Hypersensitivity reactions to monoclonal antibodies: Classification and treatment approach (Review)

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Abstract. The present paper aims to review the topic of adverse reactions to biological agents, in terms of the incriminating mechanisms and therapeutic approach. As a result of immunomodulatory therapy, the last decade has achieved spectacular results in the targeted treatment of inflammatory, autoimmune, and neoplastic diseases, to name a few. The widespread use of biological agents is, however, associated with an increase in the number of observed adverse drug reactions ranging from local erythema to systemic reactions, including life-threatening immunologically mediated events, which justifies the need for a deeper understanding of this subject. Rapid desensitization to biological agents emerges as a treatment strategy for anaphylactic (immediate or delayed) hypersensitivity reactions as well as for severe infusion reactions. Drug desensitization is the administration of progressively increasing doses of the specific preparation until reaching the therapeutic dose in order to induce immunological tolerance and is indicated when the drugs are indispensable to the therapeutic regimen of individuals with hypersensitivity reactions to the preparation, with no reasonable alternatives.

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1. Introduction

Drug allergy is the unpredictable adverse reaction that occurs as a result of the administration of a drug at a given dose, tolerated by normal subjects and based on an immunological mechanism, either immunoglobulin E (IgE)-mediated or non-IgE-mediated (through IgG or lymphocytes) (1). One or more immune mechanisms can compete in the development of allergic drug reactions (1-3).

In 1977, Rawlins and Thompson proposed the classification of adverse drug reactions into type A (‘augmented’): Predictable, dose-related and based on the pharmacological action of the drug and type B (‘bizarre’): Unpredictable, non-dose reactions or drug action (Table I) (4).

Thirty-seven years later, the World Allergy Organization (WAO) refined the classification of adverse drug reactions in relation to the onset of clinical manifestations, which broadly allows for the differentiation of IgE-mediated type I-type hypersensitivity reactions that typically start in the first hour after exposure, with some exceptions (slow absorption due to oral drug administration or concomitantly with food), and late onset reactions mediated by type II, III or IV hypersensitivity, in which manifestations occur usually after six hours of exposure and, typically, days after the initiation of treatment. WAO also suggests the use of the following terms: Immune-mediated hypersensitivity reactions and non-immune-mediated hypersensitivity reactions. The first category of ‘drug hypersensitivity reactions’ includes clinical signs and symptoms initiated by exposure to a tolerated dose by individuals under physiological conditions. According to
WAO, drug allergy defines immunologically mediated hypersensitivity reactions and includes immediate, IgE-mediated and delayed non-IgE-mediated reactions. In the second category, ‘non-allergic hypersensitivity reactions’ include non-immune-mediated immune drug responses. WAO also proposes the differentiation of adverse drug reactions (ADRs) from adverse drug events (ADEs). This latter category includes medical errors, drug side effects, and food-drug interactions (5).

Due to immunomodulatory therapy, the last decade has brought spectacular results in the targeted treatment of inflammatory, autoimmune, and neoplastic diseases, to name a few. The widespread use of biological agents is, however, associated with the increase in the number of adverse drug reactions and implicitly those which are immunologically mediated, which justifies the need for a deeper understanding of this subject.

2. Adverse reactions to monoclonal antibodies: Classification

The adverse reactions associated with biological agents vary widely and include local site reactions, infusion-related reactions, hypersensitivity reactions, blood dyscrasias, serum sickness, vasculitis, demyelinating disease, reactivation of latent infections (tuberculosis, fungal and viral infections), neoplasms or autoimmune diseases. Adverse effects associated with immunomodulatory therapy are thus potentially severe and sometimes life-threatening (6).

Since adverse reactions from biological agents differ from adverse reactions from other drugs, Pichler proposed a new classification of adverse reactions produced by biological agents in 2006, which includes five types of reactions (7).

**Alpha-type reactions.** Alpha-type reactions are caused by cytokine overload either as a result of high cytokine doses for therapeutic purposes or systemic cytokine release syndrome. Examples of alpha-type reactions include: Flu-like manifestations, myalgias, arthralgia, febrile syndrome, that occur frequently in the context of interferon (IFN) administration; multiple organ dysfunction and necrotizing vasculitis with digital gangrene to TGN1412 agent, directed against T cell surface CD28, caused by polyclonal activation of T lymphocytes and secondary cytokine storm; septic meningitis, capillary permeability syndrome and secondary pulmonary edema, encephalopathy, fever, in the context of muromonab (OK3) administration, a monoclonal antibody to CD3 expressed by T lymphocytes; hypotension and dyspnea to rituximab, a biological agent targeting CD20 from the surface of B lymphocytes (8,9). All of these monoclonal antibodies lead to increased levels of circulating cytokines, such as tumor necrosis factor (TNF)-α, IFNγ, interleukin (IL)-6 and IL-8, released by nonspecific activation of immune cells (10).

