Review

Hypersensitivity reactions during treatment with biological agents

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ABSTRACT

The recent development of biological agents, namely, anti-tumour necrosis factor alpha (TNF-α) agents (infliximab, adalimumab and etanercept), anti-CD20 monoclonal antibody (rituximab) and anti-interleukin 6 receptor (IL-6R) monoclonal antibody (tocilizumab), represents a major breakthrough for the treatment of immune-mediated disorders. Given their structural and functional differences, distinct safety profiles can be expected for each of these agents. Evidence in the literature indicates that patients treated with anti-TNF-α agents and tocilizumab are at increased risk for bacterial infections. However, an increased therapeutic use of these biological agents has disclosed other side-effects, including immediate hypersensitivity reactions, such as anaphylaxis and urticaria.

Both under-diagnosis and over-diagnosis of hypersensitivity reactions to biological agents are potential problems. Thus, it is important to identify these reactions and to adopt the right approach to manage them.

This article reviews the general aspects of adverse events during biologic treatment, focusing on IgE-mediated hypersensitivity reactions to anti-TNF-α agents, rituximab and tocilizumab, and on the tools for the diagnosis of these life-threatening reactions.

Introduction

During the last decades, the introduction of biological agents (BA) (cytokines, monoclonal antibodies and fusion proteins) has proven to be a valuable tool in the treatment of autoimmune diseases and tumours (1). Together with the more frequent therapeutic use of these agents an increased number of side-effects is observed, mostly non-immune-mediated. These side-effects are in part ascribed to the structure, morphology, pharmacokinetic properties and activity of the BA, and in part to differences in patient responses (enzymopathies, cytokine imbalance, mast cell hyper-reactivity). The ability of the BA to induce an immune response leads to the production of specific anti-drug antibodies (ADAs) that can impact therapeutic efficacy as well as induce hypersensitivity reactions (HRs) (2-4). In this review, we investigate the classification, pathogenesis and management of adverse drug reactions (ADRs) during BA treatment, focusing on immediate HRs elicited by agents commonly used in the treatment of autoimmune diseases, such as anti-tumour necrosis factor alpha (TNF-α) agents (infliximab, adalimumab and etanercept), anti-CD20 monoclonal antibody (rituximab) and anti-interleukin 6 receptor (IL-6R) monoclonal antibody (tocilizumab).

Classification of adverse drug reactions

To better understand the mechanisms underlying different side effects of BA, it is important to take into account that these agents differ from most drugs: they are not small chemical compounds, but proteins and the production strategies aim at rendering them as similar to human proteins as possible. BA are mostly naturally occurring proteins (*i.e.* cytokines) or humanised antibodies which can neutralise natural proteins (3, 5). They are not metabolised like drugs, but are processed like other proteins, and therefore need to be administered parenterally to avoid digestion in the gastrointestinal tract. Thus, taking into account that adverse drug reactions (ADRs) to these agents might differ from those elicited by traditional drugs, recently Pichler (3) classified the ADRs on the basis of the structure and

mechanisms of action of these agents, instead of the clinical manifestations. According to this classification, 5 different subclasses of ADRs have been proposed:

- *Type alpha:* immunostimulation is the cause of this ADR, and the best example is the release of high concentrations of cytokines in the circulation as result of BA activity;
- *Type beta:* this group of reactions are due to immunogenicity, defined as the ability of a molecule to induce an immune response towards itself. The HRs to drugs belong to this subclass of ADR.
- *Type gamma*: this ADR might be termed as "immunodeviation" or "immune or cytokine imbalance syndromes". They are a major group of ADRs with immunological features, unexplained by high cytokine levels or typical HRs.
- *Type delta*: these reactions are mainly due to cross-reactivity.
- *Type epsilon:* non-immunological ADRs are grouped in this class.

Type alpha

These types of reactions are due to high systemic levels of cytokines, resulting directly from the administration of these mediators as BA (*i.e.* IFN treatment) or rather due to the release of pro-inflammatory cytokines by components of the immune system (complement, macrophages, monocytes, lymphocytes and NK cells) activated by the drug (3).

