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Update: eosinophilic oesophagitis

Puesta al día: esofagitis eosinofílica

Gestione dell'allergia alimentare

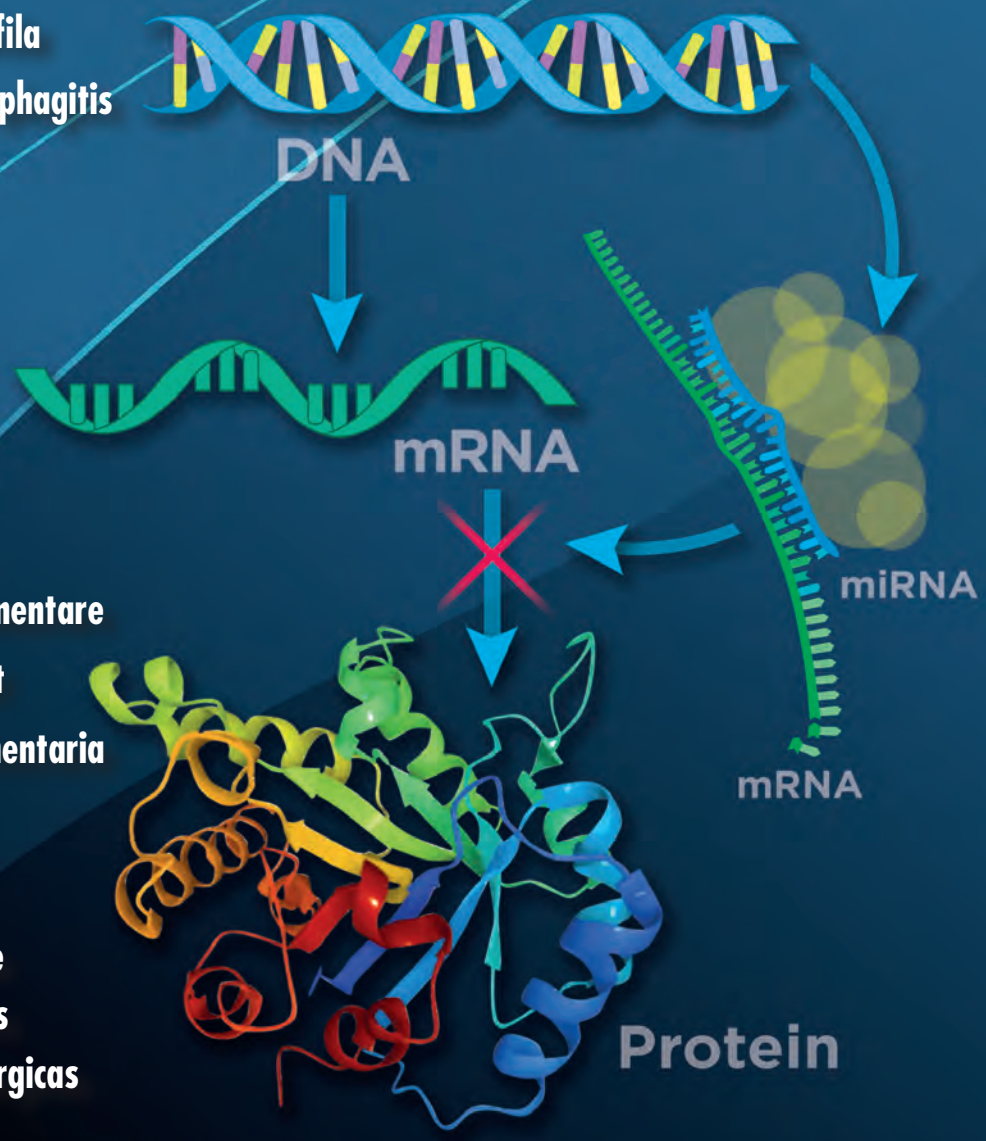
Food allergy management

Gestión de la alergia alimentaria

TSLP e malattie allergiche

TSLP and allergic diseases

TSLP y enfermedades alérgicas



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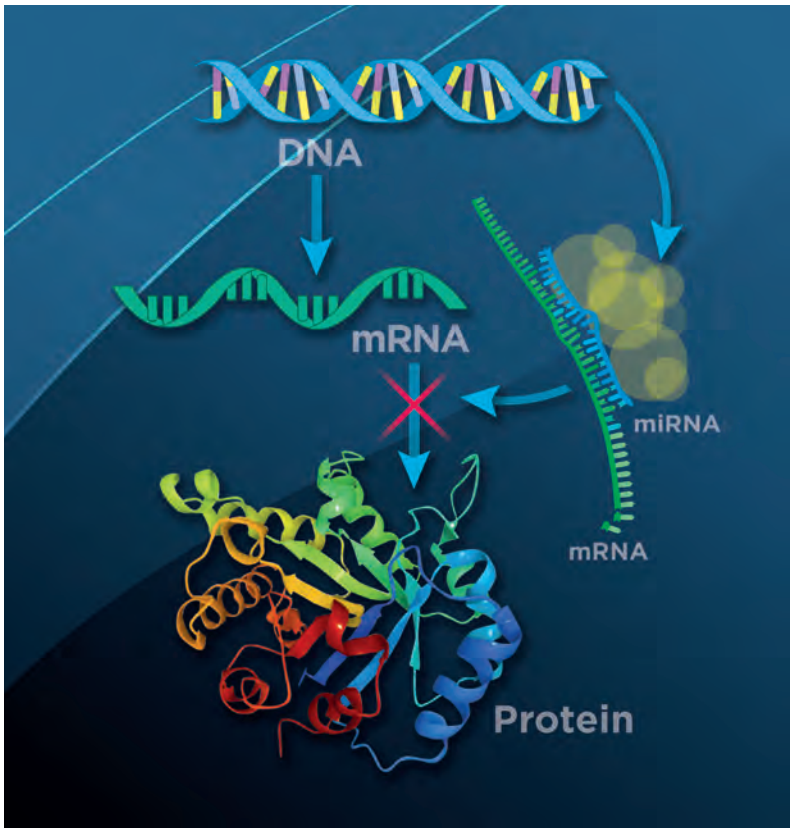

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SUMMARY

Notiziario Allergologico, 2024 Vol. 42, n. 3

Notiziario Allergologico

PDF VERSION

Notiziario Allergologico has been alive and well for over forty years. Today, it becomes international with a new layout that includes the translation of all content into three languages. The purpose remains unchanged if not implemented: to promote allergology culture by offering readers the possibility of an in-depth study and update on various allergology topics, also with a view to the future, thanks to the competence and authority of the authors of the articles published. The popular character of the articles contributes to making them accessible to a vast number of specialists, not only allergologists but also pulmonologists, paediatricians, dermatologists, etc.

ENGLISH

EDITORIAL

edited by **Gianni Mistrello**

The immune system is a sophisticated and complex network of different types of cells that, depending on their function, move to various locations such as blood, mucous membranes or organs, but remain constantly interconnected thanks to their interaction with specific receptors of particular molecules (cytokines) that provide them with instructions on how to react in certain situations. Its function is to keep the body in an optimal state of health by detecting and neutralising the various foreign agents (bacteria, viruses, allergens...) with which it comes into contact. Sometimes, however, not everything works at its best, and dysfunctions of this control system lead to the development of various pathologies. This is the case with eosinophilic oesophagitis (EoE) or allergies, the latter caused by abnormal and excessive immune responses to substances that are in themselves harmless or, in any case, non-toxic, such as food (food allergy).

Eosinophilic oesophagitis (EoE) is a chronic, immune- or allergen-mediated inflammatory disease, characterised by clinical symptoms of oesophageal dysfunction and histologically by an infiltrate of eosinophils at the level of the oesophageal mucosa, in response to the ingestion of certain allergens present in certain foods and/or inhaled substances. The rarity of the disease, coupled with patients' reduced awareness of the symptomatology often concomitant with other non-specific symptoms, made it difficult to recognise it as a clinically distinct entity, which in fact has only happened in recent times. Considerable improvements have been made in the meantime, particularly in diagnostic criteria, and this has made it possible to observe that its prevalence is steadily increasing. Dr Franceschini (SOSD Allergology and Immunology, Prato-Pistoia) discusses this comprehensively, emphasising that the diagnosis of EoE is based on a thorough evaluation of the patient's clinical history in order to highlight any allergic or gastroesophageal disorders. It should be borne in mind that very often patients with EoE also have other allergic disorders, such as allergic rhinitis or atopic dermatitis. If EoE is suspected, a definitive diagnosis of EoE requires a histological evaluation of oesophageal biopsy tissue, taken during a gastroscopy, which must show the presence of a certain percentage of eosinophils. A delay in diagnosis entails risks for the patient: EoE is a chronic progressive inflammatory disease that can evolve from a typically inflammatory phase to a much more severe fibrostenotic form characterised by obstruction of the passage of the food bolus. The author concludes by dwelling on the therapeutic approach of EoE, which involves different levels of therapy, such as acid secretion inhibitors, i.e. with anti-inflammatory action, to biologicals, without excluding the dietary/nutritional approach based on particular elimination diets.

The issue continues with a contribution by Dr Lucia Lo Scalzo and Dr Stefania Arasi (Allergology Division, Bambino Gesù Paediatric Hospital, IRCCS, Rome), who focus their attention precisely on IgE-mediated food allergy (FA). This disease now represents a major public health problem that can negatively affect the quality of life of pa-

tients suffering from it, whether paediatric or adult, if not when it causes fatal events. The authors emphasise the importance of performing a thorough and accurate case history to identify the food suspected of causing the reaction, and then confirming this by a serum search using in vitro specific IgE (sIgE) or in vivo (prick) tests, and, where necessary, by performing an oral provocation test. Once the offending food has been identified and the level of severity of the FA has been assessed, proper management of the FA is essential, which must involve the patient and his or her family with the aim of reducing patient anxiety about the risk of future allergic reactions, and promoting a sense of control over the condition. This must be done through adequate therapeutic education by the allergist to enable the patient to avoid the risk of any future episodes and, if so, how to recognise and manage them promptly. The article then continues with an overview of therapeutic strategies. In addition to the classical approach to the management of FAs based on strict avoidance of offending foods and training in the use of emergency drugs in the event of an anaphylactic reaction, the different therapeutic approaches are recalled; these can be based on the use of specific extracts administered orally (OIT) or sublingually (SLIT) and, more recently, on biological drugs such as omalizumab, a humanised monoclonal anti-IgE antibody. Finally, the authors conclude their contribution by hoping that, in the future, biomarkers can be identified to monitor the allergic state or support the prediction of natural disease evolution and prognosis.

As mentioned at the beginning of the editorial, cytokines are fundamental elements of the immune system, representing the so-called 'molecular words' through which immunocompetent cells communicate with each other to induce specific reactions. In this issue, the authors (Dr Viviana Valeri, Dr Silvia Tonon and Dr Barbara Frossi, University of Udine, Department of Medicine (DMED)), focused their attention on thymic stromal lymphopoietin (TSLP), one of the cytokines of epithelial origin that is part of the so-called alarmins, whose expression and release are increased in response to injury or immunological insults. There are numerous cellular targets of TSLP and their activation leads to the production of other cytokines, resulting in the development of T2-type inflammation. This latter aspect explains the relevance of TSLP in the context of chronic allergic diseases, i.e. where there is a continuous maintenance of this inflammatory state. As the authors point out, this cytokine is implicated in a broad spectrum of diseases, but growing interest has developed in particular in the role that TSLP produced by the lung epithelium might play in initiating and maintaining pathogenetic processes underlying severe asthma. It should be noted that TSLP is also a potential therapeutic target, and in the article's conclusion the authors report data obtained with a biological drug, tezepelumab, a humanised monoclonal antibody that inhibits the binding of TSLP to its receptor.

I wish you a good read and take this opportunity to wish everyone Happy Holidays

ENG

Update: eosinophilic oesophagitis

Dr Laura Franceschini

SOSD Allergology and Immunology, Prato-Pistoia USL Toscana Centro

1. Epidemiology

Eosinophilic oesophagitis (EoE) is a chronic inflammatory disease of the oesophagus, characterised by a spectrum of clinical manifestations that vary according to age and the fibrostenotic evolution of the inflammatory process (1-6). Although it can affect people of all ages, it tends to have a bimodal pattern, with higher incidence rates in the population aged 5-14 years and 20-45 years, and a higher prevalence in cold climates (7). The likelihood of contracting the disease is 3-4 times higher in the male gender than in the female gender (1). A family or personal history of other diseases that share the same inflammatory pattern with EoE, defined as type 2, such as allergic rhinitis, bronchial asthma, chronic rhinosinusitis with nasal polyposis, atopic dermatitis, and food allergy, is also common (8-10). A 64-fold increased risk in siblings suggests heredity of the condition (11).

Most estimates of EoE incidence and prevalence are derived from epidemiological studies conducted on predominantly Caucasian populations (7, 12, 13). North America and Europe have the highest incidence (5-20 new cases per 100,000 inhabitants per year) and prevalence (9.5-58.9 adults per 100,000 inhabitants) (12-15). In addition, epidemiological evidence indicates a progressive increase in the incidence and prevalence of the disease (16, 17), which is only partly linked to the most recent findings on the disease, the evolution of diagnostic criteria, the taking of more biopsies during endoscopy of the upper digestive tract, and the increased attention paid to its possible presence in individuals with other diseases characterised by type 2 inflammation (7, 12-19).

2. Pathogenesis

Since the identification of EoE as a clinically distinct disease in the early 1990s, understanding of the pathophysiology of the disease has made considerable progress.

Its pathogenesis can to date be considered multifactorial, and derives from the complex interaction, still largely undefined, between genetics, environment, allergenic stimuli and immune system response. The loss of epithelial barrier integrity (11, 20, 21), which is typical of all diseases characterised by type 2 inflammation, also appears to be a determining factor in triggering the inflammatory mechanisms underlying the pathogenesis of EoE (3, 22): reduced expression of tight junction components and desmoglein-1, the cause of loss of epithelial integrity, has, in fact, been highlighted in subjects suffering from EoE (23), in whom there is a genetic predisposition to defects in such integrity involving mutations in genes coding for phyllactin, calpain 12, Kaazal-type serine protease inhibitors, and the epidermal differentiation complex. The histological counterpart of this alteration/loss of barrier integrity includes dilated intercellular spaces, basal cell hyperplasia, decreased desmosomes, and profound loss of differentiation of oesophageal tissue (24).

As a result of impaired barrier function, environmental factors, including

SUMMARY

Acronyms

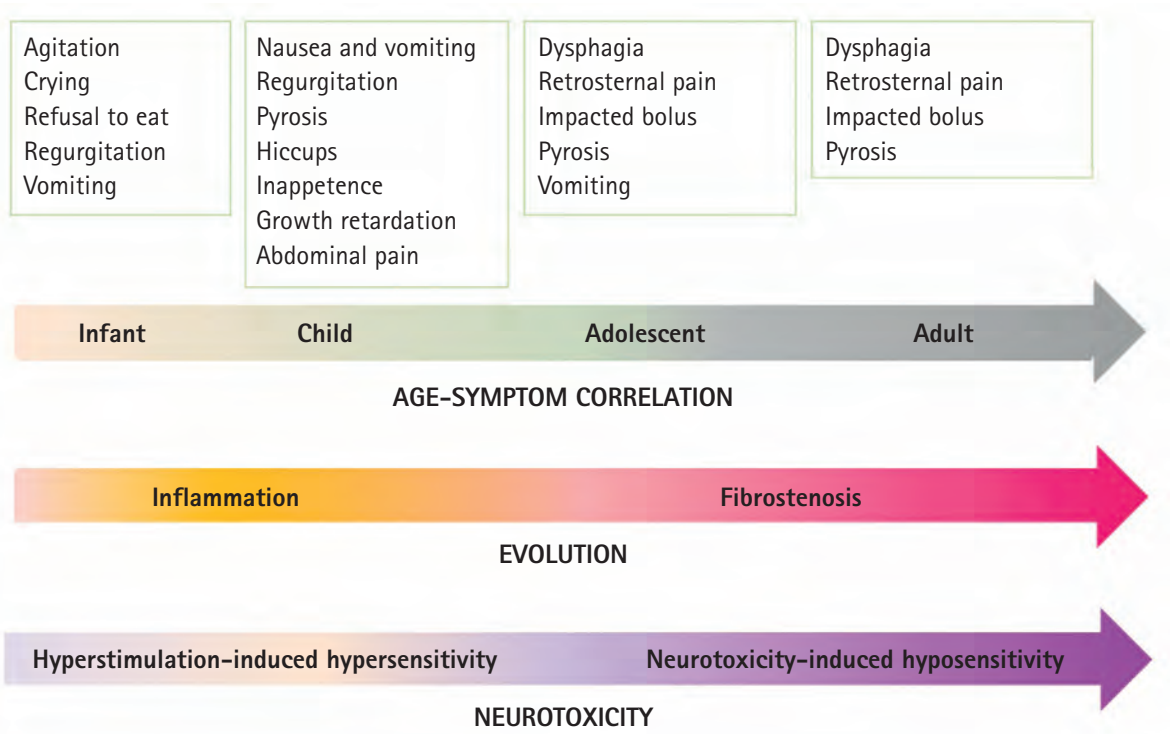
- **ECM** extracellular matrix protein
- **EMT** epithelial-mesenchymal transition
- **EoE** Eosinophilic Oesophagitis
- **FLIP** functional lumen imaging probe
- **IPP** proton pump inhibitors
- **TGF-β** transforming growth factor β

