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Review Article

Biologics in allergic diseases – challenges and new directions

Imunobiológicos em doenças alérgicas – desafios e novos rumos

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ABSTRACT

The introduction of the first monoclonal antibody for asthma treatment two decades ago marked the beginning of a new era in the management of allergic diseases. Since then, new therapies using monoclonal antibodies targeting cytokines involved in type II hypersensitivity reactions or their receptors have been successfully developed, allowing control of several immunoallergic disorders, including asthma, atopic dermatitis, eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis, chronic rhinosinusitis with nasal polyps, hypereosinophilic syndrome, and chronic spontaneous urticaria. While scientific advances provide important answers, they also raise new questions. The objective of this article was to discuss and explore these issues, including the combined use of biologics, the concept of clinical remission, their potential influence on the atopic march, and the therapeutic possibilities emerging from clinical trials of new biologics for immunoallergic diseases.

Keywords: Monoclonal antibodies, immunotherapy, sublingual immunotherapy, remission induction, spontaneous remission

RESUMO

O desenvolvimento e a disponibilização do primeiro anticorpo monoclonal para o tratamento da asma, ocorrido há duas décadas, deu início a uma nova era no tratamento das doenças alérgicas. Desde então, novas terapias foram experimentadas com sucesso utilizando-se anticorpos monoclonais direcionados contra as principais citocinas envolvidas nas reações alérgicas tipo 2 ou os seus receptores, possibilitando o controle de diversas desordens imunoalérgicas como asma, dermatite atópica, esofagite eosinofílica, granulomatose eosinofílica com poliangeíte, rinossinusite crônica com pólipos nasais, síndromes hipereosinofílicas e urticária crônica espontânea. Os avanços científicos, ao mesmo tempo que trazem respostas, levantam novas questões. O presente artigo procura discutir e aprofundar estas questões como, por exemplo, o uso combinado de imunobiológicos, o conceito de remissão clínica, a potencial influência sobre a marcha atópica e as possibilidades terapêuticas que se descortinam com os ensaios clínicos de novos biológicos para as doenças imunoalérgicas.

Descritores: Anticorpos monoclonais, imunoterapia, imunoterapia sublingual, indução de remissão, remissão espontânea.

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Introduction

Two decades ago, the development and introduction of omalizumab, the first anti-IgE monoclonal antibody approved for asthma treatment, marked the beginning of a new era in the management of allergic diseases.[1] The first clinical trials of omalizumab, which targets the Fc fragment of immunoglobulin E (anti-IgE), demonstrated remarkable efficacy in controlling asthma and allergic rhinitis, especially in patients with severe asthma receiving high-dose inhaled corticosteroids, in combination with a second or third controller, or even in oral corticosteroid-dependent patients.[2]

The enthusiasm surrounding this novel therapeutic approach was initially so great that many authors speculated that the challenges of managing asthma and other IgE-mediated conditions had come to an end. However, it later became evident that anti-IgE therapy represented only the beginning of a new era: the era of precision medicine in allergic diseases.[3,4]

Since then, new therapies have been successfully developed using monoclonal antibodies targeting key cytokines involved in type 2 allergic reactions or their receptors. These advances have improved the management of several immunoallergic disorders, such as asthma, atopic dermatitis (AD), eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndromes (HES), and chronic spontaneous urticaria (CSU).[3,4]

Recently, the Brazilian Association of Allergy and Immunology (ASBAI) published a Practical Guide on the use of biologics, covering their mechanisms of action, indications, and contraindications for the medications currently approved for allergic diseases in Brazil: omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab.[4] However, in clinical practice, scientific progress both resolves long-standing questions and raises new ones.

The objective of this study was to discuss and explore emerging issues in the use of biologics for immunoallergic diseases, including the potential for combination therapy, the concept of clinical remission, the possible influence of biologics on the atopic march, and the therapeutic possibilities arising from clinical trials of novel agents.

Biologics in combination with immunotherapy

Allergen immunotherapy (AIT) is a treatment for allergic diseases aimed at inducing immune tolerance. Despite its proven efficacy, AIT is associated with potential risks of adverse events, particularly anaphylaxis.

The combination of AIT and biologics is considered a promising approach to enhance treatment safety. Emerging evidence also suggests that this combination may improve the efficacy of AIT in the treatment of allergic rhinitis, asthma, and insect venom hypersensitivity.[5]

Rationale for the use of biologics as adjuvants in AIT

The use of biologics is based on their ability to immunomodulate the type 2 inflammatory response, thereby reducing this response and allowing patients to tolerate higher allergen doses with greater safety during the desensitization process.[5]

Anti-IgE

Omalizumab, an anti-IgE monoclonal antibody, prevents free IgE from binding to FcεRI receptors in mast cells and basophils, reducing the activation of these cells and the subsequent release of inflammatory mediators such as histamine and leukotrienes, responsible for immediate allergic reactions such as anaphylaxis. In addition, by lowering circulating

IgE levels, omalizumab decreases FcεRI receptor expression, thereby reducing cellular activation upon allergen exposure.[6] Omalizumab has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe asthma, CSU, CRSwNP, and food allergy to multiple allergens.[7] In Brazil, it is approved for all of these indications except food allergy.[4]

Anti-IL-4/IL-13 receptor

Dupilumab is a monoclonal antibody that binds to the alpha chain of the interleukin (IL)-4 receptor, also present in the IL-13 receptor, thereby blocking both receptors related to the production of key cytokines in the type 2 inflammatory pathway. Thus, dupilumab clinically reduces type 2 inflammation and can lessen the severity of allergic reactions.[8] In addition, it may positively influence immune modulation in the long-term, promoting greater allergen tolerance without requiring frequent maintenance doses.[9,10] The FDA has approved dupilumab for AD, severe asthma, CRSwNP, EoE, prurigo nodularis, and eosinophilic chronic obstructive pulmonary disease.[11] In Brazil, it is approved for all of these indications as well.[4]

Anti-IL5 / Anti-IL-5R

Mepolizumab is a humanized monoclonal IgG1/k antibody that binds human IL-5 with high affinity, inhibiting this cytokine from interacting with the alpha subunit of the IL-5 receptor (IL-5R).[6]

Benralizumab is a humanized, afucosylated, monoclonal IgG1/k antibody that binds to the IL-5R alpha subunit, preventing receptor conformation and IL-5 binding. In addition to blocking IL-5 from binding with the receptor, benralizumab interacts with natural killer (NK) cell receptors via its Fc portion, inducing apoptosis of resident and circulating eosinophils through antibody-dependent cellular cytotoxicity (ADCC).[6]

IL-5 is a key cytokine in the type 2 immune response, essential for eosinophil maturation in the bone marrow and their release into the bloodstream, thus playing a central role in eosinophilic inflammation. It may also modulate basophil and mast cell development and function, enhancing mediator release via IL-5R binding. Consequently, by inhibiting IL-5, one can minimize reactions triggered, in particular, by the degranulation of eosinophils, basophils, and mast cells.[6]

Anti-TSLP

Tezepelumab is a human monoclonal antibody (IgG2λ) that specifically binds to thymic stromal lymphopoietin (TSLP), thus inhibiting its interaction with the TSLP receptor complex on various target cells. TSLP is an innate immunity cytokine belonging to the alarmin group, acting as an activator of cellular and molecular pathways that drive airway inflammation. It interferes with the function of several immunoinflammatory and structural cells that coexpress the TSLP receptor. Together with other alarmins, such as IL-25 and IL-33, TSLP promotes the survival of type 2 innate lymphoid cells (ILC2s) and stimulates them to produce large amounts of IL-5, IL-9, and IL-13 (Figure 1).[6]

Combination of aeroallergen immunotherapy and biologics

AIT with aeroallergens provides a disease-modifying approach for allergic disorders such as allergic rhinitis and asthma. Unlike traditional medications, which offer temporary symptomatic relief, AIT aims to alter the immune system's response to allergens through the gradual administration of increasing doses of diluted allergen extracts over a recommended period of 3 to 5 years.

