

Adverse reactions to monoclonal antibodies in allergic diseases

Reações adversas aos anticorpos monoclonais para doenças alérgicas

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ABSTRACT

The use of immunobiological agents in allergy and immunology has increased in recent years, emerging as potentially effective strategies to treat allergic and hypersensitivity diseases. The use of immunobiological agents is recommended in the severe forms of allergic diseases, for which their efficacy, safety, and cost-effectiveness have been established. The purpose of this study was to summarize the most common or significant adverse effects, including hypersensitivity reactions to the main monoclonal antibodies approved for the treatment of allergic diseases that are currently licensed and marketed in Brazil.

Keywords: Monoclonal antibodies, asthma, drug-related side effects and adverse reactions, atopic dermatitis, urticaria.

RESUMO

A utilização de agentes imunobiológicos em alergia e imunologia tem sido cada vez mais frequente nos últimos anos, emergindo como potencialmente eficazes para o tratamento de doenças alérgicas e de hipersensibilidade. O uso de imunobiológicos em doenças alérgicas está recomendado nas formas graves onde a eficácia, segurança e custo-efetividade estão comprovados. O objetivo deste artigo é sintetizar os efeitos adversos mais comuns ou significativos, incluindo as reações de hipersensibilidade aos principais anticorpos monoclonais aprovados para o tratamento de doenças alérgicas licenciados e comercializados no Brasil até o momento.

Descritores: Anticorpos monoclonais, asma, efeitos colaterais e reações adversas relacionados a medicamentos, dermatite atópica, urticária.

Introduction

The use of immunobiological agents in allergy and immunology has increased in recent years, emerging as potentially effective strategies to treat allergic and hypersensitivity diseases.¹ In Brazil,

the main immunobiological agents used in the clinical practice of allergists and immunologists are polyclonal human immunoglobulins (both intravenous and subcutaneous), used in replacement therapy

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for inborn errors of immunity or in autoimmune and inflammatory diseases, and monoclonal antibodies. The use of monoclonal antibodies is more recent and is expected to increase over the next years due to their availability for the treatment of asthma in the Brazilian Unified Health System (*Sistema Único de Saúde*, SUS) and their inclusion in the List of Procedures of the Brazilian National Supplementary Health Agency (*Agência Nacional de Saúde*, ANS). Four main classes of monoclonal antibodies are currently approved for use in allergic diseases: anti-IgE (omalizumab), anti-IL-5 (mepolizumab), anti-IL-5R (benralizumab), and anti-IL-4R/IL-13R (dupilumab).¹

The use of immunobiological agents is recommended in severe forms of allergic diseases, for which their efficacy, safety, and cost-effectiveness have been established. Nearly 30% of patients with severe asthma depend on high doses of inhaled corticosteroid and frequent use of beta-2 agonists, often with frequent courses or continuous use of oral corticosteroids to maintain asthma control, despite of side effects²

Due to the impact of severe asthma, that was the first allergic disease to be treated with an immunobiological drug and is currently the condition with the greatest number of options of biological therapy.^{3,4} Subsequently, other conditions, such as urticaria, atopic dermatitis (AD), and chronic rhinosinusitis with nasal polyps (CRSwNP), have started to include this class of medications in their therapeutic arsenal.^{4,5}

The purpose of this study was to summarize the most common or significant adverse effects, including hypersensitivity reactions to the main monoclonal antibodies approved for the treatment of allergic diseases that are currently licensed and marketed in Brazil.¹

Classification of adverse reactions to biological agents

Immunobiological agents demonstrate differences from traditional drugs in terms of chemistry, mode of action, metabolism, and immunogenicity. These drugs are protein complexes obtained from cultures of bacteria, yeast, insects, plants, or mammalian cells, through genetic engineering techniques. Adverse events induced by xenobiotics (traditional drugs) are mainly linked to pharmacological effects, whereas the adverse effects of immunobiological agents

