# DUPILUMAB: A NEW ALLY FOR THE TREATMENT OF EOSINOPHILIC ESOPHAGITIS?

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## ABSTRACT

INTRODUCTION: Eosinophilic esophagitis is a chronic and immune-mediated disease of the gastrointestinal tract, resulting from the interaction between genetic, environmental and immunological factors of the affected patient. The clinical picture is characterized by esophageal dysfunction, which may present as dysphagia, chest pain, upper abdominal pain or food impaction. Treatment aims to improve clinical symptoms and prevent disease progression and subsequent complications. In this context, immunobiologicals are emerging and promising therapies, with Dupilumab being the first specific treatment approved by the FDA. It is an IgG4 monoclonal antibody, which targets IL-4R alpha and, from this, reduces protein transforylation, transcription, and the T helper 2-regulated response. The objective of this systematic review is to evaluate the efficacy of this drug in the treatment of eosinophilic esophagitis, in comparison with the options already available on the market. METHODS: PubMed searches were performed using the keywords "eosinophilic esophagitis dupilumab" and "dupilumab treatment esophagitis eosinophilic". At first, 60 results were obtained, but after exclusion by title and abstract, and by full text, 14 articles were included. RESULTS: all the articles analyzed showed improvement in patients using Dupilumab, 13 of which showed a reduction in the eosinophil count, 8 showed clinical improvement of symptoms, 8 indicated histological improvement, 7 denoted improvement in the endoscopic pattern, according to the Endoscopic Reference for Eosinophilic Esophagitis, and 4 indicated a reduction in the Dysphagia Symptom Questionnaire (QSD) score. DISCUSSION: Eosinophilic esophagitis is a rare disease, but it has the potential to progress, negatively interfering with the patient's quality of life. Thus, as the current drug therapy is nonspecific, the use of Dupilumab presents itself as an innovative and optimistic solution for the future, because it modifies the understanding of the management of the disease, expands the therapeutic options and improves the prognosis. CONCLUSION: The use of Dupilumab in the treatment of eosinophilic esophagitis has been shown to be effective. However, for treatment to be well established with regard to the doses used, frequency of administration and longitudinal monitoring, further studies are still needed.

**Keywords:** Dupilumab. Eosinophilic esophagitis. Immunobiological.

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# INTRODUCTION

## DEFINITION

*Eosinophilic GI disorders* (EGIDs) are chronic and immune-mediated diseases, characterized by inflammation triggered by eosinophils along the gastrointestinal tract, without there being a known cause for this eosinophilia, as would be the case with drug reactions, parasitic infections or malignancy, for example. This condition is associated with symptoms related to the gastrointestinal tract, which is primarily affected. This group of diseases includes eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic enteritis, and eosinophilic colitis (EC). When more than one segment of the gastrointestinal tract is affected, it is called eosinophilic gastroenteritis [1].

Eosinophilic esophagitis is the most prevalent and studied, so there is more information regarding diagnosis and treatment. Studies have suggested that this pathology results from the interaction between genetic factors, such as polymorphisms, environmental risk factors (such as diet) and the defense factors of the immune system of the affected patient [1].

In healthy patients, eosinophils are present, in small amounts, in various tissues of the gastrointestinal tract, as well as in the spleen, lymph node, thymus, and adipose tissue. Eosinophilic infiltration has only been associated with degranulation in the gastrointestinal tract, however. The amount of eosinophils increases progressively from the proximal to the distal part of the intestine. In rat biopsy, eosinophils are usually found in the lamina propria of the stomach, intestine, cecum, and colon, but not in Peyer's slide or intraepithelial locations. However, the difference between inflammatory and non-inflammatory conditions lies in the concentration of cytokines bound to the T Helper 2 lymphocyte [1].

## EPIDEMIOLOGY

The incidence of gastrointestinal eosinophilic diseases has not been accurately calculated, but it is estimated that there has been a small epidemic of these diseases in recent decades. The prevalence is approximately 0.1 to 0.2 per 10,000 people, with eosinophilic esophagitis being the second most common cause of chronic esophagitis [1]. One meta-analysis estimated a pooled overall prevalence of eosinophilic esophagitis at 22.7 per 100,000 (95% CI, 12.4–36.0), with a higher rate in adults (43.4/100,000; 95% CI, 22.5–71.2) than in children (29.5/100,000; 95% CI, 17.5–44.7) [2].

Eosinophilic esophagitis was first described in the late 1970s, but the disease, as it is defined today, only became known in the mid-1990s. Currently, it is a reasonably common finding in clinical and endoscopy and represents one of the main causes of upper

gastrointestinal morbidity. With the recent introduction of the Gastrointestinal Eosinophilic Diseases Consortium (CEGIR), it was possible to estimate the prevalence of eosinophilic esophagitis in the USA, which is approximately 39 to 56.7 cases per 100,000 people, and can reach up to 105 or 150 cases [1]. It is, therefore, a rare disease, despite the aforementioned increase in prevalence in the last two decades.

One report suggested an increase in incidence of 40% over a 4-year period between 2000 and 2003 [3]. It is likely that this increase in incidence is not only due to the greater recognition of the disease, from the performance of endoscopy with biopsy, since several studies suggest that this increase in incidence does not exceed the relatively small increase in biopsies [4]. Therefore, there may be related genetic and environmental factors. It is, therefore, a global health problem, identified in Australia, Brazil, England, Italy, Israel, Japan, Spain and Switzerland. There are still no reports of the disease in sub-Saharan Africa or India [5].

Eosinophilic esophagitis is detected in 2.4 to 6.6% of patients undergoing endoscopy for any indication [6], while in patients with dysphagia, these rates rise to 12 to 23% [7]. In this same context, in people with esophageal food bolus impaction, the identification rate is 50%, and this is the most frequent cause of such a finding in emergency services [8].