Eosinophilic oesophagitis is a chronic progressive immune-mediated inflammatory disease of the oesophagus associated with type 2 inflammation, characterised clinically by symptoms of oesophageal dysfunction and histologically by eosinophilic infiltration of the oesophageal mucosa. The increasing understanding of the pathophysiology of the disease, since its first identification some 30 years ago, has resulted in innovative diagnostic and therapeutic approaches capable of modifying the natural course of the disease. The mechanisms underlying the development and progression of the disease are influenced by several factors, such as genetics, age, type 2 comorbidities and exposure to allergens and irritants. In adults, the most characteristic symptoms are recurrent dysphagia and impacted food bolus, which may be masked by compensatory behaviour, while in paediatric age, rejection of higher consistency foods, abdominal pain, vomiting, and often growth retardation prevail. The diagnosis of eosinophilic oesophagitis is based on the clinical history and the histological finding of eosinophilic infiltration of the oesophageal mucosa in biopsies taken during endoscopy.
First-line treatment involves the use of drugs or elimination diets also in combination, while oesophageal dilatation is necessary in fibrostenotic forms to address and prevent episodes of impacted bolus feeding.
In view of the growing interest in this disease and the availability of new therapeutic approaches, we discuss here some recent scientific evidence concerning the pathophysiology, diagnosis and treatment of eosinophilic oesophagitis, and recommendations on its management based on current guidelines.

microbes and their products (pathogen-associated molecular patterns - PAMPs), allergens and/or irritants, can induce immune responses by directly activating epithelial cells, e.g. through pattern recognition receptors (PRRs), resulting in the production and release of antibacterial peptides and cytokines. In turn, epithelial cytokines, such as thymic stroma lymphopoietin (TSLP), IL-25 and IL-33, activate innate lymphoid cell type 2 (ILC2) and promote the differentiation of type 2 (Th2) T-helper cells. Th2 and ILC2 produce type 2 cytokines, in particular IL-4, IL-5 and IL-13, and promote the presence of other inflammatory mediators, orchestrating and amplifying the inflammatory response by recruiting effector cells (eosinophils, basophils and mast cells) and producing IgE. Mast cells and eosinophils also propagate the inflammatory process through the production of cytokines and inflammatory mediators (such as PGD2, leukotrienes, granular enzymes), leading to immune cell activation and epithelial changes that further impair the barrier function of the oesophageal epithelium. Thus, chronic inflammation develops that stimulates tissue remodelling in a fibrotic direction through transforming growth factor β (TGF-β), stimulation of fibroblasts and modulation of pro- and anti-fibrotic mediators such as thrombospondin-1 and tetraspanin-12, respectively. TGF-β promotes oesophageal remodelling by inducing the activation of fibroblasts and the secretion of extracellular matrix (ECM) proteins (such as collagen and fibronectin), as well as the proliferation, hypertrophy and contractility of smooth muscle cells. TGF-β also promotes the epithelial-mesenchymal transition (EMT), during which epithelial cells acquire characteristics of myofibroblasts while losing some of the characteristics of epithelial cells, allowing them to participate in ECM synthesis and deposition. Treatment

ENG

Figure 1 Temporal evolution of the clinical and pathophysiological features of eosinophilic oesophagitis



of adult patients with EoE with an anti-IL-13 monoclonal antibody significantly reduces markers of EMT in oesophageal tissue, underlining the significant role of IL-13 in the fibrostenotic evolution and oesophageal remodelling inherent to the disease (24). Furthermore, in EoE as in other diseases with type 2 inflammation, there is a complex dialogue between the immune system and the nervous system that is expressed through the release, action and modulation of certain neurotransmitters as well. Alterations in oesophageal motility could therefore be the result not only of organ remodelling, but also of oesophageal neuromuscular dysfunction induced by eosinophilia and the cytokine milieu. Consequently, the different age-dependent clinical presentation typical of the disease could also be an expression not only of the evolution from a typically inflammatory to a fibrostenotic phase, but also of an immune-mediated sensory neuronal dysfunction, which evolves from a hyperstimulation-induced hypersensitivity to a neurotoxicity-induced hyposensitivity picture (Figure 1).

Over the past decade, evidence has also accumulated regarding the possible involvement of the IgG4 antibody subclass in the pathogenesis of the disease: IgG4 deposits have been found in the oesophageal tissue of patients with EoE, as well as elevated serum levels of total and food-specific IgG4 (25, 26, 27). However, cases of EoE have also been described in patients with absolute IgG4 deficiency (28), so the exact role of IgG4 in the pathogenesis of the disease has yet to be fully elucidated

(25, 29). Finally, a recent study has also suggested a possible role for IL-18, which is regulated by the NOD-like receptor protein 3/caspase-1 system, in the pathogenesis of EoE, with the consequent therapeutic prospect of being able to use selective caspase-1 inhibitors such as Belnacasan, a small molecule that is administered orally, in the treatment of the disease (30).

3. Clinical manifestations

In adulthood, dysphagia is the most common symptom of EoE (1-3), which can lead to complete blockage of the food bolus along the oesophageal tract (6, 31). Patients may also experience retrosternal pain, heartburn or epigastralgia, which may make differential diagnosis with gastro-oesophageal reflux disease (GERD) difficult (32). In paediatric age, however, other symptoms such as abdominal pain, reflux, reduced appetite, chronic cough, growth retardation or vomiting are present (33). According to some evidence, patients may also present with some seasonal variability of symptoms, with intensity usually being lower during the winter months (34), and in such cases EoE is diagnosed more often in the spring-summer season, confirming the role of aeroallergens as a trigger for the condition (34, 35). In addition, patients who develop symptoms of EoE at a young age, and who present with allergic comorbidities, are more likely to experience the so-called 'immediate food-induced oesophageal response' (FIRE), a clinical manifestation characterised by the rapid onset of intense pain described as 'burning, choking or pressure' after consuming specific foods or beverages. The pathogenesis of FIRE syndrome has not yet been clarified, but it is unlikely to be related to an IgE-mediated mechanism (36, 37).

To correctly frame the disease, it must also be remembered that most patients (75%) have at least one type 2 comorbidity, such as food allergy, atopic dermatitis, allergic rhinitis, bronchial asthma and chronic rhinosinusitis with nasal polyposis (8-10).

Given the strong impact of clinical manifestations on quality of life, meal-related adaptive eating behaviours are common in patients with EoE, which can reduce or even minimise the frequency and intensity of symptoms, such as the ingestion of large quantities of liquids to facilitate swallowing, meticulous fragmentation of food down to a semi-solid consistency, prolonged chewing with longer mealtimes and avoidance of foods with a greater consistency, as well as drugs in solid pharmaceutical formulations (such as capsules, tablets, etc.). A series of 6 questions identified by the English acronym IMPACT can be particularly useful when collecting the anamnesis (3), in order to facilitate the identification of the pathology even in the presence of such compensation behaviour.

On the other hand, despite the increasing attention paid to EoE since it was first characterised, diagnostic delay still represents one of the most important problems related to the pathology, so much so that symptoms can not infrequently be present up to 10 years before the diagnosis is made, thus increasing the risk of an evolution in a fibrostenotic sense (5).

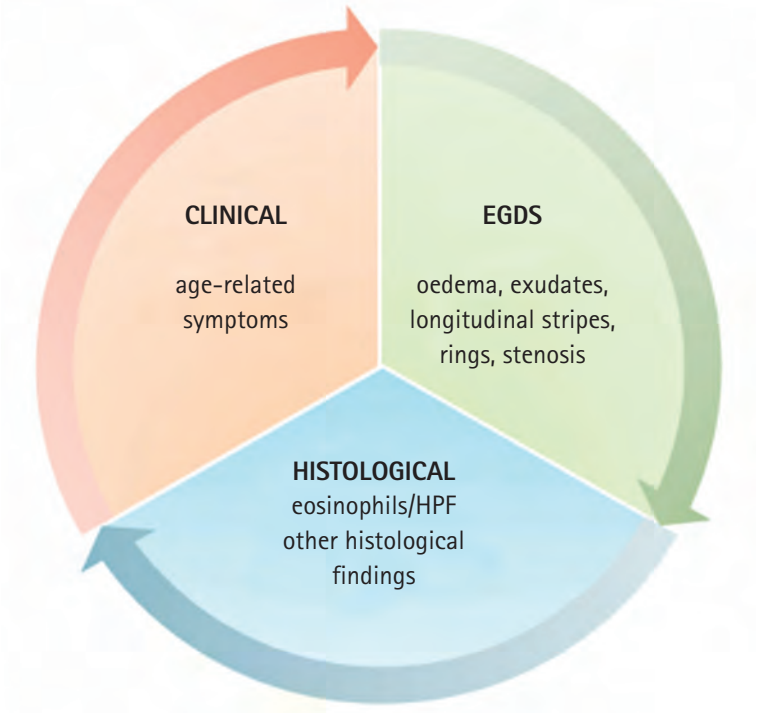
4. Diagnosis

The diagnosis of EoE is based on both the clinical history of oesophageal dysfunction and the histological finding on oesophageal biopsies of a predominant eosinophilic infiltration of the mucosa, which must be equal to or greater than 15 eosinophils per microscopic field at high magnification with or without formation of eosinophilic micro-abscesses (1-4, 6). Consequently, the gold standard for the diagnosis and follow-up of EoE remains the histopathological assessment of the number of intraepithelial eosinophils in biopsy specimens. However, additional specific histological changes of the oesophageal mucosa, such as changes in epithelial cell morphology, hyperplasia of the basal zone, presence of dilated intercellular spaces and fibrosis of the lamina propria (38), may be present, although not pathognomonic. The appearance of the oesophagus at endoscopy, on the other hand, can vary considerably and is not part of the diagnostic criteria (1, 31). Typical endoscopic features of EoE include linear furrows, oesophageal rings, white plaques, exudates and oesophageal stenosis (39).

These abnormalities may, however, be very subtle and a not insignificant number of patients with active disease may have an oesophagus of normal appearance at endoscopy (Figure 2).

Therefore, when EoE is suspected, biopsies during endoscopy of the upper

Figure 2 Clinical, endoscopic and histological features of eosinophilic oesophagitis



EGDS: oesophagogastroduodenoscopy **HPF**: high-power field

digestive tract should be performed even in the absence of obvious macroscopic changes in the oesophagus (1, 31). Given the variable endoscopic and histological appearance of EoE, at least two biopsy samples should be taken from the proximal, middle and distal oesophagus (1, 4, 31). Several studies have shown that diagnostic sensitivity increases with more biopsies taken (31).

Clinical non-response to treatment with proton pump inhibitors (IPPs) is no longer a diagnostic criterion for EoE as of 2018 (2). The British guidelines of 2022 suggest stopping IPP therapy at least 3 weeks before endoscopy to avoid masking the presence of pathology (6), whereas other guidelines do not provide such a recommendation (2, 4, 31). Finally, it must be remembered that other potential causes of oesophageal eosinophilia must be excluded before a diagnosis of EoE can be made (1, 2, 4).

5. Pathology management

Current guidelines recommend pharmacological or dietary treatment (4, 6, 31, 40, 41), while dilatation may be necessary to manage oesophageal narrowing due to stenosis and, in some cases, is performed prophylactically to prevent oesophageal obstruction. To date, no randomised controlled trial directly comparing the various treatment approaches has established the superiority of one treatment over the other. Small retrospective studies combining elimination diet and drug therapy have shown benefits in both adults and paediatric subjects (6). Despite low-quality evidence, there is a general consensus on the possibility of combining pharmacological and dietary treatments in patients with a limited response to a single therapeutic approach (6, 42).

According to most guidelines (4, 6, 31, 40, 41), the constant sharing of treatment options with the patient's preferences and expectations (shared decision making) improves the patient's quality of life, reducing frustration and increasing adherence to therapy (3, 4, 6, 40, 42). Once remission has been achieved, the current recommendation is to continue the current treatment as long as it remains acceptable to the patient (3, 6, 23, 42).

5.1 Drug therapy

The pharmacological approach is frequently the first-line treatment.

IPPs are in many cases recommended as the first treatment (1, 2, 4, 6, 23, 34), as they are easy to use, inexpensive

and have relatively few adverse effects (1, 2, 4, 6, 31, 40). In a systematic literature review from 2020, taking IPPs twice daily induced histological remission within 4-12 weeks in 41.7% of patients, compared to 13.3% of those treated with placebo (40, 41). Meta-analyses have, however, tended to classify the evidence in favour of IPP use as being of low quality, as more than two thirds of the studies had been conducted on limited case series or were retrospective in nature (43, 44).

Topical corticosteroids may be used in patients who do not respond to IPPs or as first-line therapy, especially in patients with aggressive disease (1, 2, 6, 40-41). Recent evidence indicates that topical corticosteroids are able to give histological and endoscopic remission, but are not overall superior to IPPs (2, 4, 44-48). No formulation proved superior to the others in the few direct comparisons that could be evaluated (3, 41, 44, 45). Topical corticosteroids have long been available as swallowed fluticasone propionate and budesonide, rather than inhaled through dispensers used for the treatment of asthma, or as topical oral formulations (viscous budesonide), and more recently as budesonide in orodispersible tablets. The only formulation approved in Italy, at present, only for adults with EoE, is budesonide in orodispersible tablets, available in two dosages of 0.5 and 1 mg. The most common adverse effect during treatment with topical corticosteroids is oral candidiasis, which may occur in approximately 5% of patients (49).

Biologic drugs capable of blocking cytokines and other key factors of type 2 inflammation have shown mixed results in the treatment of EoE (3, 50, 51). In May 2022, dupilumab (human monoclonal anti-IL-4/IL-13 antibody) was approved by the Food and Drug Administration for the treatment of eosinophilic oesophagitis in patients over 12 years of age and at least 40 kg body weight, at a dosage of 300 mg/week. More recently, dupilumab was also approved in paediatric patients for the treatment of children over one year of age and at least 15 kg body weight, with dosages differentiated according to weight. The European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) have approved the use of dupilumab in adults and adolescents over 12 years of age for the time being. The approval was based on a randomised controlled trial that compared dupilumab (300 mg per week) with placebo (50, 51), demonstrating histological, endoscopic and symptomatic improvement at 24 weeks of treatment (50). Importantly, in the 52-week extension of the above-mentioned study, the regimen of 300 mg every fortnight, usually adopted to treat other diseases with type 2 inflammation, was not effective in EoE. The indication of dupilumab for EoE was in fact added to those for other type 2 diseases, such as atopic dermatitis, severe asthma and chronic rhinosinusitis with nasal polyposis (50). Biological therapy with dupilumab could therefore be considered as the therapy of choice in the case of possibly coexisting other type 2 inflammatory diseases (52), as well as, of course, in the case of disease refractory to other treatments or in the presence of adverse effects and/or poor tolerance to other first-line therapies. At the moment, however, there is still open discussion about the positioning of dupilumab in a flow chart of the treatment of EoE, which considers both aspects of pharmacoeconomics and its potential in preventing and/or slowing down oesophageal remodelling, and thus the fibrostenotic evolution of the disease.

Other biologic drugs used in the treatment of severe eosinophilic asthma and other diseases with type 2 inflammation, such as mepolizumab, benralizumab and omalizumab, have shown no benefit in the treatment of EoE (6, 40, 41), just as partial results have been obtained with lirentelimab, a monoclonal antibody targeting SIGLEC-8. For the most part, these treatments have proved effective in reducing eosinophilic infiltration, without, however, leading to a significant clinical improvement, which at least calls for reflection on the actual role of eosinophils in the pathogenesis of EoE. Currently, trials are underway to evaluate the safety and efficacy, in patients with EoE, of other monoclonal antibodies such as CALY-002, an anti-IL-15, and barzolvolimab, a humanised monoclonal antibody that specifically binds the KIT tyrosine kinase receptor and strongly inhibits its activity, which is necessary for mast cell function and survival. Other treatments, including systemic corticosteroids, leukotriene

receptor antagonists and chromones, have not shown efficacy in several studies and are therefore not recommended for the treatment of eosinophilic oesophagitis (4, 6, 40-42).

5.2 Dietary interventions

The elemental diet, based on the use of liquid meal replacements of amino acids, short-chain triglycerides and maltodextrins combined with vitamins, minerals and electrolytes, is successful in inducing remission of EoE, but the degree of adherence to this type of diet is extremely low, especially in adults (53), and it is therefore reserved for patients, mainly paediatric, who are otherwise refractory to treatment (4, 6).

Diets based on the result of skin allergy tests and the search for specific IgE, on the other hand, have shown low efficacy in achieving histological remission when continued for 2-12 weeks (54).

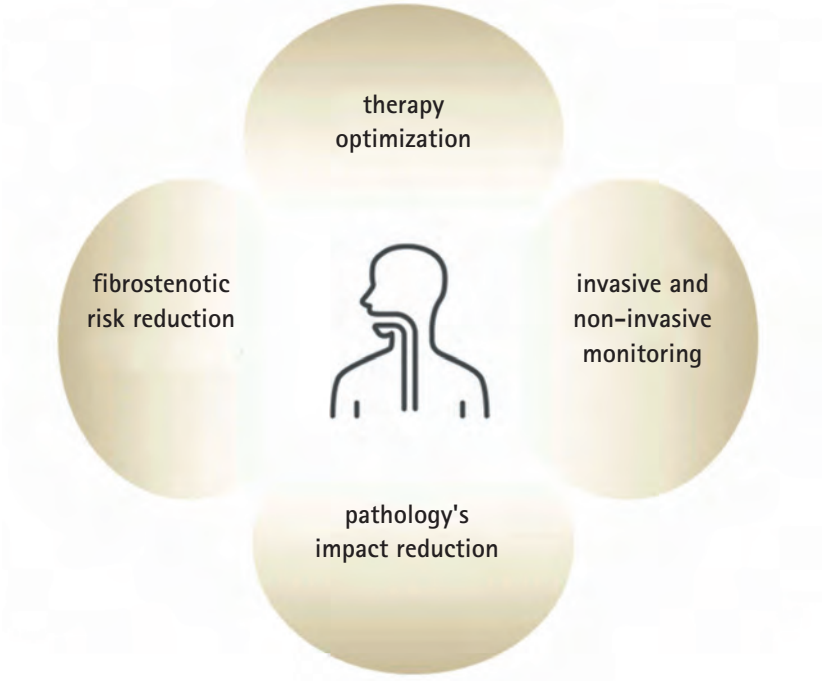
Finally, another therapeutic option are empirical elimination diets, which avoid the food groups most frequently responsible for food allergy. The 6-food elimination diet involves the elimination of milk and dairy products, wheat, soya, nuts, fish products and eggs. A systematic review of 10 observational studies, which compared a 6-week course of the 6-food elimination diet versus placebo, reported an efficacy of 68% versus 13% (40, 41).