The procedure may be administered either subcutaneously (SCIT) or sublingually (SLIT) and can be divided into two phases: an induction phase, involving gradually increasing standardized doses of specific allergens, and a maintenance phase, using fixed doses of aeroallergens. International guidelines recommend that AIT be maintained for at least 3 years to ensure sustained long-term benefits.[12]

The combination of AIT and biologics targeting the T2 response may enhance the short-term efficacy and safety of immunotherapy. Increasingly robust evidence supports the effectiveness of this approach, particularly for omalizumab.[13]

Although the approach seems promising, the indication remains under investigation, with ongoing studies aimed at assessing its long-term benefits, such as its potential to induce durable clinical and immunologic tolerance.

Omalizumab

The use of omalizumab as an adjuvant to aeroallergen AIT seems to be particularly beneficial in reducing systemic adverse reactions during the SCIT induction phase. However, it may also enhance

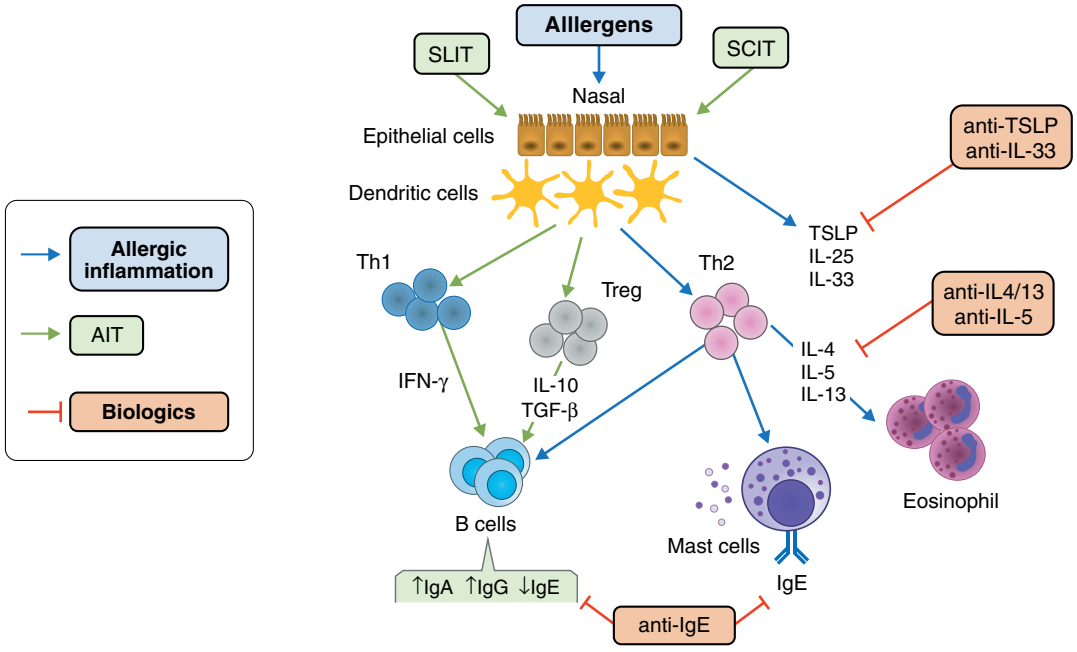

Figure 1
Interplay between AIT and biologics in modulating allergic inflammation. SLIT and SCIT shift allergic inflammation from a Th2 to a Th1 profile. Biologics target TSLP, IL-33, and IL-4/IL-13 axis, affecting epithelial alarmins and Th2 cytokines, and anti-IgE biologics prevent IgE-mediated mast cell degranulation[5]

AIT: allergen immunotherapy, IG: immunoglobulin, IL: interleukin, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy, TSLP: thymic stromal lymphopoietin.

the overall efficacy of immunotherapy. Double-blind, placebo-controlled trials suggest that combining aeroallergen SCIT with omalizumab decreases the need for rescue medication, alleviates rhinitis and asthma symptoms, and improves quality of life compared with placebo.[14-18]

In accelerated schemes, such as rush and cluster regimens, there is evidence that omalizumab improves safety, significantly reducing the rate of systemic adverse reactions.[17-19]

Table 1 summarizes the main available clinical evidence on the use of omalizumab in combination with aeroallergen AIT.[14-19]

Dupilumab

In recent years, the role of dupilumab in combination with aeroallergen AIT has been the object of research. In a double-blind, placebo-controlled trial involving patients with allergic rhinitis receiving SCIT with grass pollen in combination with dupilumab, significant improvement was observed in the nasal allergen challenge test and in total nasal symptom scores after 16 weeks of therapy, compared with patients receiving SCIT alone. The combination significantly enhanced the response to the allergen, reduced adverse events, and increased treatment tolerance, with less need for epinephrine to treat adverse reactions and a higher rate of patients achieving the maintenance dose.

Table 1
Summary of evidence on omalizumab use as adjuvant in aeroallergen immunotherapy

Study	Patients	Study design	Results
RDBPCT (Casale et al., 2006)	N = 159 Age: 18 to 50 years. Seasonal allergic rhinitis with sensitization to ragweed pollen	OMZ or placebo – 9 weeks pre-SCIT Rush SCIT + OMZ or rush SCIT + placebo – 12 weeks	OMZ group x placebo: ↓ rhinitis symptom severity score (p = 0.04) ↓ risk of anaphylaxis (p = 0.02)
RDBPCT (Kamin et al., 2010)	N = 221 Age: 6 to 16 years. Seasonal allergic rhinitis with sensitization to pollen (grass and birch)	SCIT – 12 weeks. Randomization to placebo or OMZ for 24 weeks	OMZ group x placebo: ↓ adverse reactions during SCIT (p < 0.05)
RDBPCT (Kopp et al., 2009; Kopp et al., 2013)	N = 140 Age: 11 to 46 years. Asthma and allergic rhinitis with sensitization to grass pollen	Stage 1 OMZ or placebo – 2 weeks pre-SCIT SCIT + OMZ or SCIT + placebo – 18 weeks Stage 2 SCIT maintenance after discontinuation of OMZ – 2 following years	Stage 1 OMZ group x placebo: ↓ rhinitis symptoms (p < 0.04) ↓ severity of symptoms (p = 0.004) Improved asthma control (p = 0.02) Improved QoL in asthma (p = 0.02) Improved QoL in rhinitis (p = 0.05) Stage 2 No significant difference between the two groups
RDBPCT (Massanari et al., 2016)	N = 248 Age: 18 to 55 years. Persistent asthma with sensitization to cat, dog, and house dust mite	SCIT regimen: Cluster SCIT – 4 weeks Maintenance SCIT – 7 weeks Groups: OMZ + SCIT OMZ + placebo	OMZ group x placebo: ↓ systemic adverse reactions (p = 0.01) > percentage of patients to achieve target maintenance dose (p = 0.004)
Retrospective real-world study (Valdesoiro-Navarrete et al., 2022)	N = 29 Age: 4 to 16 years. Severe asthma with sensitization to house mites, *Alternaria spp.* or pollen, after asthma control with OMZ	After OMZ for one year and controlled asthma, OMZ maintained and cluster SCIT initiated, followed by maintenance regimen (2 years)	OMZ x OMZ + SCIT: – Improvement in symptom control (p < 0.001) – Improvement in FEV_1 (p < 0.001) – Systemic adverse reactions (n): cluster SCIT – 3/64 applications maintenance SCIT – absence of reactions

FEV_1: forced expiratory volume in 1 second; OMZ: omalizumab; RDBPC: randomized, double-blind, placebo-controlled trial; SCIT: subcutaneous immunotherapy; QoL: quality of life.

