ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Practical guide for the use of immunobiologic agents in allergic diseases - ASBAI

Guia prático para o uso de imunobiológicos em doenças alérgicas - ASBAI

Filipe Wanick Sarinho[1,2], Norma de Paula Motta Rubini[3,4], Aldo José Fernandes Costa[5,2], Eduardo Costa de Freitas Silva[6,2], Fabrício Prado Monteiro[7,2], Faradiba Sarquis Serpa[8,9], Marta de Fátima Rodrigues da Cunha Guidacci[10,2], Martti Anton Antila[11,2], Nelson Guilherme Bastos Cordeiro[12,13], Rosana Câmara Agondi[14,15], Sérgio Duarte Dortas Júnior[16,2], Régis de Albuquerque Campos[17,18], Ekaterini Simões Goudouris[19,20], Fábio Chigres Kuschnir[21,22], João Negreiros Tebyriçá[23,2], Nelson Augusto Rosário Filho[24,2]

ABSTRACT

Monoclonal antibodies are a new class of drugs that represent a milestone in the evolution of therapy for severe allergic diseases. In addition to allowing targeted immunologic therapy, they can improve symptom control, reduce exacerbations, and increase quality of life and safety. The efficacy and safety of monoclonal antibodies in the treatment of allergic diseases are well documented in pivotal, extension, and real-life clinical studies. In Brazil, immunobiologic agents are currently licensed by the National Health Surveillance Agency (ANVISA) for use in asthma, atopic dermatitis (AD),

RESUMO

Os anticorpos monoclonais são uma nova classe de medicamentos que representa um marco na evolução da terapia de doenças alérgicas graves. Além de possibilitar uma terapia imunológica alvo específico, proporciona maior controle de sintomas, redução de exacerbações, melhoria da qualidade de vida e da segurança. A eficácia e a segurança dos anticorpos monoclonais no tratamento de doenças alérgicas estão bem documentadas nos estudos clínicos pivotais, de extensão e de vida real. No Brasil, estão licenciados atualmente pela Agência Nacional de Vigilância

1. Assistant Professor at the Universidade Federal de Pernambuco (UFPE) - Centro de Pesquisa em Alergia e Imunologia (HC-UFPE).
2. Member for Departamento Científico de Imunobiológicos of the Associação Brasileira de Alergia e Imunologia (ASBAI).
3. Emeritus Professor of Allergy and Immunology at the Escola de Medicina e Cirurgia at the Universidade Federal do Estado do Rio de Janeiro (UNIRIO).
4. Coordinator at the Departamento Científico de Imunobiológicos at ASBAI.
5. PhD in Nutrition at the Universidade Federal de Pernambuco (UFPE).
6. PhD in Medicine at the Universidade do Estado do Rio de Janeiro (UERJ).
7. Assistant Professor of Immunology and Genetics at the Faculdade de Medicina at the Universidade Vila Velha.
8. Professor at the Escola Superior de Ciências at the Santa Casa de Misericórdia de Vitória (EMESCAM).
9. Member for Deprtamento Científico de Asma at ASBAI.
10. Physician at the Secretaria de Saúde do Distrito Federal.
11. Preceptor physician for Programas de Residência Médica em Dermatologia, Pediatria e Otorrinolaringologia at the Pontifícia Universidade Católica de São Paulo.
12. Professor for Curso de Pós-Graduação em Alergia e Imunologia at the Hospital Central de Exército (HCE)/UNIFASE.
13. Member for Departamento Científico de Dermatite Atópica at ASBAI.
14. PhD in Sciences at the Faculdade de Medicina at the Universidade de São Paulo (USP).
15. Member for Departamento Científico de Urticária at ASBAI.
16. Physician for Serviço de Imunologia Hospital Universitário Clementino Fraga Filho at the Universidade Federal do Rio de Janeiro (UFRJ).
17. Associate Professor at the Faculdade de Medicina at the Universidade Federal da Bahia (UFBA).
18. Coordinator for Departamento Científico de Urticária at ASBAI.
19. Professor for Departamento de Pediatria of the Faculdade de Medicina at the Universidade Federal do Rio de Janeiro (UFRJ).
20. Scientific Director at ASBAI.
21. Associate Professor for Departamento de Pediatria at the Escola de Ciências Médicas at the Universidade do Estado do Rio de Janeiro (UERJ).
22. President at ASBAI.
23. Professor of Allergy and Immunology at the Universidade Federal do Estado do Rio de Janeiro (UNIRIO).
24. Professor of Pediatrics at the Universidade Federal do Paraná (UFPR).

Submitted Nov 30 2023, accepted Dec 14 2023.

Arq Asma Alerg Imunol. 2023;7(4):339-66.

http://dx.doi.org/10.5935/2526-5393.20230054-en

eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndrome (HES), and chronic spontaneous urticaria (CSU). With the incorporation of these new therapies into the daily practice of the allergist and immunologist, practical aspects will naturally emerge and require practical guidelines in light of the most current scientific evidence in order to maintain good medical practice, with judicious and conscious use by a qualified specialist. Therefore, in this practical guide, we will address the immunobiologic agents currently approved for severe allergic diseases, aiming to assist allergy and immunology specialists in the prescription and practical management of these medications, including indications, contraindications, efficacy and safety monitoring, adverse event reporting, as well as health care factors associated with vaccination, special populations, access, transport, storage, and home use.

Keywords: Monoclonal antibodies, asthma, urticaria, atopic dermatitis, eosinophilic esophagitis, nasal polyps.

Sanitária (ANVISA) imunobiológicos para asma, dermatite atópica (DA), esofagite eosinofílica (EoE), granulomatose eosinofílica com poliangeíte (GEPA), rinossinusite crônica com pólipo nasal (RSCcPN), síndromes hipereosinofílicas (SHE) e urticária crônica espontânea (UCE). Com a incorporação do uso dessas novas terapias no dia a dia do médico alergologista e imunologista, naturalmente emergem aspectos práticos que exigem orientações práticas perante as evidências científicas mais atuais, a fim de se manter a boa prática médica, com uso criterioso e consciente pelo especialista capacitado. Assim, nesse guia prático, abordaremos os imunobiológicos aprovados até o momento para doenças alérgicas graves, com objetivo de auxiliar o especialista em Alergia e Imunologia na prescrição e manejo dessas medicações, incluindo indicações, contraindicações, monitoramento da eficácia e segurança, notificação de eventos adversos, bem como aspectos associados aos cuidados com vacinas, populações especiais, acesso, transporte, armazenamento e aplicação domiciliar.

Descritores: Anticorpos monoclonais, asma, urticária, dermatite atópica, esofagite eosinofílica, pólipos nasais.

Introduction

Progress has been made in our understanding of the pathogenesis of allergic diseases and the identification of phenotypes and endotypes, in parallel with the development of target therapies, which has allowed us to apply the concept of precision medicine to treat patients with severe allergic diseases. In parallel with the development of this knowledge, a number of practical factors have had an impact on the incorporation of these new therapies into allergists' and immunologists' routine.

Immunobiologic agents are high molecular weight molecules with a complex structure, produced in organisms or live cell cultures acting on the immune system. They comprise several classes: vaccines, serums, immunoglobulins, monoclonal antibodies, fusion proteins, and human cytokines. In this guide, we will look at monoclonal antibodies, which are the most recent class and the most widely used in severe allergic diseases.[1,2] Currently, monoclonal antibodies are an emerging class of drugs and are licensed by ANVISA in Brazil for the following conditions: asthma, atopic dermatitis (AD), eosinophilic oesophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndromes (HES), and chronic spontaneous urticaria (CSU). Among the drugs licensed in the Sistema Único de Saúde (SUS, Brazil Unified Health System), only omalizumab and mepolizumab are for the treatment of severe asthma.[3] In the supplementary health care system, 4 immunobiologic agents have been incorporated onto the Agência Nacional de Saúde (ANS, Brazil National Health Agency) list of procedures: omalizumab, mepolizumab, benralizumab, and dupilumab, covering various indications.[4] In 2022, ANVISA licensed tezepelumab for the additional treatment of patients with severe asthma and it has not yet been incorporated for use in the SUS or in supplementary health care.

The efficacy and safety of monoclonal antibodies in the treatment of allergic diseases are well documented in pivotal and extension clinical studies. In addition, real-life studies (RLS) have been conducted for most biological agents and allergic conditions. Further use in clinical practice needs to be judicious, with supervision by a trained physician, monitoring during application, continuous evaluation of the response to treatment, and any potential adverse events.[5,6]

This practical guide aims to help the Allergy and Immunology specialist with the prescription of immunobiologic agents, including: indications, contraindications, monitoring efficacy and safety, reporting adverse events, and practical details of transport, storage, and application.

Immunobiologic agents

Omalizumab

Mechanism of action

Omalizumab is a humanized IgG1 monoclonal antibody whose main mechanism of action is the neutralization of circulating IgE. This immunobiologic agent specifically binds to the Cε3 portion of the circulating free IgE molecule and thus prevents it from binding to its FcεRI and CD23 receptors on the surface of mast cells, basophils, and other cell types. As demonstrated in several studies, as a result of the formation of omalizumab-IgE complexes in the circulation, a reduction in the expression of FcεRI on the surface of mast cells and basophils is observed, with a reduction in the activation and degranulation of these effector cells and the production of IgE. As a result, the recruitment of inflammatory cells to the target tissue, especially eosinophils, is inhibited and, therefore, the use of omalizumab minimizes the T2 inflammatory cascade that characterizes the pathogenesis of allergic asthma.[7-9]

Omalizumab also reduces the number of a subtype of dendritic cells that are increased in asthma exacerbations, contributing to the control of type 2 inflammation. In addition, evidence shows that patients treated with omalizumab produce more IFN-α in response to rhinovirus and influenza infections, which could be associated with a reduction in the number of exacerbations triggered by these infectious agentes.[10]

Omalizumab is effective in severe allergic asthma, as it reduces the number of exacerbations, controls symptoms, improves quality of life, reduces the use of oral corticosteroids, and improves lung function.[11]

In CRSwNP, this immunobiologic agent has shown efficacy in reducing the size of polyps, improving symptom control and quality of life.[12]

Spontaneous chronic urticaria (SCU) is currently considered an autoimmune disease, in which the presence of IgG anti-FcεRI or IgG anti-IgE autoantibodies (type IIb autoimmunity) producing mast cell degranulation is observed. Another mechanism described is the presence of IgE class autoantibodies against autoallergens (type I autoimmunity). Omalizumab exerts its effects through serum IgE level reduction, which decreases binding to IgG class anti-IgE autoantibodies, thus reducing IgE class autoantibody levels. In addition, the expression of the FcεRI receptor in cutaneous mast cells and basophils is reduced, thus decreasing the activation of these cells and reducing the action of anti-FcεRI IgG autoantibodies.[13-15] Omalizumab has been shown to be effective in SCU through reduced onset of urticaria and angioedema, skin pruritus, and a significant improvement in quality of life.[13]

Indications and contraindications

Omalizumab is indicated as an add-on treatment for adults and children (over 6 years old) with persistent, moderate to severe allergic asthma with symptoms inadequately controlled by inhaled corticosteroids (ICS). Also, 2 other indications include complementary treatment for adults (over 18 years old) with CRSwNP in which treatment with intranasal corticosteroids has not promoted adequate control of the disease; and additional treatment for adult patients and adolescents over 12 years old with spontaneous chronic urticaria refractory to treatment with H1 antihistamines.