Eliminating 6 food groups is, however, extremely challenging for the patient, as it negatively affects quality of life and can cause nutritional deficiencies (6, 53); therefore, the support of an experienced nutritionist is necessary when this dietary approach is used in the treatment of EoE. The 4-food elimination diet involves the exclusion of milk and dairy products, wheat, eggs and soy, while the 2-food elimination diet involves the exclusion of cow's milk and wheat (53). Recently, a randomised, multicentre, open-label study compared the 1-food elimination diet (milk and dairy products) with the 6-food elimination diet, demonstrating similar endoscopic, symptomatic and histological remission (55).

5.3 Dilatation

Endoscopic dilatation can be used to treat stenosis and oesophageal narrowing, reducing the risk of future episodes of impacted food bolus, particularly in patients in whom pharmacological or dietary treatment has failed. Patients with recurrent food occlusions and a narrowed oesophagus at endoscopy should be offered dilatation to reduce the risk of food bolus obstruction (31). Dilatation relieves obstructive symptoms, but does not treat the underlying inflammation; therefore, it should al-

Figure 3 Main objectives of follow-up in eosinophilic oesophagitis



ways be combined with other therapeutic approaches (3, 31, 42). In a study of patients who required dilatation, 65% of patients who underwent simultaneous pharmacological or dietary treatment showed a reduced need to repeat new dilatations 2 years later (31).

5.4 Management of acute oesophageal obstruction

Resolution of acute oesophageal obstruction caused by a food bolus can sometimes be achieved using non-invasive treatments, such as the ingestion of carbonated beverages (56). If the acute obstruction does not self-resolve, the patient must undergo emergency endoscopy to crush the bolus and allow it to progress into the stomach. Performing a chest X-ray prior to endoscopy, historically recommended to rule out oesophageal perforation, is not recommended by current guidelines due to the high rate of false negatives (57).
Once the feeding obstruction has resolved, patients must then undergo elective outpatient endoscopy, as failure to do so and the absence of follow-up greatly increase the risk of new episodes of impacted bolus feeding (7).

5.5 Patient follow-up

The patient's symptoms and endoscopic and histological findings do not always correlate with each other (31, 42). After treatment initiation, patients should undergo clinical and endoscopic follow-up with biopsies after 8-12 weeks for an overall assessment of the extent of disease remission (42, 58). Routine clinical and endoscopic follow-up should then continue once remission is achieved, but the ideal timing remains to be defined (6, 31, 42). Guidelines suggest continuing with maintenance treatment in order to avoid clinical and/or histological relapse following discontinuation of therapy (4, 6, 31, 42, 58). The eosinophilic oesophagitis severity index (I-SEE) is currently being validated with the intention that a single tool will allow physicians to stratify risk and monitor disease progression and response to treatment over time (59). Shared decision-making between physician and patient remains, however, essential to mitigate the impact on quality of life from both the disease and its treatment (6, 8, 32) (Figure 3). Recently, a classification of oesophageal function has also been proposed, based on data acquired by functional lumen imaging probe (FLIP) , an endoscopic method based on impedance planimetry, capable of highlighting oesophageal narrowing of a functional, scar or inflammatory nature (42). Through this method it is possible to define a spectrum of EoE severity from forms with a prevalent inflammatory component to more advanced forms, in which fibrostenotic aspects prevail, thus indicating the possibility of using the FLIP for the choice of the most appropriate therapeutic approach on the basis of the evolutionary state of the disease (60).

6. Conclusions

EoE is a chronic disease with an increasing incidence and prevalence. The condition affects patients' quality of life and can lead to oesophageal fibrosis and stenosis. Early diagnosis and treatment with pharmacological and dietary interventions can, if initiated at a stage of the disease when the inflammatory aspect still prevails, result in slowing the evolution of the disease towards fibrostenosis and reduce the need to intervene with dilatations. Shared decision-making is essential for long-term success in the treatment of eosinophilic oesophagitis.

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Food allergy management: Current approach and future perspectives

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Introduction

Food allergy is classically defined as 'an adverse reaction that develops from a specific and reproducible immune response to exposure to a particular food' (1). Some studies estimate an increase in the frequency of food allergies in recent decades.

A systematic review published in 2023 estimated the cumulative and point prevalence of self-reported food allergies in Europe to be 19.9% (CI 95% 16.6-23.3) and 13.1% (CI 95% 11.3-14.8), respectively. The point prevalence based on specific IgE (sIgE) is 16.6 % (CI 95% 12.3-20.8), on skin prick test (SPT) 5.7 % (CI 95% 3.9-7.4), and on oral provocation test (OPT) positivity 0.8 % (CI 95% 0.5-0.9). While the lifetime prevalence of self-reported food allergies and OPT positivity changed only slightly, the point prevalence of food allergies based on patients' self-reported food allergies, SPT and sIgE positivity increased compared to previous estimates. This could reflect a real increase, a higher level of awareness, an increase in the number of foods evaluated, or an increase in the number of studies from countries with fewer data in the first review; or again, be influenced by patient perception, where the estimate was based on patient-reported diagnosis (and not on OPT) (2). Similarly, in Melbourne, Australia, the HealthNuts study estimated a prevalence of food allergy of 11.3% (CI 95% 9.6 -13.4%) in a cohort of 1420 children recruited at 1 year of age, with repeated assessments at 6 and 10 years of age (e.g. questionnaire on symptoms and medical diagnosis of allergic conditions (International Study of Asthma and Allergies in Children); SPT, pulmonary function tests and OPT when indicated) (3). Food allergy can have a negative impact on patients and families, including effects on health-related quality of life (HRQoL), nutrition and individual and societal costs. Therefore, a relevant goal in the management of food allergy should be to increase patients' and families' autonomy in managing the risk of allergic reactions to food, reduce food-related anxiety and achieve a sense of control over their condition.

This review focuses on current knowledge and future perspectives on the management of IgE-mediated food allergy.

1. Clinic

Most paediatric food allergies are IgE-mediated, although there are other immunological mechanisms that may underlie them (e.g. cell-mediated, manifesting mainly with gastrointestinal symptoms) (4). IgE-mediated reactions are characterised by the acute onset of symptoms, usually within two hours of exposure to or ingestion of the triggering food. FAs can manifest itself with a wide range of clinical reactions: cutaneous (e.g. urticaria-angioedema); gastrointestinal (e.g. oropharyngeal itching and burning, vomiting, abdominal pain, diarrhoea); respiratory (e.g. persistent cough, hoarseness, wheezing, stridor, respiratory distress), and circulatory (e.g. pallor and flaccidity in infants and young children, hypotension, collapse) and neurologi-

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SUMMARY

Acronyms

- **AIT** allergen-specific immunotherapy
- **CMPA** cow's milk protein allergy
- **EAACI** European Academy of Allergy and Clinical Immunology
- **EPIT** epicutaneous immunotherapy
- **FA** IgE-mediated food allergy
- **FDA** Food and Drug Administration
- **HRQoL** health-related quality of life
- **OIT** oral immunotherapy
- **OPT** oral provocation test
- **sIgE** specific IgE
- **SLIT** sublingual immunotherapy
- **SPT** skin prick test

The 21st century has seen a significant propulsion in IgE-mediated food allergy (FA) research, leading to concrete changes in the clinical approach. Allergen-specific immunotherapy was recommended in clinical practice for the first time in 2018; similarly, in February 2024, omalizumab was approved by the Food and Drug Administration (FDA) for FAs from the first year of life. Further treatment methods have shown promising data, such as epicutaneous immunotherapy. Further treatment options for FAs are currently under preclinical or early clinical evaluation, such as vaccines, various biologics, and hypoallergenic foods. Efforts have been devoted to risk stratification of FAs and standardisation of the assessment of their severity. In the coming years, it is hoped that strategies capable of modifying/curing/preventing FAs will be available. The identification of reliable bio-markers and the standardisation of definitions and measurement approaches, together with the sharing of decisions with patients and families, will be crucial for the development of personalised care and for reducing the significant burden of FAs.

cal (e.g. loss of consciousness) signs and symptoms, in isolation or in association, simultaneously or at different times. The severity of allergic reactions varies from localised symptoms to severe systemic reactions, and sometimes anaphylaxis, even fatal. Although the hospitalisation rate for anaphylaxis is increasing, mortality remains low. The severity of allergic reactions depends on many factors in addition to individual reactivity, such as the quantity of the ingested allergen, co-ingestion of several food allergens, gastric emptying, type of food preparation (fresh or natural, cooked or otherwise treated). Individual reactivity can in turn be influenced by many factors: age, exercise, intake of drugs (e.g. NSAIDs, antacids), infections, stress and, in women, the menstrual cycle (5).

Proper management of FAs requires an accurate prior assessment of the severity of both the FAs as a whole and any future allergic reactions to ensure personalised and cost-effective decisions.

An international consensus on a standardised scoring system for food allergy in children and adults was published in 2023. The DEFASE (DEfinition of Food Allergy SEverity) score represents the first comprehensive classification of food allergy severity that considers not only the severity of a single reaction, but the entire spectrum of the disease. This includes elements related to symptoms, HRQoL and economic aspects, providing a more patient-centred perspective, especially considering the limitations of current predictive factors. Phase 3 will involve the validation of the scoring system in research settings and its implementation in clinical practice. The validation of this first FA severity scoring system could enable standardised patient monitoring and proper selection for clinical trials and therapeutic approaches. Future research should focus on external validation of scoring systems, adapting these models to different food allergen sources, populations and contexts (6).

2. Diagnosis

A thorough history and thorough ob-

jective examination remain essential for diagnostic suspicion, which is confirmed by the presence of IgE directed against the specific antigens of the food in question and, where necessary, by OPT. IgE-mediated sensitisation can be assessed by in vivo tests (e.g. SPT) and/or in vitro tests (sIgE): both methods are highly sensitive and have the same diagnostic capabilities. In relation to the low specificity of allergometric tests, double-blind placebo-controlled OPT is considered the gold standard for diagnosing FA. However, it is considered time-consuming and resource-intensive, and therefore remains confined mostly to research settings; open (sometimes single-blind) OPT is used in clinical practice. OPT, although safe, presents significant barriers, including the risk of severe reactions by patients and physicians; therefore, there is an unmet need for new techniques for the diagnosis and management of FA that could possibly serve as reliable and safe diagnostic alternatives to OPT. For some years now, molecular diagnostic tests aimed at determining specific IgE for a single allergenic molecule can also be used to diagnose FA. One of the main advantages lies in the possibility of detecting cross-reactivity between allergic molecules and primary sensitisations (7).
Singleplex or multiplex formats are available on the market, with a wide range of allergenic molecules available for diagnosis, which is rapidly increasing.
The potential of the basophil activation test and the mast cell activation test has recently been established, showing overall good diagnostic performance compared to OPTs (7). However, further robust data, including cost-effectiveness analyses and consensus on international standards, are still needed before these tests are ready for large-scale clinical use.
In recent years, other biomarkers have been investigated for the diagnosis of FAs, to monitor allergic status over time and help determine the need for OPT, or to support the prediction of natural evolution and prognosis. Potential biomarkers include genetic and epigenetic factors and their interaction with environmental risk factors related to FA (8).
Multi-omics approaches could potentially lead to the identification of innovative diagnostic biomarkers (9).

3. Management Options

3.1 Elimination diet and emergency drugs

The classical approach in the management of FA focuses on strict avoidance

Table 1 Contraindications to allergen-specific immunotherapy

Absolute contraindications
poor adherence
uncontrolled or serious asthma
eosinophilic oesophagitis or other gastrointestinal eosinophilic diseases
neoplasia or active systemic autoimmune diseases
pregnancy
Relative contraindications
cardiovascular diseases
remitting or organ-specific autoimmune diseases
serious atopic dermatitis
chronic urticaria
mastocytosis
use of ACE inhibitors or beta-blockers

Adapted from (20).

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Table 2 Immunotherapies for the treatment of food allergies

Characteristics	Oral (OIT)	Sublingual (SLIT)	Epicutaneous (EPIT)
Type of product used (dose of protein)	Natural allergen (300-400 mg/day)	Allergen extract drops (2-7 mg/day)	skin patch (100-500 µg)
Clinical effect - desensitization - sustained unresponsiveness	 Wide In some subgroups	 Moderate to minor Unknown	 Variable Unknown
Side effects	Oral and gastrointestinal side effects, possible anaphylaxis in the presence of cofactors	Local (oral cavity)	Local (skin)
Changes in the immune system	Significant	Minor or moderate	Minor or moderate

Adapted from (1).

of offending foods, and immediate availability and training in the use of emergency medication in the event of an allergic reaction. Limitations of an elimination diet-based management strategy include reduced food variety, potential risk of nutritional deficiencies, social restrictions that impact on the HRQoL of the patient and his or her family, and persistent anxiety due to fear of possible severe adverse reactions after accidental exposure to the offending food.

In recent years, several studies have focused on evaluating the power of the OPT in determining reactivity thresholds, demonstrating that these serve to reduce uncertainty regarding individual risk of reaction, improve anxiety and HRQoL, and broaden dietary variety through customisation of dietary restrictions (10). The challenge for the remainder of the century will be to expand this work and collaborate with the industry to define standards and improvements for food labelling, so that specific levels of allergens are labelled, instead of the dichotomous presence or absence of 'may contain traces of', thus creating more options for patients with high reactivity thresholds. This would pave the way for a renewed food and clinical offer regarding allergen avoidance, which would be customised for each patient.

In recent decades, there have been new insights into the diagnosis and treatment of cow's milk protein allergy (CMPA). Restrictive criteria for the diagnosis of CMPA have been proposed to avoid overdiagnosis and overuse of special formulas. Currently, the management of CMPA requires strict elimination of milk proteins from the patient's diet. Guidelines recommend continued breastfeeding as the ideal nutrition for allergic infants/infants, and a maternal elimination diet only in breastfed patients with persistent signs and symptoms. When breast milk is unavailable or insufficient, the latest DRACMA 2024 guidelines suggest an extensively hydrolysed (cow's milk-based) formula or a rice-based hydrolysed formula as a first choice, an amino acid-based formula as a second option, and finally a soy-based formula as a third choice. When choosing a formula with or without probiotic for patients with IgE-mediated CMPA,

the DRACMA 2024 guidelines recommend a probiotic-free formula or an extensively hydrolysed (cow's milk-based) formula containing *Lacticaseibacillus rhamnosus* (11).

In addition to the elimination diet, the other cornerstone of FA therapy is the prescription of self-injected adrenaline. When anaphylactic reactions occur, appropriate management includes the prompt administration of adrenaline as the drug of choice. One study showed that 85% of patients prescribed it always carry it, but that only 7.4% of patients who had an anaphylactic reaction actually used self-injected adrenaline (12). Therapy education is essential so that patients at risk of anaphylaxis and families can recognise and successfully manage future episodes. In 2022, the Task Force on Anaphylaxis of the European Academy of Allergy and Clinical Immunology (EAACI) recommended providing structured and comprehensive training to improve the knowledge and use of adrenaline auto-injectors in individuals at risk of anaphylaxis. Many approaches are available for training patients and families, including the use of online tutorials and other digital educational materials.

Current guidelines recommend the administration of adrenaline intramuscularly in the middle third of the anterolateral thigh region. Adrenaline doses vary according to body weight: in particular, an adrenaline dose of 0.15 mg is indicated for patients weighing between 15 and 30 kg, and a dose of 0.3 mg for those over 30 kg. If necessary, adrenaline can be repeated after 5-15 minutes (13). In recent years, alternatives to the intramuscular route are emerging to overcome mechanical problems, as well as fears associated with needles and administration errors that can cause injury. These include intranasal, sublingual, inhalation, and needle-free intramuscular administration of adrenaline. In general, intranasal administration induces minimal side effects and has few contraindications. Numerous human studies have shown that intranasal adrenaline effectively increases plasma adrenaline levels in a comparable way to intramuscular adrenaline, with faster absorption (14). In June 2024, the European Medicines Agency granted marketing authorisation in the European Union for EURneffy® (adrenaline), the first nasally administered drug for the emergency treatment of anaphylactic-type allergic reactions.

In 2006, sublingual administration of 40 mg adrenaline in tablet formulation resulted in plasma adrenaline concentrations similar to those obtained after an intramuscular injection of 0.3 mg adrenaline into the thigh. In 2021, a new fast-dispersing sublingual tablet demonstrated the feasibility of using the sublingual route for the administration of adrenaline (15).