The reactions induced by the acute release of cytokines range from flu-like reactions (fever up to 38–39.5°C, chills, fatigue, myalgia, arthralgia, headache and nausea) to cytokine release syndromes. The latter is the most severe reaction, characterised by marked hyperpyrexia (>40°C), neurological manifestations (tremor, rigour, confusion, obnubilation, seizures, aseptic meningitis and encephalopathy), gastrointestinal symptoms (vomiting, diarrhoea), and cardiovascular disturbances (drop in blood pressure, cardiovascular collapse, and even cardiac ischaemia and capillary leak syndrome with pulmonary oedema) (6).

The most common type alpha reaction is the one induced by acute infusion of the cytokine (5). It may occur at the first drug administration and may become milder or disappear at the following infusions. This reaction may resolve spontaneously or by using premedication, or reducing the infusion rate (5). According to the severity of manifestations, discontinuation of treatment may be required. Focusing on BA used in rheumatic diseases, type alpha acute infusion reactions are described for rituximab (up to 38% at first administration of the drug) and infliximab (4-21% of treated patients) (7). The local irritative reactions of BA at the injection site must be included in type α ADRs. They are very frequent but often disappear with continuation of therapy (5). In the rheumatologic field, this type of ADR is observed with any subcutaneously applied drug (7).

Type beta

BA are all potentially immunogenic because they are high molecular weight proteins, but the degree of immunogenicity depends on the following factors (3, 8):

- characteristics of molecule: oxidation, glycosylation, type of adjuvant, presence of non-human protein sequences;
- mode of administration (route, frequency);
- characteristics of patient (atopy, immunodeficiency, genetic features);
- concomitant use of traditional immunosuppressants (as methotrexate).

The immunogenicity leads to the production of ADAs in absence of HRs, or production of immune response to drug leading to HRs.

The first case occurs rather frequently. In a study with infliximab, up to 68% of the treated patients developed ADAs. These circulating ADAs may not exert any effects or may neutralise the BA, requiring a higher dose of the same BA or an alternative one to achieve the same clinical effect (3).

The immediate HRs involving an IgE-mediated mechanisms are discussed in detail below. The non-immediate/delayed HRs are caused by the production of IgG or by the recruitment and activation of T cells against the BA. IgG and the BA form immune complexes which activate complement cascade and/or neutrophils, responsible of immune complex diseases such as serum sickness, vasculitis and nephritis. In other cases, delayed infusion reactions, characterised by myalgia, arthralgia, fever, rash, pruritus, facial oedema, dysphagia and urticaria, are observed. Another Ig-associated side-effect may be thrombocytopenia, if immune complexes bind to Fc-IgG receptors on thrombocytes, which are then removed from the circulation by the phagocytic system. T cell-mediated systemic reactions (such as exanthema or hepatitis) are less frequent during BA treatment.

Type *gamma*

ADR of type *gamma* are subdivided into:

- reduction of function of the immune system, *i.e.* immunosuppression / immunodeficiency;
- alteration of the physiological balance of the immune system (3, 5).

In the rheumatology field, BA are used to reduce inflammation or dampen the immune response: thus, an impaired function of the immune system is an expected ADR. The potential consequences are the increased rate of infections, the reactivation of silent pathogens and the increase of incidence of lymphomas and solid tumours (7).

An increased frequency of severe infections as well as reactivation of tuberculosis and HBV hepatitis are well known adverse effects of anti-TNF agents and have been discussed in recent reviews (9-11). Rituximab may cause fulminant hepatitis in HBV-infected patients. Data about the risk of cancer during BA treatment in patients with rheumatic diseases are discordant (7).

Focusing on the second point, several mechanisms, such as tolerance, regulatory T cells, and Th1/Th2 balance, cooperate in the correct function of the immune system. Alteration of this physiological equilibrium results in autoimmunity, auto-inflammatory and allergic/atopic disorders. Anti-TNF antibodies lead rather frequently to autoimmune phenomena: antinuclear antibodies can be found in up to 11% of cases with etanercept, and in up to 68% with infliximab (3). However, development of lupus is a rather rare event (approximately

0.5%) (3). Demyelinating diseases, development or worsening of psoriasis, bronchial asthma and atopic dermatitis have also been observed while under treatment with anti-TNF agents (5, 7).

