

Hypersensitivity Reactions to Biologic Agents



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KEYWORDS

- Antidrug antibodies • Biologic agents • Drug allergy • Hypersensitivity reactions
- Immunogenicity

KEY POINTS

- Biologic agents (BAs) are important therapeutic tools, but their use may be limited by adverse drug reactions.
- Procedures for management of BA-induced reactions, including preventive, diagnostic work-up and desensitization, are becoming available in the clinical setting.
- The knowledge of such procedures for management of BA-induced reactions may be useful to increase the safety profile of current and forthcoming BAs.

INTRODUCTION

Many BAs have become available as new therapeutic tools, including monoclonal antibody (mAb), cytokines, and fusion proteins. Since their approval, BA therapy had a positive impact on the long-term outcomes, such as disability and mortality, associated with both inflammatory chronic diseases and cancers; thus, in a short period of time, they have entered the mainstream of their treatment.^{1,2} There is a large amount of research and development being undertaken to create BAs for many serious diseases, such as rheumatoid arthritis, multiple sclerosis, bowel inflammatory diseases, and different types of cancers.³ These medications each have their unique profile in terms of efficacy, tolerability, and adverse effects; they are not deprived in toxicity, which can impair quality of life and may occasionally be life-threatening or, more frequently, lead to the interruption of treatment.⁴

DEFINITIONS

Generally, adverse events (AEs) are defined as any untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related,

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whereas any AE caused by an injected drug is defined as an infusion reaction. The term, *allergic hypersensitivity reactions (HRs)*, refers to antibody- or cellular-mediated infusion reactions. Infusion reactions may be divided into local and systemic reactions.⁵ Local infusion reactions, which are induced by subcutaneous BAs, are referred to as injection site reactions (ISRs). Lastly, acute infusion reactions occur during or within 1 hour after infusion or within a few minutes after subcutaneous injection, whereas delayed reactions occur from 1 hour to 14 days after.^{6,7}

CLINICAL PRESENTATION: SYMPTOMS AND MANAGEMENT

The clinical manifestations of both acute and delayed reactions vary considerably, ranging from mild to severe and life threatening; thus, important clinical consequences, such as drop-out therapy or fatal cases, may occur.

Acute Infusion Reactions

Acute reactions include mainly cutaneous symptoms, such as itching, urticaria, and flushing, but sometimes anaphylaxis may occur characterized by respiratory distress, laryngeal edema, and bronchospasm, accompanied by gastrointestinal and cardiovascular involvement. In some cases, patients may display fever, skills, or myalgia.⁷ The severity of the reaction should be determined to better define the clinical management of such infusion. Mild to moderate events may be managed by reducing the infusion rate (after a temporary interruption) and administering H₁ antihistamines and corticosteroids for symptom control. In cases of severe reactions, the infusion must be stopped and rescue treatment promptly administered, such as epinephrine, liquids, oxygen supply, H₁ antihistamines, and high doses of intravenous steroids, according to the clinical features of the reaction.⁸

Acute infusion reactions may occur at the first dose or during the course of treatment, thus suggesting different underlying pathogenic mechanisms. Matucci and colleagues⁹ have recently analyzed the clinical characteristics of infliximab-induced immediate infusion reactions: severe events were 1 in 3 reactions; a majority of reactions occurred within 15 minutes after the beginning of the infusion; and cutaneous and respiratory symptoms were the most frequent clinical features.

Delayed Infusion Reactions

Delayed reactions usually occur within the first 2 weeks after the administration of a BA. They usually present with arthralgia, myalgia, exanthems, fever, urticaria, and itching.¹⁰ The clinical presentation of delayed reactions may be consistent with a classic serum sickness characterized by the production of antibody to foreign immunoglobulin with formation of antigen-antibody complexes. Patchy lung infiltrates and skin necrotizing vasculitis may be present, sustained by inflammatory infiltrates involving small blood vessels and complement deposition at immunofluorescence staining. In addition, there can be lymphadenopathy, splenomegaly, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and melena), and extremity weakness.¹¹ It has been reported that approximately 2.5% of patients receiving infliximab infusion develop serum sickness-like reactions,¹² but other chimeric molecules used to treat various conditions, such as abciximab for acute coronary syndromes, trastuzumab for breast cancer, rituximab for lymphoma, omalizumab for asthma, and natalizumab for multiple sclerosis, have been associated to these reactions.^{12–15} Some delayed reactions associated with mAb infusions may be characterized by a prevalent hematologic involvement, such as hemolytic anemia and immune thrombocytopenia.^{16,17} The course of delayed reactions is usually self-limiting, but severe acute respiratory

distress syndrome and fatal outcomes have been observed.¹⁸ Patients displaying serum sickness disease must be treated with steroids and for those most severely affected, plasma exchange may be used; serum sickness is a well-recognized indication of this therapeutic modality. On the other hand, premedication plays no established and secure role in exanthems or serum sickness and is often without effect.