It is a pathology more common in male patients, with evidence of atopy. The ratio between affected men and women is 3 to 1 [9]. A study conducted in the United States suggested a constant increase in prevalence with age, until reaching a maximum value between 30 and 44 years; then, the prevalence decreased considerably. [10]

## ETIOPATOGENIA

The etiopathogenesis of eosinophilic esophagitis is still poorly understood, but food allergies have been implicated as a major contributing factor [1]. In this sense, most patients have evidence of food allergy and sensitization to aeroallergens, identified by prick tests and/or specific allergen-IgE tests [1]. There is also a relationship between eosinophilic inflammation of the esophagus with pulmonary inflammation, presence of allergic rhinitis, hypersensitivity to grass, and atopy [1].

In addition, there are indications of a strong family component and genetic factors involved, with an increased risk of developing EEo in first-degree relatives and in the presence of certain genes, such as TSLP, CAPN14, EMSY, and eotaxin-3 [11]. In this context, ALEXANDER's study detected that monozygotic twins have a disease concordance of 44%, which represents a 2-fold increase when compared to dizigotic twins, revealing a complex genetic component [12]. This complex etiology is due to the effect of

multiple genetic loci, which affect gene expression, leading to structural and physiological changes in the function of epithelial and immune cells, increasing the risk of developing the disease, with contributions from genetic factors and environmental exposures [13].

Such exposures are more related to unknown environmental factors early in life, as well as to antibiotic use during childhood and formula feeding [13]. There are also studies that show an increased risk of developing EE when there is an association with prenatal and intrapartum factors, such as preterm labor, maternal fever, and cesarean delivery [13]. In addition, other factors that may contribute to the increase in the incidence of EE are: the decrease in the frequency of infection by *H. pylori*, a bacterium that increases the populations of Th1 and Th17, negatively regulating Th2; gastroesophageal reflux disease, which leads to injury to the intraepithelial junctions, causing greater allergenic permeability in the esophageal epithelium; and the hypothesis of bacterial hygiene and dysbiosis, relating a lower incidence of infections and bacterial exposure to microbiota alteration and epithelial permeability [1]. In contrast, having a furry pet during childhood was associated with decreased risk of developing the disease [13].

## PATHOPHYSIOLOGY

The pathophysiology of eosinophilic esophagitis mainly involves the interaction between immunoglobulin E (IgE) and T-helper lymphocyte type 2, but also includes the participation of allergens, cytokines (such as IL-5 and IL-3), microRNA, and chemokines (such as eotaxins), in addition to the loss of the functional barrier and the imbalance between protease action and inhibition, favoring pathophysiological activation [14].

Eosinophils have cytokines and chemokines that regulate the innate and adaptive immune response, such as those linked to T-helper lymphocyte 2 (IL-4, IL-5 and IL-13), T-helper 1 (such as interferon-gamma), pro-inflammatory cytokines (such as TNF, IL-6 and IL-8) and inhibitory cytokines (TGF-beta and IL-10, as well as their receptors) [14].

The type 2 inflammatory response involves the participation of T helper 2 lymphocytes, mainly for defense against parasites, worms, and toxins, and also for action in allergic diseases. Atopic diseases are based on the IgE-dependent response, so that when they encounter allergens, antigen-presenting cells pick them up and process them into peptides. They then go to the lymph nodes, where allergens are introduced to CD4 T lymphocytes [14].

In the adaptive immune response, when IL-4 dominates in that particular antigen, T helper 2 lymphocytes are recruited, capable of recognizing the cytokines IL-4, IL-5, IL-9 and IL-13. From this, B lymphocytes are called, which then initiate the production of specific IgE

antibodies, which sensitize the receptors found in basophils and mast cells. Thus, in the face of a second encounter with the allergen, these cells undergo degranulation, with the consequent release of histamine, proteoglycans, leukotrienes, and prostaglandins, which trigger the characteristic allergic clinical picture. This inflammatory response, mostly linked to Th 2, is present in several pathologies, such as asthma, rhinosinusitis with nasal polyps, atopic dermatitis, food allergies and eosinophilic esophagitis [14].

In the innate immune response, on the other hand, the epithelium activates innate ILC2 lymphoid cells, which secrete large amounts of IL-5, IL-9, and IL-13, with consequent activation of effector cells, such as eosinophils, macrophages, basophils, and mast cells. Mast cells and basophils also secrete cytokines, such as IL-4 and IL-13 [14].

Eosinophils, central to atopic diseases, are produced in the bone marrow, from the regulation of the transcription of the cytokines IL-3 and IL-5, in addition to the action of the stimulating factor of granulocyte and macrophage colonies. They have granules with proteins of toxic content to various tissues, including the intestinal epithelium. [14].

IL-5 is the most important cytokine and responsible for the differentiation of eosinophils, as well as for their exit from the spinal cord, for their arrival in the circulation and for survival, so that, in the face of high levels of IL-5, there is an increase in blood eosinophilia, while reduced levels help to decrease these cells in the blood, lung and gastrointestinal tract [14].

IL-4 and IL-13 indirectly recruit eosinophils, encouraging migration to sites of inflammation, and increase their survival, through several mechanisms, such as inhibition of apoptosis. They also influence the permeability of the epithelial barrier. They induce endothelial expression of adhesion molecules that bind to beta-1 and beta-2 integrins in eosinophils, as well as chemokines (such as eotaxins). In addition, IL-4 and IL-13 have a common signaling pathway, from the alpha subunit of the IL-4R receptor. This receptor, in its subtype II, has two portions: IL-4 alpha, to which IL-4 binds, and IL-13 alpha, to which IL-13 binds. It is present in both hematopoietic and non-hematopoietic cells. From the binding of IL-4 or IL-13 to the receptor, transforylation and activation of protein kinase begins, which uses the *Janus quiase transducer* and the transcription activator STAT-6, initiating transcription [14].

## CLINICAL PICTURE

Clinically, the condition is characterized by esophageal dysfunction and, histologically, by inflammation with a predominance of eosinophils. Initial symptoms include difficulty eating, reduced growth velocity, abdominal and/or chest pain, dysphagia, and food

impaction (defined as the retention of food, requiring extraction by endoscopy). In general, these symptoms are chronological, depending on the patient's age, so childhood eosinophilic esophagitis can progress to the adult form [1].

