REVIEW

Position Paper on the Treatment of Eosinophilic Esophagitis With Dupilumab

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Abstract

Eosinophilic esophagitis (EoE) is a chronic allergic condition affecting the esophagus and driven by food antigens. Many individuals diagnosed with EoE have other allergic conditions, such as food allergy, asthma, allergic rhinitis, and atopic dermatitis. The clinical goals of therapy in EoE include symptomatic, histologic, and endoscopic remission. The current paradigm for the treatment of EoE in Spain includes proton pump inhibitors, swallowed topical corticosteroids, and food elimination diets. These treatments have proven very effective in clinical studies. In April 2024, the Spanish Agency for Medicines and Medical Products approved dupilumab as the second drug for the treatment of EoE, thus adding this biologic to the therapeutic arsenal in EoE.

The present review includes a positioning statement by the authors, all of whom are members of the Spanish Society of Allergy and Clinical Immunology Food-EoE Working Group.

Key words: Eosinophilic esophagitis. Dupilumab. Food allergy. Outcomes. Atopy. Positioning.

Resumen

La esofagitis eosinofílica (EoE) es una afección alérgica crónica del esófago, provocada por alérgenos alimentarios. Un porcentaje muy elevado de individuos diagnosticados de EoE presentan otras enfermedades alérgicas tales como alergia alimentaria, asma, rinitis alérgica y dermatitis atópica. Los objetivos clínicos del tratamiento de la EoE incluyen la remisión sintomática, histológica y endoscópica de la misma. En España, hasta ahora, el paradigma actual para el tratamiento de la EoE incluía inhibidores de la bomba de protones (IBP), corticoides tópicos deglutidos (TCS) y dietas de eliminación de alimentos (FED). Estos tratamientos han mostrado sólidos datos de eficacia en estudios clínicos. En abril de 2024, dupilumab se convirtió en el segundo tratamiento aprobado por la AEMPS para la EoE, añadiendo este biológico a las opciones de tratamiento de la EoE.

Esta revisión incluye una declaración de posicionamiento de los autores, todos ellos miembros del Comité de Alimentación-EoE de la SEAIC.

Palabras clave: Esofagitis eosinofilica. Dupilumab. Alergia alimentaria. Resultados. Atopia. Posicionamiento.

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic and progressive type 2 inflammatory condition, with growing incidence and prevalence worldwide. In Spain, EoE affects at least 1 in every 1000 individuals. It is the primary cause of dysphagia and food impaction in children and young adults and the second most common cause of long-term esophagitis after gastroesophageal reflux [1].

The exact cause of this disease is still not completely understood. Recent studies indicate that immune cells in the esophagus, when overstimulated by antigens, release proinflammatory cytokines such as IL-4, IL-5, and IL-13, which then trigger the proliferation and recruitment of eosinophils, leading to an enhanced inflammatory response, potentially driven by factors such as food and environmental antigens [2].

EoE is diagnosed based on clinical signs of esophageal dysfunction and the presence of more than 15 eosinophils per high-power field (HPF) in esophageal mucosa biopsy samples (equivalent to 60/mm²), with no alternative causes and localized to the esophagus. The symptoms associated with esophageal dysfunction can vary widely, including poor growth or weight loss, abdominal pain, vomiting, reflux-like symptoms, dysphagia, and food impaction [2].

Treatment for EoE involves both pharmacological and nonpharmacological approaches, such as dietary therapy, proton pump inhibitors (PPIs), and swallowed topical corticosteroids (STCs). Esophageal dilatation may be necessary in the case of strictures. The primary goals of treatment are to achieve and maintain remission of eosinophilic inflammation (fewer than 15/HPF), reduce symptoms, prevent complications, and, ultimately, improve patients' quality of life [3].

Until recently, no treatments specifically targeting the underlying inflammatory mechanisms had been developed to prevent or control progression of EoE, although there is plenty of evidence that type 2 cytokines have a significant impact. Moreover, many EoE patients often have co-occurring type 2 clinical conditions [1].

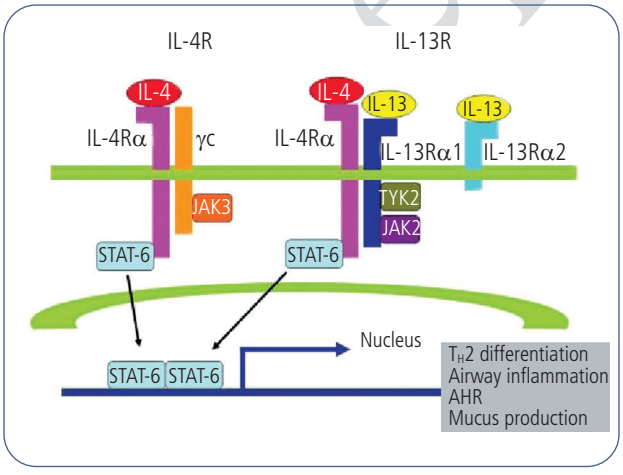

Figure 1. Schematic diagram of the interleukin (IL) 4/IL-13/signal transducer and activator of transcription factor (STAT) 6 signaling pathways. AHR indicates airway hyperresponsiveness; JAK, Janus kinase; TYK, tyrosine kinase.