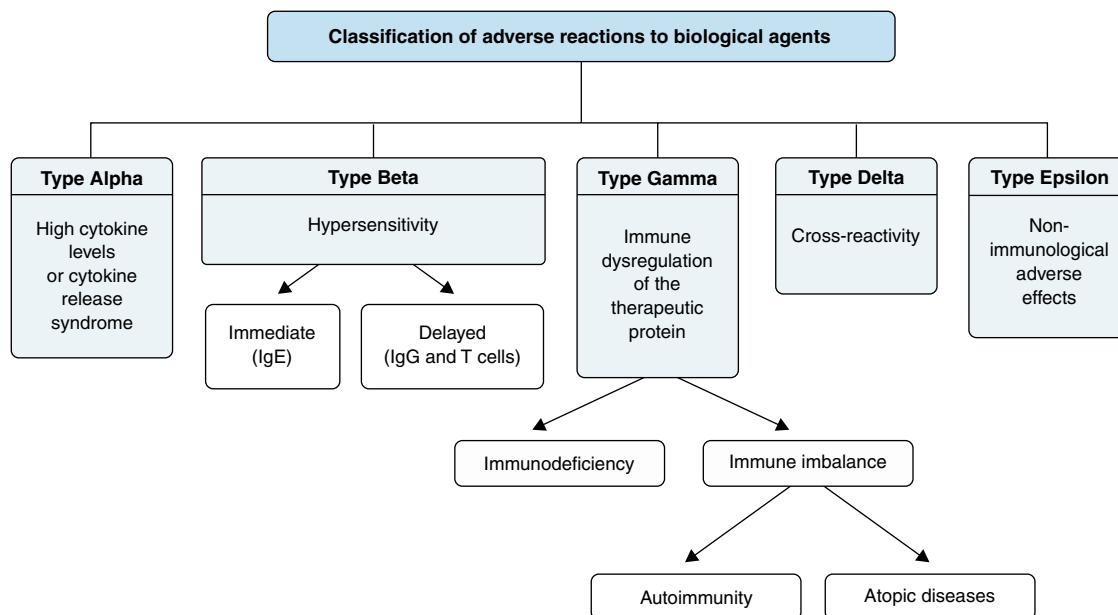
are often target-related and linked to the biological consequences of their action.⁶

Considering these differences, Pichler proposed an original classification of adverse reactions to immunobiological agents (Figure 1). Adverse reactions to these agents are classified into five groups: (1) Type alpha – induced by cytokine release, whose main manifestations are fever, asthenia, arthralgia, headache, myalgia, gastrointestinal symptoms, and cutaneous eruption mimicking a Sweet's syndrome; (2) Type beta – involves immediate and delayed hypersensitivity reactions linked to the immunogenicity of immunobiological agents, more frequent with chimeric antibodies, but that can also occur with humanized and fully human antibodies through anti-idiotypic antibodies; (3) Type gamma – related to immune dysregulation, including immunosuppression and autoimmunity; (4) Type delta – results from the co-expression of the target antigen on both pathological and normal tissue cells; (5) Type epsilon – related to new and unexpected non-immunological functions of immunobiological agents revealed by use in humans, such as neuropsychiatric disorders associated with interferon (IFN)-alpha and cardiac complications caused by anti-tumor necrosis factor (TNF)-alpha agents.⁷

Omalizumab

Omalizumab was the first immunobiological agent approved for the treatment of moderate-to-severe allergic asthma presenting with levels of total IgE from 30 to 1,500 IU/mL and IgE-specific sensitization to aeroallergens. It was initially approved for patients older than 12 years of age and, subsequently, for children over 6 years. It is a recombinant humanized monoclonal antibody that targets free serum IgE and, thus, prevents its attachment to mast cells and basophils and release of inflammatory mediators. Finally, this mechanism leads to downregulation of high-affinity IgE receptors (FcεRI) in these cells and inhibition of allergic reaction. Subsequently, omalizumab was approved for use in patients diagnosed with chronic spontaneous urticaria aged over 12 years and, more recently, it was approved for the treatment of severe nasal polyposis in patients over 18 years of age and with levels of total IgE from 30 to 1,500 IU/mL, regardless of the presence of aeroallergen sensitization.⁸

The most frequently reported adverse reactions were injection-site reaction (45%), respiratory

**Figure 1**

Classification of adverse reactions to immunobiological agents

Modified from Pichler WJ⁷.

infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%).⁹

Data from 35 phase 1 to 3 studies showed an apparent increase in malignancies among omalizumab users (0.5% vs. 0.2% in controls).¹⁰ Most consisted of solid tumors, except for a case of recurrent non-Hodgkin lymphoma. Of the 25 cases of malignancy, 4 seemed to be present before initiation of omalizumab therapy, and all cases, except for one of basal cell carcinoma, were diagnosed in the first two years of use of the biological agent. A subsequent evaluation of 32 clinical trials, conducted in 2012, did not show any association between omalizumab and risk for malignancy, which was subsequently confirmed by the Evaluating Clinical Effectiveness and Long-term Safety in Patients (EXCELS) trial.¹¹

The existing literature estimates the risk of developing anaphylaxis due to omalizumab at 0.09%,

with most cases (77%) occurring during the first 2 hours after administration of the first 3 doses.¹² Confirmation may be performed by skin tests with the drug diluted in saline and, if result is negative, an intradermal test with a concentration of 1: 100,000 (or 1.2 µg/mL) may be conducted to assess hypersensitivity.¹³ Rarely, a desensitization may be required.¹⁴ Another possibility is sensitization to other chemicals that compose the medication, such as polysorbate, used to increase drug solubility.¹⁵ Some authors suggested that pre-existing or recently developed antibodies against omalizumab could be responsible for the reactions. However, a post-marketing pharmacosurveillance using a new method to detect IgE antibodies for omalizumab did not show an apparent correlation between anaphylaxis or reactivity in the skin test or presence of antibodies of IgE isotype to omalizumab.¹⁶

Clinical studies, as well as real-life studies with the pediatric population, demonstrated an acceptable

overall safety profile. The more frequent adverse reactions were nasopharyngitis, headache, fever, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. A previously published meta-analysis of three randomized controlled studies revealed that frequency of adverse events was similar between omalizumab (76.3%) and placebo (74.2%), as well as the frequency of serious adverse events (5.2 and 5.6%, respectively). There was no evidence of increased risk for anaphylaxis, urticaria, hypersensitivity reactions, or malignant diseases.^{16,17}

A clinical trial of omalizumab for chronic spontaneous urticaria included more than 1,000 patients and did not observe any death or significant serious adverse event related to the medication. The most common adverse events after subcutaneous administration were injection-site reactions, followed by upper respiratory tract infection and headache.¹⁸

In 2018, a meta-analysis of 67 real-life studies on the efficacy of omalizumab found an average adverse event rate of 4% (1-7%) vs. 2.9-8% in clinical trials.¹⁹

In replicated studies, POLYP1 and POLYP2, on the use of omalizumab in CRSwNP, 50.4% of patients developed at least one adverse event. Most events in both studies ranged from mild to moderate intensity, and the most common ones were headache, nasopharyngitis, and injection-site reactions. Three serious cases were reported in patients using omalizumab (2.2% [1 case of snake bite, 1 hand fracture, and 1 case of asthma exacerbation/ worsening]).²⁰

Mepolizumab

Mepolizumab is a humanized IgG1 monoclonal antibody that directly targets IL-5. Thus, it prevents the attachment of this cytokine to IL-5 receptor alpha chains in eosinophils and basophils, leading to a decrease in the number of eosinophils and, thus, in eosinophilic airway inflammation.²¹ Mepolizumab is approved for the treatment of severe asthma in children over 6 years of age (40 mg/4 weeks), adolescents (≥ 12 years), and adults (100 mg/4 weeks).²²

The adverse reactions associated with the use of mepolizumab described in clinical trials were headache in 29% of patients, asthma worsening in 27%, bronchitis in 21%, and injection-site reactions in 12%. Two individuals developed severe Herpes

zoster, and for this reason, the US Food & Drug Administration recommends vaccinating patients older than 50 years with indication for using this drug. Recently, in a retrospective study on anaphylaxis related to immunobiological agents used to enhance type 2 response, Li et al. identified 102 cases caused by mepolizumab. Sixty-nine patients received mepolizumab for the treatment of severe asthma, 1 for chronic eosinophilic pneumonia, and 32 had unknown indication. Of the 102 cases, 2 (2%) resulted in death, and 31 (30%) required hospitalization.^{21,23-25}