**Beta-type reactions.** The beta-type reactions are immune-mediated hypersensitivity reactions. Variable murine regions of monoclonal antibodies (MoAbs) are complete antigens, xenonantigens, capable of inducing hypersensitivity reactions. Additionally, the MoAb protein components may induce the synthesis of clinically relevant immunoglobulins, of IgG or IgM isotypes, which are responsible for immune complex formation, complement cascade activation, anaphylatoxin synthesis and systemic release of mast cell mediators, associated with the clinical phenotype of type III hypersensitivity or with immediate reactions that mimic the clinical manifestations of type I hypersensitivity (11). Hypersensitivity reactions to biologics may be directed against excipients and not the actual biological agent. This category includes polysorbate and polyethylene glycol (12,13). Polysorbate is a non-ionic surfactant, contained in many MoAbs, and has the role of preventing aggregate formation. A series of cases of late phase hypersensitivity reactions to omalizumab have been attributed to polysorbate (14). Polyethylene glycol is an excipient found in pharmaceutical preparations, having the role of slowing down their plasma clearance. Similarly, more immediate hypersensitivity reactions to drugs are attributed to polyethylene glycol (15). Hypersensitivity to polyethylene glycol should be suspected in individuals with a history of allergic reactions to processed foods, cosmetics, various classes of drugs and other substances containing or manufactured with polyethylene glycol (16). Beta-type reactions thus encompass immune-mediated reactions through IgE, IgG and T-lymphocytes. These correspond, in fact, to the Gell and Coombs hypersensitivity reactions classification as follows:

- Type I hypersensitivity reactions, which are IgE-mediated, with immediate onset (within 1-2 h after administration), clinically ranging from urticaria and angioedema to the dramatic expression of anaphylaxis. There have also been reported cases of IgE-mediated manifestations to biological agents a few days after exposure (17-21).

- Type II and III hypersensitivity reactions are based on the synthesis of anti-MoAb isotype G antibodies, which lead to the formation of immune complexes and the activation of Fc receptors for IgG and consequently complement cascade activation, clinically resulting in vasculitis, serum sickness, nephritis and cytopenia. Type II and III hypersensitivity reactions generally have a delayed onset. IgG antibodies to the drug can also intervene by inhibiting therapeutic response and by inactivating MoAb. In such cases, administration of MoAbs will not induce side effects but will be ineffective, documenting a significant reduction in the MoAb serum concentration. The formation of anti-drug antibodies [murine anti-proteins, also called human anti-chimeric antibodies (HACA), human anti-human antibodies (HAHA)], sometimes documented during MoAb therapy, is associated with the risk of hypersensitivity reactions, insufficient response/failure of therapy or increased therapeutic dose requirements (22-30).

- Type IV hypersensitivity reactions, which are delayed, cell-mediated through T-lymphocytes, are clinically expressed by maculopapular exanthema, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), drug hypersensitivity syndrome, and acute generalized exanthematous pustulosis (31-45). Depending on the pattern of activated immune cells and cytokines involved, type IV hypersensitivity reactions have recently been subclassified into type IVa, mediated by monocyte infiltration, type IVb, involving eosinophilic inflammation, type IVc, mediated by cytotoxic T lymphocytes and type IVd, implicating neutrophilic inflammation.

**Gamma-type reactions.** Gamma-type reactions refer to the alteration of immunological equilibrium and are subdivided into: Poor immune function or immune deficiency, unmasking or generating immunologically mediated diseases, such
as autoimmunity, neoplasia, autoinflammatory diseases or allergies.

Severe infections can limit the clinical efficacy of biological agents. Anti-TNF-α therapy is associated with an increased risk of bacterial infections, especially pneumonia, reactivation of tuberculosis (TB), the Varicella-Zoosterian virus or hepatitis B virus, and opportunistic infections due to the blocking of the TNF-α, which is an essential component of the immune response against infections. Keeping this in mind, screening for latent TB infection is imperative in cases where TNF-α inhibitors are used. The response to vaccination may be altered during immunotherapy with rituximab through its effect on B lymphocytes. Thus, in cases where vaccination is recommended (anti-pneumococcal, antiviral, anti-hepatitis B), it is performed at least four weeks before the initiation of rituximab or 6 months to 1 year after cessation of immunomodulatory therapy (46-51).