Dupilumab, a recombinant IgG4 antibody, targets the α chain of the IL-4 receptor (IL-4Ra), which is a shared component of the receptors for IL-4 and IL-13. By inhibiting the signaling pathways of IL-4 and IL-13, which are key drivers of type 2 inflammation, dupilumab is effective for the treatment of several type 2 inflammatory diseases, including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, and, more recently, EoE. With the approval of dupilumab for EoE, clinicians now face the challenge of determining how best to incorporate it into treatment regimens. In this article, the Food-EoE Working Group of the Spanish Society of Allergology and Clinical Immunology (SEAIC) proposes a diagnostic algorithm for uncontrolled EoE and/or with concomitant type 2 helper T cell (T_H2) diseases, discussing various options and considerations for using dupilumab in EoE.

2. Role of IL-13 and IL-4 in Eosinophilic Esophagitis

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signaling through the type I receptor (IL-4Rα/γc) and type II receptor (IL-4Rα/ IL-13Rα), the main drivers in type 2 inflammatory diseases such as atopic dermatitis, asthma, and EoE. Knowledge of the structure and functioning of these receptors can help us to understand how dupilumab works [4].

The IL-4 receptor complex (IL-4R) is a heterodimeric structure composed of an IL-4α subunit, which pairs with auxiliary subunits to mediate the action of interleukins 4 and 13. Specifically, IL-4α pairs with the γ chain to form the high-affinity receptor IL-4R type I, which is expressed on the surface of hematopoietic cells and binds exclusively to IL-4. It also pairs with the auxiliary subunit IL-13Rα1 (receptor of low-affinity IL-13) to form the type II high-affinity heterodimeric receptor (Figure 1) [5]. This receptor mediates the action of IL-4 and IL-13 and is present on the surface of hematopoietic and nonhematopoietic cells, such as those in the airway epithelium and esophageal mucosa. This IL-4/IL-13 axis and its high-affinity receptors promote T_H2 differentiation, which is responsible for the immune response that alters the response to the presence of allergens in the air or digestive tract [6].

In the context of T_H2, exposure to allergens promotes epithelial damage and damage-associated molecular patterns (DAMPs) (Figure 2). Within the framework of this response, DAMPs promote the release of IL-33 and IL-25 (interleukin 17 family), which leads to the synthesis and release of IL-4 and IL-13 (major effective cytokine). IL-13 would in turn be responsible for the release of mediators such as eotaxins 1, 2, and 3. Eotaxin 3 is the key in this process. It is encoded by the CCL26 gene, whose increased expression enables the differential diagnosis between EoE and gastroesophageal reflux disease. These eotaxins act on the CCR3 receptor, which is present in eosinophils and mast cells. Its activation and recruitment determine the phenomenon of inflammation, which is in turn responsible for processes such as airway and digestive tract remodeling and fibrosis. In this last phase, interleukins (IL-5, IL-18, and IL-15) and other mediators (TNF-α, TGF-β1, and IFN-γ) come into play [7].