Omalizumab must not be used in patients who are hypersensitive to the active substance or any other component of the product. In the filled syringe presentation, the product contains natural latex and may cause allergic reactions in patients with latex allergy.[14]

Dosage regimens

In the treatment of asthma and CRSwNP, the doses of omalizumab are calculated according to the level of total serum IgE (IU/mL) and the weight of the patient (kg). The established dose is 0.016 mg/kg per IU/mL of total IgE ranging from 1 to 4 150 mg ampoules (150-600 mg) administered subcutaneously at intervals of 2 to 4 weeks. The dose is calculated according to the weight of the patient and baseline total IgE, with total IgE levels in eligible patients ranging 30 to 1500 IU/mL and body weight of 20 to 150 kg, according to the table in the patient information leaflet (PIL).[14]

In CSU, a fixed dose of 2 150 mg vials (total dose = 300 mg) every 4 weeks is recommended. However, the latest international consensus on urticaria established that, in the absence of improvement with the initial dose of 300 mg, the dose can be increased up to 600 mg with a 2-week interval between administrations.[15]

Adverse events

In general, omalizumab has a good safety profile as demonstrated in the initial and follow-up studies over almost 20 years of use in clinical practice. The most frequently reported adverse reactions in studies of adult patients with asthma were application site reaction, respiratory infection, sinusitis, headache, and pharyngitis.[14] The risk of developing anaphylaxis to omalizumab is low, around 0.09%, the majority (77%) occurring in the first 2 hours after administration of the first 3 doses.[16] Clinical studies, and RLS in the pediatric population, have also shown an acceptable overall safety profile with no evidence of an increased risk of anaphylaxis, urticaria, hypersensitivity reactions and malignancies.[17]

In chronic spontaneous urticaria, the most common adverse events described in pivotal studies were application site reactions, followed by upper respiratory tract infections and headache.[18] In RLS, an overall average of 4% (1% to 7%) of adverse events were reported, while in clinical trials these were reported at 2.9% to 8%.[19]

In the studies of omalizumab in CRSwNP, 50.4% of patients experienced at least 1 adverse event. Most of these were mild to moderate, the most common being headache, nasopharyngitis, and reaction at the site of application.[12]

Excipients

Excipients include sucrose, histidine, histidine hydrochloride monohydrate, and polysorbate. Each diluent ampoule contains 2 mL of water for injection, used to dissolve the powder.[14]

Table 1 summarizes the clinical use of omalizumab.

Mepolizumab

Mechanisms of action

Mepolizumab is a humanized IgG1/k monoclonal antibody of murine origin that binds with high affinity to human interleukin-5 (IL-5) and prevents the interaction of this cytokine with the alpha subunit of the IL-5 receptor (IL-5R). IL-5 is an important type 2 cytokine that can be produced by the activation of acquired immunity, namely T helper 2 lymphocytes (Th2) and also by the innate immunity pathway, that is, type 2 innate lymphoid cells (ILC2), playing a fundamental role in eosinophilic inflammation. IL-5 is essential for the maturation of eosinophils in the bone marrow

Table 1
Omalizumab - summary of clinical use

Mechanism of action	Blocks circulating IgE preventing binding to its high and low affinity receptors, resulting in reduced activation of the Th2 inflammatory cascade
Indications	Additional therapy for severe allergic asthma aged > 6 years old, CSU aged > 12 years old, and CRSwNP aged > 18 years old
Dosage regimen	Asthma and CRSwNP: dosage according to total serum IgE and patient weight, administered every 2 to 4 weeks CSU: 300 mg, subcutaneously, every 4 weeks
Main adverse events	Most commonly reported adverse reactions: headache and application site reactions. Anaphylaxis was described in initial studies and has an estimated occurrence rate of 0.09%

CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps.

and their release into the blood. In humans, IL-5 acts on eosinophils, participating in their proliferation, maturation, recruitment, activation, and survival. IL-5 appears to modulate the development and function of basophils and mast cells, increasing the release of basophil mediators by binding to IL-5R present in basophils.[20]

The efficacy of mepolizumab is well documented in severe eosinophilic asthma, with reduced incidence of severe exacerbations, symptom control, improved quality of life, reduced use of oral corticosteroids, and improved lung function. Mepolizumab significantly reduces blood and sputum eosinophilia.[21]

Indications and contraindications

Mepolizumab is indicated for the treatment of severe eosinophilic asthma (≥ 6 years old), CRSwNP (≥ 18 years old), eosinophilic granulomatosis with polyangiitis - EGPA (≥ 18 years old) and hypereosinophilic syndrome (≥ 12 years old).[22]

Mepolizumab must not be used in patients with known hypersensitivity to the drug or any of its excipients.

Dosage regimens

The dosage regimens for the indications licensed in Brazil are described below and are differentiated according to the indication and age group:

Severe eosinophilic asthma - children aged 6 to 11 years - 40 mg, subcutaneously, every 4 weeks; adolescents and adults - 100 mg, subcutaneously, every 4 weeks.

CRSwNP - 100 mg, subcutaneously, every 4 weeks.

EGPA - 300 mg, subcutaneously, every 4 weeks.

HES - 300 mg, subcutaneously, every 4 weeks.

Adverse events

Real-world pivotal and extension studies, with follow-up for 3 to 5 years, report a good safety profile for anti-IL-5 therapy. The most frequently reported adverse events include headache, upper airway infections, application site reactions, and skin rashes.[23]

Excipients

Excipients include sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate dihydrate, and water for injections.[22]

Table 2 shows the clinical use of mepolizumab.

Benralizumab

Mechanism of action

Benralizumab is a humanized, afucosylated IgG1/k monoclonal antibody of murine origin that binds to the alpha subunit of IL-5R, preventing the receptor from forming and IL-5 from binding. As a result, IL-5 cannot exert its biological effects on the target cells. In addition to this mechanism of action, benralizumab interacts with the FcγRIIIα surface receptor of natural killer (NK) cells, via its Fc portion, inducing the death of resident and circulating eosinophils by antibody-dependent cell-mediated (ADCM) cytotoxicity.[21]

Studies on benralizumab in asthma have shown efficacy in reducing severe exacerbations, controlling symptoms, improving quality of life, reducing the use of oral corticosteroids, and improving lung function. Benralizumab rapidly and significantly reduces blood and sputum eosinophilia.[24]

Indications and contraindications

Benralizumab is indicated as an add-on treatment in patients with severe eosinophilic asthma ≥ 18 years old. It is contraindicated in patients with known hypersensitivity to benralizumab or any of its excipients.[25]

Dosage regimens

The dosage regimen in severe eosinophilic asthma is 30 mg (1 syringe), subcutaneously, every 4 weeks for the first 3 doses, and 30 mg (1 syringe) every 8 weeks thereafter.[25]

Adverse events

The main adverse events described are headache, nasopharyngitis, fever, pain at the application site, hypersensitivity reactions (anaphylaxis, angioedema, urticaria), exacerbation of asthma, and pneumonia.[26]

Excipients

Excipients include histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 20, and water for injections.[25]

The clinical use of benralizumab is summarized in Table 3.

Dupilumab

Mechanism of action

Dupilumab is a fully human IgG4 monoclonal antibody with binding affinity for the alpha chain of the IL-4 receptor (IL-4Rα), which is a common chain to the type I IL-4 receptor (IL-4α/IL-2Rγ) and the type II IL-4 receptor (IL-4α/IL-13Rα1), which are receptors for IL-4 and IL-13 respectively. Thus, this antibody has a dual inhibition action on 2 key cytokines in type 2 inflammation, and synergistic action on biological effects shared by IL-4 and IL-13, such as the switch

Table 2
Mepolizumab - summary of clinical use

Mechanism of action	Binds to interleukin-5 (IL-5) preventing the interaction of this cytokine with its cell receptors, reducing eosinophilic inflammation
Indications	Additional therapy for severe eosinophilic asthma in patients ≥ 6 years old; CRSwNP ≥ 18 years old; EGPA > 18 years old, and hypereosinophilic syndromes ≥ 12 years old
Dosage regimen	Asthma: children (6 to 11 years old) - 40 mg, subcutaneously, every 4 weeks and adolescents/adults - 100 mg, subcutaneously, every 4 weeks CRSwNP: 100 mg, subcutaneously, every 4 weeks EGPA: 300 mg, subcutaneously, every 4 weeks. Hypereosinophilic syndromes: 300 mg, subcutaneously, every 4 weeks
Main adverse events	Most commonly reported adverse reactions: headache, upper airway infections, application site reactions, and skin rashes

CRSwNP = chronic rhinosinusitis with nasal polyp, EGPA = eosinophilic granulomatosis with polyangiitis.

Table 3
Benralizumab - summary of clinical use

Mechanism of action	Binds to the alpha subunit of the interleukin-5 receptor (IL-5R), preventing conformation of this receptor and interaction with IL-5. It has an additional mechanism of interaction with the FcγRIIIα surface receptor of natural killer (NK) cells, triggering the death of eosinophils by antibody-dependent cell-mediated (ADCM) cytotoxicity
Indications	Additional therapy for severe eosinophilic asthma in patients > 18 years old
Dosage regimen	First 3 applications: 30 mg, subcutaneously, every 4 weeks Subsequent applications: 30 mg, subcutaneously, every 8 weeks
Main adverse events	Most commonly reported adverse reactions: headache, upper airway infections, fever and application site reactions

in B lymphocytes to IgE production, eosinophil chemotaxis, and bronchial hyperresponsiveness.[27]

The actions of IL-4 and IL-13 on the skin in atopic dermatitis include counter-regulation of the expression of filaggrin, loricrin, and involucrin in keratinocytes, and exacerbation of epidermal barrier dysfunction.[28]

In asthma with type 2 inflammation, IL-13 has important actions on the bronchial epithelium, promoting increased mucus production by goblet cells, thickening of the basal membrane and increased smooth muscle contractility. In addition, IL-4 acts on Th0 lymphocytes, stimulating their differentiation into Th2, aggravating the process of type 2 allergic inflammation.[27]

Indications and contraindications

Dupilumab is indicated in the severe form of atopic dermatitis (AD) in children aged 6 months to 11 years old and in the moderate to severe forms in adolescents and adults, whose disease is not adequately controlled with optimized topical treatment. Topical therapy for AD can be maintained during the use of dupilumab.

Dupilumab is also indicated for the treatment of severe asthma with type 2 inflammation (≥ 6 years old), chronic rhinosinusitis with nasal polyps (≥ 18 years old) and eosinophilic esophagitis (≥ 12 years old and ≥ 40 kg).[29]

The only contraindication to dupilumab, described in the package leaflet, refers to patients with known hypersensitivity to the drug or any of its components.