Type delta

Cross-reactivity is due to the reaction of the biologic drug with the same antigen expressed on different cells or with an antigen of similar structure (3, 5). This type of ADR is typical of BA used in oncology: in fact, tumour antigens are often normal proteins, which are over expressed on neoplastic cells. Thus, antibodies against these antigens may also react with the same molecules on normal cells (3, 5). Type delta reactions during BA treatment of rheumatic diseases have not been reported.

Type epsilon

Any ADR that cannot be traced back to the direct toxic or immunologic effects and whose mechanisms are not yet clarified, are (provisionally) classified in this sub-group. Inhibition of cytochrome P450 (leading to interactions with xenobiotics), elevation of liver function test and cutaneus manifestations, such as pruritus, xeroderma and asteatotic eczema, are classified in this type of ADR (5).

Worsening of III/IV class NYHA heart failure during anti TNF treatment (3) is an example of type epsilon ADR.

Drug hypersensitivity reactions to biological agents

Drug HRs belong to type beta ADRs, which are defined by the World Health Organization (WHO) as dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans (12). Clinically, HRs to drugs are classified as immediate or non-immediate/delayed reactions, depending on the timing of their onset during treatment. Immediate HRs to drugs are possibly induced by an IgE-mediated mechanism and typically occur within one hour after the last drug administration. According to the intensity of symptoms, they range from mild to severe and can develop locally, at site of injection, or involve systemic reactions. Non-immediate/delayed HRs may occur 1 to 6 hours after the initial drug administration, but commonly occur many days after treatment and are often associated with a delayed T cell-dependent mechanism. Maculopapular exanthemas and delayed urticaria are the most common clinical presentations of non-immediate/delayed drug HRs.

Focusing our attention on immediate HRs to BA, the key event is the production, by antigen-specific B lymphocytes, of IgE specific to BA, by the same mechanisms involved in type I HRs.

IgE antibodies bind to high-affinity FcεRI receptors expressed on the surface of mast cells and basophils, creating a multivalent binding site for the drug antigen. Following subsequent drug exposure, the antigen cross-links the bound IgE, stimulating the release of preformed mediators (*e.g.* histamine, tryptase) and the production of newly generated mediators (*e.g.* leukotrienes, prostaglandins, kinins, cytokines). The preformed mediators stimulate a response within minutes, whereas inflammation due to newly generated mediators develops after several hours, time lag required for protein synthesis and recruitment of immune cells into the tissue.

Histamine is the principal mediator of IgE-mediated reactions, determining within a few minutes vasodilatation, bronchial and smooth muscle contraction, glandular secretion and pruritus. The immediate HRs can be biphasic: a second phase, normally similar but milder than the first one, can appear after some hours and newly formed leukotrienes are the principal mediators (13). The IgE-mediated reactions to BA can be local or systemic. The local reactions are confined to the injection sites, but systemic reactions may develop if therapy is not discontinued. Focusing on BA in rheumatology, local reactions are very frequent: for adalimumab 15–20% of cases, for etanercept 29-37% and for anakinra 50–80% (5). The systemic reactions induced by BA occur more rarely than the local ones. According to the drug's product label, severe HRs to cetuximab occur in 3% of patients. Among anti-TNF agents, the highest frequency and severity of HRs are observed in subjects treated with infliximab. In our experience, 60.8% of all the HRs to anti-TNF drugs were attributable to infliximab, 25.5% to etanercept, and 11.7% to adalimumab and the most serious anaphylaxis occurred in patients treated with infliximab rather than etanercept and adalimumab (14). In Phase III clinical trials on the efficacy and safety of tocilizumab in patients with rheumatoid arthritis, very rare IgE-mediated HRs were reported. Symptoms included urticaria, nausea, vomiting, hypotension, hypotensive shock, and bronchospasm (15). The results obtained in a study on IgE-mediated HRs to tocilizumab on spondyloarthritis patients (16) were consistent with those observed in the rheumatoid arthritis population.