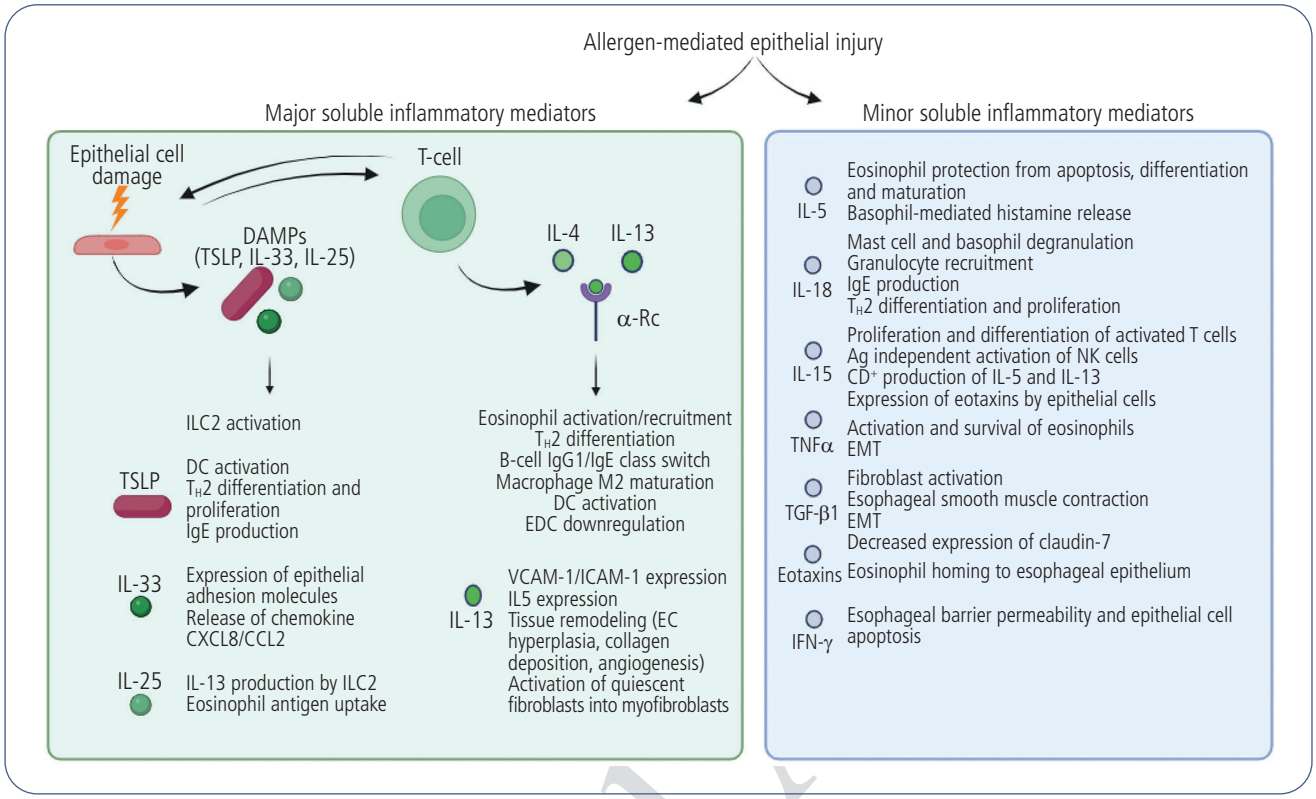

Figure 2. Functions of major and minor soluble inflammatory mediators of eosinophilic esophagitis (allergen-mediated epithelial injury). DAMP indicates damage-associated molecular patterns; DC, dendritic cell; EC, epithelial cell; EDC, epidermal differentiation complex; EMT, epithelial–mesenchymal transition; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; TSLP, thymic stromal lymphopoietin.

3. Clinical Development of Dupilumab (Phase 2 and Phase 3 Trials)

The efficacy of dupilumab in EoE is based on evidence from clinical trials.

3.1 Phase 2 Study

Study of Dupilumab in Adult Participants with Active Eosinophilic Esophagitis (EoE) (NCT02379052).

This phase 2, multicenter, randomized, double-blind, parallel, placebo-controlled study was performed in adult patients with moderate-to-severe active EoE (12 weeks' duration) to evaluate the efficacy, safety, and tolerability of repeated subcutaneous (SC) doses of dupilumab compared to placebo. A total of 47 patients were randomized (1:1) into 2 treatment groups to receive dupilumab 300 mg/wk SC (with a 600-mg loading dose) (n=23) or placebo (n=24) for 12 weeks, followed by a 16-week safety follow-up period.

In the primary efficacy endpoint analysis, dupilumab 300 mg/wk significantly reduced the Straumann Dysphagia Score Patient-Reported Outcomes (SDI PRO) score between baseline and week 10 compared with placebo (least square [LS] mean change: –3 in dupilumab 300 mg/wk, –1.3 in placebo) with improvements in the score observed from week 1.

In the analysis of secondary efficacy endpoints, dupilumab significantly improved the LS mean percentage change from baseline in the SDI PRO score compared with placebo (–45.1 [8.4] vs –18.6 [9.0]) and the LS mean change in the EoE endoscopic reference score (EREFS) total score (dupilumab 300 mg/wk –1.9 [0.3] vs placebo –0.3 [0.3]). A ≥3-point reduction in the SDI PRO score was recorded in significantly more dupilumab-treated patients than placebo-treated patients at week 10 (9 [39%] vs 3 [13%] patients) [8].

3.2 Phase 3 Study

LIBERTY EoE TREET (NCT03633617).

This was a 3-part (parts A, B, C), randomized, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of dupilumab in adults and adolescents with EoE (>12 years). Parts A and B consisted of a 24-week, double-blind treatment period. At the end of week 24, eligible patients entered part C, which consisted of a 28-week open-label treatment period. Patients were followed up for 12 weeks after the end of treatment [9].

