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Dupilumab in Gastrointestinal Allergies beyond the Esophagus

Bipneet Singh[1*], Jahnavi Ethakota[1], Palak Grover[1], Sakshi Bai[1], Parneet Hari[1], Gurleen Kaur[2]

[1]Internal Medicine, Henry Ford Allegiance, Jackson, USA
[2]Internal Medicine, Government Medical College, Amritsar, India
Email: *drbipneetsingh18@gmail.com

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Abstract

Eosinophilic gastrointestinal disorders (EGIDs) are a group of chronic inflammatory conditions characterized by eosinophil infiltration into the gastrointestinal (GI) tract, which includes eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic duodenitis (EoD), eosinophilic colitis, and other forms of non-EoE EGIDs. While EoE has been well-studied, other forms of eosinophilic gastrointestinal involvement remain rare and lack diagnostic criteria, and standardized treatment options. The recent approval of Dupilumab, an IL-4 receptor antagonist, for the treatment of EoE, has spurred interest in its potential efficacy for other eosinophilic conditions with similar histological findings. This systematic review explores the emerging role of Dupilumab in the treatment of non-EoE EGIDs, including eosinophilic gastritis, duodenitis, and colitis, by analyzing available case reports, case series, and clinical trials published from 2015 onward. A total of four studies met the inclusion criteria, involving 17 patients (13 adults and 4 children) who were treated with Dupilumab. The results from these studies suggest that Dupilumab treatment led to significant clinical improvement, including a reduction in abdominal pain, dysphagia, and iron deficiency anemia, with corresponding endoscopic and histologic remission as evidenced by a decrease in tissue eosinophilia. Additionally, patients showed improved tolerance to trigger foods and reduced reliance on steroids. The duration of treatment varied, with most patients receiving 300 mg of Dupilumab either weekly or biweekly for an average of 6 - 12 months. Despite promising results, the optimal dosing regimen, long-term efficacy, and safety profile of Dupilumab in non-EoE EGIDs require further investigation through larger clinical trials. The review also highlights the potential for Dupilumab to serve as an alter-

native to steroids, particularly for patients with steroid-resistant or dependent forms of EGID. In conclusion, Dupilumab offers a promising new therapeutic option for patients with eosinophilic gastrointestinal disorders, but further studies are essential to better define its role in the treatment of these rare and complex diseases.

Keywords

Dupilumab, Eosinophilic Gastritis, Eosinophilic Duodenitis, Eosinophilic Colitis, IL-4 Receptor Antibody

1. Introduction

Eosinophilic esophagitis (EoE) is a better-known and studied disorder among eosinophilic gastrointestinal disorders (EGID). By comparison, Non-Eosinophilic esophagitis EGID (Non-EoE-EGID) gastritis (EoG), duodenitis (EoD), jejunitis (EoJ), ileitis (EoN), and colitis (EoC) are rare and lack clear pathophysiology and treatment options [1].

These are chronic inflammatory diseases in which eosinophils infiltrate the digestive tract [1]. Pathogenesis is similar to EoE, with Th2-mediated eosinophil infiltration in response to allergen exposure, mostly food. Eosinophilia in the lamina propria releases interleukins, leukotrienes and other cytokines responsible for tissue damage producing endoscopically seen erythema, erosions and ulcers.

Currently, the focus is on steroid use and allergen limitation. Food is the most obvious trigger and identifying food antigens is crucial and can provide some relief. Given a chronic course with symptoms including nausea, abdominal pain, and diarrhea leading to malnutrition [2], early induction and long-term maintenance of remission are important for developmental prognosis, particularly in pediatric patients. 25% to 54% of the patients with non-EoE-EGIDs have atopic diseases [3]. The limitation of the current treatment regimen is difficulty with food control and increasing steroid dependence.

Dupilumab is an IL-4 targeting antibody. IL-4 plays a major role in Th2-mediated response, hence theoretically halting the chain of events. With the recent approval of Dupilumab in EoE treatment, diseases with similar pathophysiology have a potential to benefit from the same agent [4] [5]. Currently, data regarding this is limited. Therefore, in our systematic review, we aim to learn the efficiency of dupilumab in patients with non-EoE-EGID.