The reasons why a patient develops an IgE mediated response are not clear: many factors play a role including genetic predisposition (17).

However, personal or familiar history of atopy seems not to be a risk factor for HRs to BA (14, 18). Interestingly, in the IgE-mediated HRs to cetuximab, IgE antibodies against this BA were present in serum before therapy, and these antibodies were specific for galactose-a-1,3-galactose (19), suggesting that patients who developed HRs to certain BA have a pre-existent sensitisation to other substances, although they have never been exposed to the culprit drug. Thus, allergic drug reactions on first encounter are possible, and may, in some cases, be explained by cross-reactivity of IgE (20).

Diagnosis of hypersensitivity reactions to biological agents

HRs to BA have become a problem frequently encountered in clinical practice during treatment of autoimmune- and chronic inflammatory diseases. Thus, it is important to identify and classify these reactions in order to adopt the right approach to manage them. Unfortunately, studies on the diagnosis of IgE-mediated HRs to BA are so far quite limited.

According to the International Consensus on drug allergy, the diagnosis of HRs to drugs is based on history, clinical manifestations and if possible on *in vivo* and *in vitro* tests (17). Re-

garding BA, the patient history is often not sufficient to make the diagnosis of HRs. For example, a history of atopy is not predictive of an IgE-mediated HRs to a certain BA. In fact, recent studies did not demonstrate any correlation between atopy and the incidence of HRs to BA (14, 18). The common clinical manifestations of immediate HRs might be isolated symptoms such as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain), or severe systemic reactions (anaphylaxis or anaphylactic shock).

Besides collecting information on the timing of the reaction and on previous exposure to the agent, allergists use skin tests (*in vivo* tests) with the incriminated drug to confirm or exclude a drug allergy, to identify the culprit drug, or both.

In contrast with the well accepted procedures for performing and interpreting skin tests for IgE-mediated reactions to β-lactams (21), only recently the utility of *in vivo* skin testing in the diagnosis of HRs to BA has been reported (14, 22-25). On the whole, published data confirm that in the diagnosis of reactions to BA such as anti TNF agents, tocilizumab and rituximab as to any other drug, skin tests still represent the currently used tool to identify mast cell-sensitising specific IgE. In fact, detection of IgE specific to infliximab and recently to tocilizumab and rituximab has been described, but the assay has not yet been validated. A correlation between serological IgE positivity and intradermal test results has been recently reported in patients with reactions to infliximab (22). In addition, according to Matucci *et al*. (24), 30% of patients with severe reactions to infliximab display skin testing positivity. Comparing skin testing for infliximab, etanercept and adalimumab in patients who developed HRs to these BA, in our experience, infliximab seems to be responsible for IgE-mediated responses more frequently that etanercept and adalimumab (14). Recently, we have also reported that *in vivo* skin testing might be a simple and sensitive tool for the diagnosis of IgE-mediated HRs not only to anti-TNF agents, but also to tocilizumab (25). IgE specific for tocilizumab have been detected by bridging-type screening and confirmation ELISA, but positivity in the assay is not always related with the clinical manifestations (26).

Key messages

- Wider use of BA has led to an increased number of HRs.
- It is important to identify and classify the clinical manifestations of HRs to BA.
- A limited number of assays for in-vitro detection of IgE specific to BA are available.
- *In vivo* skin tests directly explore mast cell sensitisation to BA.
- For a correct diagnosis of IgE mediated reactions to BA, it is important to combine *in vivo* skin tests with the detection of IgE specific to BA.