In part A, 81 patients were randomized to dupilumab 300 mg/wk (n=42) or placebo once weekly (n=39). In Part B, 240 patients were randomized to dupilumab 300 mg/wk (n=80), dupilumab 300 mg/2 wk (n=81), or placebo once weekly (n=79). In total, 40 patients (98%) receiving dupilumab weekly in part A remained on this treatment in part C, and 37 patients (95%) receiving placebo in part A crossed over to dupilumab at a weekly dose of 300 mg in part C. Of the 240 patients from

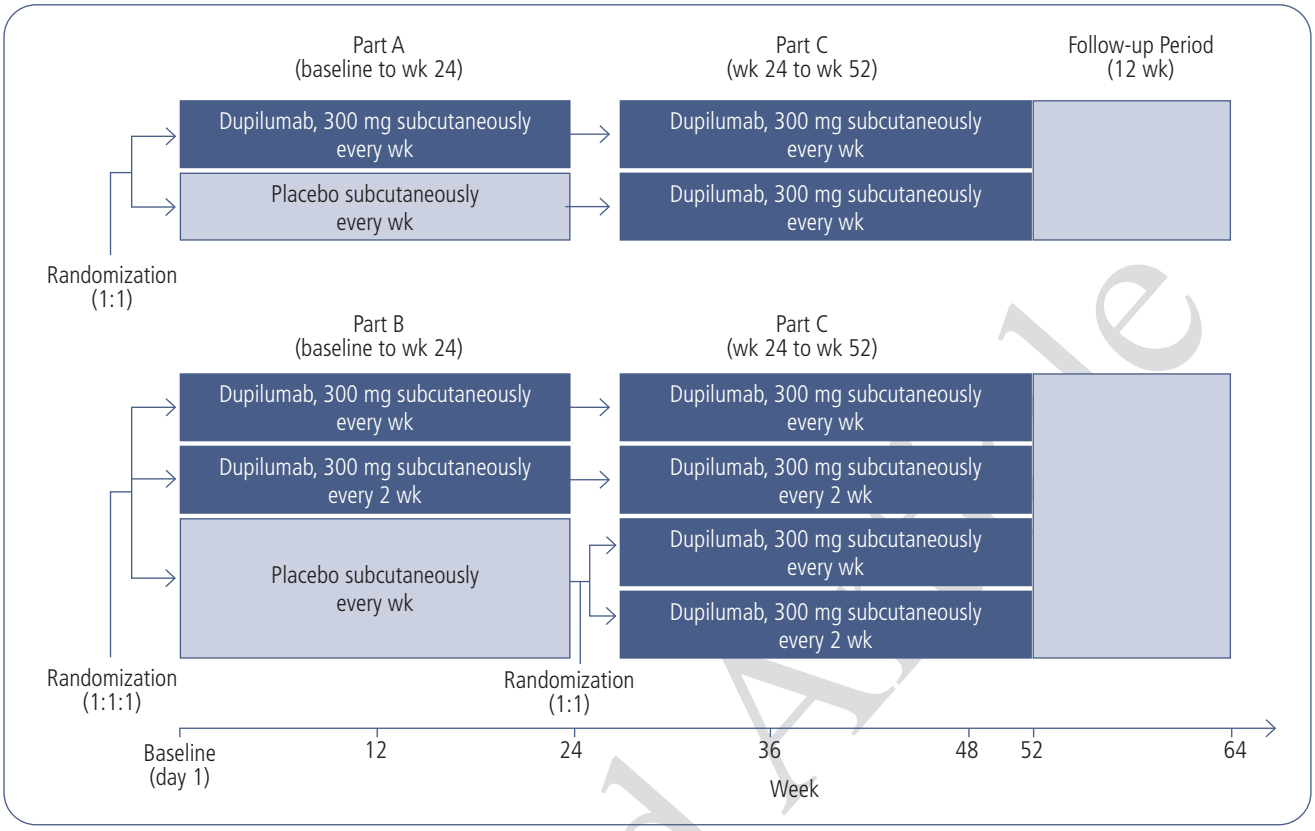

Figure 3. Phase 3 trial design. The patients who received 300 mg of dupilumab every 2 weeks in parts B and C also received placebo every 2 weeks alternating with dupilumab for regimen-blinding purposes.

part B, 227 patients continued to participate in parts B-C. Patients in parts B-C receiving dupilumab 300 mg once weekly or 300 mg/2 wk in part B received the same regimen in part C (n=74 weekly, n=79 dupilumab every 2 weeks). Patients on placebo in part B were randomized to dupilumab 300 mg every week or every 2 weeks in part C (n=74). In each case, 37 patients switched from placebo to dupilumab weekly or to dupilumab every 2 weeks (Figure 3) [9].