Dosage regimens

Dosage regimens in AD vary according to the clinical indication, age group, and body weight, and may include higher initial doses. Tables 4 and 5 describe the dosage regimens for use in patients with AD and asthma, respectively.[29]

In CRSwNP, the recommended regimen is 300 mg subcutaneously every 2 weeks, and in EoE 300 mg subcutaneously every week.[29]

Excipients

Excipients include histidine, arginine hydrochloride, sodium acetate, sucrose, polysorbate 80, and water for injections.[29]

Adverse events

Dupilumab has a good safety profile documented in pivotal studies and confirmed in 3-year extension studies in atopic dermatitis and asthma.[30,31]

The main adverse events reported with the use of dupilumab in AD are upper airway infections, conjunctivitis, headache, and application site reaction. The same profile of adverse events has been observed in studies of dupilumab for the treatment of asthma and CRSwNP, with the exception of conjunctivitis, which appears to be a specific adverse event in patients with AD. This conjunctivitis tends to be mild to moderate, affects around 10% to 23% of those treated and has a poorly understood pathogenesis. Several theories have been postulated, including ocular inflammation mediated by IL-17; eosinophilia after dupilumab administration; increased OX40L activity in the eyes; and systemic inhibition of IL-13, causing an indirect reduction in mucin production.[32]

Blood hypereosinophilia (> 1,500 cells/mm^3) is a laboratory adverse event observed in 4% to 15% of patients being treated for severe asthma with type 2 inflammation. It is often asymptomatic and does not indicate the need to stop treatment, tending to resolve after 6 months of treatment in most patients. However, 5 cases of eosinophilic granulomatosis with polyangiitis (EGPA) have been described.[6]

Dermatological changes not associated with atopy have been gradually described after the marketing of dupilumab. A recent systematic review showed that up to 45% of patients may develop a lesion not explained by the underlying disease, such as seborrheic dermatitis, rosacea-like rash, facial flushing, facial and neck erythema.[33]

Tezepelumab

Mechanism of action

Tezepelumab is a fully human monoclonal antibody (IgG2λ) that binds specifically to thymic stromal lymphopoeitin (TSLP), inhibiting its binding to the TSLP receptor complex on different target cells. TSLP is a cytokine of innate immunity belonging to the alarmin group, which acts as an activator of cellular and molecular pathways that promote airway inflammation. It is secreted by airway epithelial cells after tissue damage induced by various harmful agents including allergens, viruses, bacteria, and pollutants. TSLP interferes with the functions of several immunoinflammatory and structural cells that

Table 4
Dupilumab in atopic dermatitis: dosage regimens according to age group and weight

Age group/body weight	Initial dosing	Subsequent dosing	Dosing frequency
Adult (any weight)	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
Adolescents 12 to 17 years old			
≥ 60 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
< 60 kg	400 mg SC (2 x 200 mg)	200 mg SC	Every 2 weeks
Children 6 to 11 years old			
≥ 60 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
30 kg to < 60 kg	400 mg SC (2 x 200 mg)	200 mg SC	Every 2 weeks
15 kg to < 30 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 4 weeks
Children 6 months to < 6 years old			
15 kg to < 30 kg	300 mg SC	300 mg SC	Every 4 weeks
5 kg to < 15 kg	200 mg SC	200 mg SC	Every 4 weeks

SC = subcutaneously.

Table 5
Dupilumab in asthma: dosage regimens according to age group, weight, and comorbidities

Age group, body weight and comorbidities	Initial dosing	Subsequent dosing	Dosing frequency
Adults and adolescents	400 mg SC (2x 200 mg)	200 mg SC	Every 2 weeks
Adults with CRSwNP and/or severe AD **Adolescents with severe AD**	600 mg SC (2x 300 mg)	300 mg SC	Every 2 weeks
Children 6 to 11 years old			
≥ 15 to < 30 kg	300 mg SC	300 mg SC	Every 4 weeks
≥ 30 kg	200 mg SC	200 mg SC	Every 2 weeks

SC = subcutaneously, AD = atopic dermatitis, CRSwNP = chronic rhinosinusitis with nasal polyps.

co-express the TSLP receptor. Together with other alarmins, such as interleukin 25 (IL-25) and interleukin 33 (IL-33), TSLP prolongs the survival of type 2 innate lymphoid cells (ILC2) and stimulates these cells to produce large amounts of IL-5, interleukin 9 (IL-9) and interleukin 13 (IL- 13).[34]

In allergic asthma, by activating dendritic cells, TSLP helps promote the differentiation of undifferentiated T helper lymphocytes (Th0) into the Th2 lineage, which secrete IL-4, IL-5, and IL-13 and target B cells, eosinophils, mast cells, and airway smooth muscle cells. In nonallergic eosinophilic asthma, TSLP stimulates type 2 innate lymphoid cells to secrete IL-5 and IL-13. In neutrophilic asthma, TSLP induces dendritic cells to stimulate the development of Th17 lymphocytes, which activate neutrophils. TSLP also interacts with mast cells and airway structural cells, including epithelial cells, fibroblasts, and smooth muscle cells.[35]

Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with inflammation, such as blood eosinophils, IgE, FeNO, IL-5, and IL-13, and promotes a reduction in the frequency of severe exacerbations, emergency room visits, and hospitalizations for asthma, an improvement in pre-bronchodilator FEV_1, symptom control, and an improvement in the quality of life of asthma patients.[36,37]

Indications and contraindications

Tezepelumab is indicated as an additional therapy to maintenance treatment for patients with severe asthma aged 12 years and over, regardless of the inflammatory phenotype of the disease (T2 or nonT2).[38] It is contraindicated in patients with known hypersensitivity to tezepelumab or any of its excipients.[39]

Dosage regimens

The recommended dosage regimen for adults and adolescents (12 years and over) is 210 mg subcutaneously every 4 weeks. No dose adjustment is necessary for individuals over 65 years old or with liver or kidney dysfunction.[39]

Adverse events

In pivotal clinical studies in patients with severe asthma, the most commonly reported adverse reactions were arthralgia, pharyngitis, rash, and application site reactions.[37,40] The safety profile during the study of the drug was not evaluated. The safety profile during the long-term extension study was broadly similar to the safety profile already identified. Hypersensitivity reactions can occur after administration of tezepelumab, but no cases of anaphylaxis have been reported to date.[39]

Excipients

Excipients include L-proline, glacial acetic acid, polysorbate 80, sodium hydroxide, and water for injection.[39]

The clinical use of tezepelumab is summarized in Table 6.

Criteria for assessing efficacy

Asthma

The main clinical outcomes, which should be achieved in the treatment of severe asthma with monoclonal antibodies, are a reduction in severe exacerbations (those requiring the use of oral corticosteroids or emergency care or hospitalization), a reduction or discontinuation of the continuous use of systemic corticosteroids, an improvement in lung function, an improvement in asthma control with a reduction in symptoms and the use of rescue medication, and an improvement in the quality of life of patients, resulting in decreased use of health services (Figure 1).[41]

No criteria have been established worldwide for assessing the response to monoclonal antibodies in asthma. Some criteria, generally defined by different methodologies, involving local or regional consensus, have been suggested by different national and international groups and societies, and have yet to be better validated in real-world studies.

Table 7 describes the recently published criteria proposed by the Global Asthma Association. According to these criteria, a good response to biological therapy is considered to be when the patient meets 3 or more efficacy criteria.[42]

According to the Protocolo Clínico e Diretrizes Terapêuticas da Asma do SUS e ANS (Brazilian Unified Health System and National Supplementary Health Agency Clinical Protocol and Therapeutic Guidelines for Asthma), the criteria are similar, although they do not include potential adverse events.

Table 6
Tezepelumab: summary of clinical use

Mechanism of action	Binds to TSLP preventing its interaction with its receptor on different target cells and blocking various pathways involved in type 2 and non-type 2 asthma
Indications	Additional therapy to maintenance treatment of patients with severe asthma aged 12 years and older, regardless of the inflammatory phenotype of the disease (T2 or non T2)
Dosage regimen	210 mg dose (autoinjector), subcutaneously, every 4 weeks
Main adverse events	The most commonly reported adverse reactions were: arthralgia, pharyngitis, rash, and application site reactions

TSLP = thymic stromal lymphopoeitin.

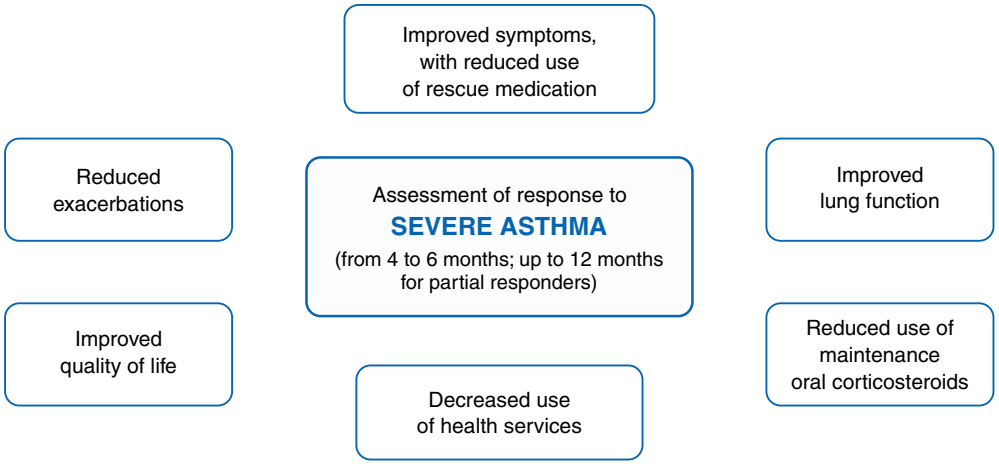

Figure 1
Objectives of biological therapy in severe asthma

The criteria proposed by Brazilian guidelines only include items 1 and 2 described in Table 7, assessed after 1 year of biological therapy.[43]

Chronic spontaneous urticaria

The main tools for assessing control and activity of CSU are the Urticaria Control Test (UCT, range 0 to 16, in which the patient is fully controlled when UCT = 16), and the 7-day Urticaria Activity Score (UAS7, range 0 to 42, in which the patient reports no urticaria activity when UAS7 = 0). The response to omalizumab should be assessed at 3 and 6 months of treatment. Around 61% of patients with CSU respond quickly to therapy within the first month of application (fast responders), and a smaller group (about 27%) responds more slowly, between month 1 and 6 of treatment (late responders).[15]

Table 7
Criteria for evaluating the efficacy of biologics in asthma

1. Reduced dose of oral corticosteroids by ≥ 50%, ideally until complete discontinuation is achieved
2. Reduced number of asthma exacerbations requiring oral corticosteroids by ≥ 50%, ideally until the absence of exacerbations is achieved
3. Minimal or no adverse events
4. Asthma control achieved: ACQ < 1.5 or ACT ≥ 20

ACQ = Asthma control questionnaire, ACT = Asthma control test.

Patients with inadequate control (UCT < 12 and/or UAS7 > 7) with the standard dosage regimen of 300 mg of omalizumab every 4 weeks should have their dosage regimen modified. The following 2 possibilities apply: reduced interval between applications to 2 weeks; or increased dose, which can be staggered, initially to 450 mg and, if necessary, subsequently to 600 mg, or increased directly to 600 mg. The treatment regimens are thus flexible and adjusted based on the assessment of disease activity and symptom control, providing patients who do not respond to the standard regimen with a better clinical response to omalizumab, with a good safety profile.[44,45]

In patients with a good clinical response to omalizumab and controlled disease, no biomarkers indicate urticaria remission. Therefore, the total duration of therapy with omalizumab in CSU has not been established, and the biological should be discontinued after complete control of symptoms to assess the possibility of disease remission. Therefore, after complete control of the CSU (UCT = 16 and UAS7 = 0) for a period of 6 months or more, the decision to discontinue treatment should follow individual medical criteria.[15]

Atopic dermatitis

Several tools are available for assessing the severity of atopic dermatitis and the response to treatment. The instruments used as primary outcomes in the pivotal studies with dupilumab were the Eczema Area and Severity Index with 75% improvement (EASI-75) and the Investigator Global Assessment Scale (IGA). Secondary outcomes included the following parameters: EASI-50, EASI-90, Severity of Atopic Dermatitis Score (SCORAD), Patient-Oriented Eczema Measure (POEM), Numerical Rating Scale for pruritus (NRS), Family Impact of Dermatitis questionnaire (FID), Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).[46-51]

Although no worldwide consensus on parameters for assessing the efficacy of dupilumab in atopic dermatitis has been established, recommendations have been made. The Portuguese guideline for the systemic therapy of atopic dermatitis recommends evaluation after 3 and 6 months of treatment, using the EASI-50 and EASI-75, NRS of pruritus and DLQI, as described in Table 8.[52]

Rhinosinusitis with nasal polyps

The expert group on chronic rhinosinusitis with uncontrolled nasal polyps and biologics of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)[53] recommends that the evaluation of the response to biologic therapy in CRSwNP should be performed after 6 and 12 months of treatment, using the following tools: olfaction assessment using a validated test, Nasal Polyp Score (NPS), Nasal Congestion Score (NCS), Sinonasal Outcome Test 22 (SNOT-22) and visual analog scale (VAS), as described in Figure 2. In addition to these instruments, the need for oral corticosteroids and a surgical approach throughout the treatment should also be assessed.