Furthermore, the use of dupilumab as an adjuvant to SCIT significantly decreased serum levels of grass pollen-specific IgE (sIgE) while increasing serum levels of allergen-specific immunoglobulin G and immunoglobulin G4 (sIgG4). Thus, the sIgG4/sIgE ratio increased compared with SCIT alone, which may explain the improved tolerability during SCIT up-dosing.[20]

An observational study assessing the use of SLIT in combination with dupilumab also reported benefits from this association. Hoshino et al. assessed 47 patients with allergic rhinitis and asthma sensitized to house dust mites over a 48-week period receiving SLIT with dust mite extracts in combination with dupilumab, and found an improvement in asthma control, better quality of life for both asthma and rhinitis, an increase in forced expiratory volume in 1 second (FEV_1), and a decrease in fractional exhaled nitric oxide (FeNO).[8]

Tezepelumab

The use of tezepelumab in combination with AIT is currently under investigation, and preliminary results seem promising.

A recent clinical trial assessed the combination of SCIT with cat dander extract and intravenous tezepelumab in patients with allergic rhinitis. When comparing patients receiving SCIT alone with those receiving the combination of SCIT and tezepelumab, the results showed that combination therapy was more effective at reducing total nasal symptom scores during the nasal allergen challenge test with cat dander, with effects sustained after one year of treatment.[21]

Thus, combining tezepelumab with conventional SCIT may potentially yield greater efficacy than SCIT alone and result in greater long-term tolerance.

Combination of venom immunotherapy (VIT) and biologics

Allergic reactions to *Hymenoptera* venom can range from localized manifestations to severe systemic responses such as anaphylaxis. It is estimated that between 0.3% and 7.5% of adults may experience a systemic reaction following insect stings.[22]

Desensitization through VIT can achieve success rates of up to 96%, depending on the insect species (bees, wasps, or ants) and the venom used.[23]

Biologics have been explored as an adjuvant option in VIT, especially in patients with severe allergies and recurrent anaphylactic reactions, for whom conventional treatment may be associated with a higher risk of severe adverse events. This combination has allowed patients to achieve and maintain VIT doses that would otherwise be intolerable.[24] However, the current evidence consists mostly of case reports and retrospective studies.

The use of omalizumab as an adjuvant to VIT has been documented in patients who experience severe anaphylactic reactions during VIT, especially among individuals with a history of multiple systemic reactions.[23]

A comparative series of 10 cases showed that combining omalizumab with a high maintenance venom dose (200-300 µg) resulted in durable tolerance to VIT in patients who had previously experienced severe adverse reactions. All 10 patients in the omalizumab group successfully tolerated the induction phase to completion, whereas in the control group (5 patients), VIT had to be permanently discontinued due to repeated systemic reactions.[25]

Recently, the American College of Allergy, Asthma & Immunology (ACAAI) published guidelines recommending the use of omalizumab to reduce the risk of anaphylaxis during VIT in select cases, particularly in patients with mastocytosis.[26]

Combination of oral immunotherapy (OIT) for food allergies and biologics

Food allergies affect approximately 4% to 8% of children and 3% to 4% of adults and may manifest with severe allergic reactions, such as anaphylaxis. Although spontaneous tolerance can occur in up to 80% of cases, some patients develop persistent and severe conditions.[27]

OIT has recently been incorporated into clinical practice as a treatment capable of inducing tolerance in persistent food allergy cases, including those with anaphylactic reactions, offering a potentially safer alternative to strict exclusion diets. However, a systematic review and meta-analysis concluded that, while OIT is effective and generally safe, it considerably increases the risk of anaphylactic reactions.[28] Therefore, safer approaches, such as the use of biologics as adjuvants, have been investigated.

A pilot study investigated the benefits of combining omalizumab with OIT in 13 patients with IgE-mediated peanut allergy at high risk for anaphylactic reactions.

The results showed the benefits of combining omalizumab with OIT, particularly regarding the likelihood of achieving the maintenance dose in a higher percentage of patients.[29]

Wood et al. conducted the first double-blind, randomized, placebo-controlled trial to assess the combination of omalizumab and OIT for cow's milk. After 32 months, sustained tolerance to the allergen was observed in 48% of patients in the OIT + omalizumab group vs. 35% in the OIT-alone group, with no statistically significant difference between the two groups (p = 0.42). However, there was a significant difference in the rate of adverse events requiring treatment, with 2.1% in the OIT + omalizumab group compared with 16.1% in the OIT-alone group (p = 0.0005).[30] These data support the role of omalizumab in improving the safety of OIT.

A phase 2 trial assessed the benefits of omalizumab combined with OIT in patients with multifood allergies. The primary endpoint was the proportion of participants who successfully completed double-blind, placebo-controlled food challenges to at least 2 of the offending foods used in OIT. A higher proportion of patients in the OIT + omalizumab group (83%) achieved the primary endpoint compared with the OIT + placebo group (33%) (p = 0.004). No serious adverse events were reported, and no statistically significant differences were observed in the overall adverse event rate between the two arms of the study. The authors concluded that in patients with multifood allergies, omalizumab was able to enhance the efficacy of multifood OIT, allowing for faster and safer desensitization.[31]

In February 2024, the FDA approved omalizumab for the treatment of food allergy, based on data from the phase 3 clinical trial "Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OUtMATCH)", which assessed the efficacy of this biologic in patients allergic to peanuts associated with at least 2 other food allergens.[7,32] The study was divided into 3 stages, but only the results from Stage 1 (omalizumab vs. placebo) have been published to date. At this stage of the study, 177 patients aged 1 to 17 years were enrolled, 118 in the omalizumab group and 59 in the placebo group. The primary endpoint was defined as the ability to ingest at least 600 mg of peanut protein without dose-limiting symptoms. The study found that 67% of patients in the omalizumab group achieved the primary endpoint, compared with only 4% in the placebo group.[33]

Additional clinical trials are ongoing and are expected to provide a higher level of evidence regarding the efficacy and safety benefits of omalizumab as an adjuvant to OIT. Table 2 summarizes the main studies investigating the adjunctive role of omalizumab in OIT.[29-33]

Combined use of biologics

Combined use of biologics in allergic diseases

Indications for biologic therapy in allergic diseases are expanding. As it develops, patients may benefit from different biologic products for the same condition, such as severe asthma, or for distinct conditions, such as CSU concomitant with AD, EoE, or nonallergic asthma.