Unlike the rest of non-EoE EGID with allergic etiopathogenesis, associations with atopic diseases, and elevated IgE levels [6] [7], eosinophilic colitis, has been known to have a different basis making the use of dupilumab in this particular condition questionable.

Other treatments, including mast cell inhibitors, IgE antibodies, and IL-5 inhibitors, have been explored without clear relief [7].

2. Methods

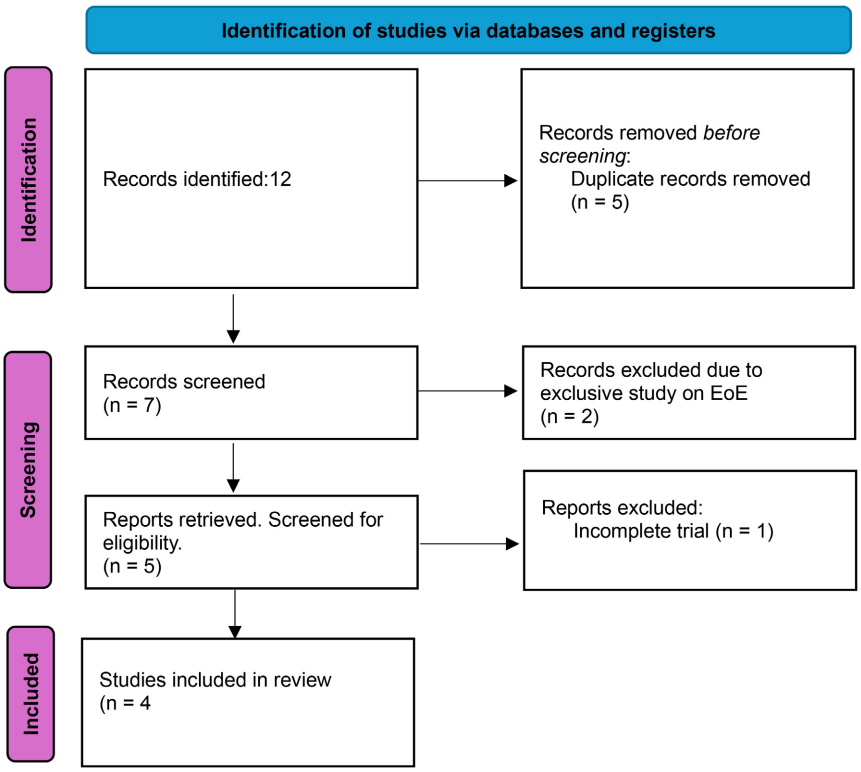

Figure 1. Prisma diagram for the systematic review.

2.1. Eligibility Criteria

The inclusion criteria for the studies were studies published in English, a diagnosis of eosinophilic gastrointestinal conditions, and treatment with Dupilumab.

Exclusion criteria were non-English publications; studies involving eosinophilic esophagitis; studies published before 2015; and studies that are not relevant to the research question.

2.2. Search Strategy and Study Selection

From 2015 to the present, a search of peer-reviewed papers was carried out in the following electronic databases: PUBMED, Google Scholar, and Cochrane Library. A review was done to look for case reports, case series, systematic reviews, meta-analyses, and randomized control trials with the terms eosinophilic esophagitis AND/OR eosinophilic gastritis, AND/OR eosinophilic jejunitis, AND/OR eosinophilic ileitis, AND/OR eosinophilic colitis, AND Dupilumab. Reviewers independently went through 12 results. 5 were duplicates and were removed.

The rest of the seven files were retrieved. Two studies focused only on eosinophilic esophagitis and were removed. One article was a randomized controlled trial that was still underway and was also removed. The remaining four articles included two case reports and two case series, which were included in the review. **Figure 1** depicts the Prisma diagram of the same.

2.3. Outcome

The primary outcomes of interest were clinical improvement, endoscopic change reversal and histological remission.

Thresholds for histologic diagnosis have been proposed at 30 eos/hpf, 40 - 50 eos/hpf, 100 eos/hpf, 85 eos/hpf, 65 eos/hpf in the stomach, duodenum and ascending descending colon, and the sigmoid colon [5]. For remission, a significant decline in eosinophils corresponding to endoscopic healing and symptom improvement can be used.