3.2.1 Results from Parts A and C of the Phase 3 LIBERTY EoE TREET Study (NCT03633617)

The primary endpoints were the proportion of patients with a peak intraepithelial eosinophil count (PEC) of ≤6/HPF and improvement in the Dysphagia Symptom Questionnaire (DSQ) at week 24. The secondary endpoints were as follows: percent change from baseline in PEC; change in the total EREFS; proportion of patients achieving a PEC of <15/HPF; percent change in the DSQ score; and absolute change from baseline in the grade and stage scores on the Eosinophilic Esophagitis Histology Scoring System (EoE-HSS, both scores range from 0 to 3, with higher scores indicating greater severity of histologic changes or greater extent of abnormal tissue, respectively).

In Part A, histologic remission was recorded at week 24 in 25/42 patients (60%) receiving weekly dupilumab and in 2/39 patients (5%) on placebo. At week 52 of part C, histologic remission was recorded in 19/34 patients (56%), and 28/34 patients (82%) had <15/HPF.

At week 24, improvements in histological findings, symptoms, and endoscopic findings were observed for dupilumab. These persisted through week 52, with an acceptable safety profile. Efficacy was similar in placebo-treated patients from part A who were switched to dupilumab in part C and in dupilumab-treated patients from part A.

3.2.2 Results from Parts B and B-C of the Phase 3 LIBERTY EoE TREET Study (NCT03633617)

In Part B, histologic remission was recorded at week 24 in 47/80 patients (59%) receiving once-weekly dupilumab, in 49/80 patients (60%) receiving dupilumab every 2 weeks, and in 5/79 patients (6%) receiving placebo. The adjusted difference in patients with <15/HPF at week 24 in part B between patients receiving dupilumab weekly and patients on placebo was 75 percentage points, and the corresponding value between patients receiving dupilumab every 2 weeks and patients receiving placebo was 72 percentage points. The LS mean change in peak eosinophil counts at week 24 between patients receiving dupilumab weekly and patients on placebo was –88.6 percentage points, and the corresponding value between patients receiving dupilumab every 2 weeks and patients on placebo was –79.2 percentage points.

At week 24, the decrease in the DSQ score was greater in patients receiving weekly dupilumab than in patients receiving placebo in part B (LS mean change, –23.78 points vs –13.86 points). There

was no significant difference in the decrease in the DSQ score between patients receiving dupilumab every 2 weeks and those on placebo (LS mean change, –14.37 points vs –13.86 points). The decrease in the number of days with dysphagia in part B was similar to that recorded in part A.

The results at week 52 were as follows: peak esophageal intraepithelial eosinophil count of ≤6/HPF in 55 (85%) patients in the weekly dupilumab/weekly dupilumab group (mean percent change in peak eosinophil count from part B baseline, –95.9%), 25 (68%) in the placebo/weekly dupilumab group (–84.2%), 54 (74%) in the dupilumab every 2 weeks/ dupilumab every 2 weeks group (–84.8%), and 23 (72%) in the placebo/ dupilumab every 2 weeks group (–91.2%) [10].

Improvements in histologic and endoscopic findings and symptoms observed after 24 weeks of weekly dupilumab were maintained or improved sequentially through week 52.

3.2.3 Subgroup Analysis

The subgroup analysis of the LIBERTY EoE TREET randomized controlled trial demonstrated that dupilumab 300 mg once weekly is a well-tolerated and efficacious treatment option for adult and adolescent patients with EoE, regardless of prior use of STCs or inadequate response, intolerance, and/or contraindication to STCs. These results indicate that previous treatment with STCs does not affect the efficacy of dupilumab in patients with EoE [11].

3.3 Phase 3 Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients With Active Eosinophilic Esophagitis (EoE) (EoE KIDS) (NCT04394351)

This is a 3-part randomized, double-blind, placebo-controlled trial to demonstrate the efficacy of dupilumab compared with placebo in pediatric patients with active EoE based on improved histology results meeting validated histologic criteria. The estimated completion date is July 7, 2025 [12].

4. Safety

Clinical trials have reported the safety of dupilumab for the treatment of multiple type 2 inflammatory diseases. The most commonly reported adverse effects are minor, such as conjunctivitis, upper respiratory tract infections, injection site reactions [13,14], and facial erythema. Other adverse effects include worsening of atopic dermatitis and herpesvirus skin infection [15], as well as blood hypereosinophilia, uveitis, blepharoconjunctivitis, inflammatory arthritis, ulcerative colitis, psoriasis, rosacea, seborrheic dermatitis, alopecia areata, erythema nodosum, and facial redness [16].

No clinical trials with dupilumab have examined safety during pregnancy and lactation, although some pregnancy outcomes were reported for participants who became pregnant while participating in clinical trials. In the TRAVERSE open-label extension study, 9 participants receiving dupilumab for asthma became pregnant: 3 miscarriages were reported in the dupilumab/dupilumab group, and none in the placebo/ dupilumab group.

