgE-mediated Non-IgE-mediated	Typically occurs after a break in therapy.
Cetuximab	Chimeric mAb – EGFR	IgE-mediated (Alpha-gal)	First-dose anaphylaxis in patients sensitized to galactose-α-1,3-galactose.
Antithymocyte Globulin	Polyclonal antibodies – Various T cell targets	IgE-mediated	Purified from rabbit, horse or goat sera. Cross reactivity between types is unknown.
Basiliximab	Chimeric mAb – IL-2Rα	IgE-mediated	First-dose anaphylaxis has been reported. In theory, anaphylaxis may occur in patients sensitized to galactose-α-1,3-galactose.
Bevacizumab	Humanized mAb – VEGF-A	No published cases	
Brentuximab	Chimeric mAb – CD30	IgE-mediated	Most commonly occurs during second infusion.
Catumaxomab	Hybrid mAb – EpCAM and CD3	No published cases	
Trastuzumab	Humanized mAb – HER2/neu	Non-IgE-mediated	Pretreatment and slower infusion rates have been effective on subsequent infusions.
TNF-Inhibitors			
Infliximab	Chimeric mAb – TNF-α	IgE-mediated (ADA, Alpha-gal) Non-IgE-mediated	Most frequently associated with anaphylaxis of all TNF-inhibitors. First-dose anaphylaxis in patient sensitized to galactose-α-1,3-galactose.
Etanercept	Fusion protein – TNF-αR	IgE-mediated Non-IgE-mediated	Lower incidence of anaphylaxis compared to infliximab.
Adalimumab	mAb – TNF-α	Unknown type	Significantly lower incidence of anaphylaxis compared to infliximab and etanercept.
Certolizumab	mAb – TNF-α	No published cases	
Golimumab	mAb – TNF-α	Unknown type	In theory, anaphylaxis may occur in patients sensitized to galactose-α-1,3-galactose.

Table 1. (Continued)

Biologic Agent	Target	Proposed Anaphylaxis Type	Special Considerations
Asthma and Allergic Disease			
Omalizumab	Humanized mAb – IgE	IgE-mediated (ADA, excipient [polysorbate]) Non-IgE-mediated	2-hour observation period with first 3 injections and 30 minute for subsequent injections. Epinephrine autoinjector prescription.
Mepolizumab	Humanized mAb – IL-5	No published cases	
Reslizumab	Humanized mAb – IL-5	Non-IgE-mediated	Close observation is recommended during and immediately after infusions.
Benralizumab	Humanized mAb – IL-5R	No published cases	
Dupilumab	Human mAb – IL-4Rα	No published cases	
B-cell Depletion and Inhibition			
Rituximab	Chimeric mAb – CD20	IgE-mediated Non-IgE-mediated	Infusion reactions during the first dose are very common; anaphylaxis remains rare.
Cardiovascular Disease			
Abciximab	Chimeric mAb – CD41	Unknown type	In theory, anaphylaxis may occur in patients sensitized to galactose-α-1,3-galactose. Anaphylaxis has been associated with severe thrombocytopenia.
Rheumatologic Disease			
Eculizumab	Humanized mAb – Complement C5	Unknown type	
Natalizumab	Humanized mAb – α4-integrin	Unknown type	
Ranibizumab	Humanized mAb – VEGF-A	No published cases	Likely comparable incidence of anaphylaxis with bevacizumab due to similarity in structure and degree of humanization.
Ustekinumab	Human mAb – IL-12 and IL-23	No published cases	In theory, anaphylaxis may occur in patients sensitized to galactose-α-1,3-galactose.
Tocilizumab	Humanized mAb – IL-6R	Unknown type	Exclusively seen in intravenous preparation. No reported cases with subcutaneous route.
Belimumab	Human mAb - BAFF	Unknown type	
Abatacept	Fusion protein – CTLA-4	Unknown type	

Table 1. (Continued)

Biologic Agent	Target	Proposed Anaphylaxis Type	Special Considerations
IL-1 Inhibition			
Anakinra	Receptor antagonist – IL-1R	IgE-mediated	Patients with anaphylaxis to anakinra have been shown to tolerate canakinumab.
Canakinumab	Human mAb – IL-1β	No published cases	
Cytokine agents			
IFN-α	N/A	Non-IgE-mediated	
IFN-β	N/A	IgE-mediated Non-IgE-mediated	Intradermal testing has been found to be useful for diagnosis.
IFN-γ	N/A	Unknown type	
Interleukin-2/Aldesleukin	N/A	No published cases	
CSF (filgrastim, lenograstim, molgramastin, pegfilgrastim, sargramostim)	N/A	Unknown type	Cross reactivity between agents is unknown.