Babies typically have difficulty eating or nursing, while school-age children often have vomiting or pain. Dysphagia predominates in adolescents. In general, in children, eosinophilic esophagitis usually manifests itself in conjunction with other atopy, such as food allergy, asthma, eczema, chronic rhinitis, and environmental allergies, which also follow a chronological order, in the so-called atopic march [1].

In adults, symptoms are often quite characteristic, including dysphagia, chest pain not linked to swallowing, food impaction, and upper abdominal pain. Dysphagia related to solid foods remains the most common symptom. Food impaction requiring endoscopy to remove the bolus occurs in 33 to 54% of adult patients with esophagitis [1].

There are no pathognomonic findings of eosinophilic esophagitis on examination or in the oropharynx, but some children may have laryngeal symptoms. In addition, there may be esophageal abnormalities on endoscopy, such as fixed esophageal rings (trachealization), exudates, edema, narrow esophageal caliber, and endoscopic-induced laceration [1].

## DIAGNOSIS

Because it is a clinical-pathological disorder, the diagnosis of eosinophilic esophagitis is based on the association of the clinical manifestations of the disease, which depend on the age of presentation (childhood or adulthood), with the endoscopic and histological findings of esophageal mucosal biopsies, and these factors should not be considered separately [15]. Thus, the gold standard for diagnosis involves esophageal biopsy findings, which demonstrate eosinophilic enlargement, requiring at least 15 eosinophils per maximal augmentation field, without concomitant infiltration in the stomach or duodenum [16]. This value has been shown to be 100% sensitive and 96% specific for diagnosis [11].

In this context, upper gastrointestinal endoscopy is the most used test, as it allows biopsies to be performed, as well as to evaluate the macroscopic characteristics of the esophagus. Thus, endoscopic findings in patients with OE consist of linear sulci, which appear as vertical lines within the esophageal mucosa; trachealization, which are concentric rings of esophageal narrowing; whitish exudates, visualized as white plaques; edema due to decreased mucosal vasculature and stenosis of esophageal size [11]. Importantly, the endoscopic appearance may be normal in 10-25% of patients with O.E. [11]. Still in relation

to endoscopy, the American College of Gastroenterology (ACG) recommends obtaining a minimum of six samples, which should be collected from the upper, middle and distal third of the esophagus, for biopsy of any patient with suspected OE [11].

The ACG established the following diagnostic criteria for O.E.: (1) Symptoms of esophageal dysfunction; (2) Concomitant atopic conditions; (3) Endoscopic findings of rings, grooves, exudate, stenosis, luminal narrowing, and mucosal fragility or crepe mucosa; (4) ≥ 15 eosinophils by HPF (60 eosinophils/mm2 ) in esophageal biopsy; (5) Eosinophilic infiltration should be isolated in the esophagus; and (6) Evaluation of disorders other than EEo that potentially contribute to esophageal eosinophilia [15].

## TREATMENT

The treatment of EEo aims to improve clinical symptoms and prevent disease progression and subsequent complications. To this end, it is based on three pillars, which are drug therapy with proton pump inhibitors (PPIs) or topical glucocorticoids, dietary changes to control the interaction of environmental factors, and esophageal dilation in cases of endoscopic complications [15]. As only the immunobiological Dupilumab was approved by the US Food and Drug Administration (FDA) on May 22, 2022, for the treatment of eosinophilic esophagitis, the choice of therapy already consolidated in the market should be made based on efficacy, ease of administration, cost, and patient preference, sharing the decision and analyzing advantages and disadvantages of each option [11, 17].

The initial dietary options for treatment of EEo are elemental diets, elimination diets guided by food allergy testing, and empirical elimination diets [11]. The elemental diet is based on a liquid formula of nutrition composed of amino acids, which is readily assimilated and absorbed; It is associated with improvement of symptoms and histological remission, but also with limitations such as poor palatability, which can lead to the need for tube use, psychological and social disorders, changes in quality of life due to lack of food, and high cost [11, 15].

The elimination diet directed by allergy tests is based on atopy tests to detect possible triggers of EEo, which will later be eliminated from the diet; The biggest triggers for adults, in order of concern, are wheat, cow's milk, soybeans, nuts and eggs, while for children, they are milk, eggs, wheat and soy, so the reintroduction should follow the opposite sequence to that of this list. A retrospective study with children associated the elimination of positive foods in allergy tests with histological response in 53% of patients, while the agreement and success of this diet were low in adults [18].

Finalizing dietary changes, the empirical elimination diet, or SFED, is based on the elimination of 6 food groups, which are cow's milk, soy, wheat, eggs, peanuts/tree nuts, and shellfish/fish, i.e., the most common allergens in the US, lasting 6 to 8 weeks [16].

Regarding drug therapy, proton pump inhibitors (PPIs) can lead to histological and symptomatic remission in 50 and 60% of cases, respectively [15]. In addition, they can be used as a first-line treatment, in high dosages, due to their low cost, tolerability, generally favorable safety profile, and ease of administration [11]. In this context, topical glucocorticoid therapy can also be used for long-term control, as is the case with inhaled fluticasone and budesonide, requiring the patient to swallow the dose for deposit to occur in the esophageal mucosa [11]. As adverse effects, glucocorticoids can cause adrenal suppression or eosinophilic candidiasis [15].

Endoscopic dilation is used in the treatment of complications subsequent to O.E., such as esophageal strictures, rings, and narrow-bore esophagus [11]. In addition, it may be a therapeutic option for patients with persistent dysphagia even after medical treatment has achieved remission of inflammation and in patients with severe dysphagia and a history of food impaction [15].