Table 8
Criteria for assessing the efficacy of dupilumab in atopic dermatitis

At 3 months of therapy
- Achieve EASI-50
- Reduced NRS by at least 3 points
- Reduced DLQI by at least 4 points

At 6 months of therapy
- Achieve EASI-75
- Achieve NRS ≤ 4 points
- Achieve DLQI ≤ 5 points

EASI-50 = Eczema Area and Severity Index with 50% improvement, NRS = Numerical Rating Scale for pruritus, DLQI = Dermatology Life Quality Index, EASI-75 = Eczema Area and Severity Index with 75% improvement.

Eosinophilic esophagitis

No standardized definition of response to the various modalities of drug therapy in EoE[54] has been established. However, the following parameters were used as primary outcomes in clinical studies of dupilumab in adolescents and adults with EoE: reduced peak eosinophil count on histopathological examination of the esophageal mucosa and reduced dysphagia symptoms assessed by the Dysphagia Symptoms Questionnaire (DSQ).[55]

The cut-off point for histological response in pivotal studies of dupilumab was 6 eosinophils/HPF (high power field). However, some authors consider 15 eosinophils/HPF to be a satisfactory response for the other therapy modalities.[56]

In studies with dupilumab, a cut-off point for reducing the DSQ score was not established, and a comparative analysis of the mean absolute reduction in the treatment group versus the placebo group was performed.[2] The DSQ evaluates a period of 14 days and the values vary between 0 and 84, with higher values indicating greater severity.[57] In clinical practice, it is necessary to set a cut-off point for a minimally significant difference. Therefore, it is reasonable to use the cut-off point proposed for other therapies, which consider a significant improvement to be a reduction of > 30% in the DSQ score.[58]

Evaluation of the clinical response to dupilumab should be performed at 3 and 6 months of treatment (the biological period in which the best response is seen).[55] In patients with a good clinical response, evaluation of histological response can only be carried out at 6 months; while in those with an absent or insufficient clinical response at 3 months, histological evaluation is also recommended at this time.[54]

In cases of discordant response between histological remission and clinical response, other parameters can be used, such as assessing inflammatory activity using endoscopy. The Endoscopic Reference Scoring System (EREFS) is the main instrument used. It assesses edema, rings, exudates, striae, and narrowing, ranging from 0 to 18, with higher scores indicating greater severity. A reduction in macroscopic inflammatory changes combined with an esophageal diameter > 15 mm has also been proposed as an outcome for clinical improvement in the endoscopic evaluation.[54,56]

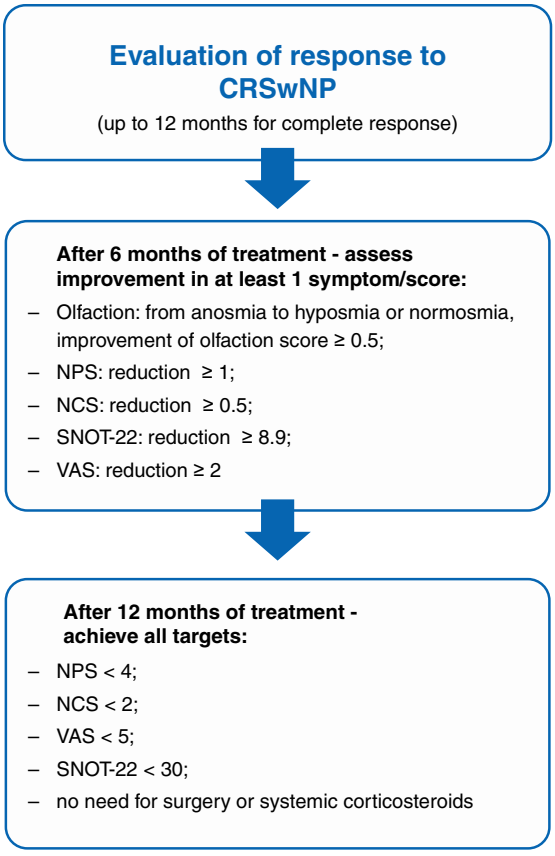

Figure 2
Assessment of response to biological therapy in CRSwNP

Olfaction = assessed by validated test (CONNECTICUT or UPSIT), NPS = nasal polyp score (Lund-Kennedy or Lund-Mackay), NCS = nasal congestion score, CRSwNP = chronic rhinosinusitis with nasal polyps, SNOT-22 (Sino-Nasal Outcome Test) = nasosinusal outcome test 22, VAS = visual analog scale.

Modified from Bachert C, et al.[53]

Hypereosinophilic syndromes

Hypereosinophilic syndromes (HSS) are a group of rare disorders characterized by high eosinophil counts in the blood (> 1,500 cells/mm^3) and/or in tissues. The clinical presentation is highly variable, involving dermatological, pulmonary, gastrointestinal, and cardiovascular manifestations.[59] Standard treatment includes corticosteroids, cytotoxic drugs, and immunosuppressive therapy. Imatinib is indicated for patients with variants sensitive to this drug. Recently, mepolizumab was approved for the treatment of patients with HSS, but criteria for response to treatment with biologics have not been established yet.[60]

However, the main primary outcomes used in the clinical studies can be applied in clinical practice as criteria for a good response, namely: 1) reduced seizures and 2) reduced dose of oral corticosteroids or maintenance immunosuppressive/cytotoxic therapy. Of course, monitoring blood eosinophilia is also important. In the pivotal clinical study, it was observed that the maximum reduction in blood eosinophil count is achieved with 8 weeks of therapy with mepolizumab.[61,62]

Monitoring, management, and reporting of adverse events

Monitoring adverse events

An adverse event (AE) with a drug can be defined as any unfavorable change to the health of the patient following their administration. They can be mild, moderate or severe, and can occur immediately after administration or after a prolonged period.[63] AEs induced by xenobiotics (traditional drugs) are mainly related to their pharmacological effects, while the adverse effects of immunobiologic agents are often related to the target molecule and the biological consequences of their actions.[26] Considering these differences, Pichler[64] proposed a special classification for adverse reactions to monoclonal antibodies, which is summarized in Figure 3.

Although pivotal and extension studies demonstrate the safety of monoclonal antibodies used in the therapy of allergic diseases and specific laboratory monitoring is not required, concerns remain about the development of adverse effects that have not been described, given the potential antigenicity of the molecules, interference with innate inflammatory response pathways, adaptive immune response and eosinophils.[5]

As for the risk of parasitosis, pre-treatment screening and monitoring during use in high-risk patients is recommended. This recommendation is based on a theoretical risk.[6]

More detailed considerations with regard to infections/parasitoses are presented in the topic developed later in this article.

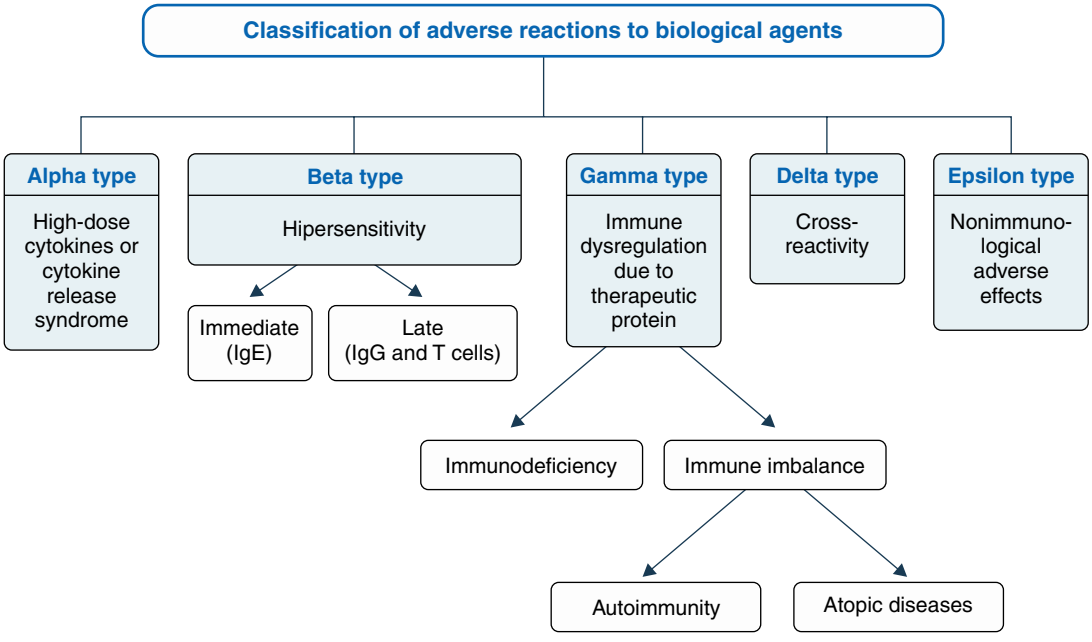

Figure 3
Classification of adverse reactions to monoclonal antibodies
Source: Pichler, 2006[64].

As for the risk of malignancy, epidemiological studies have questioned the existence of an association between cancer and some monoclonal antibodies, such as omalizumab. To date, no evidence has been found of a causal relationship between biologics used to treat allergic diseases and an increased risk of malignancies. Screening for cancer is therefore indicated according to age, sex, and specific risk factor criteria used in the general population.[6-8,11]

In summary, although no laboratory monitoring is recommended for the use of monoclonal antibodies in allergic diseases, the prescribing immuno-allergist should constantly monitor the development of the adverse events described specifically for each immunobiological (see specific section on "3 - immunobiologic agents"), and regularly update on new adverse events that may occur with the expanded use in real-world scenarios.

Table 9 compiles the most clinically relevant adverse events described to date, including systematic reviews, real-world studies, or case reports.[6,23]

Management of adverse events

Most of the adverse events (AEs) described are mild, with no need for regular laboratory monitoring or suspension of biological therapy. Local reactions in the area of application are the most common and generally do not require premedication or specific treatment.[26]

Omalizumab has an estimated risk of anaphylaxis of 0.09% and therefore prescribing physicians should talk to patients/guardians about this risk prior to treatment. Management in the event of anaphylaxis should follow guidelines established domestically and internationally.[81]

Other monoclonal antibodies have an estimated risk of nonanaphylactic hypersensitivity reactions of 1% to 2%. In mild cases, they can be managed conservatively or with symptomatic drugs such as antihistamines and/or antipyretics.[3]

Therapy with dupilumab in patients with atopic dermatitis is associated with ocular surface disease (conjunctivitis, blepharitis, and keratitis), which although frequent (14% to 23%), tends to be mild and resolve with conservative management. In some more severe or refractory cases, topical therapy should be used and joint follow-up with an ophthalmologist is recommended. Suspension of the immunobiological[66] is rarely recommended. Nonallergic skin lesions (especially on the face and neck) have been described postmarketing, but most are mild and respond to topical treatment. A systematic review estimated that 11% of these patients discontinued the medication due to this adverse event.[33]

Another concern associated with dupilumab is the presence of eosinophilia after starting treatment (up to 15% of patients). This is usually asymptomatic and tends to peak between 4-16 weeks of treatment, with a gradual decline to the baseline. Monitoring is recommended depending on the degree (see Table 9), and discontinuation is only recommended in symptomatic cases or with an alternative diagnosis (e.g. EGPA).[67,68]

As for benralizumab, it is estimated that up to 3% of patients may experience urticarial rash, although antihistamines can be used to manage this condition.[69]

Reporting adverse events

Reporting an AE is important because it allows the responsible bodies to monitor the safety of these products and identify potential risks. In general, health institutions have operational procedures for pharmacovigilance, and the physician must inform the attending pharmacist and record the AE in the medical record. In Brazil, in addition to the internal protocols of each institution, AEs involving monoclonal antibodies must be reported through the VigiMed system (available at: https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/notificacoes/vigimed), and the manufacturer of the immunobiological agent must also be notified.