In 2021, inhaled salbutamol was reported as a possible new therapeutic approach for the treatment of severe abdominal pain caused by an IgE-mediated allergic reaction to peanuts. In this case-control study, the use of salbutamol was associated with a significant improvement in abdominal pain, suggesting that it could be an effective treatment for severe gastrointestinal problems during allergic reactions. However, these observations need to be confirmed with a prospective randomised study (16).

3.2 Allergen-specific immunotherapy

Given the many limitations of the elimination diet, there has been a growing interest in the development of proactive therapeutic strategies for the treatment of FA in recent decades. In this direction, attention has focused on allergen-specific immunotherapy (AIT), a potentially disease-modifying therapy that consists of administering small, increasing doses of the allergen over prolonged periods of time, with the aim of making the subject able to take the offending food without manifesting reactions (17). The ultimate goal of AIT is to achieve clinical and immunological tolerance, i.e. no reaction to the allergen, even once therapy has been discontinued. The phrase *sustained unresponsiveness* refers to the ability to safely consume a normal portion of food containing the responsible allergen despite a period of discontinuation of treatment and, thus, absence of continuous exposure. This goal, however, takes years and is only achieved by a subset of patients anyway. A more realistic goal of AIT is desensitisation: the increase in the reaction threshold, i.e. the amount of allergen a patient can tolerate without showing any reaction. Desensitisa-

tion is normally achieved after a few months of therapy and protects the subject from the risk of severe reactions in the event of accidental contact, but requires continued intake of the allergen itself. If this is discontinued, in fact, the patient may react again to previously tolerated values. It is necessary for the patient and family to be cooperative and able to manage the complex course of AIT. For the same reasons, absolute contraindications to AIT should be considered all those social or cultural conditions that prevent them from understanding well the therapy to be conducted in case of a reaction, and from attending frequent specialist visits. The main absolute and relative contraindications are listed in Table 1.

At present, although several have been explored, there are three main routes of administration of AIT: oral, sublingual, and epicutaneous (Table 2), which are briefly discussed below.

3.3 Oral immunotherapy

Oral immunotherapy (OIT) is certainly the most widely used, being the one that has produced the best results in terms of efficacy, with higher protein contents of the allergen involved than sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT). According to this approach, small increasing amounts of the food involved are administered orally.

There are several protocols for OIT, which differ in the amount of allergen administered, the rate of escalation and the final target dose; from the available literature data, there appear to be no differences in efficacy between the various approaches (18). In general, all protocols include an initial escalation phase in hospital, administering increasing doses of allergen until a dose safe for home intake is reached. Thereafter, the patient will continue the maximum tolerated dose at home, with increases every fortnight in hospital, until a target dose for normal diet is reached, which they will continue to take regularly at home (home maintenance phase). The Canadian guidelines emphasise that there is currently no evidence that one protocol is superior to others (19).

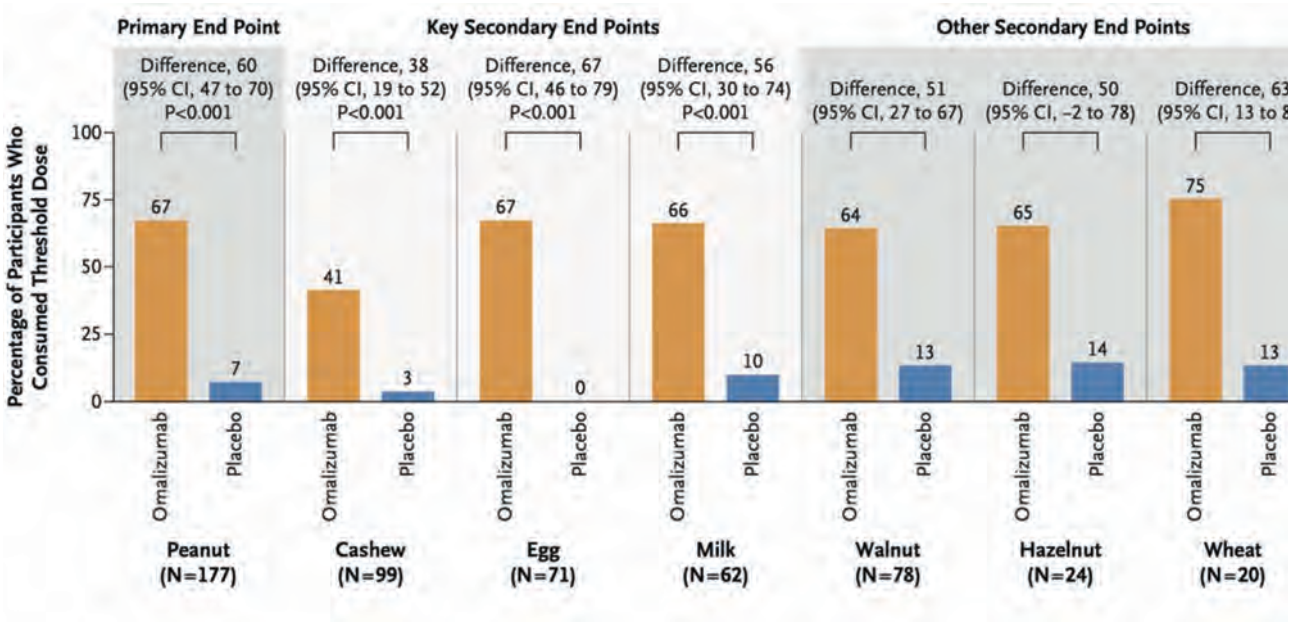
In 2018, EAACI guidelines first recommended OIT as a treatment option for persistent cow's milk, egg or peanut allergies for children aged 4-5 years (when most patients have achieved spontaneous tolerance) to increase the reaction threshold during treatment (20). Since 50-75% of children with CMPA can tolerate bakery products containing milk, and children with regular exposure to cooked milk may progress to tolerance of milk as such at a significantly accelerated rate, cooked milk has been used to attempt desensitisation with varying results, or a less rigid approach involving gradual introduction at home (the so-called 'ladder') (21).

Current evidence suggests that OIT for egg can desensitise more than 80% of children treated for egg allergy (22). The first double-blind placebo-controlled trial of OIT for egg reported that 27.5% and 50% of the group receiving OIT for egg achieved sustained unresponsiveness between the second and fourth year (23).

Since 2009, numerous studies have been conducted on OIT for peanut. A recent meta-analysis of the GA2LEN group shows that OIT induces desensitisation for peanut ($p < 0.05$, RR 9.9, 95% CI 4.5-21.4, high certainty) without increasing adverse reactions ($p = 0.06$, RR 1.1, 95% CI 1.0-1.2) or severe reactions in peanut allergy ($p < 0.05$, RR 1.6, 95% CI 0.7-3.5). Furthermore, the GA2LEN group indicates that OIT induces desensitisation for cow's milk protein allergy ($p < 0.05$, RR 5.7, 95% CI 1.9-16.7) and egg allergy ($p < 0.05$, RR 8.9, 95% CI 4.4-18). There is low evidence that OIT may increase the proportion of children able to tolerate peanut ($p < 0.05$, RR 8.8, 95% CI 1.2-61.6) and egg ($p < 0.05$, RR 7.1, 95% CI 1.7-29.4) after discontinuation of therapy (24).

In January 2020, Palforzia® (AR101), a standardised formulation of pharmaceutical-grade peanut OIT, was approved for the treatment of food allergy to peanut by the FDA in the US and in December of the same year by the European Medicines Agency (EMA). Two major studies investigated the safety and efficacy of AR101 in children with peanut allergy in North America and Europe. In the Double-Blind Placebo-Controlled Food Challenge, a significant percentage of patients in the active group (58-67%) tolerated doses of 600 mg or 1000 mg peanut protein, but not in the placebo

Figure 1 Successful consumption of the predefined threshold dose after 16 weeks of treatment with omalizumab



Taken from (32).

group (25, 26).

In a recent single-centre, single-arm pilot study, the safety and efficacy of OIT with LPP-MH (freeze-dried peanut protein-MH), a novel composition derived from peanuts in development, characterised by reduced cooking-induced allergenicity, was evaluated. Peanut-allergic children with a maximum tolerated dose of peanut protein of less than 100 mg were placed on a 40-week OIT protocol with 300 mg daily of freeze-dried and heat-treated peanut protein. An OPT with peanuts was performed after 40 weeks of treatment and during a follow-up of 6-12 months. The mean cumulative tolerated dose (MCTD) before initiation of OIT was 71.2 mg peanut protein (95% CI 45-100 mg). After 40 weeks, 32/33 patients were able to consume more than 300 mg peanut protein, with MCTD of 1709 mg (CI 365-3675 mg). After 6-12 months of daily maintenance, the MCTD was 8821 mg (CI 95% 1930-13,500 mg). The authors suggested OIT with heat-treated LPP-MH as a potentially safe and effective OIT modality for children with peanut allergy, allowing peanuts to be introduced into the diet in an age-appropriate manner (27).

Although desensitisation is often achieved during OIT, sustained unresponsiveness is not achieved in most patients. Some studies have investigated the effectiveness of OIT in children under the age of 4 (early OIT) and have shown much more favourable results in terms of the development of sustained unresponsiveness. Together with studies on food allergy prevention, which have shown high efficacy of early oral exposure to allergens, the results of early OIT studies indicate a window of opportunity in early childhood to achieve sustained unresponsiveness by allowing unrestricted dietary intake. To date, the mechanism underlying the improved efficacy of early OIT in terms of sus-

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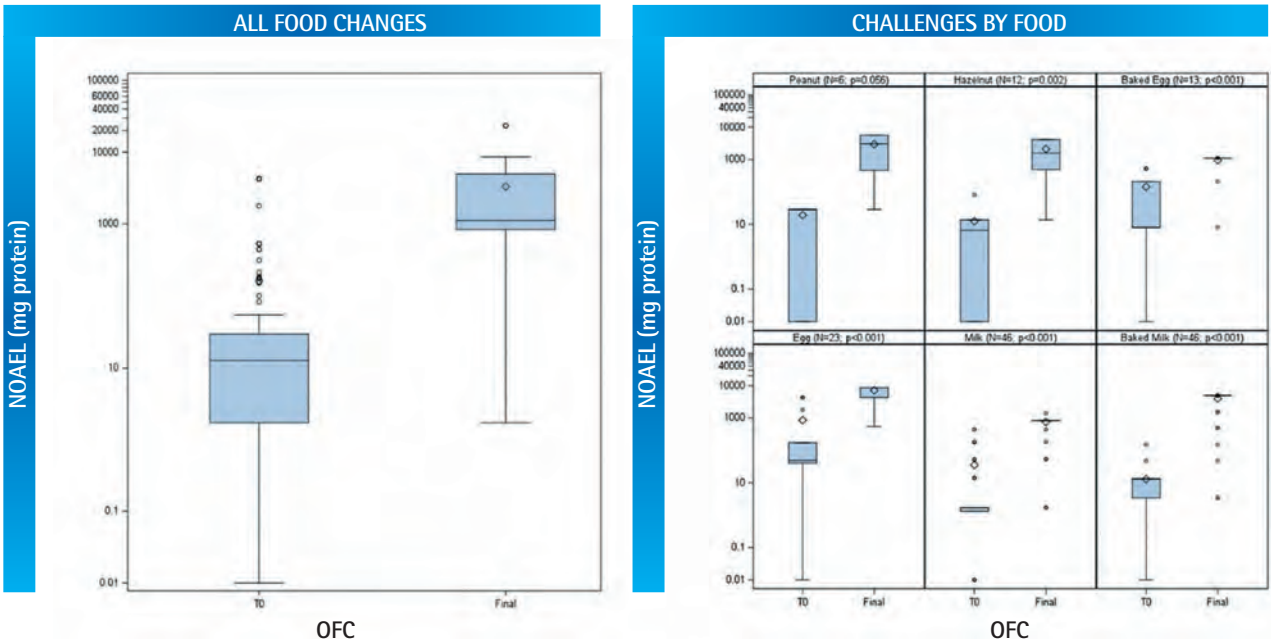
Figure 2 NOAEL before (T0) and during treatment with omalizumab



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tained unresponsiveness is not yet understood. However, both cohort and OIT studies indicate immune plasticity in early childhood. An immature food allergy response in early life seems to be a determinant of this immune plasticity, together with a more 'tolerogenic' immunological state. Future studies on the safety, feasibility, and efficacy of early OIT are awaited (28).

A number of limitations still remain. Safety is a major concern with OIT, with mainly mild side effects such as abdominal pain, but sometimes more serious ones such as anaphylaxis, and rarely eosinophilic oesophagitis. For this reason, both careful clinical monitoring and counselling are important, with a personalised action plan on how to deal with the presence of cofactors or in the event of reactions (29). The GA2LEN meta-analysis reported that OIT may increase (mild) adverse reactions in cow's milk ($p < 0.05$, RR 3.9, 95% CI 2.1-7.5) and egg ($p < 0.05$, RR 7.0, 95% CI 2.4-19.8) (17). Another meta-analysis focusing on peanuts reported a higher incidence of serious adverse reactions (RR 1.92 [1-00-3-66], I^2=0%, RD 5-7%) (30).

3.4 Sublingual and epicutaneous immunotherapy

To improve the safety profile of AIT, alternative routes (such as sublingual and epicutaneous) have been studied. These routes use tiny amounts of allergen with an extremely minimal risk of systemic reactions; they do not, however, increase the threshold of reactivity in the short term or to levels similar to those that would be obtained with OIT while maintaining the daily dose. Nonetheless, they appear to induce comparable changes in the immune response to allergens over time, suggest-

ing that they could potentially offer the same long-term benefits once therapy ends. The majority of studies focus on peanuts: the GA2LEN group indicates that EPIT increases the proportion of patients able to tolerate peanut during therapy ($p < 0.05$, RR 2.6, 95% CI 1.8-3.8) and SLIT could lead to a significant increase in the proportion of patients able to tolerate peanut during therapy ($p < 0.05$, RR 4.7, 95% CI 1.6-13.8). The GA2LEN Task Force suggests that EPIT for peanut should be considered under specialist supervision using licensed drug products, if available, for selected children aged 4-11 years with a clinical diagnosis of severe IgE-mediated peanut allergy, in order to increase the amount of peanut tolerated during therapy (24).

A recent randomised clinical trial showed that 12 months of EPIT with a daily dose of 300 µg of Viaskin® Milk resulted in a statistically significant desensitisation in children aged 2-11 years, with an excellent safety profile for CMPA (31).

3.5 Organic

Recent advances in understanding the immunopathogenesis of FA have identified the significant role of IgE and its high-affinity receptor FcεRI, as well as mast cells and basophils, cytokines and chemokines, eosinophils, lipid mediators such as leukotrienes and prostaglandins, and Th2 and B cells in mediating allergic responses. This knowledge has led to the study of biological drugs as potential therapeutic agents for FA, modulating the immune response and reducing allergic inflammation. In order to overcome the limitations of AIT for FA, research in recent years has also focused on combination with biological drugs, with promising results. Of all of them, the use of omalizumab (Xolair®) has shown the most promise. Omalizumab is a humanised IgG1 monoclonal anti-IgE antibody developed by recombinant DNA techniques. Omalizumab binds to the Cε3 constant region of circulating free IgE, preventing it from binding to high-affinity FcεRI receptors on effector cells (mainly basophils and mast cells), interfering with degranulation and the release of pro-inflammatory mediators. More recently, it has been shown that, in addition to binding free IgE, omalizumab can actively displace IgE from its high-affinity receptor. Finally, a third mechanism of action, particularly relevant in the context of FA, is the formation of IgE-omalizumab complexes. Since the Fab portion of the IgE molecule is still functional, it is able to bind the circulating allergen and thus compete for the same epitopes as the cell-bound IgE, preventing their cross-linking. This mechanism is particularly relevant for preventing systemic reactions in the context of FA.

3.5.1 Omalizumab as monotherapy

In 2024, Wood et al. investigated the efficacy and safety of omalizumab as monotherapy in a randomised double-blind placebo-controlled clinical trial in patients aged one year and older with multiple food allergies. The percentage of participants able to consume ≥600 mg peanut protein without dose-limiting symptoms was almost 10 times higher in the omalizumab-treated group than in the placebo group. Treatment with omalizumab for 16 weeks was shown to be superior to placebo in increasing the reactivity threshold for other common food allergens (cashew nuts, egg, and milk), and may protect against reactions following accidental exposure (Figure 1) (32).

A prospective real-life study evaluating the impact of omalizumab in terms of efficacy, safety, and quality of life in children with moderate/severe asthma and history of anaphylaxis to peanuts, dried fruit, fish, egg, milk and/or wheat is being published. In 65 patients allergic to 107 foodstuffs, the dose without observable adverse events at T1 (4 months after the first administration of omalizumab) increased: 243-fold and 488-fold for raw and cooked milk; 172-fold and 134-fold for raw and cooked egg; 245-fold for nuts; 55-fold for peanuts; 31-fold for wheat and 10-fold for fish. Complete tolerance was achieved in 66.4% of OPTs at T1, 58.3% and 75% at T2 and T3, respectively (8 and 12 months after the first administration of omalizumab). Ninety-five foods were liberalised ad libitum in the diet of 55 patients; the remaining 12 were introduced by at least 10 trace patients. During the study, 40/65 children obtained a free diet with a concomitant increase in the quality of life of the children and families (Figure 2) (33).