Systemic Skin Reactions

During therapy with BAs, such as rituximab and anti-TNF- α agonists, disseminated skin reactions have been reported, including exanthems (maculopapular, eczematous, lichenoid, and granulomatous) and erythema multiforme.¹⁹ A lymphocyte infiltration at the dermoepidermal junction has been reported in the case of infliximab-related generalized erythematous-squamous exanthema in patients treated for rheumatoid arthritis with infliximab, occurring 2 to 4 weeks after the treatment was introduced.²⁰ In cases of these dermatoses, clinicians may discontinue infliximab or try to continue it in conjunction with corticosteroid application or switch to a different TNF- α antagonist. Some severe systemic events, such as Stevens-Johnson syndrome after rituximab and a case of toxic epidermal necrolysis (TEN) associated with cetuximab, have been described.^{21,22} Among disseminated skin reactions related to the use of BAs, the development of psoriasiform eruption during TNF- α antagonists can be included.²³ In addition, acneiform exanthems and folliculitides during treatment with antagonists of epidermal growth factor receptor, such as cetuximab, or tyrosine kinase inhibitors, such as erlotinib, may be present.²⁴

Injection Site Reactions

Regarding subcutaneously administered BAs, even if they can also induce systemic reactions, the most common adverse events are represented by ISRs, characterized by erythema, swelling, itching, or infiltrated plaques.¹⁰ ISRs may occur within a few minutes (immediate reactions) or later (delayed reactions). Patients treated with subcutaneous TNF- α blockers, such as etanercept and adalimumab, may develop ISRs around the sites of injection, mainly reported in the first 2 months of inception of therapy, usually occurring 1 to 2 days after the last injection, and resolving within a few days. It has been observed that some patients treated with anti-TNF blockers develop recall ISRs that are reactions at sites where the BA was previously injected after the last injection.²⁵ ISRs are usually mild and disappear when the treatment is continued, uncommonly leading to the drug interruption. The use of local corticosteroids is usually sufficient in the management of ISRs along with a follow-up of the lesions to assess their severity and the compliance of patients to the treatment.

PATHOGENIC MECHANISMS OF ACUTE REACTIONS

Regarding the pathogenesis of immediate systemic HRs, they are a complex picture, not fully clarified. Non-antibody- and antibody-mediated reactions can, however, be distinguished.²⁶

Among non-antibody-mediated reactions, complement-mediated events can be presumed but not clearly demonstrated as yet, whereas cytokine release syndrome (CRS) is identified as the most defined type, usually occurring at first dose of treatment. Antibody-mediated adverse reactions (HRs) usually occur during an ongoing treatment and are unpredictable despite preventive measures, and both IgE and non IgE antibodies can be involved.²⁶

The CRS is sustained by a massive release of cytokine from different immune cells (monocytes, macrophages, cytotoxic T cells, and NK cells). Both *in vivo* and *in vitro*

studies indicate that TNF- α , interferon- γ , and interleukin 6 are the main actors of CRS.²⁷ The postulated mechanism is related to the interaction of the mAb with the Fc γ receptors of immune cells, leading to their activation and/or lysis and subsequent cytokine release.²⁸ CRS can be clinically heterogeneous, ranging from a flulike syndrome to a multiorgan failure due to a cytokine storm, but sometimes these reactions raise concern for immediate hypersensitivity, being clinically indistinguishable from an anaphylaxis. Some clinical manifestations of CRS and hypersensitivity may overlap, such as rash, fever, hypotension, dyspnea, and tachycardia.

In contrast to delayed systemic infusion reactions or ISRs, for which the role of antibody formation is still unclear, acute systemic reactions to biologicals are deeply related to the development of antidrug antibodies (ADAs). The authors' findings, obtained in infliximab-treated patients, indicate that the development of ADAs is definitely correlated with clinical outcome, in terms of infusion reactions.⁹ The authors' data confirm results previously published on a Crohn diseases patient treated with infliximab.²⁹ Patients who develop antibodies to biologicals are more likely to show immediate infusion-related reactions. Concerning antibody-dependent mechanisms, even if ADAs mainly are of IgG class, in particular IgG1 subclass, different ADA isotypes may be involved: IgE and non-IgE (Fig. 1). It is important to underline that IgE- and IgG-mediated reactions may be clinically indistinguishable. Svenson and co-workers³⁰ have clearly shown that IgG toward infliximab correlates with immediate infusion reactions. In mice models, the role of allergen-specific IgG in induction of anaphylaxis has been shown, whereas their role in humans is controversial. In the authors' opinion, adverse effects of biologicals may be an interesting model to confirm the role of this alternative pathway of anaphylaxis in humans. In mice, the IgG pathway of anaphylaxis requires a high amount of antigen and of IgG antibody; thus, human anaphylaxis induced by therapeutic mABs, after repeated infusion of high amount of the protein, may be the most likely candidates for human IgG-mediated anaphylaxis.³¹ IgG ADAs can directly activate circulating basophils, through the binding of Fc γ receptors, and indirectly they can activate tissue mast cells through activation of the complement cascade and release of anaphylatoxins.

An IgE-mediated mechanism has been described for several BAs in reactive patients, through the use of skin testing, in vitro assay for the detection of IgE, or both.^{32–35} Vultaggio and colleagues³⁶ first identified the presence of serum infliximab-specific IgE in some reactive patients. To date, among 30 reactive patients, they have identified 23 subjects as ADA positive, and 6 of them had a positive result in a *carotid artery plaque* (CAP) analysis for infliximab-specific IgE.⁹ In addition, IgE-mediated reactions seem more severe than non-IgE-mediated events. The same investigators have been able to detect circulating rituximab-specific IgE antibodies in an autoimmune patient treated with rituximab who experienced 2 infusion-related reactions.³⁷ By using a non-isotype-specific assay for the screening, they found rituximab-specific ADA, and by using an ImmunoCAP platform (ThermoFisher, Uppsala, Sweden), they defined the presence of IgE ADAs, closely time-related to the reactions. These findings confirmed data obtained in vivo (positive results of skin testing) in rituximab-reactive patients obtained by Brennan and coworkers.³⁸ In addition, these results confirm that a specific BA may trigger infusion reaction via different mechanisms according to the patient and the situation. A majority of acute infusion reactions to rituximab occur during the first exposure and are usually induced by CRS.