Despite several isolated case reports, case series investigating this approach are limited. Only one recent clinical trial has investigated the treatment of asthma with the combined use of dupilumab (anti-IL-4R) and itepekimab (anti-IL-33), and it did not find an increased risk of adverse events or any additional efficacy.[34-38]

A case series described 25 patients treated with a variety of combinations of biologics, 15 of which used combinations of biologics approved for asthma (anti-IL-5 + anti-IgE, anti-IgE + anti-IL-4/IL-13, and anti-IL-5 + anti–IL-4/IL-13). The duration of combination therapy in that study ranged from 3 to 49 months, and there were no reports of adverse events that limited treatment.[39]

Recently, Pitlick and Pongdee, in a case series, described 25 patients using combinations of biologics that included: omalizumab + mepolizumab, omalizumab + dupilumab, omalizumab + benralizumab, mepolizumab + dupilumab, and omalizumab + mepolizumab + dupilumab. The mean duration of treatment with a combination of biologics was 17.5 months (range, 1 to 60 months). No patient experienced anaphylaxis or other allergic reactions at any time during the use of multiple biologics. There were no reports of malignancies, renal or hepatic failure, pneumonia, or immune dysfunction after combination therapy, and no patient became pregnant during treatment.[40]

Other studies have described patients with severe asthma or allergic bronchopulmonary aspergillosis (ABPA) treated with omalizumab in combination with mepolizumab, benralizumab, or dupilumab. Four patients were identified as receiving combined anti-IgE and anti-IL-5 therapies after failure with single-agent

Table 2
Summary of evidence on omalizumab use as adjuvant in oral immunotherapy for food allergy

Study	Patients	Study design	Outcomes / Results
Pilot study (Schneider et al., 2013)	N = 13 Age: 8 to 16 years. High risk for peanut-induced anaphylaxis. Mean peanut-specific IgE = 229 kU/L; mean total serum IgE = 621 kU/L	OMZ before (12 weeks) and during OIT (8 weeks)	Primary: Maintenance dose – 4 g Results: – 92% of patients tolerated maintenance dose within 8 weeks. – Patients (n) with reactions to OIT during induction: Absent reaction – 3 Grade 1 – 9 Grade 2 – 2 Grade 3 – 0
		After week 21, discontinuation of OMZ and maintenance of OIT (maintenance)	– Patients with no reaction to OFC in week 32 – 85% – Patients (n) with reactions to OIT during maintenance: Absent reaction – 6 Grade 1 – 5 Grade 2 – 4 Grade 3 – 2
RDBPCT (Wood et al. 2016)	N = 48 Cow's milk	OIT+ OMZ OIT+ placebo 32 months	Primary Tolerance maintained: OIT + OMZ – 48% OIT + placebo – 35% (p = 0.42; NS) Rate of adverse events requiring treatment: OIT + OMZ – 2.1% OIT + placebo – 16.1% (p = 0.0005)
RDBPCT (Andorf, 2018)	N = 48 Age: 4 to 15 years. 2 to 5 food allergies	OIT + OMZ (N = 36) 12 weeks. OIT + placebo (N = 12) 36-week study	Primary: 2 g maintenance dose for each of 2 foods used in OIT. Results: OIT + OMZ: 83% OIT + placebo: 33% (p=0.004) No statistically significant differences compared to overall adverse event rate
Phase 3 clinical trial OUtMATCH (Wood et al., 2022) (Wood et al., 2024)	N = 177 Age: 1 to 55 years. Allergy to peanuts and at least 2 other foods (milk, egg, wheat, cashew nut, hazelnut, and nut)	Stage 1: OMZ vs. placebo. Stage 2: OMZ monotherapy vs. multiallergen OIT + OMZ. Stage 3: long-term results (12 to 36 months) including introduction of foods to induce or maintain desensitization	Primary: Ingestion > 600 mg of peanuts without limiting symptoms Secondary: – Ingestion of > 1000 mg of other food allergen without limiting symptoms. – Assessment of adverse events. Results: Stage 1: OMZ group – 67% Placebo group – 4% (p < 0.001)

OIT: oral immunotherapy; NS: not significant; OFC: oral food challenge; OMZ: omalizumab; OUtMATCH: Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy; RDBPC: randomized, double-blind, placebo-controlled trial.

monoclonal therapy. Three met the diagnostic criteria for ABPA. The authors concluded that combined anti-IgE and anti-IL-5 therapy should be considered in patients with severe asthma or ABPA who continue to require systemic corticosteroids or have frequent exacerbations despite single biologic therapy.[41]

Yang et al. conducted a study of patients with AD, in which those with refractory disease or insufficient response to dupilumab were divided into groups to receive combined treatment with JAK inhibitors (JAKi) or immunosuppressants. The authors concluded that the dupilumab + JAKi combination was significantly effective, without the occurrence of significant adverse events.[42]

Despite the small number of publications on the topic, the existing data provide preliminary evidence on safety for physicians treating patients with severe allergic diseases to consider the combined use of biologics and small molecules. However, prospective longitudinal studies are needed to determine efficacy and define the ideal patient population that may benefit from such combination therapy.

Combined use of biologics in allergic and inflammatory/autoimmune diseases

The combined use of medications in the treatment of allergic, inflammatory, and autoimmune diseases has proven to be an effective and promising approach in clinical practice, given that these conditions often share underlying pathogenic mechanisms, such as hypersensitivity mechanisms and inflammatory pathways.

The combined management of allergic diseases and inflammatory/autoimmune disorders requires a collaborative approach involving multiple medical specialties. The integration of traditional therapies with therapeutic innovations, such as biologic agents, has significantly improved outcomes for many patients with different immune-mediated diseases.

Due to the potential increased risk of infections and other adverse events, developing a personalized treatment plan involving a multidisciplinary team (allergist/immunologist, dermatologist, rheumatologist, gastroenterologist, etc.), as well as ensuring close monitoring throughout treatment, is essential. Assessing the sustained efficacy of concomitant therapies, given the high costs associated with biologic treatments, is equally important.

The association of type 2 inflammatory diseases with conditions such as psoriasis, psoriatic arthritis, rheumatoid arthritis, lupus, and inflammatory bowel disease may present a therapeutic challenge. Although rare, some patients present with 2 of these systemic inflammatory diseases simultaneously. For them, combination therapy with biologics may offer a viable solution.

The literature contains few reports on the concomitant use of omalizumab with other biologic agents. One case report described a patient treated with guselkumab (anti-IL-23α) for psoriasis and omalizumab for CSU for 21 months with no relevant adverse events or drug interactions.[43] Another report documented a patient who developed CSU while receiving adalimumab for psoriatic arthritis and subsequently received omalizumab concomitantly for 24 weeks. In this patient, omalizumab was discontinued after 24 weeks due to complete control of CSU.[44] Recently, a study assessed the combined use of omalizumab with 4 different biologics indicated for the treatment of psoriasis or hidradenitis suppurativa (adalimumab, ustekinumab, secukinumab, and ixekizumab) in 31 patients. No serious adverse events were observed with these combinations; only 1 patient experienced diarrhea after 9 months of combined omalizumab + secukinumab therapy, which resolved after discontinuation of secukinumab.[45]