Mepolizumab showed to be well tolerated in the pediatric population. However, there was the report of a case of histiocytic necrotizing lymphadenitis and another case of varicella infection after exposure to mepolizumab, both in 12-year-old patients.^{26,27}

Benralizumab

Benralizumab was the second anti-IL-5 agent approved in Brazil for severe eosinophilic asthma in patients 18 years and older. It is a humanized monoclonal antibody (IgG1 κ) that targets the IL-5 receptor alpha subunit, resulting in eosinophil and basophil apoptosis via antibody-dependent cytotoxicity and decreased formation of these cells.²⁸

It is subcutaneously administered at a dose of 30 mg every 4 weeks in the first 3 doses and then every 8 weeks.^{21,29}

In clinical trials, the percentage of patients who had an adverse event with benralizumab ranged from 65% to 75%. The most commonly reported adverse events were nasopharyngitis (12-21%) and asthma worsening (11-13%). Hypersensitivity reactions (anaphylaxis, angioedema, urticaria) occurred in approximately 3% of individuals. Li et al. found 63 reported cases of anaphylaxis by benralizumab, with a risk for prolonged hospitalization higher than that of other immunobiological agents, with reports of requirement for hospitalization in 27 (42.86%) patients. For other biological agents, the proportion was the following: omalizumab (28.92%), mepolizumab (29.81%), and dupilumab (40.32%).^{25,30}

A multicenter phase 3 extension study included patients from pivotal trials, SIROCCO and CALIMA, who received benralizumab 30 mg every 4 or 8 weeks, in addition to those who had received placebo in these studies. The latter patients were re-randomized in a 1:1 ratio, to receive benralizumab 30 mg every 4 or 8 weeks. In this two-year study, named BORA, the

most common serious adverse events were asthma exacerbation (3-4%) and pneumonia (< 1 to 1%).³¹

Despite concerns with the risk of suppression of anthelmintic immunity by immunobiological drugs targeted at IL-5, so far there is no report of cases that developed parasitic infections during or after trials of such products.³² However, we consider it advisable to perform an investigation for helminthic infestation in patients with indication for anti-IL-5 biological agents.

Dupilumab

Dupilumab is the first fully human immunobiological agent developed for allergic diseases and targets the IL-4 alpha receptor, which inhibits IL-4 and IL-13 signaling.²¹ This monoclonal antibody was approved for moderate-to-severe DA (children \geq 6 years, adolescents, and adults), severe eosinophilic asthma (\geq 6 years), and CRSwNP (\geq 18 years). The dose is variable, depending on indication.³

In a 52-week phase 3 study involving 1,902 asthmatic patients, including adolescents and adults, dupilumab showed a good safety profile.

The most common reactions, compared with placebo, were injection-site reaction (14-18% vs. 6%), oropharyngeal pain (2% vs. 1%), and eosinophilia (4.1% vs. 0.6%).³⁴ Another study observed eosinophilia in up to 14% vs. 1% with placebo.³⁵ Transient eosinophilia may reach \geq 3,000 cells/ μ L and is believed to result from inhibition of migration of these cells to tissues.^{32,34} The consequences of this hypereosinophilia were rare: two patients presented with eosinophilic pneumonia, in addition to another two patients with vasculitis compatible with eosinophilic granulomatosis with polyangiitis.³⁰ Currently, there are no recommendations on monitoring of eosinophilia in patients using dupilumab.

Dupilumab was assessed in children with severe asthma and aged from 6 to 11 years. The frequency of adverse events during the 52 weeks of the study was similar between test and placebo groups. Serious adverse events were reported in 13 patients (4.8%) in the dupilumab group and in 6 (4.5%) in the placebo group. Eosinophilia occurred in 5.9% and 0.7% of the patients in the dupilumab and placebo group, respectively. Most episodes of eosinophilia were self-limited laboratory findings without any associated symptoms. The frequency of conjunctivitis was low in both groups; one case of keratitis was reported in each group.³⁶

