The Effectiveness and Safety of Dupilumab Treatment on Adult Eosinophilic Esophagitis Patient: A Literature Review

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic allergy disorder that specifically targets the esophagus. It is caused by dietary antigens and is characterized by distinct changes in both the microscopic and visual examination of the esophagus. Eosinophilic esophagitis is characterized by a range of symptoms including retrosternal burning, dysphagia, persistent reflux, nausea, and vomiting. This review seeks to assess the current evidence on the efficacy of dupilumab in the treatment of EoE. Common therapies of EoE encompass nutritional therapy, acid suppression, and topical glucocorticoids. The initial treatment options commonly include the use of swallowed topical corticosteroids, proton-pump inhibitors, or dietary modifications. Additionally, for patients experiencing symptoms with strictures, esophageal dilatation is indicated. Dupilumab is a monoclonal antibody that specifically targets the α subunit of the interleukin-4 receptor. It has been extensively researched for its potential in treating moderate-to-severe atopic dermatitis in adults, asthma, nasal polyposis, and EoE. The drug has demonstrated promising effectiveness and safety in these conditions. It has demonstrated efficacy in treating Atopic dermatitis, severe asthma, as an adjunctive therapy to intranasal corticosteroids for adult patients with Chronic Rhinosinusitis with Nasal Polyposis, and for Prurigo Nodularis. Dupilumab can result in both minor and severe adverse effects, including injection site reactions like pain and swelling, upper respiratory infections, joint pain, and an elevated likelihood of experiencing symptoms related to oral herpes or herpes zoster.

Keywords: Dupilumab; Efficacy; Eosinophilic esophagitis; Review; Safety

INTRODUCTION

Eosinophilic esophagitis (EoE) is a persistent allergic condition affecting the esophagus, triggered by food antigens and distinguished by histological and endoscopic alterations [1-3]. Its impact spans various age groups, particularly children and adults [1]. Over the past decade, the prevalence of EoE has risen, particularly in Western nations, reaching 50 cases per 100,000 individuals. Predominantly identified in the Caucasian demographic, it also manifests in African American, Hispanic, and Asian populations [1,4,5]. The etiology of EoE is deemed multifaceted, involving environmental factors, food allergies, acid exposure, and potentially genetic influences, though the precise mechanism remains elusive [6,7], where among these contributors, food allergies are a significant factor in both adult and pediatric EoE development [8].

Various symptoms, such as retrosternal burning, dysphagia, chronic reflux, nausea, and vomiting, are associated with EoE. However, abdominal pain, vomiting, chest pain, food impaction, and heartburn are particularly typical in adult patients [1,9]. Current treatment modalities for EoE encompass corticosteroids, proton pump inhibitors, and a tailored diet to manage inflammation [2,3]. While these interventions have demonstrated efficacy in clinical trials, they lack approval from the US Food and Drug Administration for EoE treatment [3]. Notably, in 2022, dupilumab received FDA approval, marking the first sanctioned and tested method for EoE treatment [2,3].

As per reported data and phase trials, dupilumab has substantially ameliorated molecular, endoscopic, and histological aspects in EoE patients, where it has reduced symptoms like dysphagia and histologic features, including eosinophilic infiltration and inflammation, presenting itself as a safer and more effective alternative compared to a placebo [2,10,11]. Additionally, dupilumab has gained approval for atopic dermatitis, asthma, and nasal polyps [12]. Therefore, this review aims to evaluate existing evidence regarding the effectiveness of dupilumab in treating EoE.

EOSINOPHILIC ESOPHAGITIS

Definition: Eosinophilic esophagitis is a chronic, immune-mediated disorder of the mucosa with eosinophilic infiltration which causes symptoms of an impaired esophageal function [10,13]. It has become one of the leading causes of gastrointestinal morbidity among adults in recent years, and it is a disease that affects human life with an increasing incidence and occurs more frequently in men compared to women where history clearly suggests atopy or allergic diseases for those who are diagnosed with this condition [1].