A recently published study described 12 patients with AD receiving a combination of a Th2-axis inhibitor (dupilumab or tralokinumab) with an IL-23/Th17-axis inhibitor (guselkumab, risankizumab, or tildrakizumab) or an IL-12/IL-23 inhibitor (ustekinumab) for the treatment of psoriasis (8 patients), psoriatic arthritis (4 patients), and inflammatory bowel disease (5 patients). The mean duration of combination therapy was 560 days. Among participants, 75% (n = 9) showed clinical improvement of atopic dermatitis. In the remaining cases, one patient did not respond to treatment, another experienced worsening of arthritis after starting dupilumab, and a third lost response after an initial favorable outcome. Most patients received combination therapy to simultaneously treat psoriasis/psoriatic arthritis and AD (n = 8). Adverse events observed included ocular irritation and conjunctivitis in 17% (n = 2) of patients.[46]

Remission

Remission is a term used in health care to describe the reduction or absence of a disease's

signs and symptoms, associated with the reduction or suppression of underlying pathological mechanisms. When a patient is in remission, the signs and symptoms of their disease are under control or absent, and they are in stable health. Remission does not necessarily mean cure, but rather that the disease is not currently active. Therefore, disease remission is defined as a state or period of low or absent disease activity, which may occur spontaneously or be achieved through treatment.[47]

The concept of remission has long been used in certain malignancies, particularly hematopoietic cancers, in which treatment can induce complete remission of the disease, even after discontinuation. A similar principle applies to chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis, in which treatment can achieve and maintain a state of remission.[48]

With the advent of new therapeutic targets with disease-modifying potential for asthma treatment over the last 2 decades, the term remission has been proposed as a goal, in addition to the traditional objectives of symptom control and reduction of future risk.[47,49]

Remission, defined as complete control of disease symptoms and biomarkers, is an emerging therapeutic goal in the management of several chronic conditions. The recent application of this concept to the management of inflammatory airway diseases has advanced the notion of clinical remission, using a "treat-to-target" or targeted treatment approach.[50,51]

Remission in asthma

Some patients with asthma may become asymptomatic spontaneously and enter a prolonged symptom-free state, whether the underlying pathophysiological process persists or not. While spontaneous remission of asthma in pediatric populations is a relatively common phenomenon, remission in adults is less frequent, and its occurrence as a treatment outcome is a relatively new and evolving concept.[48,52,53]

The use of biologics targeting different aspects of the immunopathogenesis of asthma, as well as macrolides in select cases of severe asthma, has introduced the possibility of inducing disease remission. Given the wide variability of asthma phenotypes, remission can be interpreted in various clinical contexts: spontaneous remission without treatment as part of the natural history of the disease; remission during treatment; remission achieved during treatment and persisting after discontinuation; and remission with disease relapse, which may occur in any of the previous scenarios. Figure 2 illustrates the different possible evolutionary courses of asthma.[54]

Previous studies have used a wide range of criteria to define remission, considering symptom-free periods ranging from 6 months to 3 years, with the average generally being 1 year. A minimum duration of 12 months seems to be reasonable, as it encompasses the seasonality of disease activity. The remission rate ranged from 20% to 70% in early-onset asthma and from 2% to 17% in adult-onset asthma, reaching up to 29.7% among adults with asthma included in studies, regardless of the age of onset. Factors associated with remission included lower disease severity, better lung function, younger age, earlier onset of asthma, shorter disease duration, lower bronchial hyperresponsiveness (BHR), fewer comorbidities, and absence of smoking or smoking cessation.[53] In a Tasmanian cohort of more than 8000 participants, increased BHR and elevated blood levels of tumor necrosis factor-α (TNF-α) during spontaneous remission were associated with a higher risk of asthma relapse.[52]

In 2020, a task force of experts proposed, for the first time, criteria to define remission in asthma (Figure 2). These criteria were divided into clinical remission and complete remission, both of which may occur on or off treatment.[47]

Which tool is best suited to assess asthma symptoms for the purpose of defining remission has yet to be established, since the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT) were validated for assessing symptom control in symptomatic individuals, not in those in remission. Cut-off points of ACQ < 0.75 or ACT ≥ 20 are suggested, but the thresholds used across studies vary, ranging from 0 to 1 for the ACQ and from 20 to 25 for the ACT. For now, this variation in criteria will persist until a specific instrument is validated for this purpose (Table 3).

Some authors propose including the absence of beta-agonist use for symptom relief as a criterion for clinical remission. For complete remission, they suggest defining specific thresholds for biomarkers that indicate resolution of inflammation, such as blood eosinophils < 300/mm^3, sputum eosinophils < 3%, and FeNO < 40 parts per billion (ppb).[48] However, these biomarkers are only relevant for type 2 inflammation-driven asthma, whereas for non-type 2 asthma there

are still no defined markers of complete remission, with reduction in BHR possibly serving as a measurable parameter for this inflammatory phenotype.

In 2023, a consensus statement from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), together with experts from the American Thoracic Society (ATS), proposed an initial definition of asthma remission on treatment comprising 6 criteria (Figure 3). All criteria must be met over a minimum period of 12 months and may be applied to patients receiving biologic therapy for asthma.[55] However, applying these criteria requires the use of three different tools to assess risk and disease control, which is not common practice in Brazil. Furthermore, it allows the use of rescue medication up to once per month, a questionable choice, given that it would not meet a strict definition of disease remission.

Recently, several real-world studies have been published evaluating the response to biologics in asthma. Sposato et al., who defined clinical remission as asthma symptom control (ACT ≥ 20), absence of exacerbations, discontinuation of oral corticosteroid use, and FEV_1% ≥ 80%, observed this condition in 21.8%, 23.6%, 35.8%, and 23.5% of patients treated with omalizumab, mepolizumab, benralizumab, and dupilumab, respectively.[56]

Patients treated with omalizumab who were older, had higher body mass index (BMI), later age of asthma onset, comorbid sinusitis/nasal polyposis, hypertension/chronic heart disease, and a higher number of exacerbations were more likely to fail to achieve asthma remission. Poorer lung function and a higher number of exacerbations were associated with failure to achieve clinical remission with mepolizumab, while higher BMI and the presence of rhinitis were associated with failure to achieve remission among patients using benralizumab. Higher FeNO levels were associated with remission in patients treated with mepolizumab and benralizumab. The small number of patients treated with dupilumab in this study prevented the identification of significant differences for these factors. In the German Severe Asthma Registry, which included 443 adult patients under treatment, 210 of whom were receiving biologics, 58% were treated with IL-5-targeted agents (benralizumab, mepolizumab, or reslizumab), 15.7% with omalizumab, and 26.6% with dupilumab. Clinical remission, defined as adequate symptom control (ACT ≥ 20), absence of systemic corticosteroid use, and absence of exacerbations for 12 months or longer, was achieved by 17.2% of patients treated without biologics and by 37.6% of those receiving biologic therapy.[57]

In conclusion, with the advent of therapies that have disease-modifying potential, albeit limited to