Autoimmunity and neoplasia are also associated with biological response modifiers. Biological therapy may correlate, with an imprecise incidence, the synthesis of autoantibodies, especially antinuclear autoantibodies (ANAs), but also other autoantibodies (double-stranded anti-DNA, anti-phospholipid, anti-cardiolipin, antithyroid autoantibodies), which generally have no clinical impact. The autoimmune phenomena that occur in immunomodulatory therapy however, could be attributed to the synthesis of autoantibodies. Various systemic autoimmune disorders (systemic lupus erythematosus, systemic vasculitis, sarcoidosis, antiphospholipid syndrome, dermatomyositis/polymyositis) and organ-specific disorders (cutaneous vasculitis, psoriasis, uveitis, optic neuritis, demyelinating disorders, autoimmune hepatitis) can occur in the context of biological therapy (52-57). Demyelinating diseases have also been reported in the context of immunomodulatory therapy. The clinical aspect varies widely and includes signs and symptoms of the demyelination process such as confusion, ataxia, paraesthesia, various neurological manifestations, optic neuritis, hemiparesis, transverse myelitis, Guillain-Barre syndrome, and imaging modifications compatible with demyelination. The direct temporal relationship between exposure to biological agents and the onset of autoimmunity phenomena along with the resolution of manifestations after the cessation of treatment are arguments in favor of the cause-effect relationship between immunomodulatory therapy and autoimmunity.

| Type A                                                                 | Type B                                                   |
|-----------------------------------------------------------------------|----------------------------------------------------------|
| 85-90% of ADR                                                         | 10-15% of ADR                                            |
| Predictable, related to the pharmacological action of the drug;       | Unpredictable*;                                          |
| Can affect any individual if they are administered at a certain dose  | Independent of pharmacological action;                   |
| or at a certain rate                                                  | Immunologically mediated hypersensitivity reactions or   |
|                                                                      | mediated by other mechanisms occurring in susceptible    |
|                                                                      | patients                                                  |
| Examples: Nephrotoxicity caused by aminoglycosides,                    | Examples:                                               |
| digestive side effects secondary to NSAID therapy                      | 1. Intolerance reactions or low tolerance threshold      |
|                                                                       | 2. Idiosyncratic reactions                                |
|                                                                       | 3. Immune-mediated (allergic) reactions                  |

*With some exceptions, certain HLA haplotypes are associated with side effects to certain drugs, such as carbamazepine, abacavir, dapsone, allopurinol. ADR, adverse drug reactions; NSAIDs, non-steroidal anti-inflammatory drugs.

Table I. Classification of adverse drug reactions as proposed by Rawlins and Thompson (4).

Delta-type reactions. Delta-type reactions are represented by antibody-mediated cross-reactivity directed against specific molecular targets (e.g., tumor antigens) and their molecularly similar self-proteins (67).
Epsilon-type reactions. Epsilon-type reactions are non-immunological adverse effects that sometimes reveal unknown effects of administered biological agents or their targets (eg heart failure secondary to anti-TNF-α therapy, depression, thrombotic events, pulmonary fibrosis, granulomatous diseases, exacerbation of pre-existing bronchial asthma, pleural effusions, hepatotoxicity, skin manifestations such as psoriasis, chronic eczema, leukocytoclastic vasculitis, lichen planus or lichenoid alopecia) (68-73).

MoAbs can cause infusion-related side effects. Typical infusion reactions vary largely in severity, ranging from mild to severe, fatal forms. Infusion-related reactions cannot be classified under one pathological mechanism, however the following are suspected as being implicated: Systemic cytokine release syndrome (alpha-type reactions), IgE-mediated hypersensitivity reactions, activation of complement system (beta-type reactions), along with nonspecific degranulation of mast cells. Occasionally, infusion reactions have been correlated with the presence of anti-drug immunoglobin G and M isotypes. Clinically, infusion-related reactions may be characterized by fever, flushing, haemodynamic manifestations (hypertension/hypotension, tachycardia), dyspnoea, chest constriction, nausea, vomiting, diarrhea, and chest pain (11). The presence of angioedema, urticaria, nasal congestion, dysphonia or wheezing is an argument for the development of a true hypersensitivity reaction. On the contrary, manifestations such as fever and myalgia, make a hypersensitivity reaction unlikely (74).