The emerging treatments that are in the clinical trial phase for EEo are immunobiologicals, and the best known are IL-5 expression modulators, such as Reslizumab and Mepolizumab, two drugs that have already been approved by the FDA for the treatment of eosinophilic asthma and probably have additional applications in the treatment of atopy. The first is a neutralizing antibody against IL-5, which significantly reduced eosinophil counts in children and adults with eosinophilic esophagitis. Mepolizumab, on the other hand, drastically decreased blood eosinophilia and esophageal infiltration, but had variable effects on symptoms. In addition to these, anti-IL-13 and anti-IL-4 antibodies are also being studied, which have shown reduction of eosinophilic esophagitis and histological, endoscopic and clinical improvement. IL-13 regulates the recruitment of eosinophils at inflammatory sites, which seems to be an interesting therapeutic site, based on the antibody Iebrikuzumab, recently studied for asthma; The problem is that there seems to be a variable effect on tissue eosinophilia, leading to increased peripheral eosinophilia [19].

## DUPILUMAB

Dupilumab, the central drug of this article, was already used in the treatment of moderate/severe atopic dermatitis in uncontrolled patients and eosinophilic asthma, both of which are FDA-approved. In May 2022, this same body approved Dupilumab for the

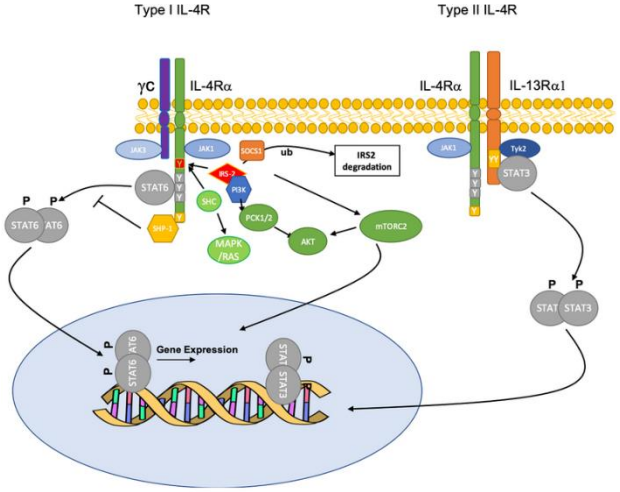
treatment of eosinophilic esophagitis in adults and adolescents over 26 years old, weighing at least 40kg, in a regimen of 300mg weekly. On January 26, 2024, FDA approval was extended to children aged 1 to 11 years, weighing at least 15kg. ANVISA (National Health Surveillance Agency) approved Dupilumab for the treatment of EoE in patients aged 12 and over, weighing 40kg or more, in April 2023. In Brazil, this drug has been marketed under the name Dupixent.

As side effects, Dupilumab can cause conjunctivitis, infection at the injection site, and localized herpes simplex infection. A small group of patients may have transient blood eosinophilia, possibly due to inhibition of the passage of eosinophils from the blood into the inflamed tissues of the skin. [14]

It is an IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain (IL-4R alpha). Type I of this receptor is specific for IL-4 and is expressed only in hematopoietic cells, predominantly in T lymphocytes, mast cells, and basophils. Type I also has the gamma portion, which interacts with other interleukins. On the other hand, the type II receptor binds to IL-4 and IL-13 (so it has two moieties: IL-4 alpha and IL-13 alpha-1) and is expressed in hematopoietic and non-hematopoietic cells, such as in the airway epithelium. Both are cytokines linked to Th2, that is, fundamental in the pathogenesis of allergy. This is because the IL-4/IL-13/IL-4R axis is related to the differentiation of Th2 cells, which modulate a pro-allergic immune response and, in addition, activate effector pathways in target tissues, such as lungs, skin, and intestines, triggering the disease phenotype [20].

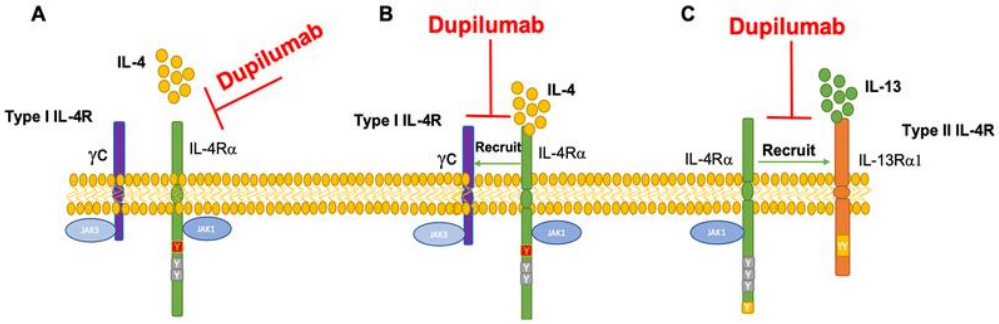
As cited in the pathophysiology of eosinophilic esophagitis, when IL-4 or IL-13 binds to receptors, transforylation and activation of  receptor subunit-associated *Janus* family protein kinases (JAKs) such as JAK1 and JAK3 at the type I receptor and JAK1 or Tyk2 at the type II receptor occurs.  a cascade of phosphorylation of tyrosine residues into IL-4R alpha occurs. Some tyrosine residues, such as human Y585 and Y603, allow recruitment of the transcription factor signal transducer and transcription factor 6, called STAT6, from the SH2 domain, which triggers the initiation of transcription. In addition to STAT 6, IRS/PI3K, mTORC2, AKT, SCH/MAPK and Ship-1 are also activated. The Box1 region and the C-terminal tail of IL-13R alpha 1 allow Tyk2 binding, with consequent phosphorylation of it and activation of STAT3 [20].

Image 1 - pathophysiological mechanism of eosiophilic esophagitis [25].




Therefore, Dupilumab is an IgG4 antibody that binds to the alpha portion of the IL-4 receptor, with consequent inhibition of both IL-4 and IL-13-induced signaling, which decreases the T helper 2-regulated inflammatory response in allergic diseases. The mechanism of action is not yet completely known, because it is not known whether it inhibits the binding of IL-4 to the type I receptor or whether it inhibits the assembly of the type II receptor (preventing the recruitment of the alpha subunit of this receptor by the alpha portion of the IL-13 receptor, after its binding to IL-13) [20].