Etiology & Pathophysiology: Eosinophilic esophagitis is marked by a persistent inflammatory condition associated with T helper type 2 (Th2) activation, characterized by a dense infiltration of eosinophils in the esophagus [1,14]. The

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underlying pathophysiology involves the coordinated action of activated eosinophils, mast cells, and cytokines IL-5 and IL-13, driven by allergic sensitization to various food sources, also, uncommon genetic syndromes have brought to light the role of barrier disruption, defective desmosomes, and dysregulated transforming factor beta (TGF-β) in the pathophysiology of EoE [14-16]. While a normal esophageal mucosa lacks eosinophils, exposure to allergens, typically food allergens, triggers EoE [14]. Both genetic and immune factors have been implicated in the onset of EoE [15]. Moreover, the esophageal epithelium, ordinarily eosinophil-free, experiences a substantial eosinophilic infiltration in EoE, resulting in symptoms like dysphagia and food impaction [17]. The contributory factors to EoE pathophysiology encompass rare genetic syndromes, barrier disruption, defective desmosomes, dysregulated TGF-β, and allergic sensitization to a variety of foods [14,18].

Prevalence & Risk Factors: Eosinophilic esophagitis is a rapidly emerging allergy-mediated condition encountered frequently in clinical practice [19], in fact, EoE affects both children and adults [20], and it is prevalent among patients with esophageal or upper gastrointestinal symptoms [21], while the frequency of EoE occurrence is escalating [22], EoE has had increasing prevalence over time, with higher levels in later years compared to earlier years [23], where the prevalence among adult population reported to be about 6.5% [24], while other studies reported a prevalence range of 10-57 cases per 100,000 individuals [19] and a prevalence of 56.7/1,00,000 were estimated in adults in the United States [25], on the other hand, in children, the incidences vary from 0.2 – 43 /100,000 and increase in food impaction or dysphagia cases [26].

Indeed, environmental factors including the timing and nature of food and allergen exposure to the developing immune system may be an important risk factor of EoE [27], where early life risk factors, such as cesarean section and antibiotic use, have also been associated with EoE [28,29], however, EoE can occur at any age and affects both children and adults [20,30], as well as EoE is recognized to exhibit a substantial level of heritability, with most of the observed variation in phenotype thought to have a genetic basis, as evidenced by genetic epidemiology investigations involving twins and familial studies [31].

Current Treatment: Common treatments of EoE encompass dietary therapy, acid suppression, and topical glucocorticoids [32], where the initial options typically involve swallowed topical corticosteroids (STCs), proton-pump inhibitors (PPIs), or dietary interventions, moreover, esophageal dilatation is recommended for symptomatic patients with strictures [33]. However, addressing the challenge of limited efficacy in managing sub-epithelial fibrosis and remodeling with currently available medications remains a significant hurdle [32-34].

Indeed, the management of EoE is complicated by issues such as dealing with refractory cases, establishing treatment endpoints, and the constrained impact of existing medications on sub-epithelial fibrosis and remodeling [35]. Furthermore, uncertainties persist regarding the treatment objectives and the methods and frequency of patient follow-up [33,35].

Dupilumab: Dupilumab, also known by its brand name Dupixent, is a monoclonal antibody that targets the interleukin-4 receptor α subunit [36], where it has been studied widely for the treatment of moderate-to-severe atopic dermatitis in adults, asthma, nasal polyposis, and EoE, where the drug has shown promising efficacy and safety profiles in these conditions [36-39].

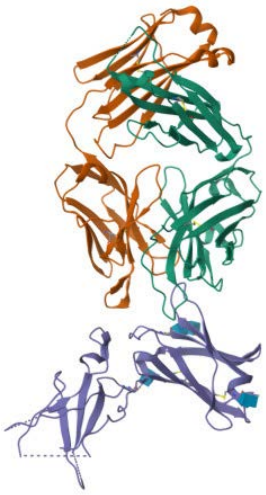

Figure 1. Dupilumab fab with Crystal Kappa design complexed with human IL-4 receptor [40]).

