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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Contents

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 dyscrasia, 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)α 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; aseptic 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, xenoantigens, 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

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

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

[a]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.

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 I interferon (INF) immunomodulatory therapy has a high potential for inducing autoimmunity (58). IFN treatment may exacerbate or uncover pre-existing or clinically silent autoimmune disorders as well as induce *de novo* autoimmune diseases. The pathological mechanisms by which IFN therapy induces autoimmunity phenomena are imprecisely defined. A number of mechanisms have been proposed, namely: Direct effect of IFN on antibody synthesis, inhibition of regulatory T lymphocytes, positive regulation of major histocompatibility complex (CMH) type I molecules expression, abnormal expression of class II MHC antigens, sequential activation of T helper lymphocytes by autoantigens, T helper 1/T helper 2 imbalance and induction of a pro-inflammatory cytokine biological microclimate (IL-6 and TNF). The risk of type I diabetes in patients with hepatitis C viral infection under IFN therapy is 18 times higher; onset could be during therapy but also delayed, after cessation of INF treatment (59,60). Neoplastic disease as a complication of biological therapy remains the subject of study and interpretation. Target inhibition of some antitumor-active molecules, such as TNF, may hypothetically increase the risk of malignancy, but the link between these is difficult to sustain. Studies on the development of neoplastic disease during anti-TNF-α therapy have demonstrated the absence of increased long-term risk, with the exception of cutaneous cancers. There are also inquiries about the long-term association of lymphomas (61-66).

MoAbs that stimulates the immune response may also cause adverse effects that mimic hypersensitivity reactions. For example, inhibitors of 'check-point' molecules reduce nonspecific tolerance to self-antigens. The anti-check-point immune action of MoAbs to block molecules that negatively regulate the activation of effector T lymphocytes explains the occurrence of these side effects (34,35).

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 immunoglobulin 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, dysphonea 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 kynase (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 dephosphorize 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 desensitisations 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

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 arrest
Others	Seizures, uterine cramps, urinary incontinence, fecal incontinence

or delayed) hypersensitivity reactions as well as for severe infusion reactions. Numerous desensitization protocols have been published for various MoAbs (adalimumab, brentuximab, cetuximab, infliximab, omalizumab, rituximab, tocilizumab, trastuzumab) (18,56,83,85-88). Signs and symptoms of immediate hypersensitivity reactions are included in Table II (89).

Desensitization is indicated in sensitized patients, confirmed by positive skin test and/or positive specific IgE (the latter being available for a series of MoAbs, respectively: Infliximab, tocilizumab, cetuximab, rituximab, trastuzumab, natalizumab, muromonab), in those who have documented elevated serum tryptase levels during acute events in the context of MoAbs administration, or when clinical history is highly suggestive of a systemic, IgE-mediated reaction (Table II). Another selection criteria for desensitization is the absence of treatment alternatives, the drug being indispensable to the therapeutic regimen. Drug challenge test is not recommended in patients with a highly suggestive clinical history of systemic IgE-mediated response due to the risk of adverse reactions. In this situation, it is advisable to start with the desensitization protocol.

Drug desensitization can be done at any age. Also, there have been reported cases of desensitization in pregnant women (90).

Desensitization is effective in cases of immediate IgE-mediated reactions, and possibly in delayed type IV hypersensitivity reactions. However, clinical history of severe hypersensitivity reactions, which do not match the typical presentation of anaphylaxis, such as Stevens-Johnson syndrome, Lyell's syndrome, are absolute contraindications for desensitization. In these situations, exposure, even at low doses, may induce severe, potentially fatal reactions. Erythema multiforme and generalized erythroderma also represent contraindications to desensitization (88,91). Desensitization is not indicated in DRESS, acute generalized exanthematous pustulosis (AGEP), serum sickness, drug-related organ damage (nephritis, hepatitis, cytopenias, hemolytic anemias, vasculitis) or other severe, non-IgE-mediated reactions. At the same time, desensitization is carried out only in situations where the patient's comorbidities permit, so that the presence of uncontrolled severe conditions (uncontrolled hypertension, hepatic failure, uncontrolled asthma) constitute contraindications to desensitization (77).