The development of ADAs usually results from repeated exposure to BAs and is associated with reactions occurring after initial doses. In particular, immunogenicity-related infusion reactions for infliximab occur within the first 10 infusions and IgE-mediated events occur early on, within the first 5 administrations.^{9,39,40} In addition,

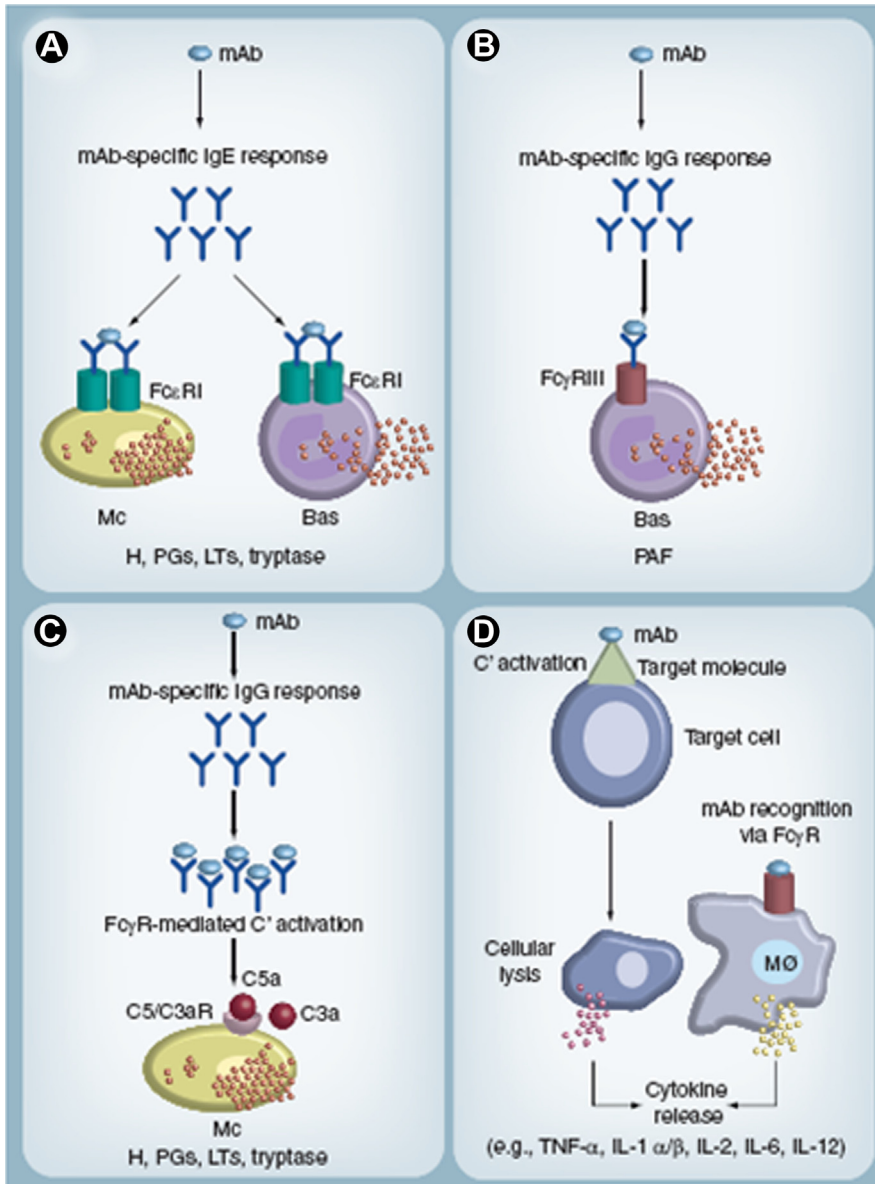


Fig. 1. Antibody (IgE and non-IgE) and non-antibody-mediated mechanisms of reactions to BAs. (A) Cross-linking of FcεRI induced by specific IgE antibodies on mast cells and basophils. (B) Activation of basophils through FcγRIII by IgG antibodies. (C) Complement activation by drug-antibodies immunocomplexes and subsequent activation of mast cells by anaphylotoxins. (D) mAb-induced cytokine release. H, histamine; LTs, leukotrienes; Mc, mast cells; PAF, platelet activation factor; PGs, prostaglandins. (From Maggi E, Vultaggio A, Matucci A. Acute infusion reactions induced by monoclonal antibody therapy. *Expert Rev Clin Immunol* 2011;7:57; with permission.)

a majority of IgE-related events occur at re-exposure after a period of interruption of the treatment, that is, a moment of risk for the development of ADAs and then of the reaction.⁹

Sometimes IgE-mediated reactions may occur as a first-dose event, as in the case of cetuximab-induced reactions, sustained by preexisting cross-reacting IgE against “foreign” glycan structures that are present on the therapeutic antibody.⁴¹ Some investigators identified the additive present in the drug formulation as the culprit factor of IgE-mediated reactions in biologicals-exposed patients. This event has been described for polysorbate in omalizumab-, erythropoietin- and darbepoetin-treated patients.^{42,43} Sensitization may be derived from previous contact with the same excipients used in the formulation of vaccines and/or cosmetics.