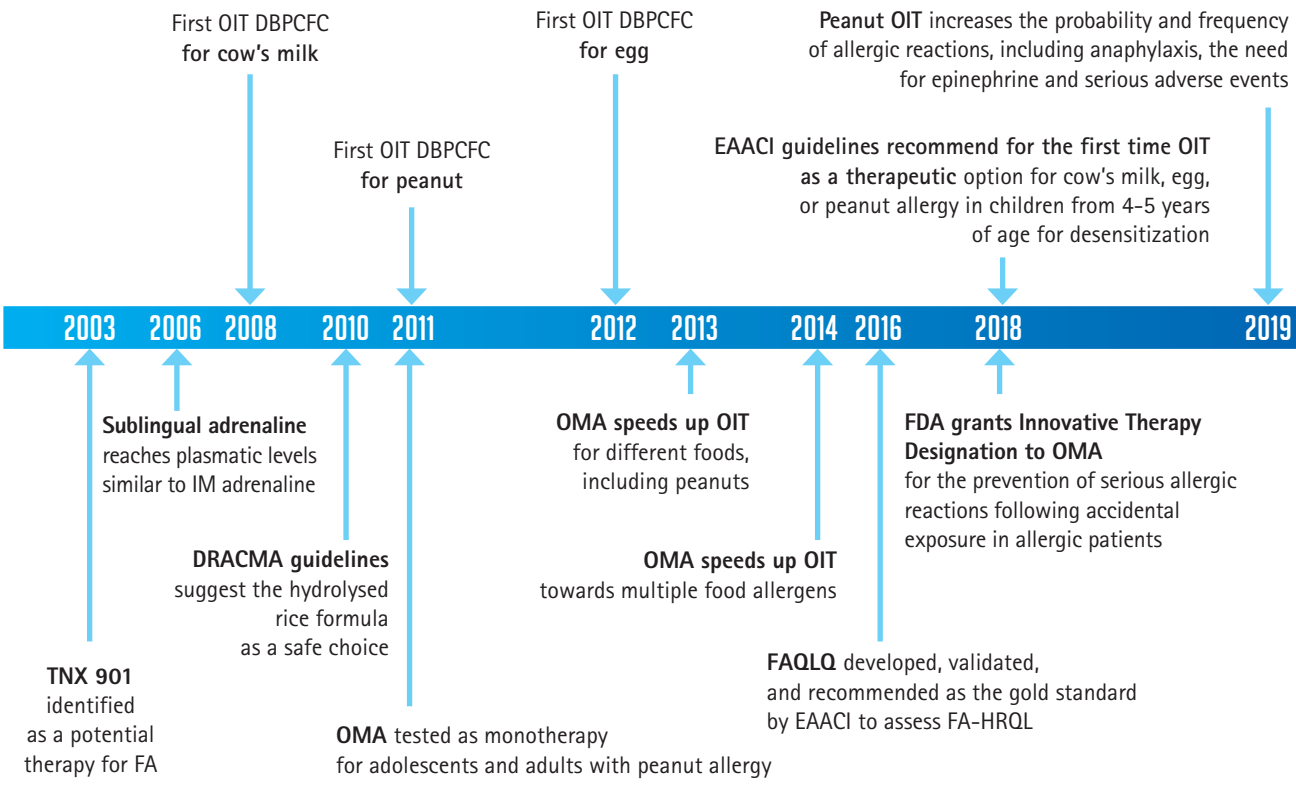
3.5.2 Omalizumab combined with OIT

There are completed clinical studies on the use of omalizumab as an adjuvant to single-food and multiple-food OIT. Wood et al. showed that the rates of sustained unresponsiveness and desensitisation were comparable with placebo at 2 years. However, omalizumab prevented the occurrence of systemic reactions during OIT (34). MacGinnitie et al. tested omalizumab as an adjuvant in an accelerated peanut OIT programme. After 14 weeks, 79% of patients in the omalizumab-treated group tolerated 2 grams of peanut protein, compared to 12% in the placebo group ($p < 0.01$, RR = 6.6) (35). Andorf et al. also tested omalizumab versus placebo as an adjuvant in an accelerated multi-food OIT programme. After 28 weeks, 83% of the treated group (compared to 33% in the control group) tolerated 2 grams of protein from at least two foods (RR = 2.5). At 8 weeks, there was a treatment failure rate of 8% versus 67% in each group, respectively (RR = 0.12) (36).

3.6 Other adjuvants

In 2023, Wang et al. demonstrated that E-B-FAHF-2, a safe and well-tolerated herbal drug for patients with FA, does not improve the outcomes of multi-OIT and omalizumab. The knowledge gained from this study sup-

Figure 3



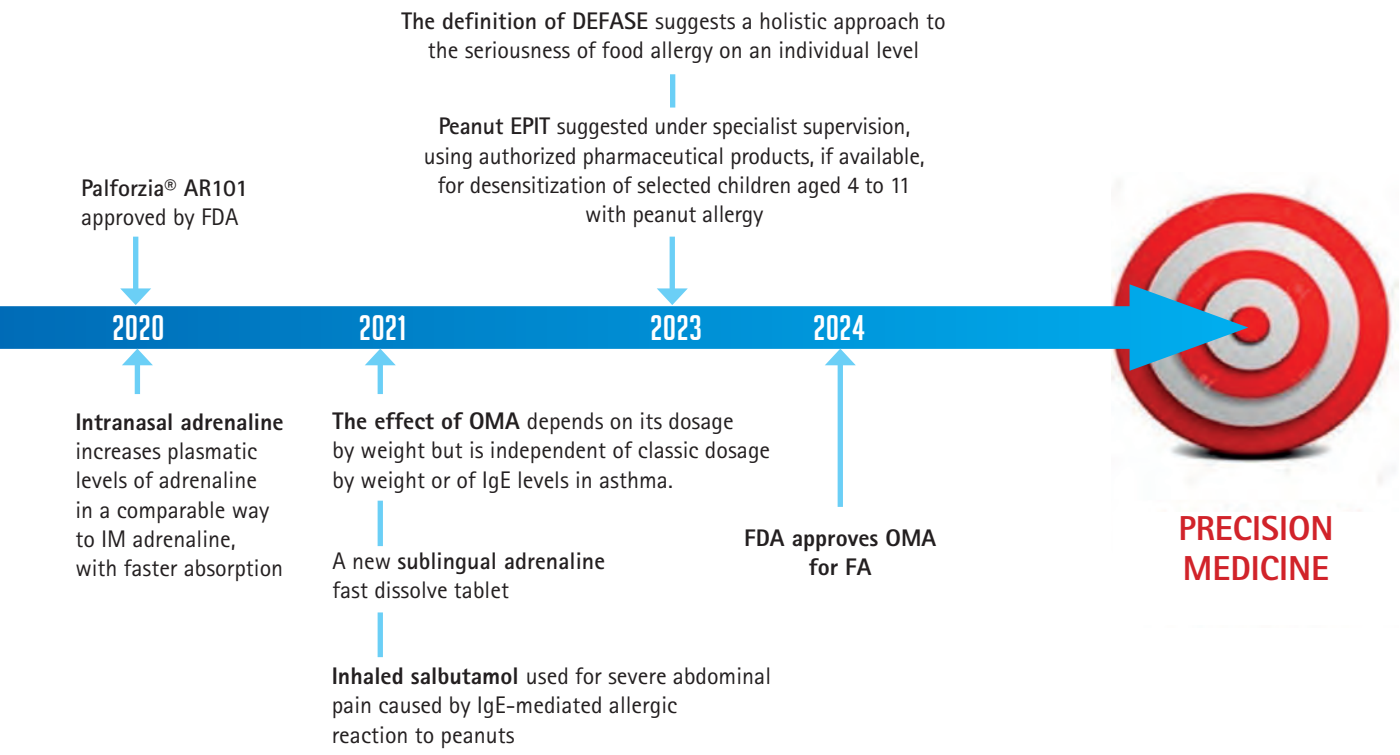
ports the safety and efficacy of omalizumab as an adjuvant to multi-OIT in the desensitisation of the majority of subjects following this treatment, and that remission at high thresholds can be achieved for some (37).

Omalizumab in February 2024 was approved for FAs in the US by the FDA starting at one year of age. In Europe, omalizumab is currently only approved for the treatment of clinically uncontrolled moderate-severe asthma from 6 years of age, and chronic spontaneous urticaria in patients older than 12 years, but not for food allergy per se.

3.7 Other biologicals

Ligelizumab, a new anti-IgE monoclonal antibody more potent than omalizumab, is currently in development for FA. In previous phase 2 trials for asthma, ligelizumab has been shown to negate skin tests, unlike omalizumab, suggesting greater potential in preventing anaphylaxis. Dupilumab is another biologic currently under investigation for FA treatment, either as monotherapy or in combination with OIT. It is an anti-IL-4 and anti-IL-13 monoclonal antibody approved for the treatment of type 2 asthma, nasal polyposis, and atopic dermatitis, also showing promise for non-IgE-mediated food allergies. Phase 2 and phase 3 studies have demonstrated its efficacy in the treatment

Management of food allergies in the 21st century



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of eosinophilic oesophagitis, and there are reports of success in the treatment of eosinophilic gastroenteritis secondary to type 4 FA. Other drugs have been investigated, but so far with limited efficacy (e.g. mepolizumab, tezepelumab), and others are under evaluation.

A new generation of treatments for FA is emerging, using different approaches. The use of biologics, either as monotherapy or in combination with AIT, represents a pioneering approach in the management of FA. However, despite the growth of research in this area, the optimal use of biologics in the treatment of FA, including timing, duration, and combination strategies, has yet to be fully elucidated.

3.8 Preclinical options

Further therapeutic approaches are being evaluated. A mention of the development of hypoallergenic products (i.e. with reduced allergenic potential) and vaccines: promising data have been published suggesting that vaccination using individual peanut allergens may represent a new therapy against peanut allergy, with a favourable safety profile (38). Further, highly anticipated studies are in progress.

4. Conclusions and future prospects

So far, the 21st century has seen significant advances in the management of FAs (Figure 3) (39). We anticipate that in the coming years, drugs currently undergoing preclinical or early clinical evaluation will finally offer the possibility of safe and effective therapies for FA in the clinical setting. In the future, the identification of reliable biomarkers and the development of standardised approaches for FA phenotyping could lead to customised approaches in the management of food allergy. Standardised and validated definitions and measurement approaches, together with shared decision-making with patients and families, will allow for more targeted support and guidance, helping to reduce the significant burden of food allergy.

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TSLP and its implications in allergic diseases

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1. Introduction

The immune system, an intricate but fascinating system of cells and soluble mediators, is our evolved weapon of defence against pathogens and the onset of certain diseases. The cells of the immune system fall into two categories: those belonging to the innate (non-specific) system include monocytes/macrophages, neutrophils, basophils, eosinophils, mast cells, dendritic cells (DCs) and innate-type lymphocytes (ILCs). These cells respond readily to external insults in a non-specific way. In contrast, the adaptive immune system includes T- and B-lymphocytes, which are capable of implementing antigen-specific responses. Allergic diseases, which are a growing public health problem worldwide, are basically caused by immune system dysfunction. As with many other diseases, genetic and environmental factors are at the root, sometimes difficult to predict (1). Allergic diseases include atopic dermatitis (AD), allergic rhinitis, allergic asthma and food allergies. Understanding the cellular and molecular

SUMMARY

Keywords
• TSLP • alarmin • allergies • immune system • asthma • tezepelumab

Acronyms
• **AD** atopic dermatitis;
• **DCs** dendritic cells;
• **IL** interleukin;
• **ILCs** innate-type lymphocytes;
• **T2** type 2 (inflammation);
• **Th** T helper lymphocytes;
• **TSLP** thymic stromal lymphopoietin;

Thymic stromal lymphopoietin (TSLP) was identified in 1994 as a factor capable of promoting the survival and differentiation of B and T lymphocytes. Originally identified as a product of thymic stromal cells, it is now described as a predominantly epithelial-derived cytokine, classified as an alarmin; it plays a primary role in the inflammatory cascade of allergic diseases, and in asthma in particular. A broad spectrum of cells of the immune system respond to TSLP binding and some of them, through a self-sustaining mechanism, are also able to contribute to its production. Given the multiple functions and pathological implications that will be described below, TSLP represents a promising therapeutic target. Indeed, therapies aimed at blocking its functionality have recently been introduced, indicated especially in patients with severe asthma that is not controlled by classical therapies. The most salient aspects of TSLP biology will be described in this article.

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Figure 1 Main target cells of TSL

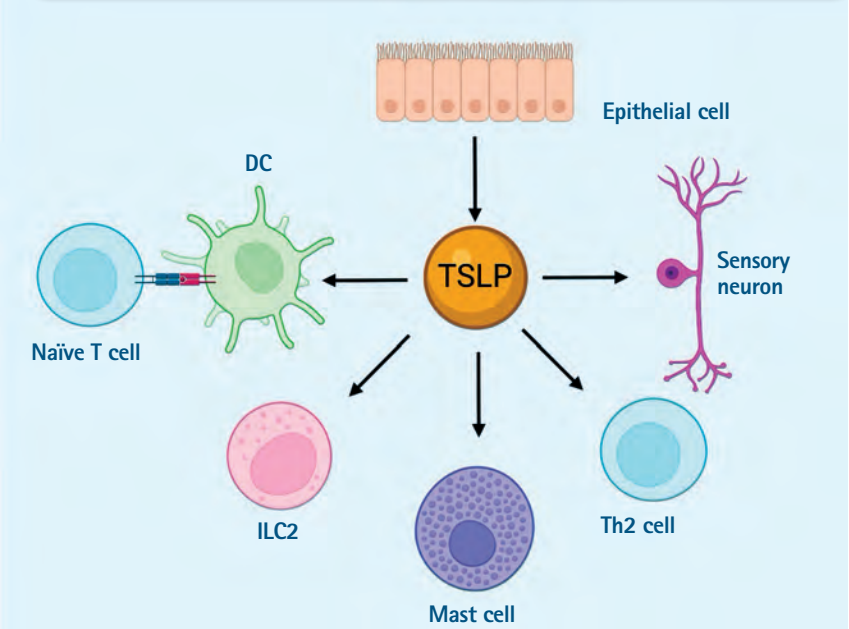

Image created on BioRender.com based on source (8).

mechanisms that fuel these deregulations is crucial, as it opens up the possibility of developing new therapeutic strategies.

2. Mediators of inflammation in allergic diseases

AD, from which mainly children suffer, is an extremely widespread inflammatory skin disease, constituting in several cases the first step in the development of the so-called allergic march characterised in particular by asthma (2). Asthma is an airway disease, generally chronic, that affects both children and adults. The treatment of asthma in the not particularly aggressive forms involves the use of bronchodilators (β-2-agonists, anticholinergics), corticosteroids, leukotriene inhibitors, mast cell stabilisers, methylxanthines and immunomodulators. A fraction of patients, between 5 and 10%, may experience severe asthma and be refractory to currently used therapies (3). Asthma and severe asthma manifest themselves with heterogeneous phenotypes, which contributes to the difficulty of treatment; therefore, the identification of new therapeutic targets and new therapies for these patients is a major field of study. In the vast majority of asthma cases, patients present with airway inflammation termed type 2 (T2) inflammation; in severe asthma, eosinophilic inflammation is present, again driven by T2 inflammation (4). An increased production of inflammation factors, in particular cytokines, such as interleukin-4, -5 and -13 (IL-4, IL-5, IL-13) leads to the establishment of T2 inflammation (5). In this inflammatory scenario, IL-4 promotes B-cell antibody isotype change and the production of immunoglobulin type E (IgE), which is more impactful in allergic states. IL-5 plays an important role in enhancing the activation and recruitment of eosinophils (which, together with mast cells, are the cells of primary relevance in allergies). IL-13 induces the production of mucus in mucus cells and also enhances IgE production (5). Factors contributing to an allergic-inflammatory microenvironment T2 include Thymic Stromal Lymphopoietin (TSLP).

3. The biology of TSLP and its roles in allergic (and other) diseases

TSLP is an epithelial - and stromal-derived pleiotropic cytokine belonging to the interleukin-2 (IL-2) family. It is a mediator that plays important roles in T2 inflammation and acquired immunity. TSLP is one of the cytokines classified as alarmins, i.e. those that are readily released following tissue damage by epithelial cells of various tissues such as skin, lungs and digestive tract.