Anyone can and should report an AE, but it is the physician responsibility to ensure that it is notified whenever known. Notification through VigiMed requires filling in an online form, which asks for information about the patient, the immunobiological, the AE, and the circumstances in which the product was administered.

Monoclonal antibodies and immunizations

Currently, no specific recommendations have been made in Brazil for patients taking monoclonal antibodies for allergic diseases. The calendar should be updated according to individual risk, at least 1 month before starting treatment with an immunobiological. As these are relatively new drugs, all the potential risks,

adverse effects, and interactions with the vaccines of the Programa Nacional de Imunização (PNI - Brazilian National Immunization Program)[70] are not yet known.

Because of the low theoretical risk, the monoclonal antibodies currently approved for allergic diseases can be used with inactivated vaccines (mRNA, conjugate, toxoid, and nonpathogenic viral vector

Table 9
Adverse events of biologics of major clinical importance in allergic diseases

Biologics	Systemic reactions	Other adverse events described
Omalizumab	Anaphylaxis Estimated rate - 0.09%	Case reports: – Arthralgia – Similar serum sickness – Eosinophilic granulomatosis with polyangiitis (EGPA)
Mepolizumab	Nonanaphylactic hypersensitivity reactions Estimated rate - 1% to 2% Anaphylaxis - 104 reported cases	Case reports: – Alopecia – Noncardiogenic chest pain – Histiocytic necrotizing lymphadenitis
Benralizumab	Nonanaphylactic hypersensitivity reactions Estimated rate - 1% to 3% Anaphylaxis - 63 cases Cytokine release syndrome (alpha type) - case reports	Case report: – Inflammatory disorders – Death in open-label extension study – patient developed hepatitis, *Aspergillus spp.* lung infection, and multiple organ failure
Dupilumab	Nonanaphylactic hypersensitivity reactions Estimated rate - < 1%	– Eosinophilia > 3,000 cells/mm^3 Estimated rate - 1.2% to 15% Recommendation: Patients with eosinophilia > 1,500 cells/mm^3 pre-treatment - monthly monitoring Patients with eosinophilia < 1,500 cells pre-treatment - monitoring every 3 months Note: Some patients may be diagnosed with EGPA – Conjunctivitis in patients with atopic dermatitis: Estimated rate – 14% to 23%; conservative or topical treatment. Follow-up with ophthalmologist in refractory or severe cases – Dermatological changes such as seborrheic dermatitis, rosacea, facial flushing appear in up to 45% of patients; specific treatment; discontinuation of dupilumab in refractory cases
Tezepelumab	Pivotal studies (NAVIGATOR and CASCADE): no cases. No other relevant data have been published in the literature	Case report: – Guillain-Barré syndrome

vaccines) and do not need to be suspended, as long as the application of the vaccines on the same day as the immunobiological is avoided (intervals of more than 7 days are recommended). Seasonal or periodic vaccines (flu or dTpa) should be administered without restrictions.[71]

It is important to note that although mRNA and viral vector vaccines work slightly differently to inactivated vaccines, none of them are live virus vaccines and can therefore be safely administered to patients receiving biological treatment for allergy. Thus, the vaccines currently available for COVID-19 are indicated for concomitant use with the monoclonal antibodies described here, whether they are inactivated virus vaccines (Sinovac/Butantan); mRNA vaccines (Pfizer-BioNTech; and Moderna); or viral vector vaccines (Johnson & Johnson, Oxford-Astra-Zeneca, and Verity Pharmaceuticals-Serum Institute of India).[72]

On the other hand, caution is required for live attenuated vaccines (Table 10). Although no data demonstrate an increased risk of attenuated vaccines in this context, this recommendation is based on the pivotal studies of dupilumab (SOLO 1 and SOLO 2) and tezepelumab (CASCADE AND NAVIGATOR), which did not include patients who had received attenuated vaccines in the 4 weeks prior to the start of the studies. When the benefit of an attenuated vaccine outweighs the risks, biological treatment can be interrupted based on the half-life of the drug (Table 11) and resumed as soon as the viremia of the vaccine is eliminated (e.g. the duration of viremia for the varicella virus is 14 days).[71-74]

Mepolizumab and benralizumab have been associated with a potential risk of herpes zoster reactivation (section 7 - monoclonal antibodies and infections/parasitoses). It is therefore recommended that patients with an indication for the herpes zoster vaccine (> 50 years old and/or with a risk condition) be immunized 4 weeks before starting treatment.[6,75]

Monoclonal antibodies and infections/ parasitoses

The main inflammatory response pathways to microorganisms and parasites are subdivided into type 1, type 2, and type 3 inflammation, which are directed at viruses and intracellular bacteria, parasites, and extracellular bacteria and fungi, respectively. The monoclonal antibodies used to treat allergic diseases mostly interfere with the type 2 inflammation pathway, via innate and/or adaptive immunity, which is the pathway involved in the response to allergens and eosinophilic inflammation, preserving the immune response against most microorganisms. However, mast cells and eosinophils play an important role in innate immunity and tezepelumab interferes with the top of the inflammatory cascade by blocking TSLP - an important alarmin of the innate immune system in response to various aggressions to the epithelium, including allergens, pollutants, viruses, and bacteria.

Clinical trials, extension studies, and real-world studies have generally not indicated an increased risk of infections and parasitoses. Nevertheless, specific recommendations regarding infections and parasitosis have been made for certain immunobiologic agents.[6]

Omalizumab

IgE may be involved in the immune response to helminthiases. As mentioned above (see section "Management of adverse events"), monitoring and specific treatment of patients diagnosed with helminthiasis is indicated during therapy with omalizumab. However, a Brazilian study demonstrated that omalizumab is safe in patients at high risk of helminth infections.[76]

Mepolizumab

A possible risk of herpes zoster reactivation was observed in 2 extension studies with mepolizumab in asthma. It is therefore recommended that patients eligible for the herpes zoster vaccine be immunized for this agent at least 4 weeks before starting therapy with mepolizumab (Table 11).[6]

Table 10
Live attenuated vaccines available in Brazil, 2023

BCG
Rotavirus
Measles, Mumps, Rubella (SCR)
Varicella (or SCR-V)
Yellow fever[a]
Poliomyelitis[b]
Herpes zoste[b]

[a] Consider epidemiological risk.
[b] Prefer inactivated vaccines: Poliomyelitis (IPV) and inactivated Herpes zoster.

Eosinophils participate in the immune response to helminthiases. Patients with preexisting helminthiases were excluded from the clinical trials developing mepolizumab. Patients living in areas endemic for helminthiasis should be screened pretreatment and treated if diagnosed prior to the start of therapy with mepolizumab. Patients diagnosed with helminthiasis during treatment who do not respond to anthelmintic treatment should consider temporarily discontinuing its use.[6]

Benralizumab

There have been reports of herpes zoster in studies with benralizumab, but no specific recommendations (Table 11). In relation to parasitosis, based on the theoretical risk, pretreatment screening and surveillance during therapy is recommended for patients living in or traveling to endemic areas.[6,25]

Dupilumab

Clinical trials have shown no evidence of an increase in the incidence of infections and parasitoses. In studies on atopic dermatitis, it was observed that approximately 0.4% to 1% of patients developed herpes zoster and 0.4% to 2% developed eczema herpeticum. However, these rates were no higher than those observed in the placebo group, nor are there any specific recommendations in the package leaflet.[29]

Tezepelumab

In the clinical trials of tezepelumab in asthma, no increased risk of infections has been reported. The risk of parasitosis is unknown and, considering the theoretical risk, the package leaflet recommends monitoring for helminthiases in patients being treated with this immunobiological.[39]

TSLP may be involved in the immune response to helminthiases. Before starting therapy with tezepelumab, investigation and treatment of preexisting helminthiases is recommended. If parasitosis is diagnosed during therapy and the patient does not respond to the anthelmintic, treatment with tezepelumab should be discontinued until the infestation is resolved.

Table 11
Immunization precautions, according to monoclonal antibodies

Omalizumab	No contraindications for live attenuated or inactivated vaccines
Mepolizumab	No contraindications for attenuated or inactivated vaccines
Benralizumab	No contraindications for attenuated or inactivated vaccines
Dupilumab	No contraindications for inactivated vaccines Live attenuated vaccines should be avoided. When indicated, administer 4 weeks after suspension
Tezepelumab	No contraindication for inactivated vaccines. Live attenuated vaccines should be avoided. When indicated, administer 4 weeks after suspension

Biological application in the presence of infections

No recommendations have been universally established regarding the use of biologics for allergic diseases in patients with ongoing or recent infections. However, considering that in the clinical studies the doses were not administered in the presence of viral and/or bacterial infections, it is advisable to postpone administering the dose by 7 to 14 days, or even skip an application, depending on the clinical condition of the patient and the severity of the infection.

These recommendations are also valid for the COVID-19 pandemic. During epidemic peaks, biological therapy should be maintained in patients without clinical suspicion and without household contagion, as the benefits of controlling severe allergic disease outweigh the risks of infection. In addition, the literature does not indicate that COVID-19 is more severe in patients with controlled allergic disease who are receiving biological therapy. In the event of recent exposure to SARS-CoV-2, the patient should be investigated and, if infection is confirmed, the application should be postponed.[23,70]

Use in special populations

Specific clinical trials in infants, older people, nephropaths, hepatopaths, or pregnant women are scarce. When available, they tend to be pooled with data from other patients. Literature data is limited and can be difficult to interpret. Therefore, recommending the use of immunological agents in these populations should be done with caution, bearing in mind possible risks and benefits that have not been adequately measured.

Before recommending immunological agents for women of childbearing age, patients should discuss their desire for pregnancy and contraception. For pregnant women, it should be emphasized that monoclonal antibodies are IgG antibodies and cross the placental barrier (in the order of greatest permeability: IgG1 > IgG4 > IgG3 > IgG2). Excretion in human milk generally occurs at a lower rate (1:10,000 to 1:100,000). It is important to note that even for medications considered safe during pregnancy, information on the long-term effects on the developing immune system is scarce.[77]

One important precaution when prescribing for children and adolescents is the form of application, as most drugs are parenteral. In general, nephropaths and hepatopaths tolerate monoclonal antibodies well, as the clearance of these drugs is through the reticuloendothelial system. However, these patients may have other associated conditions and their use should be monitored for worsening renal and/or hepatic function.[78] Table 12 compiles the main information available on use in special popu lations.[6,11,21,23,32,37,40,79,80] Currently, omalizumab (category B) is the only biological released for pregnant women.[77]

In summary, the use of monoclonal antibodies in special populations should be done cautiously, with due consideration for the risks and benefits involved. Specifically for pregnant women, some evidence shows that severe uncontrolled asthma increases the risk of preeclampsia, preterm birth, and gestational diabetes, in addition to the use of systemic corticosteroids and their specific risks. For CSU, no data has been provided on the risk of uncontrolled disease in pregnant women, although omalizumab appears to be effective and safe. For CRSwNP, alternative therapies are reasonable until the end of pregnancy.[79,80]

It is therefore recommended that the decision to use omalizumab in these populations be shared with the patient, discussing the limitations of the data, and warning of any theoretical risks. Comorbidities and adverse events should be monitored when indicated, and it is highly desirable to publicize these cases to share experiences.

General application precautions and guidance on home use, storage, and transportation

Biologicals for allergic diseases should be administered in a healthcare facility with the infrastructure (equipment and medicines) and healthcare staff trained to manage potential systemic adverse reactions, including orotracheal intubation and cardiopulmonary resuscitation procedures, to ensure patient safety (Table 13). In addition, transport and storage are necessary for the proper preservation of biologicals without compromising their efficacy. Therefore, Biologicals Infusion Centers are the ideal places for application, preferably in day hospital settings. Biologicals for allergic diseases can also be used in Allergy and Immunology clinics that have a type III consulting room, as provided for in CFM resolution No. 2153, available at: http://www.sbai.org.br/imageBank/resolucao-cfm-2153-consultorio-medico.pdf.