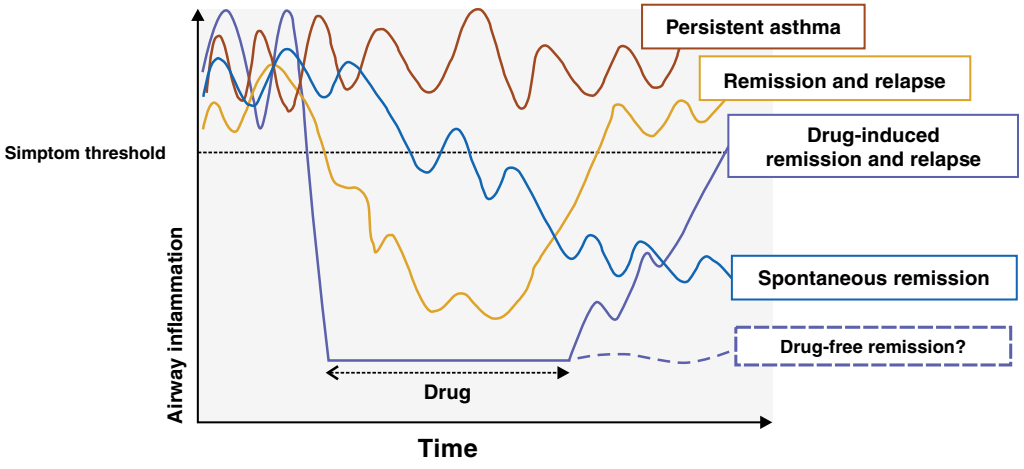

Figure 2
Possible progressions of asthma on and off treatment
Source: Cohn J.[54]

Table 3
ACAAI/AAAAI/ATS criteria for remission in treatment

1.	No exacerbations requiring a physician visit, emergency care, hospitalization, and/or systemic corticosteroids for asthma (ie, oral, injectable).
2.	No missed work or school over a 12-month period due to asthma-related symptoms.
3.	Stable and optimized pulmonary function results on all occasions, when measured over a 12-month period, with a minimum of two measurements during the year.
4.	Continued use of controllers (ICS, ICS-LABA, leukotriene receptor antagonists) ONLY at low-medium dose of ICS (or less) as defined by most recent GINA guidelines.
5.	ACT score > 20, AirQ < 2, ACQ < 0.75 on all occasions measured in the previous 12 months, with a minimum of 2 measurements during the year.
6.	Symptoms requiring reliever therapy (SABA, ICS-SABA, ICS-LABA) no more than once a month.

ACQ: Asthma Control Questionnaire; ACT: asthma control test; AirQ: Asthma Impairment and Risk Questionnaire; GINA: Global Initiative in Asthma; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; SABA: short-acting beta-agonist.
Source: Blaiss M et al.[54]

the inflammatory component of asthma and not to the structural alterations associated with bronchial remodeling, remission in asthma has become a feasible therapeutic goal, beyond mere symptom control and functional stabilization. Further studies involving the use of biologics and azithromycin in severe asthma, with larger patient populations, are needed to establish standardized criteria for clinical, functional, and complete remission. In addition, it is crucial to assess the true potential of these therapies in pursuing remission, to identify which factors or treatable characteristics predict the greatest likelihood of success with various medications, and to determine the risk factors for relapse after achieving remission.

Remission in chronic rhinosinusitis with nasal polyps

Remission in CRSwNP is defined as sustained disease control for ≥ 12 months, associated with the absence of active disease, preferably confirmed by nasal endoscopy. Remission may be achieved on or off treatment, provided there has been no use of systemic corticosteroids or surgery (within the previous 12 months). In a state of remission, patients experience no exacerbations and therefore do not require systemic corticosteroids and/or rescue surgery for nasal polyps.[58]

A Canadian consensus statement has proposed combining symptom assessment with nasal endoscopy to define successful outcomes after endoscopic sinus surgery, with outcomes considered “optimal” in the absence of symptoms combined with a normal appearance of the sinus mucosa on endoscopy.[59]

Randomized clinical trials (RCTs) of biologics in patients with CRSwNP, although not specifically designed to assess remission, have provided insights into concepts and tools that may be useful for its definition. RCTs (eg, benralizumab in the OSTRO trial; dupilumab in SINUS-24 and SINUS-52; mepolizumab in SYNAPSE; and omalizumab in POLYP-1 and POLYP-2) used several outcome measures to define clinical response. All these studies adopted as primary endpoints the change from the baseline Nasal Polyp Score (NPS) combined with the improvement in nasal congestion severity (NCS) or the Visual Analogue Scale (VAS) for nasal obstruction. Secondary endpoints included symptom improvement, quality of life assessed by SNOT-22, Lund-Mackay score on computed tomography (CT), peak nasal inspiratory flow, and the need for surgery or systemic therapy.[60-64]

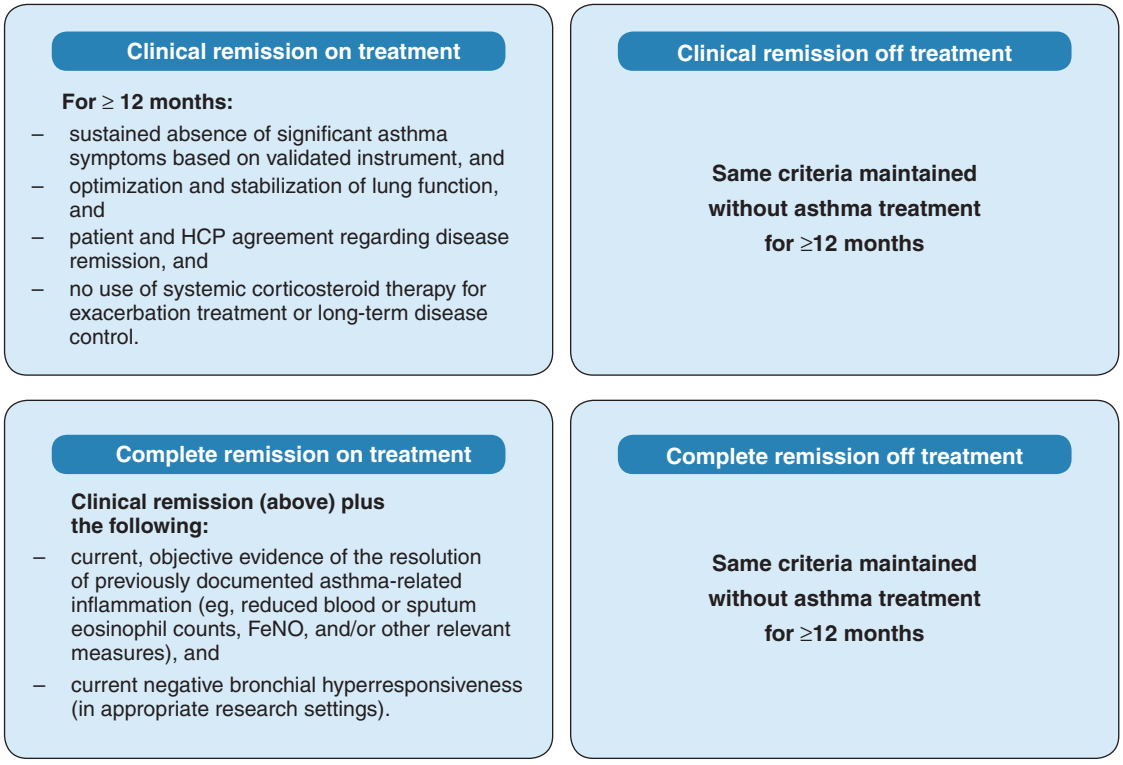

Figure 3
Suggested criteria for remission in asthma
FeNO = fractional exhaled nitric oxide.
Source: Menzies-Gow A, et al.[47]

The EPOS2020/EUFOREA expert consensus considered both patient-reported symptom control and physician assessment when defining remission. For this reason, the absence of signs of active disease, preferably confirmed through nasal endoscopy, is regarded as an important therapeutic goal. The presence of nasal discharge, edema, polypoid degeneration, and nasal polyps may be considered signs of active disease, although further research is needed to identify specific signs predictive of loss of CRSwNP control.[58]

In addition to the definition of remission in CRSwNP, the term "cure" has been proposed when remission is sustained off treatment for at least 5 years.[58] Further studies, including the identification of specific biomarkers, are needed to distinguish active from inactive nasal polyposis.