Mechanism of Action: Dupilumab is a humanized IgG4 monoclonal antibody that targets the interleukin-4 receptor alpha chain (IL-4Rα), common to both IL-4R complexes: type 1 (IL-4Rα/γc; IL-4 specific) and type 2 (IL-4Rα/IL-13Rα1; IL-4 and IL-13 specific) [41]. It inhibits IL-4 signaling induced by both IL-4 and IL-13, and down-regulates TH2 inflammation in a variety of allergic disorders [41]. Indeed, dupilumab has potentially multiple sites of action that remain to be fully established, where it can target fundamental mechanisms in TH2 cell inflammatory diseases by blocking TH2 cell IgE production by B cells, alternative macrophage activation, and other hallmarks of allergic inflammatory diseases. Furthermore, it can act on the vascular endothelium to potentially reduce cellular trafficking in inflamed tissues [41].

Dupilumab indications: Dupilumab has received approval for various indications [43-46], showcasing its versatility in addressing diverse medical conditions. Firstly, in Atopic Dermatitis (AD), it has been sanctioned for patients aged twelve and above with moderate-to-severe AD, where clinical studies have substantiated the efficacy of long-term systemic treatment with dupilumab, significantly ameliorating lesions based on extensive global assessments and achieving a noteworthy Eczema Area and Severity Index –75 [44]. Secondly, for severe asthma in patients aged 12 and older, where conventional treatments have proven insufficient, dupilumab is authorized. Specifically, it is intended for use in individuals with T2 inflammation of the airways, offering a targeted approach to asthma management [45]. Additionally, as an add-on therapy to

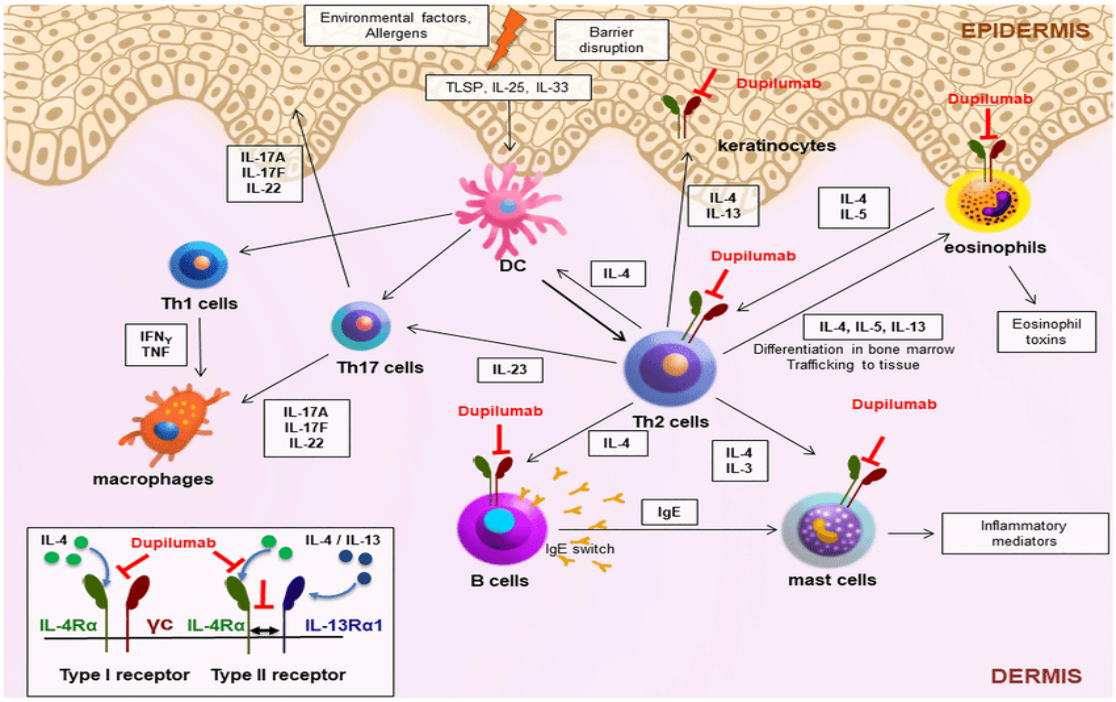

Figure 2. Mechanism of dupilumab action. Dupilumab inhibits both the binding of IL-4 to the IL-4Rα subunit shared by type I and type II receptors and dimerization of type II receptor subunits [42]).

intranasal corticosteroids, dupilumab has been recommended for adult patients with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP), especially those necessitating systemic corticosteroid treatment and/or surgery for inadequate disease control [43]. Also, in addressing Prurigo Nodularis, a chronic condition characterized by intensely itchy lesions on the extremities, dupilumab has shown efficacy in reducing these lesions, consequently alleviating the associated pruritus, as evidenced by clinical reports [46].