Abbreviations: mAb – Monoclonal antibody; CD3 – Cluster of differentiation 3; EGFR – Epidermal growth factor receptor; IgE – Immunoglobulin E; VEGF – Vascular endothelial growth factor; TNF – Tumor necrosis factor; ADA – anti-drug antibody; BAFF – B-cell activating factor

Anaphylaxis to biologic agents

The development of a consensus definition for anaphylaxis has been greatly debated. In the majority of classification schemes, it is considered a systemic reaction with typically more than one organ system involvement [4]. Anaphylaxis involves mediator release from mast cells, basophils, and other immune cells, and it clinically manifests as a constellation of cutaneous, respiratory, gastrointestinal, neurologic, and cardiovascular symptoms.

The incidence, or prevalence, of anaphylaxis has been difficult to quantify due to the lack of consensus in its defining characteristics and geographic variability. Based on a recent US study, the prevalence in the adult population is 1.6% with 35% of those due to medications [5]. When looking at fatal anaphylaxis, drugs have been identified in the overwhelming majority of cases (58.8%) [6].

The traditional notion that anaphylactic reactions must involve IgE antibodies against the offending antigen has been challenged over the past several decades. This has become even more scrutinized with the improved understanding of BAs as increasing numbers of patients are presenting with symptoms consistent with anaphylaxis without IgE antibodies to the BA in question. Because of this, the proposed classification of AEs to biologics is a very helpful