Application facilities should set up care flows, monitoring routines, and safety protocols which should be reviewed at least every 6 months. The risk of anaphylaxis and specific guidelines for medical supervision are summarized in Table 14.

The experience gained from years of using immunobiologic agents in clinical practice shows that the incidence of serious reactions during application is relatively low (< 1%), especially in patients who already use them and have no history of hypersensitivity reactions.[66]

Therefore, after the pandemic and with the advent of filled syringes, the possibility of home use of subcutaneous immunobiologic agents in low-risk patients with no history of previous reactions was considered.[6,82] Recently, the FDA authorized the use of omalizumab in a filled syringe at home in patients with no history of anaphylaxis (to any type of allergen), provided that the patient has no history of hypersensitivity reactions after receiving 3 applications initially at a health care facility. It is recommended to prescribe self-injectable adrenaline at home, a resource not readily available in Brazil.[83]

Table 12
Immunobiologic agents for special populations

Monoclonal antibodies	Pregnant women	Children	Older persons
Omalizumab	**May be recommended** Category B FDA (IgG1)	**PIL:** Asthma (≥ 6 years), CSU (≥ 12 years), CRSwNP (≥ 18 years) **Off label** CSU - retrospective study (patients ≥ 2 years)	**RCT:** up to 65 years old **RLT:** up to 83 years old
Mepolizumab	**Not recommended** Report of 1 case, with onset after first quarter	**PIL:** Severe eosinophilic asthma (≥ 6 years), EGPA (≥ 18 years), CRSwNP (≥ 18 years), HSS (≥ 12 years) **Off label:** EGPA - case report	**RCT:** up to 82 years old **RLT:** up to 80 years old
Benralizumab	**Not recommended** Not enough data	**PIL:** Severe eosinophilic asthma (≥ 12 years) **Off label:** Asthma - case report - use in 6-year-old patient	**RCT:** up to 75 years old **RLT:** up to 80 years old
Dupilumab	**Weigh risks and benefits** Report of 13 cases: no malformations; animal studies (IgG4)	**PIL:** AD (≥ 6 months), Asthma (≥ 6 years), CRSwNP (≥ 18 years), EoE (≥ 12 years) **Off label:** CSU - case report - 2 patients; Alopecia areata - case report - 2 patients	**RCT:** up to 75 years old **RLT:** up to 89 years old
Tezepelumab	**Not recommended** Not enough data	**PIL:** Severe asthma (≥ 12 years) **Off label:** HSS - case report – a 4-year-old patient	**RCT:** up to 80 years old

PIL = patient information leaflet, CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps, RCT = randomized clinical trial, RTL = real-life trial, EoE = eosinophilic esophagitis, AD = atopic dermatitis, EGPA = eosinophilic granulomatosis with polyangiitis, HSS = hypereosinophilic syndrome.

Table 13
Equipment and drugs for emergencies

Equipment for ventilatory support	Stethoscope and sphygmomanometer (adult and pediatric)
	Tourniquets, syringes, needles
	Equipment for O_2 supplementation
	Equipment for venipuncture and fluid administration
	Laryngoscope and cannulas of different sizes
	Face or laryngeal/amboo mask
	Automatic defibrillator
Drugs for emergencies	Adrenaline 1:1000 - intramuscular use
	Volume expanders: saline 0.9%
	Antihistamine - injectable use
	Bronchodilator - inhalation use
	Vasoactive drugs: noradrenaline
	Glucagon: 1 to 5 mg/dose
	Corticosteroids - injectable use

Source: Brazilian Ministry of Health, 2023.[81]

The evidence supporting the use of monoclonal antibodies at home for severe allergic diseases is based on practical experience, particularly internationally. Currently, no objective criteria have been established for the indication of treatment at home, and the physician should assess the risk, considering factors such as potential anaphylaxis, the severity of the disease, cognition and comorbidities of the patient, socioeconomic and geographical conditions, among others.[84] The choice of application site should be shared, discussed exclusively in the context of the relationship between the treating doctor and the patient, with no third party involvement, such as hospital facilities or health insurers. Patients should actively participate in this decision, once they have been explained the benefits and risks. In general, patients perceive the benefits of using medication at home to include flexibility and time optimization, less exposure to infectious agents, and the possibility of traveling for long periods, among others.[84] The risks associated with application at home include the adverse events and others discussed above. Aspects associated with the form of application, storage and transportation of the medication, living close to health facilities, and an action plan to seek immediate medical care in the event of any hypersensitivity reaction or other systemic reactions should be discussed with patients.[85,86]

Should patients have understood and decided with their physician to take the medication at home, the physician must ensure that the medication is used correctly. This includes aspects of storage, application, and disposal. Theses monoclonal antibodies must be stored in a refrigerator between 2 °C and 8 °C and cannot be frozen. Almost all monoclonal antibodies for allergic diseases can be kept out of the refrigerator for up to 14 days, provided that the room temperature does not exceed 30 °C. Benralizumab, on the other hand, should not be kept out of the refrigerator for more than 24 hours.[14,22,25,29,39]

Table 14
Risk of anaphylaxis and specific guidelines for application of immunobiologic agents

Monoclonal antibodies	Product guidelines
Omalizumab	Close medical supervision during administration and observation for 2 hours after application for the first 3 doses
Low risk of anaphylaxis	
Anaphylaxis (pivotal studies: 0.1% to 0.2%);	
EAACI Task Force: 0.09%	Close medical supervision during administration and observation for at least 30 minutes from dose 4 onwards
Most cases within 2 hours of application.	
Some cases of late onset, up to 24 hours.	
It can be triggered by any dose of omalizumab.	Home use: Only possible for patients using a filled syringe, with no history of hypersensitivity reaction after the third application.
Patients with asthma: increased risk of severe allergic reactions	Preferably carry self-injectable adrenaline.
	Precaution in patients with severe uncontrolled asthma
Mepolizumab	Close medical supervision during administration and observation for at least 30 minutes, regardless of dose number
Benralizumab	Home use: Only possible for patients using a self-injectable device, with no history of hypersensitivity reaction after the third application. Precaution in patients with severe uncontrolled asthma or still taking corticosteroids
Very low risk of anaphylaxis	
Dupilumab	Close medical supervision during administration and observation for at least 30 minutes
Tezepelumab	Home use: Evaluate home use after the third application
Extremely low risk of anaphylaxis	

In addition, patients (and their families) should be taught how to recognize the signs/symptoms of anaphylaxis and a written action plan should be prescribed. A communication channel should also be available for medical contact in the event of a reaction.[6,66,85] It is worth noting that even in the event of a reaction at home, the prescribing physician must report any adverse events (see section on "reporting adverse events").

In the absence of current case law, it is essential that prescribing physicians are aware that they may be held jointly responsible in the case of home reactions. Recording details of the discussion prior to home release in medical records is recommended, with the signing of an informed consent form (ICF) and other measures to safeguard the practitioner.

The use of monoclonal antibodies at home has peculiarities in Brazil, which should be widely discussed by health personnel, managers, patients, and their families. A thorough scientifically-based analysis can enable formal recommendations to be drawn up, including criteria that define the profile of patients suitable for using monoclonal antibodies at home. These criteria include not only clinical observations, but also sociocultural context, geographic region, logistics, and access to health services (Table 15).

Access through SUS and Supplementary Health

The incorporation of medicines into the SUS and ANS enables universal access to drug treatment, which is a fundamental right of citizens and must be guaranteed.

The development of monoclonal antibodies for the treatment of serious allergic diseases has led to the need to incorporate these technologies into the SUS and ANS. Due to their high cost, the incorporation of these drugs has become a challenge for managers, medical associations, and patients. It is crucial to promote the rational use of immunological agents to ensure the sustainability of the health system.

In the context of the SUS, 2 immunological agents for severe asthma were incorporated in the latest revision of the Ministry of Health Asthma Clinical Protocol and Therapeutic Guidelines (PCDT MS), published in 2021.[87] The immunological agents provided were mepolizumab for severe eosinophilic asthma and omalizumab for allergic asthma. The inclusion criteria in the PCDT MS are listed in Table 16.

In supplementary healthcare, the ANS has made significant progress and incorporated immunological agents for asthma, atopic dermatitis, and chronic spontaneous urticaria, creating Guidelines for use (DUT) linked to the procedure "Endovenous, intramuscular, or subcutaneous immunological therapy" (DUT No. 65), providing a regulatory framework for the use of these drugs. Benralizumab, dupilumab, and mepolizumab were incorporated for severe eosinophilic asthma[88]; dupilumab and omalizumab for severe allergic asthma[89]; dupilumab for atopic dermatitis[90] and omalizumab for chronic spontaneous urticaria.[91] Table 17 shows the different diseases, immunological agents, and their respective DUTs.

The inclusion of monoclonal antibodies for the treatment of allergic diseases in the SUS and ANS is a milestone for both public and supplementary health care in Brazil. Even with the financial and logistical

Table 15
Proposal of recommendations for the application of monoclonal antibodies for allergic diseases at home

– Assess personal risk of developing serious reactions: including individual, drug, cognitive, socioeconomic and geographical factors.
– Discuss the potential related risks; discuss the form of application and the action plan, should an adverse reaction occur
– All patients must sign an informed consent form before starting treatment
– The first 3 applications should be administered in a health care facility where emergency care can be provided, including administration of epinephrine, oxygen, bronchodilators, intravenous corticosteroids, and proceeding with emergency orotracheal intubation and/or initiating cardiopulmonary resuscitation, if necessary
– In the absence of a history of hypersensitivity reaction and after clarifying the benefits and risks, the patient wishes to have the procedure administered at home: the doctor should supervise self-application, clarifying any questions, and prescribing an action plan for adverse effects. The patient should be able to recognize anaphylaxis and treat it appropriately. Ideally, the patient should have self-injectable adrenaline
– Availability for medical contact during application hours
– Notify adverse events via the VigiMed system, available on the ANVISA website

challenges involved in these additions, the advances are promising and have the potential to transform the treatment of serious allergic diseases that were previously overlooked. Nevertheless, the rational use of these high-cost drugs is an essential strategy for maintaining the sustainability of health systems, while providing a significant improvement in the quality of medical care for patients, both in public and private services.

Final considerations

It has been 2 decades now since the first immunobiologic agents treatment for allergic diseases was licensed: omalizumab for severe asthma. Over this period, there has been a great expansion in the use of biological therapy for moderate to severe allergic diseases. Recently, access to biological therapy has become a reality in Brazil with the incorporation of

Table 16
Inclusion criteria for the use of monoclonal antibodies incorporated into the SUS and included in the Asthma PCDT MS 2021[1]

	ASTHMA PCDT MS
Drug	**Inclusion criteria**
Mepolizumab	1. Age ≥ 18 years 2. Peripheral eosinophils ≥ 300 cels/mm^3 3. At least 1 severe exacerbation in the previous year requiring a course of oral corticosteroids 4. Continuous treatment with high doses of inhaled corticosteroids (≥ 1,600 µg/day of budesonide or equivalent) associated with a LABA in the same device **OR** 5. Oral corticosteroid with a dose equivalent to at least 5mg of prednisolone daily for the last 6 months. NOTE: In item 4, some practitioners prescribe tiotropium (not incorporated into the SUS, according to Conitec Recommendation Report No. 612 - May 2021) or antileukotriene (not evaluated by Conitec) instead of oral corticosteroids
Omalizumab	1. Age ≥ 6 years 2. Weight between 20 and 150 kg 3. Total serum IgE between 30 and 1,500 IU/mL 4. Confirmation of IgE-mediated allergy through skin testing or positive specific IgE to at least 1 aeroallergen 5. At least 1 severe exacerbation in the previous year requiring a course of oral corticosteroids 6. Continuous treatment with high doses of inhaled corticosteroids (≥ 1,600 µg/day of budesonide or equivalent) associated with a LABA in the same device **OR** 7. Oral corticosteroid with a dose equivalent to at least 5mg of prednisolone daily for the last 6 months. NOTE: In item 6, some practitioners prescribe tiotropium (not incorporated into the SUS, according to Conitec Recommendation Report No. 612 - May 2021) or antileukotriene (not evaluated by Conitec) instead of oral corticosteroids

PCDT MS = Ministry of Health Asthma Clinical Protocol and Therapeutic Guidelines.