Image 2 - possible mechanisms of action of Dupilumab [25].




The results of the use of Dupilumab in the treatment of eosinophilic esophagitis seem to be promising. In 2017, a phase II clinical trial was carried out for the use of Dupilumab in this pathology, which showed a 3-point reduction in the score of the Straumann Dysphagia Instrument, which assesses patients' swallowing difficulty, from the use of 300mg of Dupilumab weekly, compared to 1.3 points reduction in the placebo group [21].

## JUSTIFICATION

This research on the use of Dupilumab in the treatment of eosinophilic esophagitis is justified because it is a rare disease, but considered a global health problem, with an increase in prevalence and incidence in recent years. In addition, eosinophilic esophagitis is the second most common cause of chronic esophagitis and a leading cause of upper gastrointestinal morbidity. If not treated properly, its progression can progress to esophageal stenosis, severe dysphagia, and food impaction, greatly affecting the patient's quality of life. Dupilumab is an innovation in the treatment of eosinophilic esophagitis and shows promising results in clinical trials, which may change the treatment perspective and prognosis of the disease.

## OBJECTIVES

**General objective:** to evaluate the efficacy of the drug Dupilumab in the treatment of eosinophilic esophagitis, in comparison with the treatments already consolidated and available on the market.

**Specific objectives:**

- To analyze the indications for the use of Dupilumab;
- To evaluate the main advantages and disadvantages of the use of Dupilumab in relation to treatments with diet, proton pump inhibitors, topical glucocorticoids and endoscopic dilatation, which are already consolidated, in the context of eosinophy esophagitis;
- To compare Dupilumab with other immunobiologicals available for the treatment of the pathology, such as IL-5 expression modulators, such as Reslizumab.

## METHOD

Initially, two simultaneous searches were carried out using PubMed (https://pubmed.ncbi.nlm.nih.gov/) by two different researchers. The first of them used the keywords "eosinophilic esophagitis dupilumab", while the second used "dupilumab treatment esophagitis eosinophilic". Both were carried out between September 12 and 13, 2023 and added, as a filter, articles published in the period between 2020 and 2023.

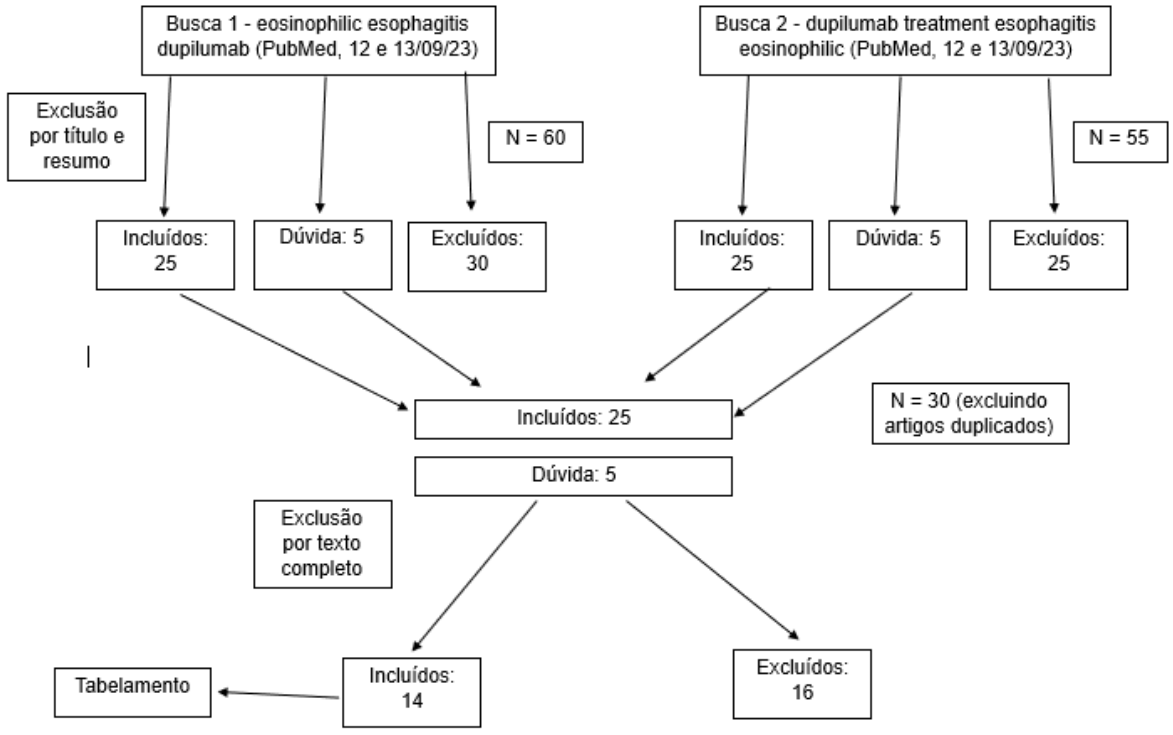
The exclusion, at this initial moment, was carried out based on the reading of the title and abstract of the articles. The inclusion criteria involved: approach to the results of the treatment of eosinophilic esophagitis with Dupilumab, articles in English and studies of adults and/or children. The exclusion criteria, on the other hand, were: articles in languages other than English, lack of consideration of Dupilumab or the outcome of treatment with this

drug, articles dealing only with esophagitis (not the drug under study), focus on other atopic diseases, and texts structured as comments. In the first search, 60 articles were initially obtained, 25 of which were included in the study, 30 were excluded and 5 left doubts. In the second search, 55 articles were found, of which 25 were included, 25 were excluded, and 5 left doubts. All of these 55 articles obtained in the second search were repeated, compared to the first search, including, in the sum of the two title and abstract analyses, 25 articles categorized as included and 5 in doubt.