Infusion-related and cytokine storm reactions may occur from the first or second infusion, while IgE-mediated reactions must have previous exposures to allow sensitization. Exceptions to this rule are pre-sensitized patients (for example, reactions upon first exposure to cetuximab in individuals previously sensitized to α-gal) (75). Hypersensitivity reactions become more severe with subsequent exposures, while infusion-related reactions become less severe over time.

Subcutaneous administration of MoAbs is often associated with local reactions at the site of administration, including erythema, edema, pruritus, induration, ecchymosis and pain that usually occur in the first month of treatment and remit within a few days (3-5 days) of subcutaneous administration. These are generally not followed by systemic reactions and have rarely been associated with T-lymphocyte-mediated late phase hypersensitivity reactions (76). Seldom, reactions may occur at a distal site from the site of administration and occasionally, their severity calls for the cessation of therapy.

3. Therapeutic approach: Rapid drug desensitization

Drug desensitization is the administration of progressively increasing doses of the specified preparation until reaching the therapeutic dose in order to induce immunological tolerance and is indicated when the drugs are indispensable to the therapeutic regimen in individuals with hypersensitivity reactions to the preparation, with no reasonable alternatives.

Desensitization mechanisms are currently insufficiently elucidated. In the case of IgE-mediated reactions, desensitization induces the temporary immunological tolerance or hyporesponsive state of mast cells and basophils to the incriminated drug (77). In most patients following desensitization for IgE-mediated reactions, the reduction in skin reactivity was documented, while in some individuals, skin testing becomes negative to the incriminated drug once the desensitization protocol has been successfully completed (18,78,79).

One of the mechanisms that could explain the induction of temporary drug tolerance during desensitization is that of altering the level of surface receptor expression. In vitro studies have shown that antigen doses below the tolerance threshold make mast cells and basophils non-responsive to that specific antigen but responsive to other activating stimuli (80,81). Reduced doses of antigen, below the tolerance level, bind monomeric high affinity IgE receptors (FcεRI) from the surface of the sensitized mast cells. The initiation of IgE mediated hypersensitivity reactions involves an essential step of cross-linking at least two adjacent IgE receptor molecules, a situation encountered when exposed to high doses of antigen. Monomeric binding of IgE receptors thus prevents the activation and degranulation of mast cells, events that coincide with the initiation of IgE-mediated, immediate hypersensitivity reactions (77). Studies have shown that reduced doses of an antigen induce structural changes in the cell membrane of sensitized mast cells, and subsequent impairment of the internalization of antigen/IgE/FcεRI complexes from sensitized mast cell surface, which protects against anaphylaxis. Compared to anaphylaxis, where these complexes are internalized, during desensitization, they remain on the surface of the mast cells, preventing their activation (77,82).

Another mechanism of inducing tolerance by desensitization is the skewing of the immune balance in favor of specific immunoglobulin G synthesis. After desensitization, antigen-specific IgE and IgG levels increase. IgE levels increase as a result of antigenic exposure, but the dynamic increase in specific IgG levels generally coincides with the development of immunological tolerance. It is also possible that the high titers of IgG neutralizes drug epitopes and inhibits their ability to induce IgE mediated responses. Some authors have shown that drug desensitization induces increased levels of CD4+CD25+ T cells and CD4CD25FoxP3 regulators, suggesting the role of allergen-specific regulatory T lymphocytes in inducing drug tolerance (83).

Recent studies have argued in favor of altering some mast cell and basophil signaling pathways (77). In vitro desensitization studies of mast cells and basophils have shown a reduction in the level of signal molecule expression, such as syk kinase (spleen tyrosine kinase). Syk is involved in the activation of mast cells and basophils after cross-linking high affinity immune receptors for IgE with antigens. It has been shown that syk-deficient basophils, which are naturally produced, do not respond to drug antigens, which supports the importance of syk expression in desensitization. In addition, IgG receptors, Fc-gamma-RII can competitively inhibit binding of IgE, Fc-epsilon-RI receptors, and phosphatases can dephosphorylate syk and other early signal molecules so that mast cells and basophils receive negative activation signals. Blocking of calcium influx and actin filament polymerization also seems to be also critical in the desensitization process (77,84).

With other adverse reactions, such as type IV hypersensitivity, drug desensitizations have been reported. In such cases, immunological mechanisms are yet to be elucidated.