PATHOGENIC MECHANISMS OF DELAYED REACTIONS

Systemic

Serum sickness-like reactions seem to be associated with the presence of ADAs, related to the formation of complement-binding immune complexes (type III HR). Immune complexes deposition lead to complement cascade activation; reduction of serum concentration of C3, C4, and total complement; and subsequent inflammatory infiltration around small vessels. Immunofluorescence of skin specimens shows the presence of complement deposition around vessels.¹¹

The pathomechanism of delayed disseminated skin reactions has not been well studied; most probably, it constitutes an AE sustained by cellular-specific mechanisms as suggested by results obtained in an analysis of 2 infliximab-induced maculopapular exanthemas.⁴⁴ A maculopapular exanthem due to abciximab with a positive intracutaneous test after 48 hours has been published,⁴⁵ which might also correspond to a cellular-mediated mechanism. Some AEs may result, however, from the inherent effects on the immune system as a direct molecular target-dependent event. This is the case of cutaneous AE induced by epidermal growth factor receptor (EGFR) antagonists or of exacerbation of psoriasis²¹ during TNF- α antagonist.

Local

Histologic examination of biopsy specimens obtained from ISRs show an inflammatory infiltrate composed of predominantly lymphoid cells and some eosinophils in a perivascular cuffing pattern without signs of vasculitis.^{46,47} Few and controversial data regarding a further characterization have been reported in literature; in some cases, the infiltrating cells are predominantly DR⁺CD3⁺CD4⁻CD8⁺ cells, and in others, T cells bearing a CD4⁺ phenotype are mostly composed of the inflammatory infiltrate. In addition, epidermal keratinocytes show strong expression of HLA-DR antigen. So ISRs may be an example of T-lymphocytes-mediated delayed-type HRs. Waning of reaction overtime is frequently observed, thus suggesting eventual induction of tolerance.

VALUE OF SKIN TESTING FOR ACUTE REACTIONS

Skin tests are usually done and are of great importance in the diagnosis of drug allergy because they potentially reproduce IgE-mediated reactions or T-cell-mediated events. In vivo tests, however, are not currently standardized and approved for BAs; in this field of drug allergy, up to now, exact diagnostic tools to identify potentially reactive patients have not been defined.

Even if data in literature about skin testing for BAs are limited, during the last few years positive skin testing has been reported in patients with immediate HR caused

by BAs,^{32–34,38} such as rituximab, anti-TNF agents, and trastuzumab. More importantly, few studies involving small case series reported results of skin testing confirmed by in vitro tests, such as RAST or ImmunoCAP.^{35,36} Regarding in vivo tests for BAs, there is insufficient evidence to recommend appropriate drug concentration as well as the timing to perform it. Some data on nonirritant concentrations for anti-TNF agents and other BAs are reported in literature (Table 1).

The utility of skin testing in 23 patients who have experienced infliximab-related reactions has been recently evaluated.⁹ The investigators showed that it was essential to perform intradermal test in immediately reactive patients, because the prick test is usually negative. Seven of them (30.4%) had a positive result at an immediate-reading intradermal test and 6 of them displayed ImmunoCAP, positivity thus showing a great correlation between serologic IgE positivity and in vivo results. Considering that immediate intradermal tests for BAs had a specificity of approximately 100% in that small case series, they seem to be a useful method for the diagnosis of immediate type I HRs to BAs; however, they show a sensitivity of 30%, similar to the performance characteristics of in vitro IgE detection for BAs. The overall lack of sensitivity of IgE assay (in vivo and in vitro) could be explained by non-IgE-mediated hypersensitivity to BAs, as discussed previously.

It is an obvious factor that for skin testing the time between the reaction and the evaluation (Fig. 2) is a crucial point, due to temporary unresponsiveness of the skin mast cells after massive activation during the reaction. In addition, IgE specific for BAs displays a rapid decrease over time and, accordingly, Matucci and co-workers⁹ reported that none of the patients had positivity when studied 8 months after the first analysis, suggesting that the allergological work-up of reactive patients should be performed early. The authors, however, do not have any negativization rate of skin testing for BAs. Concerning safety, there were also no unexpected adverse reactions to the in vivo procedures with BAs in patients experiencing severe reactions.

Easy clinical application, their safety, and high specificity may offer a new tool for the diagnosis of at least IgE-mediated HR. There is an urgent need, however, to establish, standardize, and share practical procedures in this field of drug allergy. These procedures could be used to design multicenter studies aimed at defining the diagnostic accuracy of skin testing for BAs in a prospective manner, which are lacking.

Table 1
Concentrations and dilutions for mAb skin testing

Biologic Agent	Concentration (mg/mL)	Dilutions	
		Prick Test	IDT (0.02 mL)
Infliximab ^{9,36,38}	10	1:100–1:1	1:1000–1:10
Adalimumab ^{48,68}	50	1:100–1:1	1:1000–1:10
Etanercept ^{34,48}	25	1:100–1:1	1:1000–1:10
Rituximab ^{37,38}	10	1:100–1:1	1:1000–1:10
Cetuximab ⁷³	5	1:100–1:1	1:1000–1:10
Trastuzumab ³⁸	21	1:100–1:1	1:1000–1:10
Natalizumab ³⁵	20	1:100–1:1	1:1000–1:10

Maxima and minima dilutions are reported for each BA based on literature data. For delayed reactions, reading at 24–48 h can be suggested.