In the case of the airway epithelium, their release is induced by environmental insults in response to allergens, viruses, bacteria or pollutants (6). The alarmins also include interleukin 33 (IL-33) and interleukin 25 (IL-25), cytokines that also play important roles in allergic diseases and T2 inflammation (7, 8). There are multiple mediators that positively regulate TSLP release, including IL-4, IL-5, IL-13, as well as tumour necrosis factor (TNF), interleukin 1 β (IL-1β) and IL-25 (9). This last aspect explains the relevance of TSLP in the context of chronic allergic diseases, i.e. where there is a continuous maintenance of this inflammatory state. Several cells produce and release TSLP: these include mast cells (cells of the innate immune system classically known to be activated in allergic contexts), which are also an important regulator of inflammation. Indeed, it has been shown that mast cells activated by IgE binding to the high-affinity receptor, which they express in the membrane, release high levels of TSLP (10). It has been reported in the literature that DCs stimulated via toll-like receptors (TLRs) and IL-4 are also able to produce TSLP, as well as being responsive to it; this has been observed both by in vitro stimulation of cells and in an in vivo allergy model (11).
Two isoforms of TSLP are described in the literature: a long form, consisting of 159 amino acids, also corresponding to the murine form, which is found increased in inflammatory states, and a short form, consisting of 63 amino acids and constitutively produced by epithelia (12, 9). The long form is believed to be most responsible for the exacerbation of allergic states; conversely, in certain oncological diseases such as ovarian and endometrial cancer, the short form appears to be responsible for promoting tumour growth (13).
The diverse functions of TSLP can be explained by the fact that there is a broad spectrum of cells in the immune system (and beyond) on which TSLP can bind, influencing their biological functioning. In addition to B- and T-lymphocytes, the long list includes DCs, neutrophils, mast cells, eosinophils, basophils, ILCs belonging to

Figure 2 TSLP receptor and intracellular signal leading to cytokine production of T2 inflammation

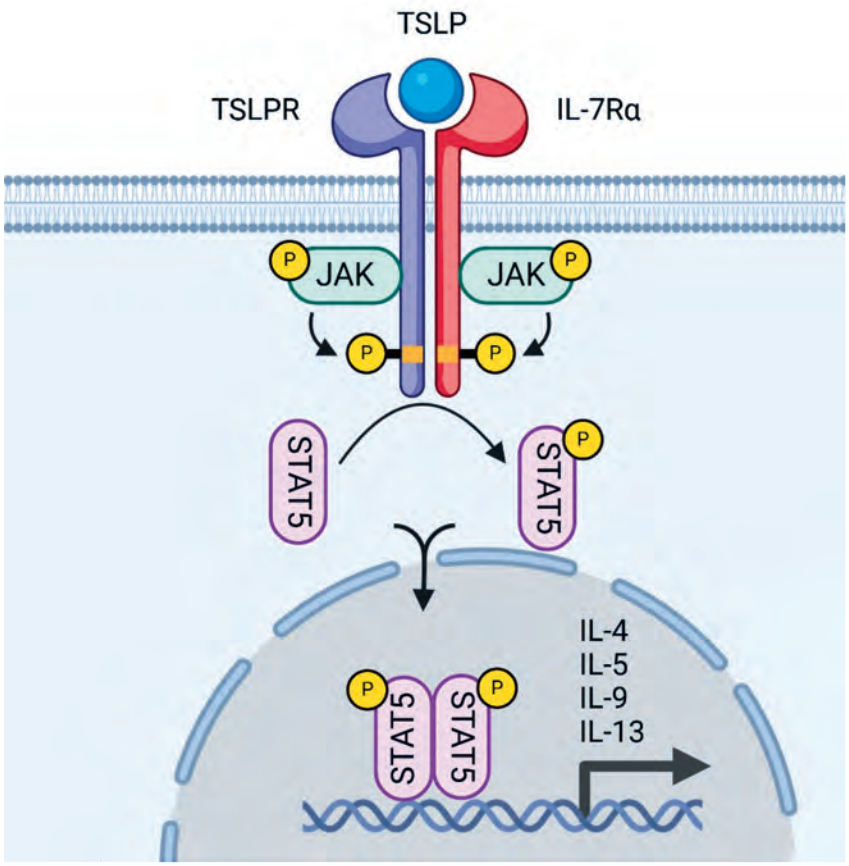

Image created on BioRender.com based on source (9).

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Table 1 Therapies for patients with severe asthma

Monoclonal antibody	Molecular target
Omalizumab	anti-IgE
Mepolizumab, Reslizumab	anti-IL5
Benralizumab	anti-IL5R
Dupilumab	anti-IL4Rα

R Receptor

group 2 (ILC2s), natural killer T-cells, as well as muscle cells and tumour cells (9) (Figure 1).

TSLP is paralogous to interleukin 7 (IL-7) with which it shares the ability to bind to the IL-7Rα receptor (14). Intracellular signalling is mediated by TSLP's binding to its own receptor, a heterodimer composed of IL-7Rα and TSLPR (TSLP receptor), which activates important intracellular signalling pathways such as the Janus kinase (JAK) pathway, which in turn activates activator of transcription 5 (STAT5) and signal transduction pathways such as MAP kinase. As an end result, target cells produce increased levels of the cytokines IL-4, IL-5, IL-9, IL-13, thus creating a kind of loop that exacerbates allergic inflammation (Figure 2).

TSLP, therefore, plays a major role in the context of allergic-type diseases, where T2 inflammation is a characteristic feature. A type 2 inflammatory state tends to occur in a precise temporal sequence: first there is the development of atopic dermatitis, followed by the onset of food allergies, to evolve in certain cases into a (chronic) pathology of the airways that can lead to asthma.

TSLP, in concert with the other epithelial cytokines, is considered both a promoter and propagator of allergic states (8). The allarmins underlying T2 inflammation in this context are induced by exposure to allergens and are therefore critical elements of allergic states. Similarly to the action of IL-33, TSLP induces increased expression of co-stimulatory molecules on DCs thus in turn favouring the polarisation of T helper (Th) type 2 cells (15). Th2 cytokine release is also induced by direct binding of TSLP on mast cells, ILC2s and macrophages.

Before moving on to the description of TSLP's roles in allergic contexts, to complete the descriptive picture of TSLP's functions, let us recall that the cytokine, by enhancing T2 responses, also participates in the resolution of staphylococcal and streptococcal bacterial infections, helminth infections and viral infections, all by orchestrating the functions of the cells of the immune system (9).

3.1 TSLP in atopic dermatitis and food allergies

AD is a generally chronic inflammatory skin disorder characterised by itching and skin erythema. TSLP is highly expressed in AD lesions; TSLP gene variants have been identified as being associated with less AD development in children, while other variants are associated with increased risk of developing the disease (16, 17, 9). From a therapeutic point of view, it is interesting to note that some TSLP gene mutations are associated with greater disease persistence despite concomitant therapeutic treatments (10, 16). As far as symptomatology is concerned, TSLP seems to play not only an indirect role in the induction of itching (i.e. by activating cells capable in turn of acting on neuronal stimulation), but also a direct pruritogenic one. There are, in fact, data showing that TSLP is directly responsible for the activation of TRPA1-positive sensory neurons (18). Food allergies tend to develop early in children and frequently occur following the development of AD. From these observations, it has been hypothesised that skin sensitisation to allergens is crucial in the context of food allergies. However, in contrast to TSLP's roles as an important inducer of AD, in allergic responses of the intestinal tract it has been hypothesised that TSLP may play less of a role in induction (where, for

example, IL-33 seems to be more decisive), but rather in maintenance (19).

3.2 TSLP in asthma

There is a strong association between elevated levels of TSLP, IL-33 and T2 inflammation cytokines in patients suffering from uncontrolled asthma (20). As with previously described conditions, correlations have emerged between the existence of mutations in the TSLP gene and the risk of developing asthma (21, 22); it has been observed that gene isoforms of TSLP may play a role in the manifestation of uncontrolled asthma (23). In asthmatic patients, there is increased expression of the TSLP receptor on ILC2s, which innately release T2 cytokines. In this context, TSLP synergizes and enhances IL-33- and IL-25-mediated activation. In severe asthma, higher levels of ILC2 are observed compared to more moderate forms, despite the high levels of corticosteroids used in treatment. There is work suggesting a function of TSLP in inducing resistance of ILC2 to corticosteroids; specifically, the inhibitory effects of the anti-inflammatory drug dexamethasone on ILC2 would be reduced in the presence of high levels of TSLP and IL-7 (24). In severe or uncontrolled asthma, eosinophils are increased in number and found in an activated state, a critical feature in driving physiological changes and airway remodelling. TSLP plays a primary role in the activation of eosinophils, promoting their survival and accumulation in the tissue and inducing the release of other pro-inflammatory cytokines and chemokines such as IL-6, CCL2, CXCL8 (20). In eosinophilic asthma, patients typically have elevated levels of IL-4 in the airway epithelium; this cytokine not only plays direct roles in promoting epithelial damage by altering permeability, but also by directly increasing TSLP and IL-33 levels and further exacerbating the Th2 response (25). Mast cells that release the con-

Figure 3 Multiple targets of anti-TSLP antibodies vs. classically used antibodies in asthma treatments

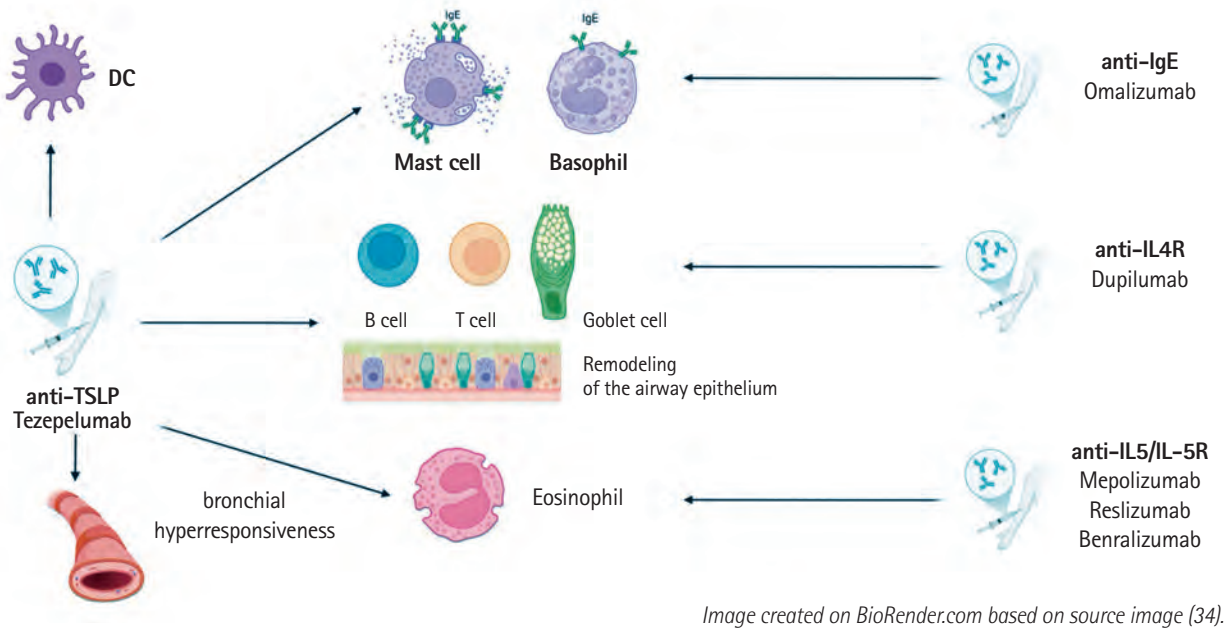

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Table 2 Clinical trials involving tezepelumab in allergic diseases

Name of the clinical trial	Trial code (clinicaltrials.gov)	Phase	No. of participants	Pathology	Main conclusions of the trial
	NCT01405963	1b	31	Mild atopic asthma	Decreased allergen-induced bronchoconstriction and airway inflammation.
UPSTREAM-COPD	NCT05507242	2	40	Asthma in adult patients treated with ICS (+/- LABA)	Decrease in eosinophils in the respiratory tract and blood. Improvement of airway irritability.
CASCADE	NCT03688074	2	116	Asthma (moderate to severe)	Improvement of airway irritability. Reduction of eosinophils in the airway submucosa.
	NCT03809663	2	251	Atopic dermatitis	The study did not reach predetermined efficacy levels for the patient population examined.
PATHWAY	NCT02054130	2b	550	Asthma (moderate to severe)	Reduction of annual recurrences of eosinophilia and the inflammation marker FeNO
NAVIGATOR	NCT03347279	3	1061	Asthma (moderate to severe)	Reduction of annual recrudescences, eosinophil counts and the inflammation marker FeNO.
NOZOMI	NCT04048343	3	65	Asthma (moderate to severe)	Efficacy and safety confirmed in Japanese asthmatic patients
DESTINATION	NCT03706079	3	966	Asthma (moderate to severe)	Long-term efficacy and safety data are confirmed.
SOURCE	NCT03406078	3	150	OCS-dependent asthma	Reduced annual recrudescence and reduced OCS for patients with eosinophilia ≥150 cells/µl.
VECTOR	NCT05062759	3b	70	Adolescents and young adults with asthma (moderate to severe asthma) vaccinated for influenza	There was no suppression of the antibody response in adolescents and young adults vaccinated for influenza during treatment with tezepelumab.

ICS inhaled corticosteroids; **LABA** long-acting β agonists; **FeNO** exhaled nitric oxide; **OCS** oral corticosteroids.

tents of their granules through IgE-dependent activation (i.e. histamine, heparin, cytokines, leukotrienes etc.) play a key role in promoting the onset of allergic and eosinophilic asthma. As already mentioned, mast cells are both responsive to the binding of TSLP and the source of the cytokine itself: a kind of autocrine inflammatory circle is thus established. The mast cell is therefore an important target to treat TSLP-fuelled asthma. Another cell type of the immune system that represents a target of TSLP in allergic asthma are the macrophages of the airways. This is explained by the fact that TSLP promotes differentiation, production of cytokines and pro-angiogenic factors such as endothelial growth factor (VEGF) by macrophages, thereby promoting bronchial remodelling. Not only that, it has also been shown that TSLP can be produced by appropriately stimulated macrophages (via, for example, lipopolysaccharide and IL-4), thus outlining another 'vicious' circle of self-feeding inflammation (26). DCs are another important target of TSLP, which can induce the expression of co-stimulatory molecules on these cells that are in turn crucial in mediating the differentiation of T-cells to Th2 cells. It is also reported that TSLP can induce polarisation of Th2 cells via direct binding (27).

Finally, there are both moderate and severe asthma phenotypes that are not characterised by eosinophilic inflammation, but instead mediated by neutrophils and IL-17-producing T lymphocytes. TSLP also comes into play in these contexts; indeed, it has been observed that TSLP promotes the differentiation of Th17 cells through the activation of DCs (20).

3.3 TSLP and cancer

A deregulated TSLP signal has not only been observed in allergic-type inflammatory contexts. There are tumour contexts in which predominant T2 inflammation is associated with a poorer prognosis, and deregulations of TSLP itself have been correlated with the onset and maintenance of both solid and haematological tumours. Several years ago, interesting work analysing the immune tumour microenvironment in pancreatic cancer patients revealed that there was a poorer survival of patients with TSLP-induced type 2 inflammation. Specifically, it was determined that TSLP was produced by tumour-associated fibroblasts stimulated by TNF-α and IL-1β. In addition, TSLP-stimulated DCs were observed in the tumour stroma and tumour-draining lymph nodes. DCs, in turn, would promote the activation of Th2 presenting specificity towards tumour antigens, ultimately responsible for the pro-tumour fibrotic action (28). In the context of metastatic breast cancer, TSLP's role as a pro-tumour factor produced by the tumour cells themselves, capable of shaping a Th2-type tumour microenvironment, has also emerged (29). However, it is fair to point out that other researchers have questioned whether TSLP plays such a decisive role in the context of breast cancer (30). Gene mutations inducing increased expression of TSLPR have also been shown in a good percentage of paediatric patients with acute lymphoblastic leukaemia, particularly in those with the so-called Philadelphia chromosome (i.e. with BCR-ABL 9-22 gene translocation) (31, 32). Therapeutic strategies aimed at targeting TSLPR over-expressed in lymphoblastic leukaemia cells have been successfully tested in a murine xenograft model (i.e. by transplantation of human tumour cells injected intravenously into mice) by exploiting chimeric T-cell antigen receptor (CAR T) technology. This represents a new and promising type of immunotherapy involving the engineering of T lymphocytes (of the subject to be treated) to express in the membrane the antigen receptor to be targeted on tumour cells; the CAR-Ts, once re-infused into the patient, detect the tumour antigen and attack the cancer cells. In this specific study, CAR-Ts recognise the TSLP receptor and induce leukaemic cell death (33).

4. Tezepelumab: monoclonal antibody directly targeting the TSLP receptor

Patients with severe asthma are at risk of hospitalisation. For such patients, who present with allergic asthma with a highly inflammatory phenotype (T2), there are therapies involving monoclonal antibodies designed to neutralise IgE, sequester individual cytokines such as IL-5, or block the signal induced by binding to IL-5 and IL-4 receptors (34) (Table 1).

Recently, tezepelumab, a monoclonal antibody designed to neutralise the ac-

tion of TSLP, has been developed. Specifically, it is a monoclonal antibody that prevents the binding of TSLP to its receptor. The drug was approved in 2021 by the US Food and Drug Administration (FDA) as a treatment for asthma, followed by Japan in 2022. The antibody tezepelumab (trade name Tezspire®), authorised in 2022 by the European Medicines Agency (EMA), is expected to treat asthma in adults and adolescents over 12 years of age with severe asthma, in particular asthma not controlled by high-dose inhaled corticosteroids in combination with another drug intended for the treatment of asthma (https://www.ema.europa.eu/en/medicines/human/EPAR/tezspire).

The most important advantage of treating asthma with tezepelumab is its broad spectrum of action, i.e. the fact that a single drug is able to suppress a variety of inflammatory cascades by simultaneously inhibiting the activation of mast cells, basophils, eosinophils, B- and T-cells, dendritic cells and bronchial hyperresponsiveness (34) (Figure 3).

This may help to significantly suppress T2 inflammation compared to other monoclonal antibody treatments, as proposed by meta-analysis studies (35).

It should be emphasised that the monoclonal antibodies listed in Table 1, having cytokines or antibodies closely related to T2 inflammation as targets, are of little use in the treatment of uncontrolled non-T2 asthma. In contrast, tezepelumab appears to be a valid treatment for patients with no T2 inflammation but with inflammation more driven by Th17. The biological explanation would lie in the fact that in these patients TSLP promotes differentiation into Th17 cells producing IL-17, IL-21 and IL-22. This effect is mediated by the action of the cytokines IL-1β, IL-6, IL-23 and TGF-β. In particular, Th17 cytokines, contributing to the pathogenesis of non-T2 bronchial asthma, act directly on epithelial cells to promote the production of factors that in turn promote neutrophilic inflammation (35-37). To date, in patients with moderate eosinophilic asthma, anti-TSLP therapy has been successful in mitigating airway bronchoconstriction and reducing the number of eosinophils circulating and present in sputum (38). In 2021, a major phase 3 study (NAVIGATOR trial) demonstrated the efficacy of treatment with tezepelumab for patients with severe asthma compared to the control group in terms of lung function and inflammation (even in cases with lower levels of eosinophilia) (39).