Remission in atopic dermatitis

The natural history of AD encompasses several trajectories, which can be subdivided into the following main patterns: (1) early onset transient, (2) early onset persistent, and (3) late onset persistent. Remission may occur spontaneously, particularly in pediatric patients. Analysis from the GUSTO cohort (Growing Up in Singapore Towards Healthy Outcomes), which followed 1,152 patents from three months of age to eight years, evaluated the prevalence and natural history of AD and estimated that 43% of pediatric patients exhibited the transient early-onset phenotype.[65]

There is still no established definition of remission in AD either during treatment or after discontinuation of biologics, and the available data come mostly from extension studies. Blauvelt et al. investigated

the rate of clinical remission both during and after discontinuation of dupilumab therapy in adolescents in a 52-week extension study including 102 patients, where clinical remission was defined as clear or almost clear skin sustained for 12 weeks. Among participants aged 12 to 17 years, 29.4% achieved sustained remission during therapy and stopped medication. Of these, 43.3% maintained remission without therapy, while 56.7% required reinitiation of dupilumab over a median follow-up of 18 weeks.[66]

A similar study assessing the clinical remission rate of AD in 254 children aged 6 to 11 years over a 52-week period, using comparable remission criteria, found that 28.7% achieved sustained remission while on dupilumab. Among them, 60.3% maintained clinical remission after discontinuing treatment for a median period of 15.7 weeks.[67] These data suggest a higher likelihood of sustained remission after discontinuation of treatment in children compared to adolescents. In both studies, the 12-week period used to define clinical remission was quite short, especially considering that AD alternates between periods of improvement and exacerbation in most patients. Furthermore, the follow-up period after discontinuation of treatment (ranging from 15 to 18 weeks) also seems inadequate to reliably estimate remission rates off treatment.

Miyamoto et al. conducted a study assessing sustained clinical remission in 109 adolescent and adult patients with AD after discontinuing treatment with dupilumab. The criterion for remission was defined as controlled disease for 6 months with proactive topical therapy, and documented a 20% sustained remission rate, with a mean duration of 40 weeks. Dupilumab levels declined gradually, with complete elimination in 8 to 10 weeks. When comparing baseline characteristics of patients with sustained remission versus those with recurrence of AD, the only parameter to display a significant difference was a younger age in the sustained remission group.[68]

A real-world study from Japan examined clinical remission rates during treatment with dupilumab and its maintenance after discontinuation in adults treated for up to 5 years. Fifty-eight patients were analyzed, of which 25 (43%) achieved significant control of AD after at least 12 months of treatment and discontinued therapy. Among them, 18 (31%) required reinitiation of dupilumab due to disease exacerbation, while only 7 (12%) maintained clinical remission after discontinuation. The authors conducted a comparative analysis to compare patients with sustained remission after discontinuing dupilumab and the group that required reinitiation due to exacerbation of AD. Patients with sustained remission after dupilumab discontinuation had, before treatment, lower Patient-Oriented Eczema Measure (POEM) and VAS scores for pruritus, lower serum thymus and activation-regulated chemokine (TARC) levels, and longer treatment duration (mean of 2 years) before discontinuation, compared with the group who had exacerbations after discontinuing biologics (mean of 1 year).[69]

The currently available data are still preliminary and do not allow for definitive conclusions; therefore, its is necessary standardized criteria for defining clinical remission in AD. Equally important is the identification of biomarkers of inflammatory activity that can be applied to assess treatment response as well as serve as predictors of sustained clinical remission.

Influence of biologics on the atopic march

The concept of the atopic march was proposed in 2003 to describe the axis of immune dysregulation shared by atopic diseases, the risk of developing respiratory allergies in patients with AD, and the typical progression of atopic manifestations—AD, asthma, and allergic rhinitis.[70] Subsequently, IgE-mediated food allergy was incorporated into the atopic march, as it frequently follows the onset of AD.[71] More recently, the inclusion of EoE in the atopic march has been proposed due to its strong association with atopic diseases, leading to a change in the term to “allergic march.” In most cases, EoE represents the final manifestation in this sequence.[72]

The allergic march does not always follow the classical pattern proposed initially; multiple trajectories are possible in the development of 2 or more clinical manifestations of atopic conditions, either sequentially or concurrently, depending on genetic predisposition, environmental exposures beginning in utero, and socioeconomic conditions, as illustrated in Figure 4.[73] Although there may be various trajectories, AD is the first manifestation in the majority of cases. It has been hypothesized that type 2 inflammation and epithelial barrier dysfunction in AD promote cutaneous sensitization to both food and airborne allergens.[74]

The rationale for the use of biologics in the treatment of allergic diseases includes, among other benefits, preventing the development of additional atopic comorbidities. This effect stems from the ability of biologics to act on multiple points of the type 2

inflammatory pathway, including a reduction in alarmin production in response to environmental stimuli (tezepelumab), a decrease in IgE sensitization specific to food and aeroallergens (dupilumab), and restoration of the skin barrier in AD (dupilumab).[75-77]

Given that AD is the first manifestation of atopy in nearly all cases, and that dupilumab is approved for use from 6 months of age with proven efficacy across multiple atopic comorbidities, this biologic theoretically has the greatest potential to disrupt the allergic march.

A retrospective population-based cohort study (TriNet Collaborative Network US) investigated whether dupilumab reduced the risk of developing asthma and allergic rhinitis in pediatric patients (<18 years of age) with AD and no pre-existing respiratory allergy at treatment initiation. The study included 2190 patients treated with dupilumab and 2192 patients in the control group receiving conventional AD therapy over a 3-year period. There was a 40% reduction in asthma and a 31% reduction in allergic rhinitis in the dupilumab group compared to the control group. Moreover, among patients who did develop asthma and/or allergic rhinitis, symptom severity and use of maintenance or rescue therapy were lower, suggesting a disease-modifying effect on respiratory allergy severity.[78]

A meta-analysis including 12 clinical trials and assessing 3525 patients over the age of 12 with AD (dupilumab group = 2296; control group = 1229) assessed both the risk reduction for developing new allergic diseases and the improvement in control of existing atopic comorbidities over a 52-week period. Treatment with dupilumab reduced the overall risk of developing new allergic diseases in 37% of patients. The study also found better control of concomitant allergic diseases and a significant reduction in serum IgE levels in patients treated with dupilumab compared with the control group.[79]

A prospective study conducted in the Netherlands (Dutch Bioday Registry) assessed the impact of dupilumab on the control of atopic comorbidities in patients undergoing treatment for AD. Among patients with a history of food allergy, there was a 70.5% to 82.5% reduction in food allergen-specific IgE levels (peanut, hazelnut, almond, and cashew) and a 60% reduction in allergic symptoms following accidental ingestion of these foods. In patients with allergic rhinitis and/or asthma, there was also a significant reduction in aeroallergen-specific IgE levels, ranging from 61.3% to 89.1%.[80]