For each test, positive (histamine) and negative controls (saline) must be used.

Abbreviation: IDT, intradermal test.

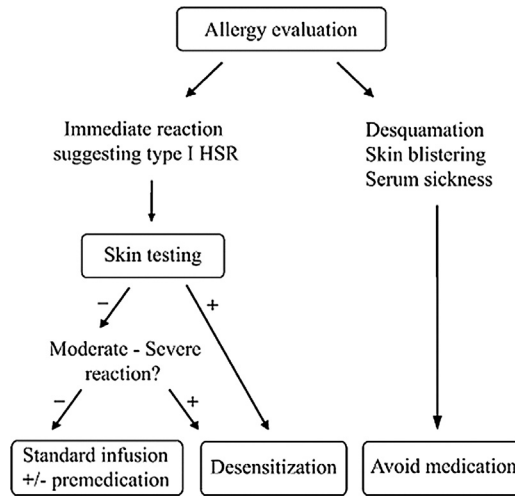


Fig. 2. Allergological evaluation of reactive patients to be submitted to desensitization procedure. (From Brennan PJ, Bouza TR, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124:1260; with permission.)

MANAGEMENT OF BA-INDUCED REACTIONS: PREVENTIVE MEASURES AND DIAGNOSIS

Considering the increased use of the biologic therapies in different pathologic conditions, the management of BA-induced reactions is becoming an unavoidable necessity in the clinical practice. The management of these reactions means defining their pathogenic mechanism as well as identifying patients at risk. If the authors deal with patients with previous reactions, the aim is to define the pathomechanism, whereas if the authors have patients with no previous reaction, it is to identify patients at risk and reduce the risk itself. The common clinical outcome is the prevention of further or first-time reactions.

Preventive Measures

Recognition of patients at risk

The identification of patients at risk is a key point in clinical practice. Taking a thorough history, in particular, including atopic status and any previous allergic reactions, is one of the most useful risk-assessment tools in allergy. Data show that there is no correlation between the atopic status and the incidence of HRs during therapy with TNF- α blocking agents; a similar prevalence of atopy and previous adverse drug reactions in reactive and unreactive patients also was seen.^{39,48}

Excellent data have highlighted the associations between ADAs and adverse clinical outcomes; risk factors for immunogenicity represent risk factors for HRs. In particular, the presence of antibodies against anti-TNF mAbs confers a risk of development of HRs in all immune-mediated inflammatory diseases. The combined use of anti-TNF mAbs and disease-modifying antirheumatic drugs reduces the development of antibodies and subsequent risks; information on other BAs is fragmentary.⁴⁹ A higher incidence of infliximab reactions in rheumatoid arthritis patients than in patients suffering from seronegative ankylosing spondyloarthritis and vasculitis confirmed that the underlying disease itself can be an important factor in the context of developing an

unwanted immune response toward the therapeutic agent.³⁹ Concordantly, a higher detection rate of antirituximab antibodies in systemic lupus erythematosus than in lymphoma patients suggests that chimeric antibodies may be more immunogenic in autoimmune disease because of the highly activated B-lymphocytes status.^{50,51} The high expression of costimulatory molecules on dendritic cells in patients with immune-mediated diseases may accelerate the development of ADAs.⁵² Some reports indicate an increased proportion of BA reactions in patients who have discontinued therapy.⁵³ Adults and children with Crohn disease experienced severe systemic reactions when a distant reinfusion interval was attempted.⁵⁴ Patients receiving regularly scheduled infliximab infusions have a decreased likelihood of forming ADAs. On the contrary, intermittent therapy may favor ADA formation and increase the likelihood of infusion reaction.⁵⁵

It is likely that regular drug infusion may induce a high-dose tolerance through efficient peripheral mechanisms, which need the continuous antigen intake. Thus, the avoidance of long intervals between infusions represents a useful strategy to increase BA safety.

CRS seen during the treatment of tumors is largely dependent on the disease burden; for example, in patients treated with rituximab suffering from non-Hodgkin lymphoma, the severity of reactions is related to the numbers of CD20⁺ circulating cells.

Premedication

Prophylactic medication with acetaminophen and/or H₁ antihistamines could prevent infusion reactions in HRs even though solid evidence is lacking and there are controversial data.⁵⁶ Premedication seems to be not protective in patients who have already developed ADAs³⁹; pretreatment with acetaminophen plus H₁ antihistamines, however, is recommended as prophylaxis for CRS induced by mAbs used in cancer therapy. The incidence and severity of CRS may also be reduced by premedication with high-dose steroids given before the administration of the first dose of the BA.⁵⁷

Choice of the infusion rate

Specific guidelines of use and administration, including flow of infusion, for each BA are usually provided, aimed at significantly reducing the risk of reaction. Many mild-to-moderate events can be successfully managed by reducing the rate of infusion, although, at least for infliximab-induced events, it seems to be useful in ADA-negative but not in ADA-positive patients.^{36,39}

In addition, in contrast to type I HRs, CRS may be managed by short-term cessation of the mAbs infusion (fractionized dosing) and restarting the infusion at a slower rate. These reactions can also be minimized by cautious incremental increases in the rate of infusion and ensuring appropriate hydration and diuresis.