The dupilumab package insert indicates that hypersensitivity reactions occur in <1% of patients. These include generalized urticaria, serum sickness, rash, erythema nodosum, and anaphylaxis [16].

There is insufficient evidence to suggest a causal relationship between dupilumab and malignancy, and the certainty of evidence of serious adverse reactions related to the drug is low to very low. However, cases of eosinophilic pneumonia related to dupilumab have been published [17].

Long-term studies on the efficacy and safety of dupilumab in children under 12 years of age and in patients with EoE are required.

5. Use of Dupilumab in T_H2 Diseases and in EoE in Particular

Dupilumab is currently used for a wide variety of T_H2 immune-mediated inflammatory diseases. The drug was first approved in March 2017 by the United States Food and Drug Administration (FDA) as a treatment for severe atopic dermatitis. Afterwards it was approved for the treatment of severe asthma with a type 2 phenotype.

Dupilumab has also been approved for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis who required multiple courses of systemic corticosteroids and/ or experienced a relapse after surgery [18].

In the latest updates from regulatory agencies, the approved age range for dupilumab has been expanded, so that it can now be used for moderate-to-severe atopic dermatitis in patients aged >6 months. It is also authorized for patients aged >6 years with severe type 2 asthma who are refractory to treatment with high-dose inhaled corticosteroids combined with another asthma medication.

Dupilumab can be used off-label in other T2 diseases, such as allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia. Muñoz Bellido et al [19] published a review of off-label uses of dupilumab for other T2 diseases, finding that in allergic bronchopulmonary aspergillosis, the drug reduced severe exacerbations, total IgE, and specific IgE against *Aspergillus fumigatus*.

EoE is the most recent disease for which dupilumab was approved. In May 2022, the FDA approved dupilumab for EoE, making it the first biologic therapy for this disease [20].

In April 2024, dupilumab was authorized for treatment of EoE by the Spanish Agency for Medicines and Medical Products (AEMPS) in patients aged >12 years weighing ≥40 kg who fail to respond to classic therapy.

With the approval of dupilumab for EoE, physicians must assess in which situations its use is most appropriate. Dupilumab may be indicated for the treatment of EoE in the following circumstances [21]:

– Patients with multiple atopic conditions, of which 1 is poorly controlled and for which dupilumab is approved. These would be patients who have EoE and severe asthma, atopic dermatitis, or chronic rhinosinusitis with nasal polyposis that cannot be controlled with usual treatment and require biologic therapy. Thus, 1 medication would treat multiple diseases.

– Persistence of continuous symptoms of esophageal inflammation despite conventional treatment in patients refractory to exclusion diets, PPIs, and STCs.
– Clinical presentation with severe involvement:
  - Patients with severe esophageal stenosis. Although these cases were initially excluded from dupilumab clinical trials, the drug has proven effective in reducing severe stenosis in real-life studies. Lee et al [27] studied a group of 46 patients with severe fibrostenotic EoE that was refractory to conventional therapy. After treatment with dupilumab, most patients improved in clinical and histological terms, with a significant increase in their esophageal diameter. Therefore, dupilumab could be useful in reducing the need to perform esophageal dilatations in severely ill patients.
  - Patients at risk of malnutrition or with significant weight loss due to severe dysphagia and frequent choking, which make it difficult for them to feed themselves. In certain cases, malnutrition is conditioned by treatment with overly stringent diets.
  - Complications of the disease such as esophageal perforation.
– Poor adherence to daily medication. The lower dosing frequency of dupilumab (a weekly injection) may improve adherence [20].

Treatments for EoE are subject to a series of adverse effects.

STCs can cause oral and esophageal candidiasis in 16% of patients. Consequently, dupilumab could be a suitable alternative for patients with candidiasis that is resistant to antifungal treatment.

STCs also carry a low risk of adrenal suppression, growth impairment, decreased bone mineral density, and visual disturbances (eg, cataracts, glaucoma). However, these risks increase when corticosteroids are administered through other routes to treat concomitant atopic diseases. STCs can also lead to rare but serious adverse effects, such as central serous chorioretinopathy [28], which requires treatment to be discontinued. Therefore, alternative therapy with dupilumab should be considered in these cases.

Furthermore, dietary therapy may also have significant adverse effects, including eating disorders, malnutrition, and anxiety disorders. In such situations, dupilumab should be considered as a potential treatment option.

Finally, it is uncommon for PPIs to be replaced, as they are generally considered safe drugs with mild and infrequent adverse effects. However, extended use can lead to enteric infections, making dupilumab a potential alternative in such cases.