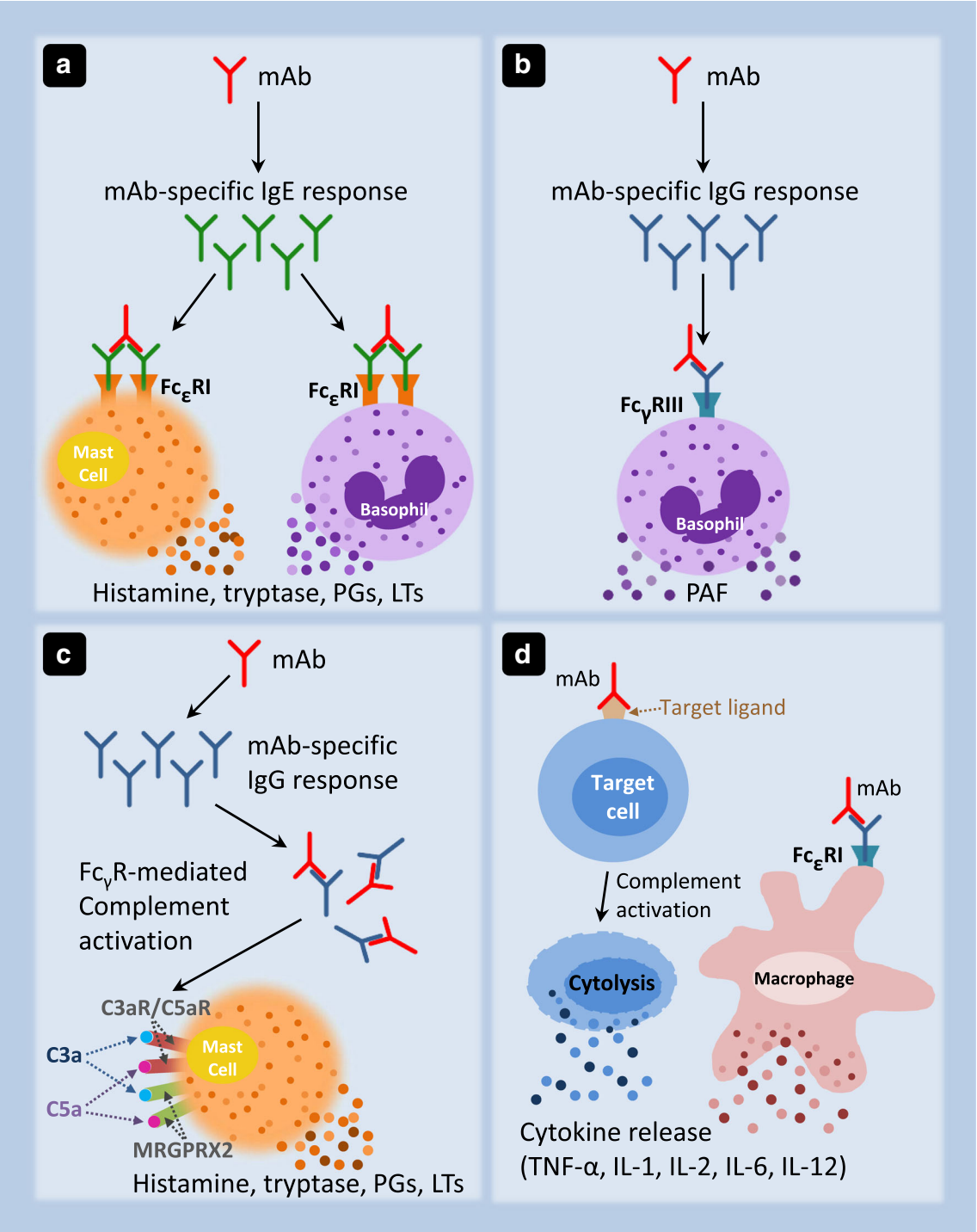

Fig. 1. Proposed mechanisms of anaphylaxis with the use of biologic agents including IgE-mediated (**a**), IgG-mediated (**b**), mast cell degranulation through complement receptor and MRGPRX2 receptor activation (**c**), and cytokine release syndrome (**d**). Adapted from Vultaggio and Castells [7].

tool in understanding the multiple mechanisms likely involved [2, 3]. Both type α (cytokine release syndrome) and type β (IgE-mediated and non-IgE-mediated hypersensitivity) reactions can present with symptoms that meet the criteria for anaphylaxis and will be discussed individually in this article (Table 1). As the mechanisms of non-IgE-mediated hypersensitivity reactions and cytokine release syndrome (CRS) are not clear, there is likely some degree of overlap when attempting to classify these life-threatening reactions (Fig. 1).

Understanding how to diagnose and manage these patients will become increasingly important as not only do anaphylactic reactions pose a significant risk to the patient in the near-term, but they are also a major reason for treatment discontinuation which can considerably affect a patient's clinical course in the long-term [8].

IgE-dependent anaphylaxis

IgE-mediated reactions are uncommon causes of AEs but have been noted to occur with the use of several BAs (Fig. 1). One of the earliest cases of IgE-mediated anaphylaxis in a BA was noted by Abramowicz and colleagues after anti-muromonab IgE was detected in a young patient that developed anaphylaxis after his second course of the medication [9]. Since then, both in vitro assays and skin prick testing used as a surrogate have been implemented to evaluate for the presence of IgE in patients with anaphylactic-like reactions. Omalizumab, cetuximab, infliximab, and rituximab have all been implicated as having an IgE-mediated pathway that may contribute to its allergenicity [10–14].

When evaluating for hypersensitivity reactions to BAs, the understanding of three main categories is essential: (1) degree of humanization; (2) excipients involved in its formulation; (3) cell line derivation.