However, it is important to point out that tezepelumab did not show particularly encouraging results in phase 2 clinical trials in the treatment of severe to moderate AD (40). Moreover, for the sake of completeness, it is useful to consider that, since many of TSLP's functions overlap with those induced by increased IL-33 levels, therapeutic strategies aimed at interfering with the biological activity of the latter alarmin are equally interesting and promising for the treatment of allergic states, and in particular severe asthma (41). The most relevant clinical trials involving tezepelumab in allergic diseases, well summarised in reviews (9, 34), are listed in Table 2.

5. Conclusions

TSLP, being implicated in a broad spectrum of diseases but also in the maintenance of immune homeostasis, is an important predictive marker of disease severity as well as a promising therapeutic target. Clinical data concur in indicating TSLP as a driver of asthma. By interfering with its action, a restoration of homeostatic conditions in the airways can be achieved. Among the most important scientific evidence is the encouraging result of anti-TSLP treatment with tezepelumab in uncontrolled cases of eosinophilic asthma. Moreover, the benefits obtained in the treatment of non-eosinophilic asthma also shed light on how TSLP may contribute not only in T2-independent inflammation as has long been thought, but also in T2-independent inflammation. This finding is promising, since to date no alternative therapies with proven efficacy are available for these patients. However, a number of elements remain to be investigated: for instance, it is not entirely clear whether the shorter isoform of TSLP (whose functions are not yet fully delineated) is also the target of anti-TSLP antibodies in the clinic. Moreover, the efficacy and safety of long-term treatment (for periods of more than two years), as well as systemic interference with TSLP (i.e. at anatomical sites distal to the airways), need to be properly assessed. Indeed, it should be remembered that TSLP, in some contexts, has functions that are considered protective, such as in defence against certain types of infection.

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Anaphylaxis to airborne allergens: an invisible enemy

Airborne anaphylaxis: highlighting an invisible enemy

Ridolo et al. Current Opinion in Allergy and Clinical Immunology, 22(5), 283-290 (2022). DOI: 10.1097/ACI.0000000000000848

In this review, the authors draw attention to an often underestimated problem: anaphylaxis induced by airborne allergens (*airborne anaphylaxis*, AA). Anaphylaxis, the most severe of allergic reactions, can be life-threatening and requires immediate intervention. It is most commonly caused by food ingestion, drug use and hymenoptera stings, but in some cases can be triggered by inhalation of airborne allergens. There are no epidemiological data on AA in adults, but it has been observed that in children with anaphylactic reactions to food, about 6% of cases were due to exposure to food allergens in aerosol form (8% by ingestion, 16% by skin contact).

Works in the literature on AA are rather limited and mainly present single clinical cases. The authors collected and ordered the available data to provide an overview of potential causes of AA. The studies are presented according to allergenic source: the most important are food, which is also a major cause of anaphylaxis in general, and drugs, with interesting overlaps between the two classes. A short section at the end of the paper is dedicated to published reviews on the subject.

Regarding food allergens, in a study of 1411 Canadian children with peanut allergy, the annual incidence rate of allergic reactions after accidental exposure to peanuts was 12.5%, with 4.8% of reactions due to inhalation. The induction of allergic reactions (with clinical signs of anaphylaxis) to peanuts by inhalation was also confirmed in a study on mice exposed to peanut meal intranasally. The potential risk of peanut-related AA is also behind the decision of several airlines to no longer offer peanuts as a snack to passengers.

The dispersion of airborne food allergens and subsequent exposure to them can occur by different routes; one of the main ones is related to the cooking of food, as exemplified by two cases of AA related to exposure to lentil cooking vapours, and the case of an 8-year-old child with severe AA caused by inhalation of rice cooking vapours. Another route of exposure to airborne food allergens in cooking is the use of powdered preparations. The authors report the case of two children with an egg protein allergy who had a severe anaphylactic reaction just because they were in the same room (without direct contact) where a pavlova, a meringue-based dessert, was prepared using a preparation containing powdered egg white; or, as in the case of two children, aged 6 and 3, accidentally exposed to American ginseng powder (SPT positive for American ginseng for the first patient, while in the second the oral provocation test did not induce IgE-mediated allergic reactions).

The authors then report other curious cases, such as that of a woman with a food allergy to dill who experienced symptoms just from the smell of food prepared with this aromatic herb, and the case of a child with severe reactions to figs (itching of the upper limbs and face, oedema of the eyelids and lips, coughing, dyspnoea and dysphagia) while hitting the fruit under a fig tree with a tennis racket.

Allergy to airborne food allergens also occurs in the occupational context: an example is that of a worker at a *Pleurotus ostreatus* mushroom farm, who developed an AA as a result of constant exposure to the mushroom and its spores. The specific allergy was confirmed by prick-to-prick tests and inhalation provocation tests.

It should be emphasised that sometimes the trigger of AA is not easily identifiable because it is not immediately traceable to the food. An example of this is parasites: the paper reports the case of a patient who developed AA after inhaling dust from peas infested with the beetle *Bruchus pisorum*, and that of a patient with an allergy to *Anisakis simplex* (a parasite of fish and other fish products) who developed itching, tongue oedema,

coughing and breathlessness just by standing in front of a fish shop.
Conversely, some food-borne allergens may actually be the basis of drug-borne AA. This is the case, for example, of milk proteins contaminating lactose used as an excipient in various pharmaceutical formulations. Mention is made of the case of a milk-allergic paediatric patient who experienced AA after taking a drug in powder form for inhalation (Inavir®) against influenza. Laboratory investigations revealed the presence of traces of β-lactoglobulin in the drug. A similar reaction was described for soya lecithin used as an excipient in some drugs with inhaled bronchodilator activity (ipratropium bromide). In this case, the patient was allergic to soya and peanuts. Other experimental studies in mice seem to suggest that respiratory viruses may also play a role in triggering AA.
Drugs per se constitute another important group of factors capable of inducing AA. The clinical cases identified by the authors relate in particular to anaesthetics such as aerosol lidocaine and sevoflurane. Occupational exposure can also play a role in triggering an AA, as in the case of three subjects with reactions to chlorhexidine, i.e. the case of a nurse exposed to low doses of the inhaled drug cefuroxime taken to treat respiratory infections.
The authors then report interesting cases related to other agents such as latex (often linked to the use of gloves in hospital settings) and allergens derived from companion animals such as guinea pig and rabbit.
In conclusion, the authors emphasise that AA can remain undiagnosed or underestimated, and only a detailed medical history can help identify the underlying cause. Furthermore, it is important to refer the patient to an allergy specialist who can help him/her both to recognise the symptoms quickly and manage the acute phase and to inform him/her to avoid exposure to specific risk factors (e.g. vapours from cooking food or inhaled drugs) that may also be present in common environments such as the home or workplace.

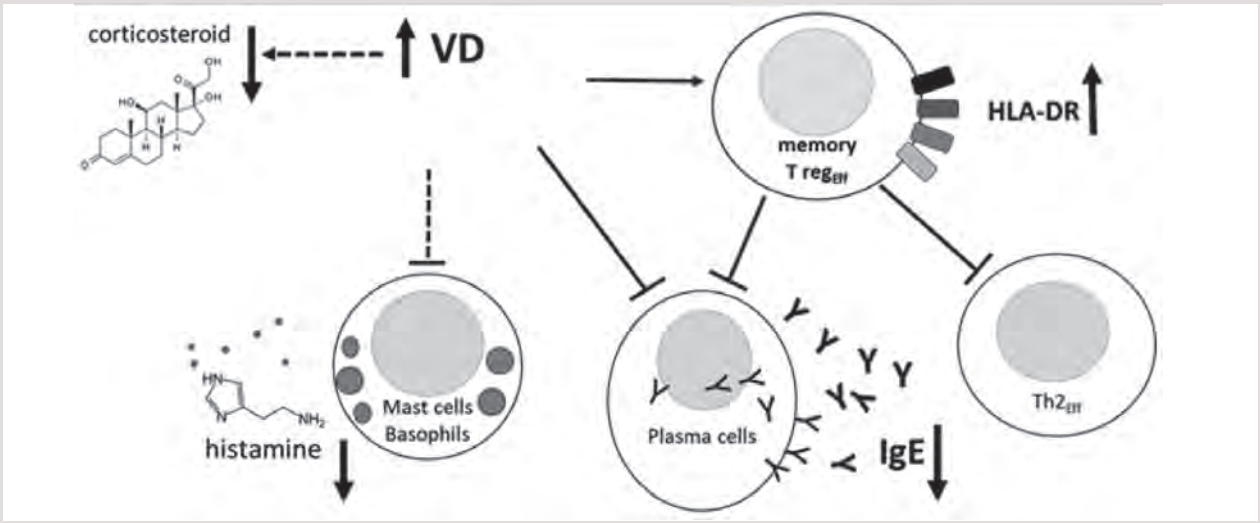
Role of endogenous vitamin D in allergen-specific immunotherapy

Vitamin D Role in Childhood Mite Allergy and Allergen Immunotherapy (AIT)

Petrarca C, Viola D. Biomedicines. 2023;11(6):1700. doi: 10.3390/biomedicines11061700

In this paper, the authors present a study aimed at clarifying the possible influence of vitamin D (VD) on clinical outcomes of allergen-specific immunotherapy (AIT) for *house dust mite* (HDM) allergy in paediatric patients. AIT is able to modify the course of the allergic disease by inducing a lasting tolerance to the triggering allergen. AIT appears to act by promoting the differentiation, activation and maturation of allergen-specific regulatory T cells (Treg), which consequently increase the production of the inhibitory cytokine IL-10 and TGF-beta. AIT induces a switch of the immune response from Th2 to Th1 type, reducing the production of IgE antibodies and increasing the levels of blocking antibodies, such as IgG4 antibodies. In a previous work, the authors demonstrated the efficacy of AIT for HDM by sublingual injection (SLIT) in promoting an increase in memory-functional Treg, characterised by an increased number of functional surface inhibitory markers associated with significant suppressive activity (1).
However, it must be considered that AIT can last up to five years and may not be successful in all patients. In an attempt to develop a therapeutic approach that can enhance the immunomodulating activity of AIT and promote its therapeutic effects, the focus has been on vitamin D3 (1,25-dihydroxyvitamin D; VD3), the active form of vitamin D (VD), which is known for its ability to modulate the immune response. Studies have shown that VD promotes Treg maturation by inducing surface expression and/or secretion of inhibitory cytokines, which play a significant role in allergy control; it also appears to exert an indirect blocking activity on Th2 effector cell

Figure 1 Possible role of VD in the context of effective AIT in children with low VD



proliferation and inhibit B-cell proliferation and their differentiation into antibody-secreting cells. In a study on a mouse model of HDM allergy, Petrarca and co-workers observed an adjuvant effect of VD3 supplementation when administered in combination with immunotherapy with the major allergen of *D. pteronyssinus*, *Der p 1* (2). The role of endogenous VD in improving AIT has not been considered so far. This article presents the results of a retrospective (*post-hoc*) analysis of children with respiratory allergy to HDM, conducted to assess the influence of VD on the clinical outcome of AIT and/or Treg cell function. The study included 165 paediatric patients (age 10.4 ± 3.1 years; 51.5% male), diagnosed with HDM allergy, symptomatic, treated at the Paediatric Allergology and Pneumology Unit of the University Hospital of Chieti (Italy) between September 2019 and June 2021. The children had undergone standard therapy or SLIT with the monomeric allergoid LAIS® (Lofarma S.p.A).

Data from three different patient cohorts were retrospectively analysed:

- *Post-hoc analysis 1*: 70 patients treated only with standard therapy for symptom control (all with oral antihistamines and 44 with inhaled corticosteroids/long-acting beta-2-agonists, ICS-LABA). *Der f* IgE and Der p IgE were 48.5 ± 35 kUA/L and 59.3 ± 33.6 kUA/L, respectively. The mean serum VD value at diagnosis (22 ng/mL), measured by ELISA, was taken as *cut-off* to define the two groups with lower (N=38) and higher (N=32) VD. Comparative statistical analysis (by Wilcoxon's rank-sign test) showed that the group with lower VD had a significantly higher ($p < 0.05$) level of IgE (total and specific), needed ICS-LABA more frequently (84% vs 37.5%), and reported more severe symptoms (on a visual analogue scale, VAS, from 0 to 10).

- *Post-hoc analysis 2*: 60 patients treated with AIT for 12 months, with pre-AIT *Der f* IgE and *Der p* IgE values of 49.4 ± 33 kUA/L and 60.2 ± 34.1 kUA/L, respectively; all children were taking oral antihistamines and 64% also ICS-LABA. To define two subgroups, the mean value of endogenous post-AIT VD (27 ng/mL) was considered as *cut-off*. The analysis showed no significant differences between the two groups in the overall clinical outcome of AIT based on an improvement in respiratory clinical scores nor in IgE levels, but showed a greater reduction in oral antihistamine use and VAS score in

patients with VD ≥ 27 ng/mL.
- *Post-hoc analysis 3*: 35 children undergoing AIT for 12 months were divided into two groups: one that had received vitamin D3 supplementation (+VD3 = 19 pts) and the other not (-VD3 = 16 pts). VD3 supplementation led to a significant increase in serum VD levels (from 25.2 ± 2.4 pre-treatment to 36.1 ± 2.8 ng/mL). AIT was effective in both groups, irrespective of VD3 levels, with improvement in all relevant clinical parameters (severity of rhinitis, drug use) and an induction of peripheral memory effector Tregs was observed in both patient groups. However, it should be noted that the +VD3 patients showed the greatest improvements in symptoms, with a more important reduction in corticosteroid and antihistamine use and *anti-Der f* IgE levels. An additional increase in peripheral memory effector Treg was observed in this group.
Overall, the analyses revealed an inverse association between endogenous serum VD levels and allergy severity and medication use. AIT proved effective in all patients; however, the most significant improvements were observed in children with fully sufficient VD levels (>27 ng/mL). This suggests that VD3 supplementation might be useful as a supplement in VD-deficient children undergoing AIT and characterised by a high need for symptomatic medication. The authors point out that VD could enhance the inhibitory function of effector memory Treg and present the hypothetical mechanism in a figure (Figure 1), and that this role deserves further investigation to assess its actual importance.

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Spontaneous chronic urticaria: do sex and gender differences play a role?

Is there a difference between women and men in chronic spontaneous urticaria? A systematic review on gender and sex differences in CSU patients

Preis S, et al. World Allergy Organization Journal, Vol. 17(11), 100974. 2024. doi:10.1016/j.waojou.2024.100974.

Gender medicine, or gender-specific medicine, studies the influence of biological (sex-based) and socio-economic and cultural (gender-based) differences on people's state of health and illness. In recent years, there has been a significant increase in interest for this topic in clinical research, with a growing understanding of gender and sex differences in the prevention, diagnosis and treatment of diseases.
The work of Preis and colleagues fits into this context. The authors note that in outpatient clinical practice more women than men present with chronic spontaneous urticaria (CSU); however, there are no systematic literature reviews addressing gender differences in CSU. This inflammatory skin disease manifests itself with itchy wheals and may be associated with angioedema, and lasts for more than 6 weeks (Figure 1). The pathogenesis is linked to two forms of autoimmunity: type I (IgE antibodies against autoallergens) and type IIb (IgG antibodies against the IgE/FcεRI complex). Changes in the levels and expression of sex hormones may favour the development of immunological imbalances responsible for the onset and course of CSU. While oestrogens can stimulate humoral immunity and antibody synthesis, androgens tend to have an immunosuppressive action.
This paper represents the first systematic review of the available literature on CSU that examines sex and gender differences in different aspects of the disease (epidemio-

logy, clinical features, diagnostics, comorbidities, response to treatment and quality of life). The authors followed the PRISMA guidelines (1). For the search of publications on PubMed Medline, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL), a combination of terms referring to chronic urticaria and gender/sex was used, without setting time limits. Randomised controlled trials, prospective and retrospective cohorts and case-control studies were included, while case reports, reviews, abstracts and letters were excluded. Only studies on adults were included. Screening of the identified papers was conducted independently by two of the authors. The search yielded 513 results, 354 after removal of duplicates. A further 263 studies were excluded on the basis of title and abstract because they were not relevant. After full-text analysis, 26 papers published between January 2004 and April 2023 were selected.

The results of epidemiological studies showed a higher incidence and prevalence of CSU in women than in men. The prevalence of CSU was higher in women between 40 and 49 years of age, while there were no differences between the sexes with regard to the age of onset. In women, the disease lasted longer than in men and was more often associated with angio-oedema. Female sex was also associated with greater severity of CSU, based on the mean 7-day Urticaria Activity Score (UAS7). At the diagnostic level, women also had a higher ASST (autologous serum skin test) positivity rate and a significantly lower number of eosinophils in the blood than male patients. An association was found between eosinopenia and ASST positivity.

Studies on comorbidities also showed differences between the sexes. For example, certain autoimmune diseases were reported more frequently in females with CSU (such as thyroiditis, vitiligo, systemic lupus erythematosus, rheumatoid arthritis), whereas males had higher rates of Kawasaki disease and inflammatory bowel disease.

The current treatment protocol for CSU involves second-generation H1 antihistamines and, in severe cases, omalizumab (anti-IgE monoclonal antibody) and then cyclosporine. Several studies have evaluated gender differences in the treatment of CSU, showing partially contradictory results.