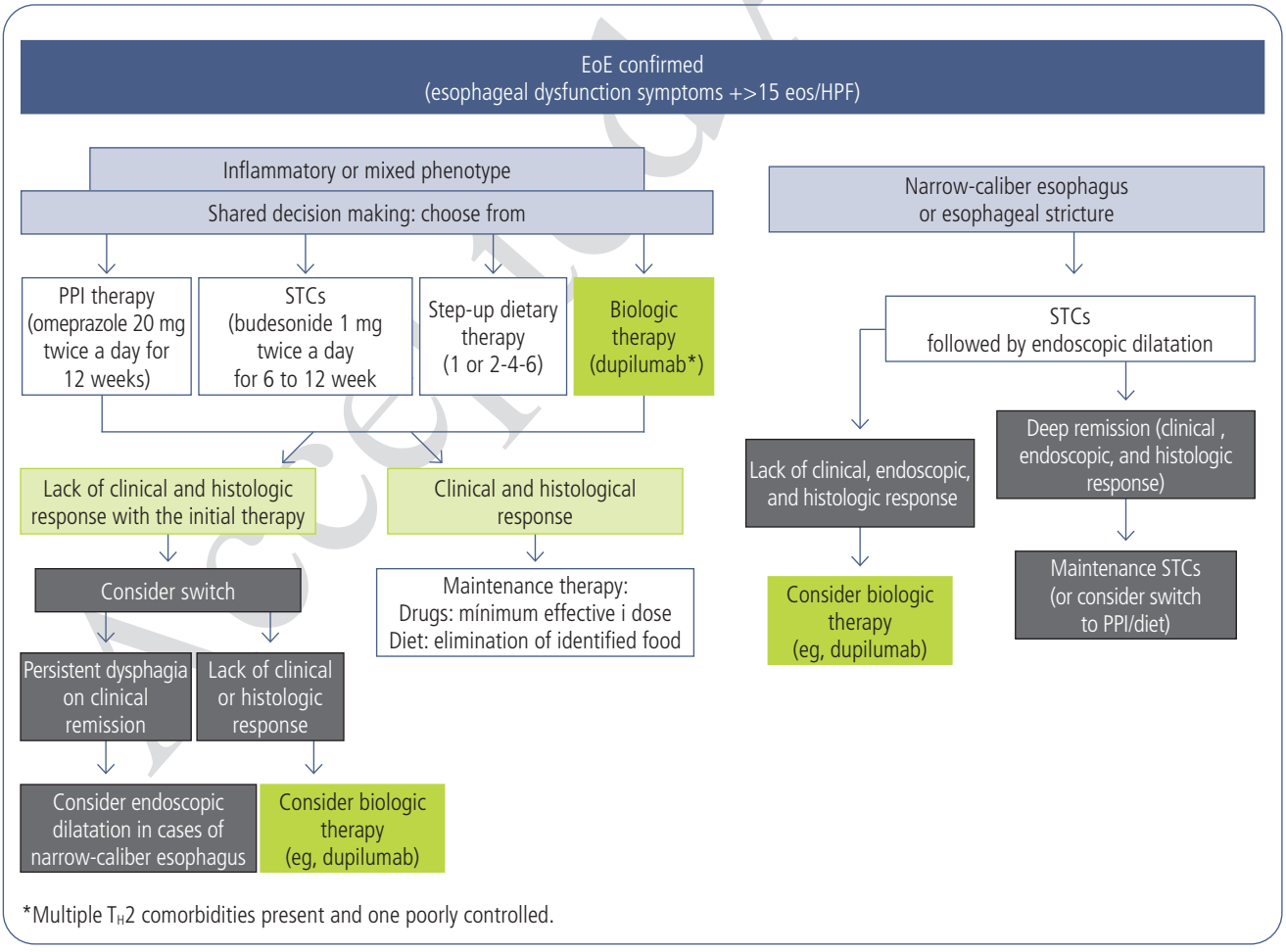

Figure 4. Algorithm for the use of dupilumab in patients with EoE. PPI indicates proton pump inhibitor; STC, swallowed topical corticosteroid.

6. Discussion

The cytokines IL-4 and IL-13 play an essential role in the T2 response. The monoclonal antibody dupilumab acts by blocking the transmission of IL-4 and IL-13 signals, thus affecting the permeability of the epithelial barrier. In addition, IL-4 and IL-13 influence barrier function by reducing filaggrin expression and altering the permeability of the epithelium [19].

Dupilumab has been approved for patients aged ≥12 years with severe asthma that is not controlled with high-dose inhaled corticosteroids and for severe atopic dermatitis. It is also approved as adjunctive therapy with intranasal corticosteroids for the treatment of adults with chronic rhinosinusitis with nasal polyposis in whom treatment with systemic corticosteroids and/or surgery does not provide adequate disease control. Although it has been approved for years by the FDA and the European Medicines Agency, it was not approved in Spain by the AEMPS until this year. While the summary of product characteristics currently includes an indication for EoE, the drug is only approved for patients aged >12 years and weighing >40 kg whose disease is not adequately controlled with conventional drugs [9,18].