Table 2. Excipients with allergenic potential in biologic agents. Updated from Corominas et al. [15]

Polysorbate	Mannitol	Albumin	Latex	Trometamol	Papain
Adalimumab	Adalimumab	Interferon β-1a (Avonex)	Adalimumab	Etanercept	Abciximab
Alemtuzumab	Basiliximab	Interferon β-1b (betaferon)	Anakinra		
Belimumab	Etanercept	Interferon α-2b (IntronA)	Etanercept		
Benralizumab	Interferon β-1a (rebif)				
Canakinumab	Interferon β-1b (betaferon)				
Dupilumab	Interferon γ-1b				
Infliximab	Lenograstim				
Mepolizumab	Palivizumab				
Natalizumab					
Omalizumab					
Tocilizumab					

Over time, the degree of humanization of mAbs has evolved with early mAbs having higher foreign antigen content. Accordingly, their immunogenicity has also decreased, although not completely. Studies have shown that even completely human mAbs can produce human anti-human antibody (HAHA) production due to the detection of non-self-sequences [2].

Moreover, additives may be a cause of hypersensitivity reactions seen with certain BAs (Table 2). Polysorbate, used in many pharmacologic products to promote solubilization, was implicated as a possible cause of omalizumab-related hypersensitivity in a case series of two patients, although this association has not been reproduced [16].

The vast majority of IgE-mediated reactions occur from repeated exposure to allow for sensitization, but noteworthy exceptions exist. First-dose anaphylaxis to cetuximab, an epidermal growth factor receptor inhibiting mAbs, was discovered to be considerably more common in the Southeastern US compared to the Northeast [11]. Investigating this geographic oddity, Chung et al. uncovered that IgE antibodies specific for galactose-α-1,3-galactose, an oligosaccharide found in mammalian meats and the Fab portion of the cetuximab heavy chain, were the principal cause. These moieties are formed from the glycosylation involved in SP2/0 murine cells which is a shared process in several BAs [15].

IgE-independent anaphylaxis

IgE-independent anaphylaxis, also referred to as anaphylactoid reactions, are clinically indistinguishable from IgE-mediated anaphylaxis. For years, the underlying physiology of these types of reactions was unknown; however, recent advances have proposed two possible pathways (Fig. 1).

First, murine models have demonstrated that antigen-specific IgG can lead to macrophage and basophil activation through the FcγRIII [17]. This causes substantial platelet-activing factor (PAF) release and the development of shock. Interestingly, PAF levels have been shown to directly correlate with the severity of human anaphylaxis [18]. Differing from IgE-mediated reactions, large quantities of antigen are needed to provoke an IgG-mediated anaphylactic reaction in mice which does occur with mAb infusions. While this pathway's importance in human non-IgE-mediated anaphylaxis is unclear, there is some data, though very limited, that infliximab-specific IgG antibodies are present in some patients with anaphylaxis during infliximab infusions [19, 20]. In addition, infliximab-specific IgM antibodies have also been seen in these patients, but its significance remains unknown.

Second, complement activation can trigger mediator release from mast cells, basophils, and phagocytic cells through their complement receptors. Furthermore, MRGPRX2 is a recently discovered mast cell receptor which can be activated by C3a and C5a (key complement cleavage products) as well as breakdown products from several drugs [3, 21–23]. MRGPRX2 has been implicated as a possible contributor in cases of first-exposure drug-induced anaphylaxis with antimicrobials (e.g., vancomycin, ciprofloxacin) and neuromuscular blocking agents [22]. Whether BAs can also activate MRGPRX2 is unclear.

Cytokine release syndrome

The term cytokine release syndrome (CRS) was first described in patients given murine anti-CD3 mAb (muromonab) for the management of transplant

rejection [24, 25]. While the mechanism is not entirely clear, CRS is thought to be an exaggerated systemic immune response to BAs with the potential release of over 150 inflammatory mediators through the activation of multiple cell types, including monocytes/macrophages, T cells, and B cells [26]. Symptom onset is normally within 1–2 h after infusion and is most commonly seen during the first dose; although a smaller, yet significant, risk does persist on subsequent doses [27]. Patients often experience fatigue, headache, pruritus, dyspnea, sensation of throat swelling, flushing, fever, tachycardia, hypotension, arthralgias, nausea, vomiting, diarrhea, and altered mental status [28].