The pathogenesis of conjunctivitis associated with dupilumab is still not totally elucidated. An association between pre-existing ocular diseases related to AD may be responsible for the increased incidence of conjunctivitis in patients treated with dupilumab, but it was not identified in studies on other type 2 diseases. A possible explanation would be an increase in expression of IFN γ , the Th1 cytokine, which would cause secretory dysfunction and loss of conjunctival goblet cells, worsened by IL-13 inhibition due to dupilumab.³⁷

Other ocular complications occurred in 1-10% of patients in the form of blepharitis, ocular pruritus, keratitis, and dry eye. Orofacial herpes simplex infection was also reported in 1-10% of patients. Hypersensitivity reactions, especially generalized urticaria, occurred in 0.1-1%. Much rarely, there was the development of serum sickness (< 0.01%).³⁰

As for anaphylaxis, a recently published study identified 62 patients who developed anaphylaxis due to dupilumab, most of which used this drug for AD (23; 37%) and severe asthma (19; 30.6%). The others received dupilumab for the following indications: 2 (3.2%) for aspirin-exacerbated respiratory disease; 1 (1.6%) for CRSwNP; and 1 (1.6%) for unknown indication.²⁵

In phase 3 trials with dupilumab for CRSwNP, adverse events were rare. In the trial that lasted for 24 weeks, LIBERTY NP SINUS-24, the more common events were nasopharyngitis, CRSwNP worsening, headache, asthma worsening, epistaxis, and injection-site erythema. In the LIBERTY NP SINUS-52 trial, which assessed use of dupilumab for 52 weeks, the most frequent adverse events were cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions.³⁸

Recently, a systematic review was conducted to evaluate the association between use of dupilumab and development or worsening of psoriasis symptoms. Twenty-six studies with 47 patients met the review inclusion criteria. All patients were adults (age range, 24-92 years), and most of them (43; 91%) were given dupilumab for AD. The remaining patients were given dupilumab for asthma (1), alopecia areata (1), and other dermatitis (2). The interval from initiation of dupilumab to development/worsening of psoriasis was 3.7 months. Psoriasis led to cessation of dupilumab in 16 of the 33 patients (48%) for which cessation vs. continuation was reported. The accurate immunological mechanism through which dupilumab induces the development of psoriasis in certain

patients remains unknown. This is believed to be due to the fact that IL-4 levels were high in AD, and that this cytokine downregulates T-helper 1 and T-helper 17 lymphocytes, both of which are increased in patients with psoriasis. Dupilumab may prevent this inhibition by blocking IL-4 signaling, which promotes the occurrence of psoriatic inflammation. This explanation is consistent with the already known observation that coexistence of psoriasis and AD in the same patient is less common than expected based on the prevalence of the two diseases.³⁹

Close remarks

Increased prevalence of asthma and allergic diseases resulted in the need for investigations on new treatments to better control symptoms, improve quality of life, and reduce serious crises and hospitalizations. Advances in knowledge on pathogenic mechanisms allowed for identification of different endotypes and phenotypes, as well as new therapeutic targets involved in allergic inflammation. Availability of effective immunobiological agents to control these diseases is extremely important, but patient safety is always the primary goal.

The main adverse events of immunobiological agents that act on type 2 response are mostly mild, such as injection-site reaction, respiratory tract infection, and headache. The mechanisms of action of these immunobiological agents have low potential for immunosuppression, with good safety profiles with regard to infections. We emphasize frequency or severity of respiratory tract infection, including SARS-CoV-2, are not statistically higher, compared to placebo, in subjects using immunobiological agents described here.

A small risk for anaphylaxis has also been described; thus, we highlight the importance of using these medications in day-hospitals, with medical supervision.

In the future, the development of biomarkers can help prevent the risk for adverse events, especially immediate reactions, for which protocols of investigation and desensitization need to be improved and standardized. Therefore, it is important to perform clinical and laboratory monitoring of adverse events (e.g., eosinopenia or eosinophilia).

Finally, it is worth highlighting that the use of immunosuppressive agents, occasionally used in the treatment of allergic diseases, is associated

with adverse events. With the development of precision medicine, immunobiological agents have been increasingly incorporated into the practice of allergists and immunologists. These drugs cause hypersensitivity reactions, but, fortunately, most of them have low severity.

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