Figure 1 Typical presentation of chronic spontaneous urticaria

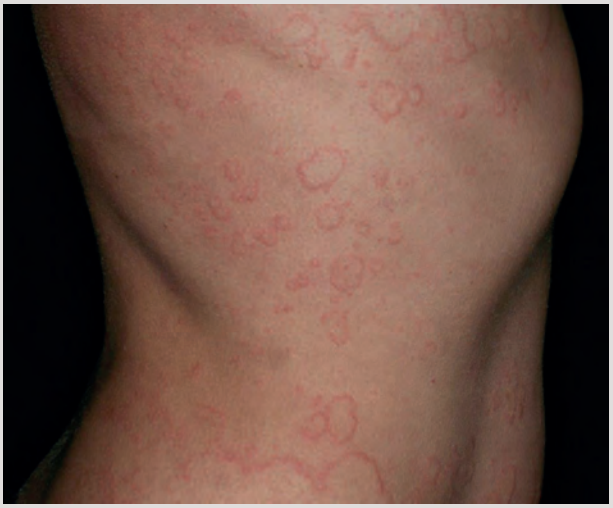

Image used with permission from ECARF. From source (2).

A significantly higher frequency of relapse was observed in females (77.4% vs 36.4% in males); moreover, most patients who did not respond to omalizumab and cyclosporine A were female.

CSU can significantly reduce patients' Quality of Life (QoL), and the study revealed significant differences between genders in patients' needs and expectations and in the impact of the disease on their QoL. Needs related to the ability to accept one's condition, obtain a clear diagnosis, heal skin defects and feel less powerless against the disease were found to be more relevant for the female gender. In general, it was found that CSU has a greater impact on QoL in women, especially in relation to daily activities, energy levels, emotional role, psychological health and sexual dysfunction. For example, 55.3% of females with CSU reported chronic fatigue, compared to 29.6% of males.

Overall, the results of the systematic review showed gender and sex differences in different aspects of CSU (epidemiology, clinical features, diagnostics, comorbidities,

treatment responses and QoL). These differences should be considered in the clinical management of patients with CSU, starting with the establishment of updated and specific guidelines for the diagnosis and treatment of associated comorbidities. The authors emphasise the need to introduce gender-specific screening methods and conduct further research on gender-differentiated responses to therapy, not only for CSU but also for other skin diseases, to ensure better therapeutic outcomes.

Preis and colleagues point out that in dermatology it is difficult to distinguish whether differences in disease or behaviour result from sex or gender, as they are deeply intertwined. Women may perceive skin conditions such as CSU more negatively, with an impact on their psychological health and QoL that does not always correspond to clinical severity. Furthermore, only studies focusing on patients' subjective well-being and QoL took both biological and sociocultural aspects of gender into account in their discussions. In none of the included studies were data provided on the number of patients who chose a gender identity other than their biological sex.

In conclusion, the authors point out that in the era of personalised medicine, it cannot be ignored that women and men have different disease progression, and that both sexes deserve specific diagnoses and treatments.

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Provide information, create a profession

Edited by **Franco Frati**

Specialist in Paediatrics, Allergology and Clinical Immunology
Director of Lofarma Academy

Four years of Lofarma Academy

Dr. Frati Franco
Director of Lofarma Academy

An interactive day in Milan on 15 October 2024 marked the end of the dissemination, update and training project dedicated to the 4th year residents of Italian schools of Allergology and Clinical Immunology: Lofarma Academy.

The Italian schools involved in 2024 were: Ancona, Bari, Bologna, Brescia, Cagliari, Chieti, Florence, Genoa, L'Aquila-Teramo, Messina, Milan, Milan-Humanitas, Milan-San Raffaele, Modena, Naples, Padua, Parma, Pavia, Pisa, Rome-Policlinico Gemelli, Rome-University La Sapienza, Rome-UniCampus, Turin, Treviso, Verona.

More than 400 trainees participated in this year's training.

The web training, a series of 8 webinars divided into a basic course (1st year) and an advanced course (2nd, 3rd and 4th year of specialisation), were delivered by leading scholars and experts in our subject, both scientifically and practically:

- **Dr. Franco Frati**, specialist in Paediatrics, Allergology and Clinical Immunology, Director Lofarma Academy;
- **Dr. Danilo Villalta**, specialist in Allergology and Clinical Immunology, Pneumology;
- **Prof. Enrico Heffler**, specialist in Allergology and Clinical Immunology;
- **Dr. Sara Manti**, specialist in Paediatrics;
- **Dr. Giovanni Coniglio**, specialist in Allergology and Clinical Immunology, Diseases of the Respiratory System;
- **Prof. Massimo Landi**, specialist in Paediatrics and Clinical Pathology;
- **Dr. Maurizio Andreanò**, SEO specialist and Digital Marketing consultant for the health sector.

The topics covered in 2024 were:

- Respiratory allergies from correct framing to choice of therapy;
- Skin prick tests;
- Immunophlogosis of the respiratory tract: role of FeNO determination in adults and children;
- Framing of children with allergy;
- Use of spirometry and methacholine testing in allergology practice.

A special and innovative aspect of the Lofarma Academy project was the creation of a major web portal, https://lofarma.academy, a dedicated platform to which around 400 students have joined and which has enabled them to get to know each other, appreciate each other and exchange ideas and proposals, creating a large virtual community.

The Academy's dedicated website contains the most significant teaching materials from the various lectures, a very useful innovation for all trainees.

ENG

Figure 1. Group photo of the participants of the Lofarma Academy closing event on 15 October 2024.

Participant satisfaction was high, with very positive comments. In addition to being recorded and available on video, the lectures have been carefully transcribed and edited, so that in 2025 they will be part of a volume: 'Notes on Practical Allergology', with contributions from the various lecturers.

The key word of the entire Academy is indeed clinical practice, and as such all lectures have always maintained this characteristic.

As a complement to the academic course that individual university postgraduate schools normally provide, Lofarma Academy has included a space to enable these postgraduates to get to know the set of knowledge and technical skills that are the driving force behind a modern company in the sector.

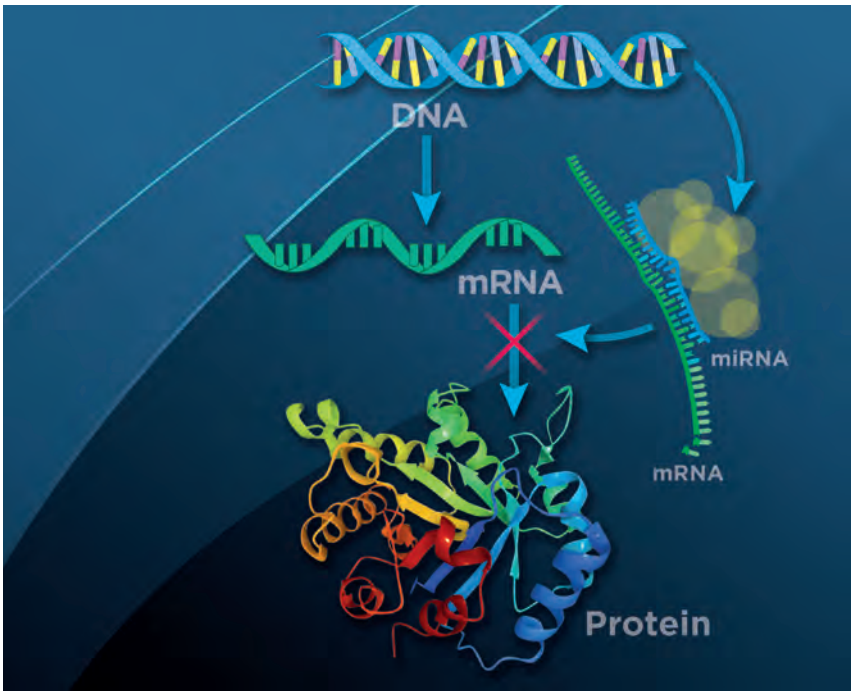
An important day in the 2024 training course was the final day on 15 October 2024 in Milan, which was attended by 50 Italian fourth-year postgraduates.

The Presidents of SIAAIC and AAIITO, Prof. Mario Di Gioacchino and Dr. Lorenzo Cecchi, were also present as lecturers; Prof. Paolo Luperto, who held a mini-course on Nasal Cytology; finally, Dr. Lorenzo Romagnoli, head of Lofarma's Acarology department, explained the main characteristics of dust mites from a morphological and allergological point of view to those present, also discussing the main activities of the Acarology department and how it fits into Lofarma's production reality.

In addition to these topics, Dr. Franco Frati, Director of Lofarma Academy, gave an interactive presentation of emblematic cases of respiratory allergology with a discussion of specific immunotherapy, from precision diagnosis to the choice of the right allergen and route of administration, and follow-up.

Finally, I would like to emphasise Lofarma's overall commitment to this important project.

Since the 1970s, Lofarma, a leading company in the sector, has always been willing to open its laboratories to the then nascent experts in the field with visits and cultural exchanges in order to rapidly disseminate modern acquisitions in the field of a rapidly evolving subject; even today, by founding this Academy in the sector, it perpetuates this policy by demonstrating that it always wants to be at the side of young trainees, the future immunoallergology specialists.



più "digeribile" si è scelto quindi di minimizzare questo stadio, mettendo in evidenza solo la fase terminale che culmina con il legame del miRNA all'mRNA con un blocco della trascrizione e la conseguente produzione della proteina. L'impatto di questa scoperta ha generato un diluvio di ricadute. Alcune migliaia di miRNA sono stati nel tempo identificati nell'uomo, e numerose evidenze dimostrano il ruolo che alcuni di essi possono avere ruoli in varie patologie, dai tumori alle malattie cardiovascolari o neurovegetative fino alle malattie allergiche. Gli miRNA rappresentano oggi un filone di ricerca in continua evoluzione con l'obiettivo sia di individuare futuri biomarkers in grado di migliorare la fase diagnostica di una malattia che di usare gli stessi come possibili target nello sviluppo di nuovi farmaci, una volta compresa la base molecolare della malattia che si vuole curare.

Come noto, il corredo genetico (DNA) delle cellule è uguale tra loro; viceversa, le caratteristiche morfologiche e funzionali possono essere molto diverse. Questo dipende dai meccanismi di regolazione genica, in base ai quali alcuni geni vengono trascritti e tradotti in proteine e altri, al contrario, rimangono invece silenti. Va sottolineato che fino a qualche anno fa il meccanismo in grado di silenziare determinati geni, fondamentale per esempio nella fase di differenziamento cellulare, non era ancora noto. L'immagine scelta per la cover di questo numero vuole in qualche modo rendere omaggio ai due ricercatori (Victor Ambros e Gary Ruvkun) a cui è stato riconosciuto il premio Nobel 2024 per la Medicina. Il loro merito è stato quello di aver intuito per primi che alcune brevi sequenze di RNA (da qui il nome microRNA o miRNA) a singolo filamento, prodotte da alcuni geni (la cui funzione era del tutto sconosciuta fino ad allora) rappresentavano il tassello mancante del puzzle relativo alla regolazione genica a livello post-trascrizionale. In particolare, i due ricercatori, studiando lo sviluppo temporale delle larve di un particolare nematode (Caenorhabditis elegans), scoprirono come le suddette sequenze di miRNA (non codificanti per alcuna proteina) fossero in grado di legarsi in maniera specifica a sequenze di RNA messaggero (mRNA) codificanti per proteine e di modularne la quantità prodotta nella cellula in rapporto alle necessità della stessa. In altre parole, gli miRNA fungono da interruttori dell'espressione di proteine. La biogenesi che porta alla produzione dei miRNA è molto complessa e difficilmente traducibile in un'immagine di cover. Per rendere la stessa

As is well known, the genetic makeup (DNA) of cells is the same; conversely, their morphological and functional characteristics can be very different. This depends on gene regulation mechanisms, whereby some genes are transcribed and translated into proteins and others, on the contrary, remain silent. It should be emphasised that until a few years ago the mechanism capable of silencing certain genes, crucial for example in cell differentiation, was not yet known. The image chosen for the cover of this issue is intended in some way to pay tribute to the two researchers (Victor Ambros and Gary Ruvkun) who were awarded the 2024 Nobel Prize in Medicine. Their merit was that they were the first to realise that certain short, single-stranded RNA sequences (hence the name microRNA or miRNA) produced by certain genes (whose function was completely

unknown until then) represented the missing piece of the puzzle relating to gene regulation at the post-transcriptional level. In particular, two researchers, studying the temporal development of the larvae of a particular nematode (*Caenorhabditis elegans*), discovered that these miRNA sequences (not coding for any protein) were able to bind specifically to messenger RNA (mRNA) sequences coding for proteins and to modulate the amount produced in the cell according to the cell's needs. In other words, miRNAs act as switches of protein expression. The biogenesis that leads to the production of miRNAs is very complex and difficult to translate into a cover picture. In order to make it more 'digestible', it was therefore decided to minimise this stage, highlighting only the terminal phase that culminates in the binding of the miRNA to the mRNA with a transcription block and the subsequent production of the protein. The impact of this discovery generated a deluge of spin-offs. Several thousand miRNAs have been identified over time in humans, and a wealth of evidence demonstrates the role some of them may play in various diseases, from cancers to cardiovascular or neurovegetative diseases to allergic diseases. Today, miRNAs represent an evolving strand of research with the aim of both identifying future biomarkers that can improve the diagnostic phase of a disease and using them as possible targets in the development of new drugs once the molecular basis of the disease being treated is understood.

Como es bien sabido, la composición genética (DNA) de las células es la misma; en cambio, las características morfológicas y funcionales pueden ser muy diferentes. Esto depende de los mecanismos de regulación génica, por los que algunos genes se transcriben y traducen en proteínas y otros, por el contrario, permanecen en silencio. Cabe destacar que hasta hace unos años, aún no se conocía el mecanismo capaz de silenciar determinados genes, fundamental, por ejemplo, en la fase de diferenciación celular. La imagen elegida para la portada de este número pretende de alguna manera rendir homenaje a los dos investigadores (Victor Ambros y Gary Ruvkun) que han sido galardonados con el Premio Nobel de Medicina 2024. Su mérito ha sido ser los primeros en darse cuenta de que determinadas secuencias cortas de RNA monocatenario (de ahí el nombre de microRNA o miRNA) producidas por determinados genes (cuya función era completamente desconocida hasta entonces) eran la pieza que faltaba en el *rompecabezas* de la regulación génica a nivel postranscripcional. En concreto, los dos investigadores, estudiando el desarrollo temporal de las larvas de un determinado nematodo (*Caenorhabditis elegans*), descubrieron cómo las mencionadas secuencias de miRNA (que no codifican ninguna proteína) eran capaces de unirse específicamente a secuencias de RNA mensajero (mRNA), que por su parte codifican proteínas, y modular la cantidad producida en la célula en función de sus necesidades. En otras palabras, los miRNA actúan como interruptores de la expresión de proteínas. La biogénesis que lleva a la producción de los miRNA es muy compleja y difícil de plasmar en una imagen de portada. Por ello, para hacerlo más "digerible", se decidió minimizar esta etapa, destacando únicamente la fase terminal que culmina con la unión del miRNA con el mRNA con un bloqueo de la transcripción y consiguiente producción de la proteína. El impacto de este descubrimiento ha generado una avalancha de consecuencias. A lo largo del tiempo se han identificado varios miles de miRNA en los seres humanos, y numerosas pruebas demuestran que algunos de ellos pueden desempeñar funciones en diversas patologías, desde cánceres a enfermedades cardiovasculares o neurovegetativas, pasando por enfermedades alérgicas. En la actualidad, los miRNA representan una línea de investigación que evoluciona continuamente con vistas tanto a identificar futuros biomarcadores capaces de mejorar la fase diagnóstica de una enfermedad como a utilizarlos como posibles dianas en el desarrollo de nuevos fármacos, una vez comprendidas las bases moleculares de la enfermedad que se desea tratar.

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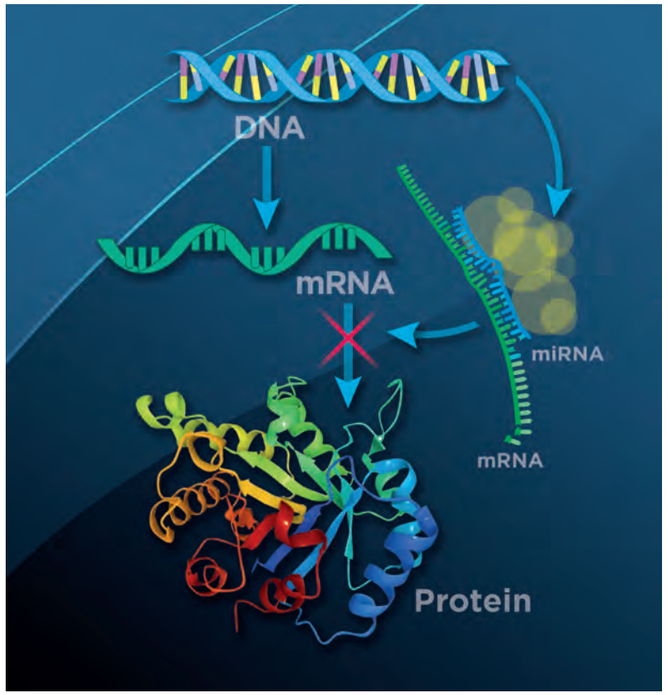

Scopri la storia dell'immagine di copertina a pagina 139
Discover the story of the cover image on page 139
Descubre la historia de la imagen de portada en la página 140

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