These 30 articles were read in their entirety below. Each of the principal investigators was responsible for 15 of them. From this, 14 were considered adequate to be included in the tabulation, and 16 were not included, and 9 of these exclusions were due to being paid articles, while the others were made using the same criteria described in the previous paragraph.

Finally, these 14 articles were analyzed in greater depth and included in a table collecting the following information: title, DOI, year of publication, origin of the article, type of study, total number of patients studied, classification of the study population (age group, gender, ethnicity, and presence of comorbidities), treatment prior to Dupilumab, and results with the use of medication (which were subdivided into improvement and recurrence/side effect).

Image 3 – illustrative scheme referring to the method adopted in the work.



## RESULT

A total of 14 articles were analyzed, after applying the exclusion criteria detailed in the study methodology. Of these, one was published in 2023, 8 in 2022, one in 2021, three in 2020 and one in 2019. This denotes that the application of Dupilumab in the treatment of eosinophilic esophagitis is quite recent, a context in which a relationship was established between the pathophysiology of EoE and the mechanism of action of the drug, which was already used in the treatment of other pathologies with atopic characteristics, such as asthma and atopic dermatitis.

Regarding the origin of the article, three continents (Europe, America and Oceania) were considered. However, there was a predominance of studies carried out in the United States, since 13 of the 14 articles were carried out, at least partially, in that country, one of which was multicenter (also applied in Australia, Canada and Europe) and another involved both Europe and North America, while the others were carried out only in the United States. One of the tabulated articles did not specify the origin.

In terms of the type of study, there was a predominance of reviews and case reports, with 5 of each of these, in all. There were also 3 double-blind randomized clinical trials, one of them phase 3, another phase 2 and a third unspecified. A retrospective study of medical record review was also found.

The total number of patients studied ranged from 1 in 4 of the 5 case reports found to 321 in the multicenter study. In the phase 2 clinical trial, there were 47 patients; in another clinical trial, whose phase was not specified, 240 people were studied; in the retrospective study, 7 were contemplated; In the only case report that did not include a single patient, there were 3 in all. Three of the review articles did not specify the number of patients covered. The other two review articles covered 47 patients in the analyses.

Regarding the age group, the clinical trials covered patients aged 12 years and over, 18 to 65 years and 12 to 66 years, while the case reports analyzed patients aged 7, 9, 14, 17 and 42 years; The retrospective study had a range from 6.9 to 25.4 years. Three articles did not specify the age of the patients under study and two classified only as "adults", without further details.

With regard to gender, of the 7 patients studied in clinical trials, there was only one female patient (14.2%) compared to 6 males (85.7%), while in the retrospective study, there were 5 boys (71.4%) and 2 girls (28.5%). In the clinical trials, there was a predominance of male participants, ranging from 57, 60, 68 and 73% depending on the study, while women represented 32, 37, 40 and 43%. 5 articles did not provide data on the gender of the patients.

Of the articles analyzed, 11 did not specify the race of the patients in question, and only 3 detailed this information. Of these articles, one clinical trial had 100% of the white patients in the Dupilumab group and 87.5% in the placebo group, while a second trial had a great predominance of white race (96% in part A and 90% in part B of the study); One of the case reports involved a Caucasian patient.

Regarding the presence of comorbidities, the data are presented in the following table. Only 5 articles did not report on comorbidities

Table 1 – Comorbidities of the patients included in the articles analyzed.

| **Study design and total patients** | **Presence of comorbidities** |
|---|---|
| Phase 3, randomized, double-blind clinical trial with 321 patients [22] | 285 (89%) had a history of allergic disease with type 2 inflammatory response, 217 (67%) with allergic rhinitis, 175 (54%) with food allergy, 115 (36%) with asthma, and 63 (20%) with atopic dermatitis |
| Randomized double-blind phase 2 clinical trial with 47 patients [23] | 79% (19 patients) of the placebo group and 87% (20 patients) of the Dupilumab group had 1 or more additional atopic diseases, 31 (66%) with food allergy and the same amount with allergic rhinitis, 20 (43%) with asthma, 10 (21%) with chronic rhinosinusitis, 8 (17%) with atopic dermatitis, and 6 (13%) with allergic conjunctivitis |
| Case report of 1 patient [24] | Atopic dermatitis, asthma and allergic rhinitis |
| Case report of 3 patients [25] | Patient 1: severe atopic dermatitis and food allergy<br>Patient 2: severe asthma<br>Patient 3: severe atopic dermatitis. |
| Case report of 1 patient [26] | Rhinitis allergy and asthma |
| Case report of 1 patient [27] | Asthma, chronic urticaria, allergic rhinitis, and eczema/atopic dermatitis. Food impaction. |
| Retrospective study of 7 patients [28] | Asthma or atopic dermatitis |
| Case report of 1 patient [29] | Tracheostomy, gastrostomy, extreme prematurity (26 weeks gestational age), chronic lung disease, tracheal and subglottic stenosis. No personal or family history of atopy |
| Phase 2, Randomized, Double-blind, Placebo-controlled Study With Dupilumab With 47 Patients [30] | Allergic rhinitis or food allergy |

In the context of previous treatment, all clinical trials included the use of proton pump inhibitors (PPIs), and in one of them, 38% (7 patients) had already used PPIs in high doses or twice a day for at least 8 weeks [23]. In a second study, 71% (231 patients) had previously used high-dose PPIs for 8 weeks, and the pump inhibitor was maintained

throughout the study; In addition, 38% (122) of patients already had a previous esophageal dilatation and 38% (122) had a history of diet with elimination of certain foods [22]. Regarding the retrospective study, topical corticosteroid therapy, including budesonide, fluticasone, and mometasone, was used in 85.7% of the patients, PPIs were used in 100% of the cases, elementary formula in 33.3%, and esophageal dilatations in 16.6% of the patients [28]. In the randomized, double-blind, parallel-group, multicenter, placebo-controlled study, 43% of the subjects in part A and 37% of the subjects in part B had a history of previous esophageal dilatations [17].