Diagnosis: In Vitro and In Vivo Tests

In vitro tests useful in the clinical setting for the evaluation of BA-induced reactions are focused on the detection of ADAs. Different methods can be used, but solid-phase or solution ELISA is the most frequently used, generally displaying sensitivity, accuracy, and reproducibility.⁵⁸ Even if these assays are relatively simple, shortcomings related to matrix effects and detection of low-affinity ADAs, are present, leading to false-positive or -negative results. Thus, the initial ADA screening assay, able to detect all ADA-positive samples, should be followed by a confirmatory assay for distinguishing between true and false-positive results. For example, false-positive results can be due to rheumatoid factors cross-linking with the capture antibody⁵⁹ as well as drug

interference, and rapidly dissociating or low-affinity antibodies may lead to an underestimation of the number of patients producing ADAs (false-negative results). Serum samples should be taken shortly before a new dose of drug, because in currently used assays, ADA detection is only possible if the production of ADAs exceeds the amount of drug present in a patient's serum due to the formation of ADA-drug complexes. In addition, sample pretreatment methods with acid, for dissociation of drug-antidrug complexes, may be used to improve free drug tolerance in ADA assays.⁶⁰ The evaluation of drug levels in parallel with the ADA detection could be necessary to understand ADA assay's results.

Although ADAs are mostly represented by IgG class,⁶ multiple isotypes (IgM, IgE, and IgG) and subclasses (IgG1–4) can be produced during humoral antidrug response. Thus, a multitier testing strategy for assessment of immunogenicity is recommended, including the isotype definition of confirmed positive samples. The identification of BA-specific IgE may be difficult because these antibodies are usually quantitatively lower than all other isotypes, and IgG ADAs can deeply interfere with the detection of the low amounts of IgE. The ImmunoCAP platform is characterized by a high and reproducible binding capacity, leading to its ability to identify ADAs independently of their affinity and in the presence of interfering IgG.

Among other tests, the measurement of serum tryptase, the classical mediator accounting for mast cells activation, is currently used, and high levels are consistent with a true anaphylactic reaction. Tryptase levels within normal range, however, do not exclude IgE-mediated anaphylaxis, as described in patients with acute systemic reactions to BAs.³⁶ In these cases, the attention has been focused on basophils that express high-affinity FcεRI and, after stimulation, release mediators but not tryptase. The measurement of serum cytokine levels as well as complement fractions may be supposed in the *in vitro* evaluation of acute BA-induced reactions, but they are not routinely performed as yet.

Taking into account that patients developing ADAs are more likely to show acute reactions, whereas definitive data on their role in the induction of delayed reactions are lacking, no clear indications about the usefulness of ADA detection in patients with delayed reactions to BAs are available. Finally, to date, the role of *in vitro* T-cell analysis remains to be defined in the clinical setting for both acute and delayed BA-induced reactions.

Besides the value of skin testing for acute reactions already reported, there are few data regarding *in vivo* allergological tests for delayed HRs.^{61,62} They have been carried out largely in patients with interferon-induced reactions. Controversial data are reported, however, and conclusive results are lacking.

DESENSITIZATION

Risk, Safety, and Outcomes

There is an inherent risk to the administration of an mAb to which a patient has had an HR and the risk should be weighed against the benefit of using the medication when the offending agent is the best option and can improve the quality of life. Rapid drug desensitization (RDD) is a groundbreaking treatment option, allowing patients to receive their full target doses while protecting them against severe HRs and anaphylaxis. RDD is contraindicated in patients whose reactions suggest Stevens-Johnson syndrome or TEN, drug reaction with eosinophilia and systemic symptoms, or acute generalized exanthematous pustulosis. RDD has not provided benefit for the treatment of serum sickness-like reactions or hemolytic anemia. RDD is a temporary phenomenon that inhibits mast cell activation and the release of mediators, such as

histamine leukotrienes and prostaglandins, which are responsible for the symptoms of anaphylaxis. Whether RDD can induce long-term tolerance needs further study, and current outcomes indicate that patients have to be redesensitized at each medication exposure. RDD is a safe and effective treatment option to increase the life expectancy and quality of life for indicated patients with HRs to mAbs. RDD can address infusion reactions consistent with cytokine storms and type I HRs, including anaphylaxis. Skin testing is a useful tool to provide evidence of IgE mechanism and validate the indication of RDD, although most mAbs skin tests have not been validated in large series and their negative predictive value is unknown. Different protocols are available for RDD and large series of patients are required for their validation. Trained allergists, nurses, and pharmacists are required for successful RDD to mAbs.

Rituximab

Rituximab is a chimeric mAB against CD20 effective in lymphomas, leukemias, transplant rejection, and autoimmune and inflammatory disorders. Desensitization to rituximab was initially described as part of a case series of 413 RDDs in 98 patients by Castells and colleagues.⁶³ Three of the 98 patients had 7 successful RDDs to rituximab; 2 patients had initially presented with rash and severe pruritis during the infusion of rituximab; and a third patient had presented syncope, preventing the completion of the rituximab infusion. The RDD protocol included three 250-mL solutions with 10-fold increasing concentrations and 12 steps in which the dose was advanced every 15 minutes by increasing the rate and/or the concentration. Reactions during the desensitizations were mild and occurred during this last step.