CRS can be difficult to distinguish from hypersensitivity reactions as they share many clinical features. However, the management of CRS compared with hypersensitivity reactions is drastically different, so all attempts should be made to identify the type of reaction before proceeding. Patients with CRS can be treated by temporary cessation of the biologic infusion and restarting at a slower rate [29, 30]. In addition, pretreatment with antihistamines, montelukast, systemic steroids, acetaminophen, and adequate hydration are often used to reduce the risk during subsequent infusions although randomized trials have not been performed to support this practice [28]. This would not be a reasonable option for patients with hypersensitivity reactions, specifically IgE-mediated, as the risk of subsequent anaphylaxis is high and premedication regimens are not typically helpful. Lastly, some authors have recommended rapid drug desensitization for CRS reactions though whether these approaches truly induce some type of tolerance is not clear [31].

Notable biologic agents

Malignancy, organ transplant, and rheumatologic conditions

Muromonab

Muromonab was the first completely murine mAb approved in the USA by the FDA for the management of acute rejection in organ transplant patients [32]. The most common forms of AEs reported with muromonab are caused by cytokine release including fever, chills, headache, and pulmonary edema [33]. However, multiple reports of IgE-mediated anaphylaxis have also been noted which typically have occurred on subsequent administrations after a break in therapy [9, 34–36]. Two reports have been published of first-dose anaphylaxis to muromonab with at least one being a non-IgE-mediated process [37, 38]. Unfortunately, underlying mechanisms were not further investigated in either case.

Cetuximab

The chimeric mouse-human monoclonal antibody, cetuximab, is directed against epidermal growth factor receptor (EGFR) and is FDA-approved in the treatment of metastatic colon cancer and squamous cell cancer of the head and neck. The risk of anaphylaxis with cetuximab varies considerably with geography as studies have shown rates of grade 3/4 infusion reactions (consistent with anaphylaxis) to be approximately 1% in Europe but as high as 22% in the Southeastern US [29, 39–41]. Chung et al. investigated this phenomenon by detecting IgE antibody against galactose-α-1,3-galactose (alpha-gal) in 17 of 25 patients that had hypersensitivity reactions on their first infusion of cetuximab [11].

Alpha-gal is an oligosaccharide epitope found in the major blood groups of non-primate mammals [42]. IgE against alpha-gal can develop in humans after a bite by a lone star tick, *Amblyomma americanum*, which has a high prevalence in the Southeastern US [43]. Although the exact mechanism of sensitization is not known, patients with alpha-gal IgE may subsequently develop delayed anaphylaxis with ingestion of mammalian meats such as beef, lamb, and pork.

Alpha-gal was also found to be present in the Fc and Fab domains of cetuximab. van Bueren et al. demonstrated the high avidity of IgE for the bi-alpha-galactosylated biantennary complex glycans present on the Fab domain which allows for IgE cross-linking and mast cell activation [44]. The high alpha-gal content of cetuximab was determined to be the most likely explanation of the high frequency of anaphylaxis noted in patients with preformed anti-drug IgE [11]. Additionally, cetuximab is glycosylated with alpha-gal in the mouse-derived SP2/0 cell line which is also used for abciximab, basiliximab, canakinumab, infliximab, golimumab, and ustekinumab [44, 45]. Based on a common derivation, risk for anaphylaxis to any of these BAs may be elevated in patients with known alpha-gal IgE, although this association has only been reported with infliximab [42].

Prospective studies have also looked at identifying patients with alpha-gal IgE prior to starting cetuximab to reduce the risk of severe infusion reactions [46, 47]. Based on negative predictive values ranging from 99 to 100%, experts have proposed the routine use of in vitro assays for alpha-gal IgE in areas of high alpha-gal sensitization prevalence before initiating cetuximab therapy [11, 46].

TNF-inhibitors

Infliximab

Infliximab is a chimeric mouse-human monoclonal antibody against TNF-α which is frequently used in inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Acute infusion reactions are relatively common with up to 27% of patients developing them during their treatment course [48]. The exact incidence of anaphylaxis is not known, but both IgE-mediated and non-IgE-mediated anaphylaxis have been reported [19]. The presence of anti-drug antibodies (ADAs), including non-isotype-specific, IgG, IgM, and IgE, have been associated with hypersensitivity reactions with infliximab and could be used to predict the risk of reaction [49, 50]. Additionally, patients with IgE ADAs and/or skin test positivity typically have earlier (within the 3rd dose) and more severe reactions [19, 49]. Correlation between skin testing and serological IgE positivity has been established with the proposed use of both assessments in predicting the risk of severe reactions [51].