Table 17
Monoclonal antibodies incorporated by the Brazilian National Supplementary Health Agency and criteria of the guidelines of use

Indication	Drug	DUT number	DUT criteria
Severe eosinophilic asthma	Benralizumab Dupilumab Mepolizumab	65.9	a. Uncontrolled asthma, despite the use of inhaled corticosteroids associated with long-acting beta 2 agonists; **and** b. eosinophil count ≥ 300 cels/mm^3 in the last 12 months; **and** c. continuous use of oral corticosteroids for asthma control in the last 6 months or > 3 asthma exacerbations requiring oral corticosteroid treatment in the last year.
Severe allergic asthma	Dupilumab Omalizumab	65.10	a. Uncontrolled asthma despite the use of inhaled corticosteroids associated with long-acting beta 2 agonists; **and** b. evidence of sensitization to at least 1 perennial aeroallergen documented by prick skin testing or *in vitro* specific serum IgE dosage; **and** c. total serum IgE, before starting treatment, > 30 IU/ml; **and** d. continuous use of oral corticosteroids for asthma control in the last 6 months **OR** > 3 asthma exacerbations requiring oral corticosteroid treatment in the last year
Atopic dermatitis	Dupilumab	65.14	Severe atopic dermatitis with indication for systemic treatment with failure, intolerance, or contraindication to cyclosporine, which meet at least 1 of the following criteria: a. Atopic Dermatitis Activity Score - SCORAD > 50; **OR** b. Eczema Area and Severity Index - EASI > 21; **OR** c. Dermatology Life Quality Index - DLQI > 10
Chronic spontaneous urticaria	Omalizumab	65.11	Urticaria and/or angioedema for a period of more than 6 weeks, if all the following criteria are met: a. 7-day urticaria activity score (UAS7) > 28; **and** b. refractoriness to treatment with second-generation antihistamines for at least 2 weeks; **and** c. prescription by a dermatologist, immunologist or allergist **Note:** – Omalizumab treatment should be discontinued if no satisfactory therapeutic response is observed up to the fourth dose; – Following dose 6, discontinue treatment to check for spontaneous remission. If the disease recurs after discontinuation, treatment with omalizumab may be restarted at the discretion of the treating physician

various immunobiologic agents into the SUS and supplementary health care.

Currently, the prescription of immunobiologic agents is part of the therapeutic arsenal of all allergists and immunologists. In addition to theoretical and technical knowledge, the prescription of immunobiologic agents in allergic diseases must involve reflection on aspects of clinical practice, such as monitoring response, adverse events, care with application and access, as well as the cost-benefit balance.

New advances are continually being made, including the development of new monoclonal antibodies, expansion of the age range for use, and new indications for monoclonal antibodies that have already been licensed. In addition, some patients may benefit from the combined use of 2 monoclonal antibodies for concomitant allergic conditions (e.g. atopic dermatitis and urticaria) or for the potentiation of effects in the treatment of a single allergic condition (e.g. asthma), involving multiple pathogenic mechanisms.[92] Furthermore, patients with allergic diseases and other illnesses are also indicated for monoclonal antibodies therapy (e.g. asthma and Crohn's disease).[93] However, experience is still quite limited, and the combination of monoclonal antibodies should be reserved for exceptional cases, based on a shared decision between the prescribing physicians and the patient.

Finally, it should be emphasized that immunobiologic agents are new drugs and, therefore, some of the recommendations contained in this guide have not reached the desired scientific robustness yet. As such, they should be interpreted in the light of current evidence and local experiences, and should be updated periodically.

References

1. Solé D, Sano F, Rosário NA, Antila MA, Aranda CS, Chong-Neto HJ, et al. Guia prático de atualização: medicamentos biológicos no tratamento da asma, doenças alérgicas e imunodeficiências. Arq Asma Alergia Imunol. 2019;3:207-58.
2. Morita H, Matsumoto K, Saito H. Biologics for allergic and immunologic diseases. J Allergy Clin Immunol. 2022;150:766-77.
3. Ministério da Saúde. Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde – SCTIIE. Protocolo Clínico e Diretrizes Terapêuticas da Asma [Internet]. Brasília, 98 p, 2021. Available from: https://www.gov.br/conitec/pt-br/midias/consultas/relatorios/2021/20210526_pcdt_relatorio_asma_cp_39.pdf. Accessed Oct 30 2023.
4. Agência Nacional de Saúde Suplementar (ANS). Rol de Procedimentos e Eventos em Saúde. Anexo II. Diretrizes de Utilização para a Cobertura de Procedimentos na Saúde Suplementar [Internet]. Rio de Janeiro, 191 p, 2022. Available from: https://www.gov.br/ans/pt-br/arquivos/assuntos/consumidor/o-que-seu-plano-deve-cobrir/Anexo_II_DUT_2021_RN_465.2021_tea.br_RN473_RN477_RN478_RN480_RN513_RN536_RN537_RN538_RN539_RN540_RN541_RN542_RN544_546_550_553_571.pdf. Accessed Oct 30 2023.
5. Agache I, Cojanu C, Laculiceanu A, Rogozea L. Critical Points on the Use of Biologicals in Allergic Diseases and Asthma. Allergy Asthma Immunol Res. 2020;12:24-41.
6. Sitek AN, Li JT, Pongdee T. Risks and safety of biologics: A practical guide for allergists. World Allergy Organ J. 2023;16:100737.
7. Guntern P, Eggel A. Past, present, and the future of anti-IgE biologics. Allergy. 2020;75:2491-502.
8. Bousquet J, Wahn U, Meltzer EO, Fox H, Hedgecock S, Thomas K, et al. Omalizumab: an anti-immunoglobulin E antibody for the treatment of allergic respiratory diseases. Eur Respir Rev. 2008;17:1-9.
9. Hanania NA, Wenzel S, Rose K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the Effects of Omalizumab in Allergic Asthma: An Analysis of Biomarkers in the EXTRA Study. Am J Respir Crit Care Med. 2013;187:804-11.
10. Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol. 2018;141:1735-43.
11. Bousquet J, Humbert M, Gibson PG, Kostikas K, Jaumont X, Pfister P, et al. Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies. J Allergy Clin Immunol Pract. 2021;9:2702-14.
12. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146:595-605.
13. Bauer A, Dickel H, Jakob T, Kleinheinz A, Lippert U, Metz M, et al. Expert consensus on practical aspects in the treatment of chronic urticaria. Allergo J Int. 2021;24:1-12.
14. Xolair® – bula profissional [Internet]. Available from https://portal.novartis.com.br/medicamentos/wp-content/uploads/2021/10/Bula-XOLAIR-solucao-injetavel-Medico.pdf. Accessed Oct 30 2023.
15. Zuberbier T, Latiff AHA, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77:734-66.
16. Barakat L, Torres MJ, Phillips EJ, Caminati M, Chang YS, Caimmi D, et al. Biological treatments in allergy: prescribing patterns and management of hypersensitivity reactions. J Allergy Clin Immunol Pract. 2021;9:1396-9.
17. Baker DL, Nakamura GR, Lowman HB, Fischer SK. Evaluation of IgE Antibodies to Omalizumab (Xolair®) and Their Potential Correlation to Anaphylaxis. AAPS J. 2016 Jan;18:115-23.
18. Urgert MC, Van den Elzen MT, Knulst AC, Fedorowicz Z, Van Zuuren EJ. Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment. Br J Dermatol. 2015;173:404-15.
19. Tharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K, et al. Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "Real-world" Evidence. JAMA Dermatol. 2019 Jan 1;155(1):29-38.
20. Varrichi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. Curr Op Allergy Clin Immunol. 2016;16:186-200.
21. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI recomendations on the use of biologicals in severe asthma. Allergy. 2020;75:1023-42.

22. Nucala® - Bula profissional [Internet]. Available from https://br.gsk.com/media/6289/nucala-solução-injetável.pdf. Accessed Oct 30 2023.
23. Jappe U, Beckert H, Bergmann KC, Gülsen A, Klimek L, Phillip S, et al. Biologics for atopic diseases: Indications, side effect management, and new development. Allergologie Select, 2021;5:1-25.
24. Saco TV, Pepper AN, Lockey RF. Benralizumab for the treatment of asthma. Expert Rev Clin Immunol. 2017;13:405-13.
25. Fasenra® - Bula profissional [Internet]. Available from: https://www.azmed.com.br/content/dam/multibrand/br/pt/azmed-2022/home/bulas-profissionais/bulas/Fasenra_Bula_Profissional.pdf. Accessed Oct 30 2023.
26. Dortas-Junior SD, Costa AJF, Guidacci MFRC, Sarinho FW, Serpa FS, Silva EC, et al. Reações adversas aos anticorpos monoclonais para doenças alérgicas. Arq Asma Alerg Imunol. 2022;6:318-24.
27. Harb H, Chatila TA. Mechanisms of Dupilumab. Clin Exp Allergy. 2020;50:5-14.
28. Fania L, Moretta G, Antonelli F, Scala E, Abeni D, Albanesi C, et al. Multiples roles for cytokines in atopic dermatites: from pathogenic mediators to endotype specific biomarkers to therapeutic targets. Int J Mol Sci. 2022;23:2684.
29. Dupixent®- Bula profissional [Internet]. Available from: https://www.4bio.com.br/wp-content/uploads/2019/06/Dupixent.pdf. Accessed Oct 30 2023.
30. Beck LA, Thaçi D, Deleuran M, Blauvelt A, Bissonnette R, de Bruin-Weller M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21:567-77.
31. Weshley ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med. 2022 Jan;10:11-25.
32. Agache I, Akdis CA, Akdis M, Brockow K, Chivato T, Del Giacco S, et al. EAACI Biologicals guidelines-dupilumab for children and adults with moderate-to-severe atopic dermatitis. Allergy. 2021;76:988-1009.
33. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: A systematic review. J Am Acad Dermatol. 2021;84:1339-47.
34. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: Its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets. 2020;24:777-92.
35. Pelaia C, Pelaia G, Crimi C, Maglio A, Gallelli L, Terracciano R, et al. Tezepelumab: A Potential New Biological Therapy for Severe Refractory Asthma. Int J Mol Sci. 2021 Apr 22;22(9):4369.
36. Kurihara M, Kabata H, Irie M, Fukunaga K. Current summary of clinical studies on anti-TSLP antibody, Tezepelumab in asthma. Allergology International. 2023;72:24-30.
37. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B, et al. Efficacy of Tezepelumab in Severe, Uncontrolled Asthma: Pooled Analysis of the PATHWAY and NAVIGATOR Clinical Trials. Am J Respir Crit Care Med. 2023 Jul 1;208(1):13-24.
38. Global Initiative of Asthma – GINA Report 2023 [Internet]. Available from: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed Oct 30 2023.
39. Tezspire® – Bula profissional [Internet]. Available from: https://www.azmed.com.br/content/dam/multibrand/br/pt/azmed-2022/home/bulas-profissionais/bulas/Tezspire_Bula_Profissional.pdf. Accessed Oct 30 2023.
40. Menzies-Gow A, Wechsler ME, Brightling CE, Korn S, Corren J, Israel E, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. Lancet Respir Med. 2023;11:425-38.
41. Pepper AN, Hanania NA, Humbert M, Casale TB. How to Assess Effectiveness of Biologics for Asthma and What Steps to Take When There Is Not Benefit. J Allergy Clin Immunol Pract. 2021 Mar;9(3):1081-8.
42. Papaioannou AI, Fouka E, Bartziokas K, Kallieri M, Vontetsianos A, Porpodis K, et al. Defining response to therapy with biologics in severe asthma: from global evaluation to super response and remission. Expert Rev Respir Med. 2023;17:481-93.
43. Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos em Saúde. Protocolo Clínico e Diretrizes Terapêuticas da Asma 2021 [Internet]. Available from: https://www.gov.br/conitec/pt-br/midias/protocolos/20210830_pcdt_asma_pt14.pdf/view. Accessed Oct 30 2023.
44. Giménez Arnau AM, Valero Santiago A, Bartra Tomás J, Jáuregui Presa I, Labrador Horrillo M, Miquel Miquel FJ, et al. Therapeutic strategy according to differences in response to Omalizumab in patients with chronic spontaneous urticaria. J Investig Allergol Clin Immunol. 2019;29:338-48.
45. Agache I, Akdis CA, Akdis M, Brockow K, Chivato T, Del Giacco S, et al. EAACI Biologicals Guidelines-Omalizumab for the treatment of chronic spontaneous urticaria in adults and in the paediatric population 12-17 years old. Allergy. 2022;77:17-38.
46. Simpson EL, Bieber T, Guttman-Yassky E, Beck L, Blauvelt A, Cork MJ, et al. SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab vs. placebo in atopic dermatitis. N Engl J Med. 2016;375:2335-48.
47. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebocontrolled, phase 3 trial. Lancet. 2017;389:2287-303.
48. Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol. 2018;178:1083-101.
49. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156:44-56.
50. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020 Nov;83(5):1282-93.
51. Paller AS, Simpson EL, Siegfried EC, Cork MJ, Wollenberg A, Arkwright PD, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2022;400:908-19.
52. Torres T, Gonçalo M, Lopes MJP, Claro C, Ramos L, Selores M, et al. Portuguese recommendations for the treatment of atopic dermatitis with biologic therapy and JAK inhibitors in adult patients. Drugs Context. 2021;10:2021-9-5.
53. Bachert M, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. J Allergy Clin Immunol. 2021;147:29-36.
54. Dhar A, Haboubi HN, Attwood SE, Auth MKU, Dunn JM, Sweis R, et al. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic esophagitis in children and adults. Gut. 2022;71:1459-87.
55. Dellon ES, Rothemberg ME, Collins MH, Hirano I, Chehade M, Bredenoord AJ, et al. Dupilumab in adults and adolescents wuth eosinophilic esophagitis. N Engl J Med. 2022;387:2317-30.
56. Hirano I, Furuta GT. Approaches and Challenges to management of pediatric and adult patients with eosinophilic esophagitis. Gastroenteroloy. 2020;158:840-51.