References

1. LEE S J, KAVANAUGH A: Adverse reactions to biologic agents: focus on autoimmune disease therapies. *J Allergy Clin Immunol* 2005; 116: 900-5.
2. SCIRE' CA, CAPORALI R, SARZI-PUTTINI P *et al*.: Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet database. *Clin Exp Rheumatol* 2013; 31: 857-63.
3. PICHLER WJ: Adverse side-effects to biological agents. *Allergy* 2006; 61: 912-20.
4. ATZENI F, TALOTTA R, SALAFFI F *et al*.: Immunogenicity and autoimmunity during anti-TNF therapy. *Autoimmun Rev*. 2013; 12: 703-8.
5. SCHERER K, SPOERL D, BIRCHER AJ: Adverse drug reactions to biologics. *J Dtsch Dermatol Ges J Ger Soc Dermatol* 2010; 8: 411-26.
6. DESCOTES J: Immunotoxicity of monoclonal antibodies. *MAbs* 2009; 1: 104-11.
7. FAVILLI EG, CAPORALI R, SINIGAGLIA L *et al*.: Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology II. Safety. *Clin Exp Rheumatol* 2011; 29: S15-27.
8. PURCELL RT, LOCKEY RF: Immunologic responses to therapeutic biologic agents. *J Investig Allergol Clin Immunol* 2008; 18: 335-42.
9. RAMIRO S, GAUJOUX-VIALA C, NAM JL *et al*.: Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis*. 2014; 73: 529-35.
10. VASSILOPOULOS D, CALABRESE LH: Management of rheumatic disease with comorbid HBV or HCV infection. *Nat Rev Rheumatol* 2012; 8: 348-57.
11. KEYSTONE EC: Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: a review of longterm data. *J Rheumatol* 2011; 38: 1552-62.
12. DEMOLY P, ADKINSON NF, BROCKOW K *et al*.: International Consensus on drug allergy. *Allergy* 2014; 69: 420-37.
13. HOLGATE ST, CHURCH MK, LICHTENSTEIN L M: (Eds) *Allergy* 2006. Third Edition. 2006. 157-66.
14. PUXEDDU I, GIORI L, ROCCHI V *et al*.: Hypersensitivity reactions during treatment with infliximab, etanercept, and adalimumab. *Ann Allergy Asthma Immunol* 2012; 108: 123-4.
15. SCHIFF MH, KREMER JM, JAHREIS A *et al*.: Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011; 13: R141.
16. SIEPER J, PORTER-BROWN B, THOMPSON L *et al*.: Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. *Ann Rheum Dis*. 2014; 73: 95-100.
17. MIRAKIAN R, EWAN PW, DURHAM SR *et al*.: BSACI guidelines for the management of drug allergy. *Clin Exp Allergy* 2009; 39: 43-61.
18. BENUCCI M, MANFREDI M, SAVIOLA G *et al*.: Correlation between atopy and hypersensitivity reactions during therapy with three different TNF-alpha blocking agents in rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 333-6.
19. CHUNG CH, MIRAKHUR B, CHAN E *et al*. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008; 358: 1109-17.
20. HAUSMANN O, SCHNYDER B, PICHLER WJ: Etiology and pathogenesis of adverse drug reactions. *Chem Immunol Allergy* 2012; 97: 32-46.
21. TORRES MJ, BLANCA M, FERNANDEZ J *et al*.: Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; 58: 961-72.
22. VULTAGGIO A, MATUCCI A, NENCINI F, *et al*. Skin testing and infliximab-specific antibodies detection as a combined strategy for preventing infusion reaction. *Intern Emerg Med* 2012; 7 (Suppl. 2): S77-9.
23. VULTAGGIO A, MATUCCI A, NENCINI F *et al*.: Drug-specific Th2 cells and IgE antibodies in a patient with anaphylaxis to rituximab. *Int Arch Allergy Immunol* 2012; 159: 321-6.
24. MATUCCI A, PRATESI S, PETRONI G *et al*.: Allergological *in vitro* and *in vivo* evaluation of patients with hypersensitivity reactions to infliximab. *Clin Exp Allergy* 2013; 43: 659-64.
25. ROCCHI V, PUXEDDU I, CATALDO G *et al*.: Hypersensitivity reactions to tocilizumab: role of skin tests in diagnosis. *Rheumatology* (Oxford) 2014; 53: 1527-9.
26. STUBENRAUCH K, WESSELS U, BIRNBOECK H *et al*.: 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.* 2010; 32: 1597-609.