Dupilumab Side Effect: Dupilumab may cause mild or serious side effects, including reactions where the drug is injected, such as pain and swelling, upper respiratory infection, joint pain, and increased risk of symptoms of oral herpes or herpes zoster [47,48], as well as drug-induced alopecia has also been reported [49], also, it was found that dupilumab can lead to ocular surface disease, particularly in patients with atopic dermatitis [50].

DUPILUMAB & EOE TREATMENT

Clinical Studies and Trials: Several clinical studies and trials have investigated the use of dupilumab in adult patients with EoE, indeed, phase 2 trial investigating dupilumab's effectiveness in patients with active EoE yielded positive results, where the study revealed a decrease in esophageal eosinophil count, histologic activity, and symptomatic improvement, as well as a reduction in the peak esophageal intraepithelial eosinophil count, EoE-histologic scoring system severity score, and endoscopic reference score. Additionally, dupilumab demonstrated the capacity to enhance esophageal distensibility [11].

Moreover, in a Phase 3 trial published in the New England Journal of Medicine in 2022, a comprehensive three-part investigation established that weekly subcutaneous administration of dupilumab significantly enhanced histologic outcomes and mitigated symptoms in both adults and adolescents diagnosed with EoE [10].

Results from the clinical trials consistently indicate the efficacy of dupilumab in enhancing histologic outcomes, decreasing esophageal eosinophil count, and relieving symptoms in adult EoE patients [10,11,51]. Also, the safety profile of dupilumab remained generally favorable, with no occurrence of serious adverse events reported in the studies [11]. In terms of patient outcomes, individuals treated with dupilumab exhibited symptomatic improvement, reduced histologic activity, and enhanced esophageal distensibility compared to those receiving a placebo [10,11].

Dupilumab & EoE current treatment: The approved use of dupilumab for EoE treatment and its effective results make it a feasible and acceptable option for clinicians and patients [2,3], where an advantage of dupilumab is that it can reduce eosinophil counts in tissue by different mechanisms, including eotaxin and vascular cell adhesion molecule 1 (VCAM1) down-regulation, thus inhibiting eosinophil chemotaxis and tissue infiltration [52].

Observational studies suggest that Proton Pump Inhibitors (PPIs) are frequently employed as the initial therapeutic approach for EoE owing to their anti-inflammatory effects, cost-effectiveness, and favorable safety profile [34]. Despite reports of PPIs inducing prolonged disease remission, it is noteworthy that they lack FDA approval for EoE treatment [46]. In contrast, the approval of dupilumab, designed to address various type 2 inflammatory conditions, including EoE, has demonstrated notable treatment outcomes. These include significant improvements in histologic,

molecular, and endoscopic aspects, along with the alleviation of EoE symptoms in patients [10]. Comparative experimental studies further highlight dupilumab's efficacy, showcasing a reduction in the peak of esophageal intraepithelial eosinophil count and superior activity compared to a placebo [2].

CONCLUSION & FUTURE RESEARCH

Future research on dupilumab in EoE treatment should prioritize long-term efficacy and safety assessments, investigating potential late-onset side effects and optimizing management strategies, where comparative effectiveness studies comparing dupilumab with existing treatments will enhance our understanding of its position in the treatment landscape. Also, exploring genetic markers associated with dupilumab response can facilitate personalized treatment approaches and identify subgroups with enhanced therapeutic benefits. Additionally, in-depth investigations into the precise mechanisms of dupilumab's action in EoE, particularly its modulation of immune responses and interactions with genetic factors, are warranted for a comprehensive understanding of its therapeutic effects. Overall, a multifaceted research approach addressing these recommendations will contribute to refining the use of dupilumab in EoE treatment and advancing patient care.

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