In the largest study to date, Puxeddu et al. reported 21 anaphylactic episodes in 225 patients using infliximab [52]. Of these, 8 had skin testing performed with 5 being positive which may indicate that both IgE- and non-IgE-mediated processes are at play.

As previously indicated, first-dose anaphylaxis has been documented due to the presence of IgE antibodies against galactose-α-1,3-galactose [42]. The alpha-gal content of infliximab is 4.6 times less than that of cetuximab, and its relatively protected location on the BA likely explain its rarity in causing anaphylaxis compared with that seen with cetuximab [44]. Careful

consideration should be taken when starting infliximab in patients with known mammalian meat allergy, and alternative medications should be considered.

Etanercept

Etanercept is a recombinant DNA fusion protein that inhibits the TNF-α receptor which is approved for the use in several autoimmune conditions. Fusion proteins in general do not produce as robust of an immune response compared with mAbs which may in part explain the lower reported rate of anaphylaxis with etanercept compared with infliximab. Fewer studies have been conducted on defining the underlying pathophysiology of anaphylactic reactions with etanercept. Puxeddu et al. reported 2 episodes of anaphylaxis in the 245 patients that received etanercept at their institution between 2000 and 2009 [52]. Other reports of anaphylaxis have also been published but mainly as case reports [53, 54].

Skin testing has been used for evaluating hypersensitivity reactions with data supporting both IgE- and non-IgE-mediated reactions [52]. Its use in the management of etanercept-induced anaphylaxis has not been adequately investigated.

Adalimumab/certolizumab/golimumab

Rare reports of anaphylactic reactions to adalimumab exist, although the frequency appears to be significantly lower than that of infliximab and etanercept [55, 56]. Skin testing has been used in cases of hypersensitivity but its reliability remains unknown [52]. Isabwe reported on a patient who was desensitized for a severe reaction to golimumab but the exact nature of the reaction was not indicated [31]. We are not aware of any reports of anaphylaxis with the use of certolizumab.

Asthma and allergic diseases

Omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody used in both allergic asthma and chronic idiopathic urticaria (also known at chronic spontaneous urticaria). As the first BA approved for asthma in 2003, the cumulative exposure to patients far outnumbers that of other BAs. Postmarketing studies have demonstrated that approximately 70% of the cases occurred during the first three doses [57–59]. In addition, approximately 63% of anaphylactic reactions took place within 60 min of administration of the medication with rare cases of delayed onset at over 24 h after administration being reported. Over 90% of anaphylactic reactions included respiratory compromise but no deaths have been reported.

Due to this unique presentation with delayed or protracted onset of symptoms, the Omalizumab Joint Task Force was formed between the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Executive Committees to examine the clinical trials and postmarketing data on omalizumab-associated anaphylaxis. In their 2007 report, based on a calculated anaphylaxis rate of 0.09% (35 of 39,510 patients) and timing of these events, it was recommended that patients be observed for 2 h during their first three injections and 30 min for each

subsequent injection [10]. A follow-up report in 2011 found that approximately 77% of anaphylactic reactions fell within the recommended waiting periods [60]. Additional measures such as informed consent, anaphylaxis education, epinephrine autoinjector prescription and education, and preinjection health assessment were also recommended.

The underlying mechanism of anaphylaxis with omalizumab is unknown with likely multiple pathways contributing. As it does possess 5% polypeptides from a murine source, it is very possible that IgE antibodies against these sequences are a factor [61]. Omalizumab is the only biologic for which non-irritating concentrations for drug skin testing have been systematically determined [62]. However, due to the lack of published data, the usefulness of skin testing with calculated positive and negative predictive values has not been established.

When evaluating the risk of hypersensitivity in patients beginning omalizumab therapy, certain populations, specifically those with a prior history of anaphylaxis not associated with omalizumab, may be at particular risk with an anaphylaxis rate as high as 0.62% of patients [59, 63]. In addition, 2 cases have been described of IgE-mediated anaphylaxis due to an excipient (polysorbate) found in the formulation of omalizumab, although this has not been reported elsewhere [16].