Rapid desensitization to biological agents may be considered as a treatment strategy for anaphylactic (immediate
Drug desensitization is done subcutaneously or intravenously, starting with sequential administration of three drug solutions, at a fixed time interval of 15 min, namely 1/100, 1/10 and undiluted preparation. For those experiencing adverse reactions at 1/100, the starting dose is changed to 1/1000. Some protocols recommend re-administering doses that induce adverse effects until the reaction becomes unresponsive. Desensitization is done subcutaneously or intravenously, depending on the mode of administration of the specific drug, until the therapeutic dose is administered.

Because the tolerance status is transient and maintained only in the context of daily drug administration, desensitization to biological agents at a different rate of administration, such as weekly, is a real challenge for both the clinician and the patient alike. For MoAbs, desensitization may be necessary at each administration. Patients should be informed of the temporary nature of desensitization. MoAbs remain in circulation longer than most low-molecular-weight drugs, but their clearance is variable and does not correctly predict whether desensitization at each administration is necessary or not. Desensitization is also dose-dependent. Thus, tolerance at higher doses than those achieved with desensitization is unlikely. In some patients, desensitization also depends on the concentration of the substance, it is thus recommended that the final solution is the undiluted substance or the therapeutic concentration.

Premedication is intended to prevent and/or reduce the severity of adverse reactions during desensitisation and varies according to the protocol. Most protocols include anti-H1 and anti-H2 antihistamines, some include steroids, aspirin or montelukast. Some authors advocate for avoiding premedication during desensitization to avoid masking early signs of anaphylaxis. Other authors support the efficacy of aspirin and montelukast in the prevention of skin and respiratory manifestations, suggesting the role of prostaglandins and leukotrienes in mediating these reactions. Recently published studies advocate the benefit of administering omalizumab as premedication. Omalizumab remains an option for patients who cannot desensitize after the standard protocol.

Allergic reactions during desensitization remain a dreadful obstacle. Therefore, desensitization is only done in intensive care units, by trained medical personnel and experienced

Table II. Clinical manifestations of allergic reactions (90).

| Manifestations          | Reactions                                      |
|-------------------------|------------------------------------------------|
| Muco-cutaneous manifestations | Flushing, erythema, pruritus, urticaria, angioedema |
| Pulmonary manifestations | Dry cough, dyspnea, wheezing, stridor, dysphonia    |
| Digestive manifestations | Nausea, vomiting, abdominal pain, diarrhea       |
| Cardiovascular manifestations | Hypotension, tachycardia, cardio-respiratory diarrhea |
| Others                  | Seizures, uterine cramps, urinary incontinence, fecal incontinence |
in emergency therapy of anaphylaxis. If anaphylactic-type adverse reactions occur, rapid serum tryptase dosing is recommended within 30-120 min of the onset of reaction to confirm the IgE-mediated mechanism. In general, desensitization is well tolerated, and most often induces mild, cutaneous reactions (for intravenous agents) or local reactions at the site of administration (for subcutaneous preparations). If the adverse reaction requires treatment, re-administration of the drug will be done after the resolution of the manifestations, starting with the last tolerated dose or with the previous dose. Allergic reactions during biological desensitization (rituximab, infliximab, trastuzumab) occur in up to 20% of cases. Most of these are mild in severity, but patients with a history of severe systemic reactions have a high risk of anaphylaxis. Occasionally, delayed reactions, including serum sickness, hemolytic anemia, nephritis, thrombocytopenia, have been reported. No fatal anaphylaxis has been reported during desensitization. Regarding the evolution after desensitization, a study by Brennan et al showed a high rate of success with 104 desensitizations from 105 patients in the study (18).

4. Conclusions
The use of biological agents has inaugurated a new era in the therapy of autoimmune, allergic, and neoplastic diseases. Sometimes the clinical utility of MoAbs is limited due to the occurrence of adverse effects. Immunomodulatory therapy influences immune response as well as other biological functions, which also explains the clinical benefits but also the immune and non-immune adverse effects. Adverse reactions to MoAbs are impediments to first-line treatments. Rapid drug desensitization has the potential to induce transient immunological tolerance, which allows for safe administration of the culprit drug in incremental doses until the full therapeutic dose is reached. Successful immunomodulating therapy is conditioned by appropriate patient selection and knowledge about the potential side effects in correctly addressing the patient with the indication of biological therapy. Moreover, a better understanding of the immune mechanisms underlying drug desensitization is the premise for success of this method.

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