Finally, in the case reports, the first included previous use of PPIs, which was maintained during the study, in addition to Betanecol and Fluticasone, which was changed to Budesonide [24]; in a second report with 3 patients, the first used Budesonide, PPIs, milk and gluten elimination, 6-food elimination diet (milk, gluten, soy, fish/shellfish, peanuts, tree nuts, and egg) and glucocorticoids; the second, PPIs and budesonide; and the third had undergone previous treatment only for severe atopic dermatitis, whose medication was not informed [25]. In a third case report, PPIs, topical glucocorticoids, milk-elimination diets, and esophageal dilatations were previously used [26]; in the last report, only ingested fluticasone (110 µg/performance), 2 oral inhalations twice a day, and esomeprazole 20 mg a day [29] were used. 5 articles did not provide information on prior treatment.

All the articles analyzed demonstrated improvement in patients using Dupilumab, 13 of which showed a reduction in the eosinophil count, 8 showed clinical improvement of symptoms, 8 indicated histological improvement, 7 denoted improvement in the endoscopic pattern, according to the Endoscopic Reference for Eosinophilic Esophagitis, and 4 indicated a reduction in the Dysphagia Symptom Questionnaire (QSD) score.

HIRANO [23] indicated that the mean QSD score was 6.4 at baseline involving 47 patients, and was reduced to a mean value of 3 at week 10 in the group that received 300 mg of dupilumab weekly, compared to the 1.3 reduction in placebo. In addition, 9 patients treated with Dupilumab (39%) had a reduction of 3 points or more in the Dysphagia Symptom Questionnaire (QSD) compared to 3 patients on placebo. At week 12, compared with placebo, Dupilumab reduced peak eosinophil count by an average of 86.8 per high-rise field; The histological score was reduced by 68.3% and the endoscopic reference by 1.6. In addition, there was an increase in esophageal distensibility in 18% of those who received Dupilumab. Finally, 13% of patients treated with Dupilumab had histological and symptomatic remission, compared with none on placebo, at week 10.

BEVERIDGE [31] studied patients who received subcutaneous injections of placebo or dupilumab with a loading dose of 600 mg and then maintenance with 300 mg weekly for

12 weeks. Of the patients who received Dupilumab, 83% achieved an eosinophil count of less than 15 per high-magnification field, at week 12, compared to 0% of those receiving placebo. 39% of patients who received Dupilumab had symptomatic improvement at week 10, compared to 13% who received placebo. Oesophageal distensibility also improved significantly with Dupilumab, compared with placebo at week 12.

Al-HORANI [17] conducted a randomized study in which, in parts A and B, patients received 300 mg of Dupilumab or placebo for 24 weeks. In part A, 60% of patients achieved less than 6 eosinophils per high-magnification field, compared to 5% in the placebo group, and achieved an average improvement of 22 points in the QSD score, compared to only 10 points for patients in the placebo group. In part B, 59% of patients achieved less than 6 eosinophils per high-magnification field, compared to 6% of the placebo group. The average improvement was 24 points in the QSD score, compared to only 14 points for patients in the placebo group. In this same context, LUCENDO [32] studied the use of placebo compared to a loading dose of 600mg, followed by 300mg of Dupilumab weekly, for 12 weeks. As a result, the maximum eosinophil count was reduced by 91.8% with Dupilumab, compared with 15.1% with placebo. In addition, 82.6% of patients treated with Dupilumab achieved less than 15 eosinophils per high-magnification field, and 65.2% achieved less than 6 eosinophils. There was also improvement in endoscopic scores and symptomatic improvement of dysphagia in 45% of patients, compared to 19% of the placebo group, according to QSD.

Still with regard to clinical improvement, it is interesting to note that the multicenter clinical trial concluded that histological and symptomatic remission was evident only in the weekly treatment with Dupilumab, since, in the biweekly regimen, the results were not considered significant, since there was no difference at baseline of the Dysphagia Symptoms Questionnaire (QSD) between those who took Dupilumab fortnightly and those who received placebo.  perhaps due to the divergence of serum concentration between the weekly and fortnightly regimens [22]. In part A of this study, 25 of 42 patients (60%) who received 300mg of Dupilumab weekly had histological remission, as did 2 of 39 who received placebo, while in part B, 47 of 80 patients (59%) who received Dupilumab weekly had histological remission, as did 49 of 80 (60%) who received 300mg of Dupilumab every 2 weeks and 5 of 79 (6%) who received placebo. On the Dysphagia Symptom Questionnaire (QSD), the score improved with weekly Dupilumab, compared with placebo (difference of -12.32 in part A and -9.92 in part B); on the QOD scale, there was no significant improvement with biweekly dupilumab. The reduction in eosinophil count was greater in those who received Dupilumab weekly, in part A, than in placebo, with a

difference of 68.3 percentage points. In part B, the difference was 88.6 points between those who received the weekly drug and the placebo, and 79.2 between those who received the biweekly treatment and the placebo. Regarding the ERFES endoscopic score, in part A, the difference between patients who received weekly Dupilumab and those who took placebo was -2.9; in part B, -3.8 in the weekly regime and -3.9 in the biweekly regime. The serum concentration of the drug in weekly use was more than double that of the biweekly drug. These findings are consistent with the FDA's recommendation of 300 mg of Dupilumab weekly for the treatment of EoE.

The case reports also had promising results. NAMBIAR [26] studied a 14-year-old patient who was admitted to the ER with esophageal food impaction, inability to tolerate oral secretions and progressive dysphagia for 2 years, and esophageal stenosis and ring trachealization were observed at endoscopy. The narrowest portion of the esophagus was smaller than 5.4 mm. Glucocorticoids and PPIs were started at high doses thereafter, but stenosis remitted after 3 months. New treatments were tried the following year, without symptomatic, histological and stenotic resolution, which culminated in the initiation of Dupilumab. As a result, EREFS went from 7, in July/20, when it was admitted to the ER, to 5, in March/22, with the patient using 300mg of Dupilumab weekly since December/21.