Mepolizumab/reslizumab

Both mepolizumab and reslizumab are humanized monoclonal antibodies against IL-5 which play a role in eosinophilic recruitment, and they are FDA-approved for use in severe eosinophilic asthma. The majority of the AEs that have been reported with mepolizumab and reslizumab are local injection site reactions, headache, back pain, pruritus, and worsening of asthma [64, 65]. The prescribing information for mepolizumab reports the risk of hypersensitivity reactions with its use. While no reports of anaphylaxis have been published in its phase III trials, anaphylaxis has been reported in postmarketing data [64, 66]. Two cases of reslizumab-associated anaphylaxis were reported in their phase III trials, and ADA testing was negative [65, 67, 68]. These patients were removed from the study, but no additional details are available.

Benralizumab

Benralizumab is a recently FDA-approved humanized monoclonal antibody against the IL-5 receptor α chain for the management of severe eosinophilic asthma. Hypersensitivity has been rarely reported in approximately 1–2% of patients, and no cases of anaphylaxis have been published [69–71]. It does not appear that ADAs have been associated with hypersensitivity reactions, although limited data is available.

Dupilumab

FDA-approved for both atopic dermatitis and severe eosinophilic and/or steroid-dependent asthma, dupilumab is a fully human monoclonal antibody against the IL-4Rα. As only human-derived sequences are used, the theoretical risk for IgE-dependent hypersensitivity reactions should

be lower, although not absent. HAHAs could theoretically develop with the use of dupilumab; however, anaphylactic reactions have not been reported to date [72–74].

B cell depletion and inhibition

Rituximab

Rituximab is a chimeric mAb that is used in the treatment of B cell lymphomas and many rheumatologic diseases. It targets the surface molecule, CD20, which is expressed on B cell precursors and mature B cells. Infusion reactions are common with the vast majority occurring during the first infusion [75]. Anaphylactic reactions are rare but the presence of positive skin testing and the detection of IgE ADA has occurred in select cases [13, 51]. Basophil activation testing has also been shown to provide useful information in determining risk of hypersensitivity reactions [76].

Cytokine therapy

Reports of anaphylactic-like reactions have occurred with interferons (IFN), interleukins, and colony-stimulating factors (CSF) (Table 1). These reactions are not nearly as well studied as with mAbs, and the underlying mechanisms are not well understood with both IgE and non-IgE pathways likely playing a role.

Several cases of anaphylaxis have been published with the use of IFN-α, including one death [77–79]. Skin testing in all of these cases was either not performed or negative, and no IgE ADAs have been discovered in these patients. IFN-β, on the other hand, has had 2 reported cases of intradermal skin test–positive anaphylactic reactions [80–82].

IgE-mediated hypersensitivity reactions have been reported with interleukin therapy, although no reports of anaphylaxis have been published [83]. Both granulocyte-CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) have been implicated in anaphylactic reactions. Cases have been reported with filgrastim, lenograstim, sargramostim, and pegfilgrastim [84–89]. The underlying pathways of anaphylaxis have not been well established in these cases due to the rarity of these reactions. Further investigation is needed to better characterize these hypersensitivities.

Conclusion

Biologic agents will continue to remain an increasingly significant part of medical practice. Their safety profile varies significantly from traditional drugs due to their inherent immune-mediating effects. While not the most frequently seen AE, anaphylaxis remains significant as it remains a major reason why medication is stopped, affecting long-term care. IgE, non-IgE, and cytokine release have all been proposed as possible mechanisms of anaphylaxis, and further research is needed to better appreciate each process. In addition, it will be very important to obtain a more comprehensive understanding of the role of various factors such as the degree of humanization, excipient involvement, and how the BA was developed, in determining its allergenicity.

Compliance with Ethical Standards

Conflict of Interest

Dr. Khan reports other from Genentech, other from Aimmune, outside the submitted work. Shyam R. Joshi declares 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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- • Of importance
- •• Of major importance

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