Desensitization involves administering the target drug in progressive incremental doses. The starting dose varies from one to another, ranging from 1/10 to 1/4,000 of the final concentration (92). From the authors' experience, the starting dose for desensitization is adjusted according to the individual reactivity threshold and may need to exceed the initial dilution level of 1/4,000. In some cases, the starting dilution may be that which did not induce a positive skin reaction during cutaneous drug testing.

Brigham and Women's Hospital (Dana Farber Cancer Institute) proposed a 12-step desensitization protocol, which starts 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 1/1,000. 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 (92).

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 serum 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 (82,88,90).

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 (93). 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 (94). Recently published studies advocate the benefit of administering omalizumab as premedication. Omalizumab remains an option for patients who cannot desensitize after the standard protocol (95).

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

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, inflixmab, 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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Competing interests

The authors declare that they have no competing interests.

References

1. International drug monitoring: The role of national centers. Report of a WHO meeting. World Health Organ Tech Rep Ser 498: 1-25, 1972.
2. Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, Brockow K, Pichler W, Torres MJ, Terreehorst I, *et al*: Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. Allergy 64: 194-203, 2009.
3. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W, *et al*: International consensus on drug allergy. Allergy 69: 420-437, 2014.
4. Rawlins MD and Thompson JW: Pathogenesis of adverse drug reactions. In: Textbook of adverse reactions. Davies DM (ed), Oxford University Press, pp44, 1977.
5. Thong B and Vervloet D: Drug Allergies. WAO. Available from: https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/drug-allergies, 2007.
6. Hausmann OV, Seitz M, Villiger PM and Pichler WJ: The complex clinical picture of side effects to biologicals. Med Clin North Am 94: 791-804, 2010.
7. Pichler WJ: Adverse side-effects to biological agents. Allergy 61: 912-920, 2006.
8. Sunthralingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner M D and Panoskaltsis N: Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 355: 1018-1028, 2006.
9. Vasquez EM, Fabrega AJ and Pollak R: OKT3-induced cytokine-release syndrome: Occurrence beyond the second dose and association with rejection severity. Transplant Proc 27: 873-874, 1995.
10. Wing M: Monoclonal antibody first dose cytokine release syndromes-mechanisms and prediction. J Immunotoxicol 5: 11-15, 2008.
11. Cheifetz A and Mayer L: Monoclonal antibodies, immunogenicity, and associated infusion reactions. Mt Sinai J Med 72: 250-256, 2005.
12. Shelley WB, Talanin N and Shelley ED: Polysorbate 80 hypersensitivity. Lancet 345: 1312-1313, 1995.
13. Steele RH, Limaye S, Cleland B, Chow J and Suranyi MG: Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. Nephrology (Carlton) 10: 317-320, 2005.
14. Price KS and Hamilton RG: Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. Allergy Asthma Proc 28: 313-319, 2007.
15. Jover Cerdá V, Rodríguez Pacheco R, Doménech Witek J, Marco de la Calle FM and de la Sen Fernández ML: Immediate hypersensitivity to polyethylene glycols in unrelated products: When standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary. Allergy Asthma Clin Immunol 15: 9, 2019.
16. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, Hemler JA and Phillips EJ: Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 7: 1533-1540.e8, 2019.
17. Stubenrauch K, Wessels U, Birnboeck H, Ramirez F, Jahreis A and Schleypen J: Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clin Ther 32: 1597-1609, 2010.

18. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE and Castells MC: Hypersensitivity reactions to mAbs: 105 Desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 124: 1259-1266, 2009.
19. Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S and Maggi E: Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. Allergy 65: 657-6561, 2010.
20. Mezzano V, Giavina-Bianchi P, Picard M, Caiado J and Castells M: Drug desensitization in the management of allergy and anaphylaxis to chemotherapeutic agents and monoclonal antibodies. BioDrugs 28: 133-144, 2013.
21. Georgitis JW, Browning MC, Steiner D and Lorentz WB: Anaphylaxis and desensitization to the murine monoclonal antibody used for renal graft rejection. Ann Allergy 66: 343-347, 1991.
22. Proctor L, Renzulli B, Warren S and Brecher ME: Transfusion medicine illustrated. Monoclonal antibody-stimulated serum sickness. Transfusion 44: 955, 2004.
23. Krishna M and Nadler SG: Immunogenicity to biotherapeutics-the role of anti-drug immune complexes. Front Immunol 7: 21, 2016.
24. Han PD and Cohen RD: Managing immunogenic responses to infliximab: Treatment implications for patients with Crohn's disease. Drugs 64: 1767-1777, 2004.
25. Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, Stapel S, Tak PP, Aarden L and Dijkmans L: Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 54: 711-715, 2006.
26. Baert F, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A and Rutgeerts P: Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 348: 601-608, 2003.
27. Haraoui B, Cameron L, Ouellet M and White B: Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. J Rheumatol 33: 31-36, 2006.
28. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X and Marcelli C: Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: A real issue, a clinical perspective. Ann Rheum Dis 72: 165-178, 2013.
29. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL and Bendtzen K: Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 68: 1739-1745, 2009.
30. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, Dijkmans BA, Aarden L and Wolbink GJ: Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 305: 1460-1468, 2011.
31. Abdullah SE, Haigentz M Jr and Piperdi B: Dermatologic toxicities from monoclonal antibodies and tyrosine kinase inhibitors against EGFR: Pathophysiology and management. Chemother Res Pract 2012: 351210, 2012.
32. Rauer S, Stork L, Urbach H, Stathi A, Marx A, Süss P, Prinz M, Brück W and Metz I: Drug reaction with eosinophilia and systemic symptoms after daclizumab therapy. Neurology 91: e359-e363, 2018.
33. Bouman CA, van Herwaarden N, van den Hoogen FH, Fransen J, van Vollenhoven RF, Bijlsma JW, Maas AV and den Broeder AA: Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-Year data of the DRESS study-a randomised controlled pragmatic non-inferiority strategy trial. Ann Rheum Dis 76: 1716-1722, 2017.
34. Shah KM, Rancour EA, Al-Omari A and Rahnama-Moghadam S: Striking enhancement at the site of radiation for nivolumab-induced Stevens-Johnson syndrome. Dermatol Online J 24: Jun 6, 2018 (Epub ahead of print).
35. Salati M, Pifferi M, Baldessari C, Bertolini F, Tomasello C, Cascinu S and Barbieri F: Stevens-Johnson syndrome during nivolumab treatment of NSCLC. Ann Oncol 29: 283-284, 2018.
36. Saw S, Lee HY and Ng QS: Pembrolizumab-induced Stevens-Johnson syndrome in non-melanoma patients. Eur J Cancer 81: 237-239, 2017.
37. Demirtas S, El Aridi L, Acquitter M, Fleuret C and Plantin P: Toxic epidermal necrolysis due to anti-PD1 treatment with fatal outcome. Ann Dermatol Venereol 144: 65-66, 2017 (In French).
38. Didona D, Paolino G, Garcovich S, Caposiena Caro RD and Didona B: Successful use of etanercept in a case of toxic epidermal necrolysis induced by rituximab. J Eur Acad Dermatol Venereol 30: e83-e84, 2016.