We reviewed the efficacy of dupilumab in the treatment of EoE based on a 3-part protocol consisting of 2 separate randomized, double-blind, parallel-group, multicenter, placebo-controlled, randomized studies with 24 weeks of treatment (parts A and B) and an active treatment extension phase of an additional 28 weeks (part C). The randomized, placebo-controlled phase 3 trials highlight the therapeutic efficacy of dupilumab 300 mg weekly in terms of histologic remission and symptom relief in adults and adolescents with EoE, as well as its favorable safety profile [22].

Expert opinion [21] has considered dupilumab for use in EoE that does not respond well to standard therapies based on the rationale that biologic therapies are generally newer and more expensive options and involve a broad, systemic immunomodulatory approach with decreased long-term safety. However, there are potential clinical situations in which dupilumab could be a first-line option, as follows: patients with multiple comorbid atopic disorders involving mild, severe, persistent, or refractory asthma or moderate, persistent, or refractory atopic dermatitis; difficult-to-control chronic sinusitis with nasal polyposis; patients who would prefer to avoid dietary restriction or topical corticosteroids; step therapy for hard-to-treat EoE; patients with failure to thrive, poor growth, or substantial weight loss due to EoE; patients who frequently use rescue medications (oral systemic corticosteroids, esophageal dilatations); patients with severe dietary restrictions, clinically significant esophageal stricture, or narrow-caliber esophagus; and patients whose condition is refractory to current first-line therapy (owing to the persistence of symptoms, poor adherence, persistent adverse effects, poor tolerance).

The currently recommended approved dose for dupilumab in EoE is 300 mg/wk, although doses administered for the treatment of other primary atopic diseases (300 mg/2 wk) have also proven effective in EoE [23,24,25], thus reducing the cost of this therapy. Dupilumab is indicated for long-term treatment, although dosing beyond 52 weeks has not been studied [18]. Data show a worsening in the DSQ score 12 weeks after discontinuation of dupilumab. Although the data indicate that dupilumab 300 mg/wk continued for 1 year was generally well tolerated, it is unclear whether this frequency of administration is necessary after the patient achieves remission or after the first year of therapy.

All patients with EoE should be monitored after changes in treatment. Monitoring involves esophagogastroduodenoscopy with multiple biopsies. In the case of dupilumab, a repeat esophagogastroduodenoscopy can be considered 6 months after starting treatment, although clinical symptoms may improve 4 weeks after starting treatment.

The safety of dupilumab in the 300-mg/wk regimen has already been evaluated in trials for other indications (atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis), with approximately 3000 exposed patients. No new safety signals associated with the use of dupilumab in patients with EoE have been identified to date. The rate of serious adverse events and/or events leading to treatment discontinuation has been low in all treatment groups, and no clear pattern has been identified to indicate their association with the study treatment. In general, the safety profile in adolescents is similar to that in adults, although with a somewhat higher frequency of adverse events.

Weekly treatment of EoE with dupilumab 300 mg has demonstrated clinically relevant benefits in both adult and adolescent patients with substantial disease burden. In addition, dupilumab is currently the only drug with an approved indication for the treatment of EoE in patients under 18 years of age. It is also often reserved for use in treatment-refractory patients who have not responded adequately to conventional therapies and may be an option for individuals who have experienced significant adverse effects from long-term corticosteroid use [26].

The long-term efficacy of dupilumab is unknown. It is effective for up to 1 year. However, we do not know if the time intervals of administration could be suspended or extended after this time, if there will be relapses, or if concomitant treatments should be withdrawn and in what way. Such questions should be answered in future research studies.

The limitations of treatment with dupilumab are its high cost and the lack of data on long-term safety and efficacy. Considering cost and safety profile, we continue to recommend PPIs as initial treatment, even though a histologic response occurs in only 30%-50% of cases. For patients who do not respond to PPIs or those who respond and do not wish to be treated with PPIs in the long term, we recommend a patient-specific approach, taking into account efficacy, patient preferences, cost, tolerability, and adherence. These options include elimination diets, STCs, and, now, dupilumab. As stated above, we currently consider dupilumab to be the first choice for patients with uncontrolled concomitant T2 allergic conditions, those who do not respond to other therapies, and those with poor adherence or who experience adverse effects with other EoE therapies. As more evidence and other treatments emerge, this paradigm will continue to evolve and provide patients with safe and cost-effective therapies for EoE (Figure 4).

In conclusion, dupilumab is a promising therapeutic option for EoE, particularly in specific patient populations affected by

EoE with an atopic phenotype or disease with a concomitant T_H2 profile, where it may be prescribed as the first choice.

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Conflicts of Interest

J Doménech Witek reports conference fees from Thermo Fisher, AstraZeneca, and GSK. The remaining authors declare that they have no conflicts of interest.

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