The 3 patients were able to complete full treatment doses over 7 RDDs with no severe reactions. No patient experienced any reaction during RDD that was more severe than the initial presenting reaction. Brennan and colleagues³⁸ described a group of 14 additional patients who experienced HRs to rituximab as part of a review of 105 RDDs to mAbs in 23 patients who had reactions to mAbs. The protocol for infusions and treatment of reactions was identical to that described but adapted to dosing of mAbs (rituximab, infliximab, and trastuzumab). Eleven of 14 rituximab-sensitive patients developed a reaction on their first exposure and had no known prior exposure to any other mAB. Data on rituximab skin testing were collected, but the sensitivity and specificity have not been on a larger scale and a negative skin test did not preclude desensitization over a strong clinical history of HR. One patient in the study converted from a positive to a negative skin test and was able to tolerate a subsequent rituximab infusion without RDD. Consistent with the findings of Castells and colleagues,⁶³ a majority of reactions that occurred to rituximab RDD occurred during the last step (#12, comprising approximately 90% of the therapeutic dose) with a majority of reactions consisting of mild cutaneous symptoms (flushing and hives), and all reactions were less severe than the initial presenting HR.

Infliximab

Infliximab is a chimeric mouse-human IgG1 mAB that binds with high affinity and specificity to tumor necrosis factor α (TNF- α) and is used primarily in the treatment of inflammatory bowel disease and rheumatoid arthritis.

To address acute infusion reactions, slowing the infusion rate has been shown helpful as has the use of premedication with steroids, antihistamines, and acetaminophen, but severe infusion reactions are not prevented by these premedications. RDD protocols have been successfully applied to treat infliximab hypersensitivity. Puchner and colleagues⁶⁴ first reported successful desensitization for anaphylactic reactions in 2 patients who were desensitized to infliximab with an 11-step protocol with 2-fold

increase at each step starting at 1/100,000 of the final dose. The dose was increased every 15 minutes and the infusion was completed in 4 hours. Cheifetz and colleagues,⁶⁵ in a retrospective analysis of 165 patients who received a total of 479 infusions of infliximab, described a slow infusion protocol starting at 10 mL/h for 15 minutes, then doubled every 15 minutes to 20, 40, 80, and 100 mL/h after which the patient was continued at 150 mL/h for 30 minutes. There were 26 acute reactions of which 15 (58%) were mild, 6 (23%) were moderate, and 5 (19%) were severe. All patients with mild or moderate reactions were able to continue infliximab. Of the 4 patients who had severe reactions, 2 were able to continue treatment with desensitization, 1 had a breakthrough severe reaction, and 1 withdrew from further treatments. In 2006, Duburque and colleagues⁶⁶ reported their experience with desensitization in 14 patients with Crohn disease who had developed severe infusion reactions despite prophylactic administration of hydrocortisone and for whom infliximab was considered the only therapeutic option. The investigators used an 11-step protocol in which the final target dose was 5 mg/kg with a total infusion time of 2 hours and 45 minutes. Of the 14 patients studied, all were able to receive at least 1 full infliximab treatment. Three patients had mild reactions, 1 patient had angioedema necessitating stoppage of the protocol, and 1 patient had a delayed reactions consisting of generalized arthralgias, myalgias, and fever and requiring treatment with corticosteroids. Brennan and colleagues³⁸ reported 6 patients who had immediate-type HRs to infliximab. Four patients (67%) had a positive intradermal skin test at either 0.1 or 1.0 mg/mL concentration and all patients undergoing RDD had reactions after several exposures to infliximab. The same protocol used for rituximab RDD was used successfully for infliximab desensitization, with a majority of reactions occurring during the last step and consisting of mainly cutaneous symptoms of flushing, pruritis, and/or hives. All patients were able to receive their full treatment dose and no delayed reactions were observed.

Other Monoclonal TNF- α Inhibitors

Although local reactions with hives, local swelling, and pruritus are the most common allergic reaction with the injectable TNF- α inhibitors, systemic reactions after adalimumab administration have also been reported. Skin testing has been used to document the IgE-mediated mechanism of reactions to both etanercept and adalimumab. Rodriguez-Jimenez and colleagues⁶⁷ performed a successful desensitization in a patient with plaque psoriasis who had poor responses to methotrexate and etanercept. Infliximab was also tried but discontinued secondary to a cardiac dysrhythmia associated with its use. Adalimumab was effective but induced generalized urticaria and rhinitis after 6 doses. The patient was skin test positive to full strength adalimumab (50 mg/mL) compared with 10 negative control patients. Adalimumab was given over 6 injections spaced 60 minutes apart starting with a 0.5-mg dose. Each subsequent injection was an approximate doubling of the prior step. By the end of the 6-hour desensitization, the patient had received a full dose of 44.25 mg. Bavbek and colleagues³⁴ recently reported a successful desensitization to etanercept in a patient with ankylosing spondylitis who became sensitized to both adalimumab and etanercept. The patient had developed local swelling, diffuse pruritus, and shortness of breath after his 26th adalimumab injection and was then switched to etanercept. He developed a local reaction followed by a disseminated urticarial rash after his 22nd etanercept injection. The patient was positive on intradermal skin test to 1/100 dilution of etanercept compared with 2 negative control patients. An attempt to prevent a reaction with antihistamines was unsuccessful secondary to a breakthrough disseminated urticarial rash. The patient was then desensitized after a 3-day protocol and

received 6 injections on each day spaced by 30 to 90 minutes starting at 1/100 dilution of the final dose and doubling the dose with each step. The patient achieved the target dose and was subsequently maintained on etanercept twice weekly as a single injection with only small (<3 cm in diameter) local ISRs. The same investigators describe a 26-year-old woman with rheumatoid arthritis and severe generalized urticaria associated with adalimumab who had a positive skin test at 0.05 mg/mL and was desensitized successfully with 6 doubling doses reaching the target dose of 55 mg in 3, 5 hours.⁶⁸