39. Fallon MJ and Heck JN: Fatal Stevens-Johnson syndrome/toxic epidermal necrolysis induced by allopurinol-rituximab-bendamustine therapy. J Oncol Pharm Pract 21: 388-392, 2015.
40. Wang CY, Khoo C, McCormack CJ, Xu W and Pan Y: Acute localised exanthematous pustulosis secondary to pembrolizumab. Australas J Dermatol 58: 322-323, 2017.
41. Maranduca MA, Branisteanu D, Serban DN, Branisteanu DC, Stoleriu G, Manolache N and Serban IL: Synthesis and physiological implications of melanic pigments. Oncol Lett 17: 4183-4187, 2019.
42. Hwang SJ, Carlos G, Wakade D, Sharma R and Fernandez-Penas P: Ipilimumab-induced acute generalized exanthematous pustulosis in a patient with metastatic melanoma. Melanoma Res 26: 417-420, 2016.
43. Blendea A, Georgescu CV, Ţolea I, Brănişteanu DE and Costache A: An unusual cutaneous malignant melanoma arised de novo: A case report. Rom J Morphol Embryol 56: 1217-1221, 2015.
44. Suga H, Sugaya M, Tamaki Z, Yamamoto M, Tada Y and Sato S: Varicella like generalized pustulosis induced by adalimumab. Int J Dermatol 52: 890-892, 2013.
45. Bosanquet DC, Davies WL, May K, Harding KG and Patel GK: Acute generalised exanthematous pustulosis following intravitreal Ranibizumab. Int Wound J 8: 317-319, 2011.
46. Popa C, Leandro MJ, Cambridge G and Edwards JC: Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology (Oxford) 46: 626-630, 2007.
47. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese EC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, *et al*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 54: 2793-2806, 2006.
48. Koo S, Marty FM and Baden LR: Infectious complications associated with immunomodulating biologic agents. Infect Dis Clin North Am 24: 285-306, 2010.
49. Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester GR, Dougados M, Ferraccioli G, Jaeger U, Klareskog L, *et al*: Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 66: 143-150, 2007.
50. Gelinck LB, Teng YK, Rimmelzwaan GF, van den Bemt BJF, Kroon FP and van Laar JM: Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis 66: 1402-1403, 2007.
51. Kelsey A, Chirch LM and Payette MJ: Tuberculosis and interleukin blocking monoclonal antibodies: Is there risk? Dermatol Online J 24: 13030/qt58j4n38m, 2018.
52. Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ and Khamashta MA, BIOGEAS Study Group: Autoimmune diseases induced by biological agents: A double-edged sword? Autoimmun Rev 9: 188-193, 2010.
53. Perez-Alvarez R, Pérez-de-Lis M and Ramos-Casals M; BIOGEAS study group: Biologics-induced autoimmune diseases. Curr Opin Rheumatol 25: 56-64, 2013.
54. Grange JD, Duquesne N, Roubeyrol F, Branisteanu D, Sandon K, Fleury J, Gerard JP, Chauvel P, Pinzaru G, Jean-Louis B and Bievelez B: Double irradiation for macroscopic radioresistance or recurrence of melanomas of the posterior uvea: Clinical, ballistic, therapeutic and prognostic aspects: Series of 19 cases among 462 patients. J Fr Ophtalmol 22: 1054-1063, 1999 (In French).
55. Brănişteanu DE, Mihaila G, Alupoaei A, Ciubotariu E, Cherciu M and Brănişteanu DE: Options and therapy limits in a case of severe psoriasis. J Eur Acad Dermatol Venereol 24: 40, 2010.
56. Khobzey K, Liskova I, Szegedi A, Pavlovsky L, Lunder T, Kingo K, Miljković J, Péč J, Bohinc M and Hojnik M: Effectiveness of adalimumab in the treatment of scalp and nail affection in patients with moderate to severe plaque psoriasis in routine clinical practice. Acta Dermatovenerol Alp Pannonica Adriat 26: 11-14, 2017.
57. Brănişteanu DE, Voicu CM, Creţu A, Dimitriu A, Luca MC and Sălăvăstru CM: Adverse reactions of biological therapy for psoriasis. Rev Med Chir Soc Med Nat 119: 38-44, 2015.
58. Lin JE, Reddy S, Shah VV and Wu JJ: A review of neurologic complications of biologic therapy in plaque psoriasis. Cutis 101: 57-60, 2008.