The use of Dupilumab, even as a primary indication for other pathologies, allowed the remission of eosinophilic esophagitis, as demonstrated by SYVERSON [28], in which 7 patients with EoE were treated with subcutaneous Dupilumab 200mg (4/7) or 300mg (3/7), every 2 weeks, for the primary indication of asthma or atopic dermatitis. At follow-up endoscopy performed during Dupilumab therapy, the median maximum esophageal eosinophil count was 2 eosinophils per high-power field (IQR 0–5 eos/CGA), with the presence of edema and exudate in 2 patients and absence of rings, grooves, or strictures in all of them. Follow-up endoscopy was performed on average 5.3 months (IQR 4.6–9.8) after initiation of Dupilumab, with all patients off topical corticosteroid therapy, 4 of 7 had reintroduced one or more food groups into their diet, and 6 of 7 had dysphagia improvement. In this same context, BUENDIA [24] demonstrated a patient with atopic dermatitis and EoE, who had clinical and histological remission of EoE, after 4 months of use of Dupilumab as the primary indication for atopic dermatitis. A loading dosage of 600 mg was performed, followed by maintenance with 300 mg fortnightly. The number of eosinophils per field reached 12, and it had already been close to 105.

Regarding relapse and adverse effects, Dupilumab was well tolerated, with no serious adverse events or deaths. In clinical trials, the most frequent were injection site reaction (ranging from 2.36%, 35%, and 38%) and nasopharyngitis in two studies (17% of

patients in both); conjunctivitis (3.1%), upper respiratory tract infection (18%), arthralgia (2%), and herpes viral infections (2%) were recorded in a single trial; One of the clinical trials showed no adverse effects and there are no records of recurrences in all of them. Only 1 patient discontinued treatment for a serious non-study related event (nail disorder).

Also in this context, the case reports presented varied results, including two cases without recurrence and without side effects; one case of a patient who relapsed twice after starting Dupilumab, with worsening dysphagia and an eosinophilic count of 55 per high-power field, requiring the association of low-dose Budesonide and maintenance of PPI for complete resolution and histological remission (10 eosinophils/CGA) after a 4-month follow-up [24]; and one case without histological remission after initiation of Dupilumab, with normal eosinophil count, but active EoE in the distal esophagus, with improvement of symptoms and esophageal appearance, with no identification of new stenosis; the patient had been on Dupilumab for 1 year, without any side effects other than lack of appetite [26]. Finally, a review article cited adverse reactions such as injection site reactions, upper respiratory tract infections, herpes viral infections, and arthralgias, without further details [19]; 4 articles did not provide data on adverse reactions and relapses.

## DISCUSSION

The results of this research found that the studies included patients in a variable age range between 7 and 66 years. With this, it is possible to infer that Dupilumab was safely used from the pediatric population to the adult population. In addition, as suggested in previous studies, there was a predominance of males [10] and a great relationship with other atopic diseases, such as allergic rhinitis and asthma [9]. Regarding previous treatments, there was a preponderance of the use of proton pump inhibitors (PPIs).

The results demonstrated by Dupilumab are undoubtedly promising, in the context of EoE, in terms of histological, clinical, endoscopic remission and eosinophil count, which can have a great impact on improving the quality of life of these patients. In addition, there were no serious adverse effects recorded.

However, there was divergence among the studies regarding the dose and appropriate frequency of treatment, considering that HIRANO [23] and AL-HORANI [17] proposed a weekly regimen of 300 mg of Dupilumab, as recommended by the FDA, while BEVERIDGE [31] and LUCENDO [32] used 600 mg of loading dose, with maintenance at 300 mg for 12 weeks. These two regimens were well effective in terms of clinical, histological, and endoscopic remission. However, the biweekly treatment regimen with 300mg of Dupilumab did not modify the baseline Dysphagia Symptom Questionnaire (QSD)

score, compared to placebo, despite the fact that there was histological improvement and reduction in endoscopic score, as demonstrated by DELLON [22].

Longitudinal monitoring of patients with this pathology is essential, even for the introduction of new therapies, when necessary, such as immunobiologicals. However, there is a lack of studies that deal with the transition from conventional pathologies to Dupilumab. It is also worth mentioning that, as much as the weekly treatment with 300mg of Dupilumab, as approved by ANVISA and the FDA, has shown superior results, compared to the biweekly regime, this drug has been marketed, under the name of Dupixent, for approximately 10 thousand reais and, from what was ascertained, it is not distributed in the Unified Health System (SUS) as a primary indication for the treatment of EoE, so that access to it becomes quite limited.

## CONCLUSION

In summary, the pathophysiology of eosinophilic eosphagitis is mainly permeated by the action of the T-heper 2 lymphocyte, the recognition of interleukins (especially IL-4, IL-5 and IL-13, with regard to allergic diseases), the differentiation of eosinophils and the production of IgE antibodies [14]. Dupilumab, the central drug of this study, targets the alpha chain of the IL-4 receptor, called IL-4R alpha. From this, Dupilumab inhibits IL-4 and IL-13 induced responses, so as to reduce protein transforylation, transcription (sustained mainly from STAT 6) and T helper 2-regulated response, in the context of atopic diseases [20].

The primary objective of this systematic review was to evaluate the efficacy of Dupilumab in the treatment of EoE. It is a chronic and immune-mediated disease, probably triggered by the relationship between genetic factors, environmental risks and the patient's defense system. The results were promising, with evidence of improvement in all patients included in the studies analyzed, with no association with serious adverse effects.

However, it is worth noting that further studies are needed to better clarify the longitudinal monitoring of patients with eosinophilic esophagitis, with regard to both the transition from conventional treatment to immunobiologicals and the appropriate treatment time with Dupilumab and subsequent maintenance therapy. Despite having been approved by ANVISA and having had very promising results, in research, this drug has not been distributed by the Brazilian Unified Health System, which makes access to it quite restricted, due to its high price, so that, for its use to be expanded, it is necessary to wait for it to become available in the health system.

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