57. Dellon ES, Irani AM, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther. 2013 Sep;38(6):634-4.
58. Hirano I, Collins MH, Katza DA, Mukkada VA, Falk GW, Morey R, et al. Clin Gastroenterol Hepatol. 2022;20:525-34.
59. Requena G, Van den Bosch J, Akuthota P, Kovalszki A, Steinfeld J, Kwon N. Clinical Profile and Treatment in Hypereosinophilic Syndrome Variants: A Pragmatic Review. J Allergy Clin Immunol Pract. 2022;10:2125-34.
60. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária – ANVISA. Nucala (mepolizumabe): nova indicação [Internet]. Available from: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/nucala-mepolizumabe-nova-indicacao. Accessed Oct 30 2023.
61. Roufosse F, Hahn JE, Rothember ME, Wardlaw AJ, Kilon AD, Kirby SY, et al. J Allergy Clin Immunol. 2020;146:1397-405.
62. Gleich GJ, Roufosse F, Chupp G, Faguer S, Walz B, Reiter A. Safety and Efficacy of Mepolizumab in Hypereosinophilic Syndrome: An Open-Label Extension Study. J Allergy Clin Immunol Pract. 2021;9:4431-40.
63. Carbonnel F, Wending D. The complexity of adverse side effects to biological agents. J Crohns Colitis. 2013;7:257-62.
64. Pichler WJ. Adverse side-effects to biological agents. Allergy. 2006 Aug;61:912-20.
65. Guex-Crosier Y, Di-Lucca J, Hausermann P, Laffitte E, Saulite I, Smitd-Grendelmeier et al. Management of dupilumab-associated ocular surface diseases in atopic dermatitis patients. Swiss Med Weekly. 2021;151:w30020.
66. Baddini-Martinez J, Filho FSL, Caetano LSB. Riscos anafiláticos associados a agentes imunobiológicos na terapia da asma Rev Assoc Med Bras. 2023;69:367-9.
67. Bavbek S, Pagani M, Alvarez-Cuesta E, Castells M, Dursun AB, Hamadi S, et al. Hypersensitivity reactions to biologicals: An EAACI position paper. Allergy. 2022;77:39-54.
68. Associação Brasileira de Alergia e Imunologia – ASBAI. Departamento Científico de Imunobiológicos 2023-2024. Esclarecendo ASBAI nº 3, junho 2023 [Internet]. Available from: https://asbai.org.br/esclarecendo-no-3/ . Accessed Oct 30 2023.
69. Chow TG, Oppenheimer J, Joshi SR. A Review of Adverse Reactions to Biologics Used in Allergy-Immunology Practice. J Allergy Clin Immunol Pract. 2022;10:3075-86.
70. Associação Brasileira de Alergia e Imunologia – ASBAI. Departamento Científico de Imunobiológicos 2021-2022. Recomendações de vacinação para COVID-19 em pacientes em uso de medicamentos imunobiológicos [Internet]. Available from: https://asbai.org.br/wp-content/uploads/2021/03/2021-03-22-Imunobiolo%CC%81gicos_COVID-19_PAPEL-CARTA.pdf. Accessed Oct 30 2023.
71. Martinez-Cabriales SA, Kirchhof MG, Constantinescu CM, Murguia-Favela L, Ramien ML. Recommendations for Vaccination in Children with Atopic Dermatitis Treated with Dupilumab: A Consensus Meeting, 2020. Am J Clin Dermatol. 2021;22,443-55.
72. Simonetti O, Rizzetto G, Molinelli E, Diotallevi F, Radi G, Cirioni O, et al. Safety and Efficacy of Vaccines during COVID-19 Pandemic in Patients Treated with Biological Drugs in a Dermatological Setting. Healthcare. 2021;9:401.
73. Fan R, Cohen JM. Vaccination Recommendations for Psoriasis and Atopic Dermatitis Patients on Biological Therapy: A Practical Guide. Yale J Biol Med. 2022;95:249-55.
74. Sociedade Brasileira de Imunizações. Guia de Vacinação da Sociedade Brasileira de Imunizações (SBIm) 2023-2024 [Internet]. Available from: https://sbim.org.br/images/calendarios/calend-sbim-pacientes-especiais.pdf. Accessed Oct 30 2023.
75. Mishra AK, Sahu KK, James A. Disseminated herpes zoster following treatment with benralizumab. Clin Respir J. 2019 Mar;13(3):189-91.
76. Cruz AA, Lima F, Sarinho E, Aire G, Martin C, Fox H, et al. Safety of antiimmunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. Clin Exp Allergy. 2007;37:197-207.
77. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol. 2015 Feb;135(2):407-12.
78. Kulthanan K, Rujitharanawong C, Munprom K, Trakanwittayarak S, Phumariyapong P, Prasertsook S, et al. Prevalence, clinical manifestations, treatment, and clinical course of chronic urticaria in elderly: A systematic review. Journal of Asthma and Allergy, 2015;15:1455-90.
79. Jacoby TV, Shah N, Asdourian MS, Thompson LL, Otto TS, LeBoeuf NR, et al. Dermatology evaluation for cutaneous immune-related adverse events is associated with improved survival in cancer patients treated with checkpoint inhibition. J Am Acad Dermatol. 2023 Mar;88(3):711-4.
80. Narváez-Fernández EJ, Entrala A, Nin-Valencia A, Mir-Ihara P, Losantos-García I, Domínguez-Ortega J, et al. Long-Term Omalizumab in Elderly Patients with Chronic Urticaria: Is It a Safe Therapy? Int Arch Allergy Immunol. 2023;184(10):1003-9.
81. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de Imunizações e Doenças Imunopreveníveis. Manual dos Centros de Referência para Imunobiológicos Especiais. 6a ed. Brasília: Ministério da Saúde; 2023. 176p [Internet]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/manual_centros_referencia_imunobiologicos_6ed.pdf. Accessed Oct 30 2023.
82. King C, Cox F, Sloan A, McCrea P, Edgar JD, Conlon N. Rapid transition to home omalizumab treatment for chronic spontaneous urticaria during the COVID-19 pandemic: A patient perspective. World Allergy Organ J. 2021 Oct;14:100587.
83. Novartis United States of America. Novartis receives FDA approval of Xolair® (omalizumab) self-injection with prefilled syringe across all indications for appropriate patients [site na Internet]. Available from: https://www.novartis.com/us-en/news/media-releases/novartis-receives-fda-approval-xolair-omalizumab-self-injection-prefilled-syringe-across-all-indications-appropriate-patients. Accessed Oct 30 2023.
84. Flokstra-de Blok B, Kocks J, Wouters H, Arling C, Chatelier J, Douglass J, et al. Perceptions on Home-Administration of Biologics in the Context of Severe Asthma: An International Qualitative Study. J Allergy Clin Immunol Pract. 2022 Sep;10(9):2312-2323.e2.
85. Lombardi C, Bagnasco D, Passalacqua G. Biological agents for severe asthma: the evolution of the at-home self-injection approach. Curr Opin Allergy Clin Immunol. 2020 Aug;20(4):421-7.
86. Li L, Wang Z, Cui L, Xu Y, Guan K, Zhao B. Anaphylactic risk related to omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. Clin Transl Allergy. 2021;11(4):e12038.
87. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas da Asma. Portaria Conjunta Nº 14, de 24 de agosto de 2021 [Internet]. Available from: https://www.gov.br/saude/pt-br/assuntos/protocolos-clinicos-e-diretrizes-terapeuticas-pcdt/arquivos/2021/portal-portaria-conjunta-no-14_pcdt_asma_.pdf. Accessed Oct 30 2023.
88. Brasil. Ministério da Saúde. Agência Nacional de Saúde Suplementar. Resolução Normativa Nº 513, de 31 de março de 2022 [Internet]. Available from https://bvsms.saude.gov.br/bvs/saudelegis/ans/2022/res0513_01_04_2022.html. Accessed Oct 30 2023.
89. Brasil. Ministério da Saúde. Agência Nacional de Saúde Suplementar. Resolução Normativa Nº 550, de 4 de novembro de 2022 [Internet]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/ans/2022/res0550_09_11_2022.html. Accessed Oct 30 2023.

90. Brasil. Ministério da Saúde. Agência Nacional de Saúde Suplementar. Resolução Normativa Nº 571, de 8 de fevereiro de 2023 [Internet]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/ans/2023/res0571_10_02_2023.html. Accessed Oct 30 2023.

91. Brasil. Ministério da Saúde. Agência Nacional de Saúde Suplementar. Resolução Normativa N° 465, de 24 de fevereiro de 2021 [Internet]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/ans/2021/res0465_02_03_2021.html. Accessed Oct 30 2023.

92. Pitlick MM, Pongdee T. Combining biologics targeting eosinophils (IL-4/IL-5R), IgE and IL-4/IL-13 in allergic and inflammatory diseases. W Allergy Org. 2022;15:100707.

93. Gisondi P, Maurelli M, Costanzo A, Esposito M. The combination of dupilumab with other monoclonal antibodies. Dermatol Ther. 2023;13:7-12.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Filipe W. Sarinho
E-mail: filipe.sarinho@ufpe.br