59. Nakamura K, Kawasaki E, Imagawa A, Awata T, Ikegami H, Uchigata Y, Kobayashi T, Shimada A, Nakanishi K, Makino H, *et al*: Type 1 diabetes and interferon therapy: A nationwide survey in Japan. Diabetes Care 34: 2084-2089, 2011.
60. Zornitzki T, Malnick S, Lysyy L and Knobler H: Interferon therapy in hepatitis C leading to chronic type 1 diabetes. World J Gastroenterol 21: 233-239, 2015.
61. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R, Walsh C, Lawson R, Reynolds A and Emery P: Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: A systematic review and meta-analysis. Ann Rheum Dis 70: 1895-1904, 2011.
62. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH and Symmons D: Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: Meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 20: 119-130, 2011.
63. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB and Gelfand JM: The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 64: 1035-1050, 2011.
64. Thompson AE, Rieder SW and Pope JE: Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheum 63: 1479-1485, 2011.
65. Parakkal D, Sifuentes H, Semer R and Ehrenpreis ED: Hepatosplenic T-cell lymphoma in patients receiving TNF-α inhibitor therapy: Expanding the groups at risk. Eur J Gastroenterol Hepatol 23: 1150-1156, 2011.
66. Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K, Dreyer L, Hetland ML, Cordtz R, Hyrich K, *et al*: Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: A European registries collaborative project. Ann Rheum Dis 76: 2025-2030, 2017.
67. Peréz-Soler R and Saltz L: Cutaneous adverse effects with HER1/EGFR-targeted agents: Is there a silver lining? J Clin Oncol 23: 5235-5246, 2005.
68. Kwon HJ, Coté TR, Cuffe MS, Kramer JM and Braun MM: Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 138: 807-811, 2003.
69. Khasnis AA and Calabrese LH: Tumor necrosis factor inhibitors and lung disease: A paradox of efficacy and risk. Semin Arthritis Rheum 40: 147-163, 2010.
70. Dixon WG, Hyrich KL, Watson KD, Lunt M; BSRBR Control Centre Consortium and Symmons DP; British Society for Rheumatology Biologics Register: Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: Results from the British society for rheumatology biologics register. Ann Rheum Dis 69: 1086-1091, 2010.
71. Collamer AN and Battafarano DF: Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: Clinical features and possible immunopathogenesis. Semin Arthritis Rheum 40: 233-240, 2010.
72. Brănişteanu DE, Pintilie A, Andreş LE, Dimitriu A, Oanţă A, Stoleriu G and Brănişteanu DC: Ethiopatogenic hypotheses in lichen planus. Rev Med Chir Soc Med Nat Iasi 120: 770-776, 2016.
73. Brănişteanu DE, Brănişteanu DC, Stoleriu G, Ferariu D, Voicu CM, Stoica LE, Căruntu C, Boda D, Filip-Ciubotaru FM, Dimitriu A and Radu CD: Histopathological and clinical traps in lichen sclerosus: A case report. Rom J Morphol Embryol 57 (Suppl 2): S817-S823, 2016.
74. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Greenhawt M, Khan DA, *et al*: Anaphylaxis-a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol 145: 1082-1123, 2020.
75. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Murphy BA, Satinover SM, Hosen J, Mauro D, *et al*: Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 358: 1109-1117, 2008.
76. Torres MJ, Chaves P, Doña I, Blanca-López N, Canto G, Mayorga C and Blanca M: T-cell involvement in delayed-type hypersensitivity reactions to infliximab. J Allergy Clin Immunol 128: 1365-1367. e1, 2011.
77. de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M and Castells MC: Drug hypersensitivity and desensitizations: Mechanisms and new approaches. Int J Mol Sci 18: 1316, 2017.