Cetuximab

Cetuximab is a human-murine chimerized IgG1 mAB that targets the extracellular ligand-binding domain of the EGFR. It was the first Food and Drug Administration–approved mAB directed against EGFR and is approved for metastatic colorectal cancer and squamous-cell carcinoma of the head and neck. It carries a black box warning of severe infusion reactions, which have been reported to occur in 3% of patients, with 90% of those reactions occurring during the first infusion with rare fatalities (<1:1000). These reactions occurred despite the use of prophylactic antihistamines, and the reactions that developed were consistent with a type I HR with bronchospasm, hypotension, and/or urticaria. Most reactions to cetuximab occur with the first infusion. An unusually high rate of severe infusion reactions in North Carolina and Tennessee prompted an investigation, which led to the discovery of a high prevalence of preformed anticetuximab IgE directed against galactose- α -1,3-galactose in patients who had first-time infusion reactions and who had tick bites prior to the infusion. Cetuximab is generated in a mouse cell line, SP2/0, which expresses α 1,3-galactosyl-transferase, which is present on the Fab' portion of the cetuximab heavy chain, which is shared by the tick.⁴¹

The first published desensitization to cetuximab was a case report describing a female patient with metastatic breast cancer and preexisting anti-cetuximab-specific IgE. A 5-solution, 20-step protocol was used and four 10-fold serial dilutions were used in succession, starting from most the most dilute (0.0002 mg/mL) to the final, most concentrated solution (2 mg/mL), and each step doubling the prior step's dose, starting with 0.001 mg. The patient presented several reactions during desensitization but was able to complete the infusion.⁶⁹

The 12-step RDD protocol has been successfully used to desensitized more than 10 patients with type I hypersensitivity symptoms, and skin testing to cetuximab was found positive in these patients during first administrations.⁷⁰ There have even been reports of successful readministration of cetuximab after an HR during the first administration using a premedication regimen of H₁ and H₂ antihistamines, steroids, and a test dose; however, caution needs to be exercised in the interpretation of these case reports because the underlying mechanism for the initial reactions are not described.

Trastuzumab

Trastuzumab is a humanized mouse IgG1 mAB with selective affinity for the human epidermal growth factor 2 protein, HER2. Trastuzumab is approved for the treatment of HER2-overexpressing metastatic breast cancer. Rates of severe HR to trastuzumab range from 0.6% to 5% with the bulk of reports in the literature reporting mild-to-moderate infusion reactions characterized by fevers or chills in 40% of patients.⁷¹ The current recommendation of the manufacturer is to permanently discontinue trastuzumab in those who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. The first reports of desensitization to trastuzumab in 2002 were in 2 female

patients with metastatic breast cancer: one who developed urticaria and palmar pruritus after her third infusion and severe flushing, vaginal itching, nausea, vomiting, rigors, and angioedema of the face, lips, and tongue at the fourth infusion. Positive intradermal skin testing (0.5 mg/mL) was consistent with type I hypersensitivity. The second patient developed diffuse pruritus after 10 months of therapy with trastuzumab and then had throat tightness in the first minute of her infusion. Skin testing on prick and intradermal was negative. Desensitization protocols first 5 steps involved dose escalation starting with a 5- μ g/mL solution and the final 10 steps used a 1-mg/mL solution. Both patients experienced hypersensitivity symptoms, the first with angioedema of the tongue and urticaria and the second diffuse pruritus during the desensitization protocol.⁷²

Brennan and colleagues³⁸ described 3 patients and, unlike rituximab, HRs to trastuzumab occurred after multiple exposures to trastuzumab. Skin testing was positive in the 3 patients; they underwent 29 successful RDDs. Melamed and Stahlman⁷² reported the induction of tolerance by performing weekly subcutaneous immunotherapy with trastuzumab. Two patients who underwent a 15-step desensitization were continued on subcutaneous injections with trastuzumab. During the first week, patients received daily injections of 15 mg and increased the frequency to 3 injections over the second week. During weeks 3 to 10, 20-mg injections were given twice weekly followed by weekly 20-mg injections thereafter for as long as patients were on trastuzumab therapy. This protocol worked for 1 patient with postinfusion reactions of rigors, chills, and occasional hives for several months, who was able to continue on trastuzumab infusions for 3 years with no further allergic symptoms.

This approach suggests that the desensitized state can be maintained as long as continuous exposure to the agent is not limited by its toxicity but the risk of antibody formation may limit its therapeutic efficacy.

SUMMARY

BAs are important therapeutic tools, but their use may be limited by adverse drug reactions. Procedures for management of BA-induced reactions, including preventive diagnostic work-up and desensitization, are becoming available in the clinical setting. The knowledge of such procedures may be useful to increase the safety profile of current and coming BAs.

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