Omalizumab blocks circulating IgE and the signaling through the IgE receptor, thereby inhibiting both immediate and late-phase allergic responses, and its efficacy in asthma is well established. Furthermore, it helps reduce asthma exacerbations during viral seasons and enhances interferon-α (IFN-α) release in response to rhinovirus infection, which may provide an additional protection against the development of asthma, since rhinovirus is one of the main triggers for the onset of persistent asthma in children.[81] In addition, omalizumab has been shown to raise the threshold for clinical reactivity to food allergens and was recently approved by the FDA for the treatment of patients (aged >1 year) with IgE-mediated multifood allergies, indicating potential for food allergy prevention.[7,33] Currently, the Prevention of Asthma in High-Risk Kids (PARK) study is underway, aiming to investigate the prevention of asthma development and reduction of disease severity risk in children aged 2 to 3 years at high risk for developing allergies.[82]

New biologics

Despite the significant advances achieved with the use of biologics in patients with severe allergic diseases, there are still gaps and unmet needs. The heterogeneity of allergic diseases makes it difficult to standardize treatment for all individuals. Personalizing therapies based on phenotypes and endotypes is essential to improve efficacy. Some patients do not meet the eligibility criteria for currently available biologics, while others show partial or no response to current biologics, and some have mixed phenotypes with overlapping inflammatory pathways. Moreover, adverse reactions can occur, including the development of anti-drug antibodies (ADAs). The development of innovative therapies remains essential and continues to progress as new research sheds light on the inflammatory pathways involved in allergic processes and identifies potential new therapeutic targets.[6,83-85]

Among the newly available biologics, lebrikizumab (anti-IL-13) stands out for the treatment of moderate-to-severe AD in patients aged ≥12 years, having recently been approved for use in Brazil. Lebrikizumab is a monoclonal antibody that binds to soluble IL-13, preventing the formation of the IL-13Rα1/IL-4Rα signaling complex. In pivotal studies, it showed efficacy based on the Investigator Global Assessment (IGA), with 43.1% (ADvocate1) and 33.2% (ADvocate2) of patients achieving IGA 0/1, and Eczema Area

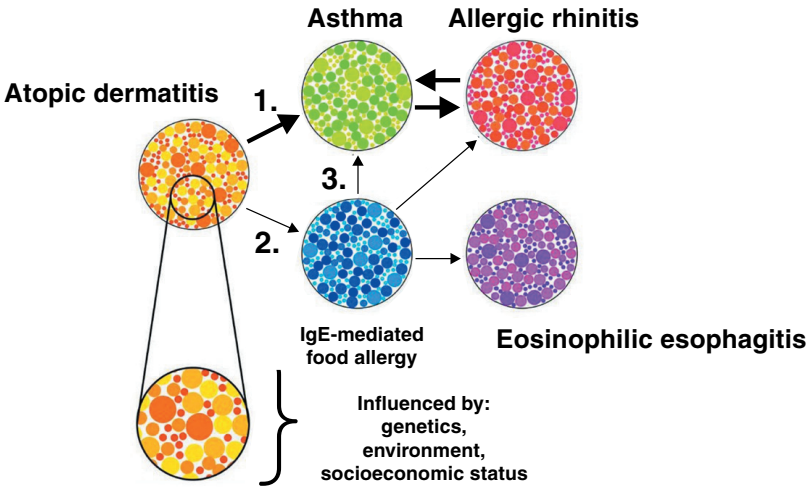

Figure 4
Atopic march trajectories
Source: Gabryszenski SJ & Hill DA.[73]

and Severity Index (EASI-75) responses in 58.8% (ADvocate1) and 52.1% (ADvocate2) of patients after 16 weeks of treatment. The most common adverse event (> 5%) was conjunctivitis, occurring in 7.4% (ADvocate1) and 7.5% (ADvocate2) of patients.[86]

As for the main biologics under investigation, there are new agents for old targets, such as anti-IL-5 (depemokimab) and anti-IL-13 (cendakimab), as well as biologics for novel targets, such as anti-IL-31R (nemolizumab), anti-IL-33 (etokimab, itepekimab, and tozorakimab), anti-OX40 (rocatinlimab, telazorlimab), and anti-OX40L (amlitelimab).[6,83]

Nemolizumab antagonizes the IL-31 receptor (IL-31RA), a key therapeutic and anti-inflammatory target in AD. IL-31 has been identified as one of the major cytokines involved in the origins of pruritus, and its serum levels correlate with AD severity. IL-31R is expressed in C-fiber nerve endings, keratinocytes, and neurons of the dorsal horn of the spinal cord. It also contributes to epidermal barrier disruption in AD, promotes nerve fiber elongation and branching, and activates pruriceptive neurons, which release neuropeptides. These neuropeptides, in turn, enhance local skin inflammation, attracting Th2 cells. Nemolizumab has been approved in Japan for patients aged ≥13 years. Clinical trials with nemolizumab found a 66% reduction in pruritus and a 78% reduction in EASI scores. The main adverse event reported was nasopharyngitis (33.9%). Additional phase 3 trials are ongoing, as well as phase 2 studies in children (aged 2-11 years) with moderate-to-severe AD.[87]

The OX40 pathway represents a promising target for therapeutic intervention in AD and bronchial asthma. OX40, a costimulatory molecule, is significantly expressed on activated T cells in patients with these conditions. The interaction of OX40 with its ligand (OX40L) drives Th2 differentiation and promotes the clonal expansion, survival, and production of memory T cells.[6] Phase 2 clinical trials of anti-OX40 antibodies

(eg, rocatinlimab and telazorlimab) and an anti-OX40L antibody (amlitelimab) have shown encouraging results in patients with moderate-to-severe AD and moderate-to-severe bronchial asthma.[88] These findings suggest that modulating the OX40 pathway may offer a novel and effective strategy for managing these conditions.

Final considerations

Biologics represent one of the most significant innovations in the treatment of allergic diseases. They have revolutionized the management of several immunoallergic conditions, such as asthma, AD, EoE, CRSwNP, and chronic urticaria. Real-world experience has confirmed the efficacy and safety of biologics in treating severe allergic diseases, substantially improving the quality of life of patients and their families.

This therapeutic modality continues to expand, with ongoing efforts to deliver broader and more effective solutions for a growing number of individuals with immunoallergic conditions. New challenges have emerged, including the combined use of biologics, the concept of clinical remission during biologic therapy, their potential influence on the atopic march, the advantages of combining biologics with allergen-specific immunotherapy, and the broadening of indications and age ranges for their use. Conducting clinical trials in children remains a challenge that research centers and the pharmaceutical industry must address to extend the benefits of biologic therapy to the pediatric population. On the other hand, for some allergic diseases multiple biologic options are available, and the challenge lies in making a judicious selection based on personalized medicine and shared decision-making. In addition, the high cost of biologic therapy limits access for a substantial share of the population, especially in low- and middle-income countries.

Research into novel therapeutic targets and the development of new biologics is rapidly expanding. Although beyond the scope of this review, in addition to biologics, small molecules also represent an important advance in the treatment of moderate-to-severe AD. Currently, new molecular classes are under investigation, such as nanobody compounds, including lunsekimig, a bispecific compound that targets the inhibition of TSLP and IL-13.[89] Fortunately, scientific progress is ongoing, and additional safe and effective treatment options for allergic diseases will become available in the near future. It is essential that specialists in Allergy and Immunology stay informed and up to date on the latest developments in their field.

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