78. Cortellini G, Mascella F, Simoncelli M, Lippolis D, Focherini MC, Cortellini F, Cherubini C, Gavioli B and Ballardini G: Effective desensitization to tocilizumab in delayed hypersensitivity reaction. Pharmacology 102: 114-116, 2018.
79. Quercia O, Emiliani F, Foschi FG and Stefanini GF: Adalimumab desensitization after anaphylactic reaction. Ann Allergy Asthma Immunol 106: 547-548, 2011.
80. Pruzansky JJ and Patterson R: Desensitization of human basophils with suboptimal concentrations of agonist. Evidence for reversible and irreversible desensitization. Immunology 65: 443-447, 1988.
81. MacGlashan D Jr and Lichtenstein LM: Basic characteristics of human lung mast cell desensitization. J Immunol 139: 501-505, 1987.
82. del Carmen Sancho M, Breslow R, Sloane D and Castells M: Desensitization for hypersensitivity reactions to medications. Chem Immunol Allergy 97: 217-233, 2012.
83. Aydogan M, Yologlu N, Gacar G, Uyan ZS, Eser I and Karaoz E: Successful rapid rituximab desensitization in an adolescent patient with nephrotic syndrome: Increase in number of Treg cells after desensitization. J Allergy Clin Immunol 132: 478-480, 2013.
84. Macglashan D and Miura K: Loss of syk kinase during IgE-mediated stimulation of human basophils. J Allergy Clin Immunol 114: 1317-1324, 2004.
85. Görgülü B, Toprak SK and Bavbek S: Successful desensitization to brentuximab after anaphylactic shock. J Investig Allergol Clin Immunol 28: 352-354, 2018.
86. Pérez-Rodríguez E, Martínez-Tadeo JA, Pérez-Rodríguez N, Hernández-Santana G, Callero-Viera A, Rodríguez-Plata E and García-Robaina JC: Outcome of 490 desensitizations to chemotherapy drugs with a rapid one-solution protocol. J Allergy Clin Immunol Pract 6: 1621-1627.e6, 2018.
87. Erdogan T, Yasar Bilge NS and Kasifoglu T: Successful slow tocilizumab desensitization in a patient with adult onset Still disease. Biologicals 55: 17-18, 2018.
88. Bavbek S, Kendirlinan R, Çerçi P, Altıner S, Soyyiğit Ş, Çelebi Sözener Z, Aydın Ö and Gümüşburun R: rapid drug desensitization with biologics: A single-center experience with four biologics. Int Arch Allergy Immunol 171: 227-233, 2016.
89. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, Ellis A, Golden DB, Greenberger P, Kemp S, *et al*: Anaphylaxis-a practice parameter update 2015. Ann Allergy Asthma Immunol 115: 341-384, 2015.
90. Madrigal-Burgaleta R, Vazquez-Revuelta P, Marti-Garrido J, Lleonart R, Ali FR and Alvarez-Cuesta E: Importance of diagnostics prior to desensitization in new drug hypersensitivity: Chemotherapeutics and biologicals. Curr Treat Options Allergy 7: 1-13, 2020.
91. Creţu A, Dimitriu A, Brănişteanu D and Branişteanu DE: Erythema multiforme-etiopathogenic, clinical and therapeutic aspects. Rev Med Chir Soc Med Nat Iasi 119: 55-61, 2015.
92. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, Laidlaw TM, Legere HJ, Nallamshetty SN, Palis RI, *et al*: Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 122: 574-580, 2008.
93. Herrero T, Tornero P, Infante S, Fuentes V, Sánchez MN, De Barrio M and Baeza ML: Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. J Investig Allergol Clin Immunol 16: 327-330, 2006.
94. Breslow RG, Caiado J and Castells MC: Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. Ann Allergy Asthma Immunol 102: 155-160, 2009.
95. Ojaimi S, Harnett PR and Fulcher D: Successful carboplatin desensitization by using omalizumab and paradoxical diminution of total IgE levels. J Allergy Clin Immunol Pract 2: 105-106, 2014.