For endoscopic remission, improvement in ulcers, erosions and erythema on subsequent endoscopy was used. The time frame for repeat endoscopy was vastly different, so improvement in any subsequent endoscopy was agreed upon.

Clinical improvement focused on improvement in food tolerability and abdominal pain.

2.4. Data Extraction and Risk of Bias Assessment

Two independent authors removed duplicates, extracted data, evaluated the entire texts, checked the titles and abstracts, and determined the bias risk. The reviewers resolved their points of conflict to an agreed point. ROBINS-I tool was used to assess the risk of bias, as mentioned in the plot in **Figure 2**.

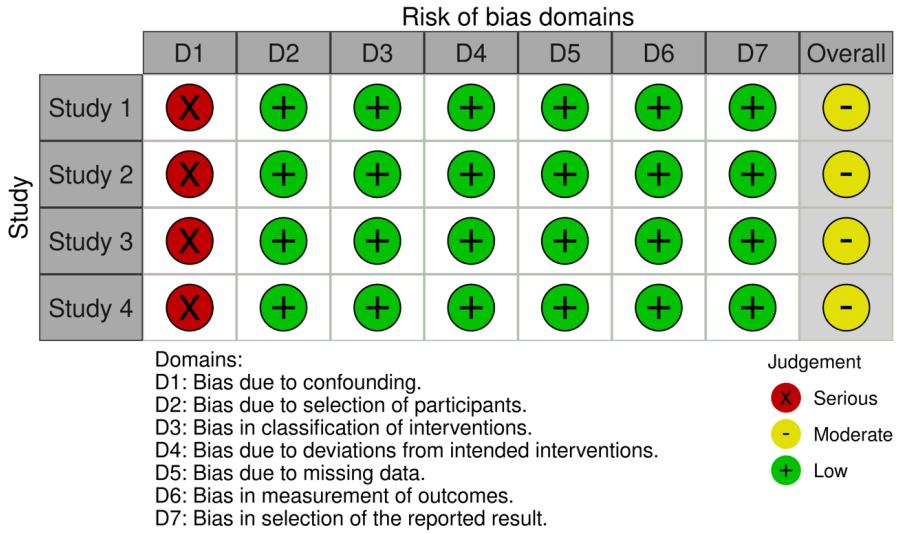

Figure 2. ROBINS-I RoB diagram.

2.5. Limitations

The absence of higher-quality studies, such as randomized controlled trials or prospective cohort studies, limits an analysis of the outcomes. The absence of a control group to look for statistically significant outcomes limits this study to comment on the null hypothesis and comment on the efficiency of Dupilumab in the population. The limitations posed by relying primarily on case reports and case series further include a lack of randomization, low power, and vastly different demographics limiting generalizability.

3. Results

The names of the respective articles and the organ system involvement are shown in Table 1**.** All four studies have gastroduodenal involvement, counting for higher incidence amongst non-EoE-EGID. Relative incidence of lower gastrointestinal involvement till ileum is rare, however it might be clouded by lack of endoscopic approach.

Table 1. Included studies.

Name	Type	Organ involvement
Dupilumab Can Induce Remission of Eosinophilic Gastritis and Duodenitis [8]	Case series (CS)	Gastritis and duodenitis
A Case Series on the Use of Dupilumab for Treatment of Refractory Eosinophilic Gastrointestinal [9]	CS	Gastritis, duodenitis, ileitis, colitis
Successful use of dupilumab for egg-induced eosinophilic gastroenteritis with duodenal ulcer: a pediatric case report and review of literature [10]	Case report (CR)	Gastroenteritis
Effective use of dupilumab for eosinophilic gastritis concomitant with severe asthma [11]	CR	Gastritis

There was a total of 17 cases with 13 in the adult age range and four in the pediatric range. The average age for adults was 37 years and 11.5 years for children. There were 12 men and five women. All of the patients were treated with dupilumab (Table 2).

Table 2. Demographics.

Number	Male%	Mean age
(8 for subgroup analysis)	60% (75%)	37 years (35 years)
3	100%	10 years
1	100%	13 years
1	100%	35 years

With regards to the first study, patients presented with nonspecific symptoms, as in Table 3, dupilumab was started at 300 mg weekly with symptom improvement or at least no worsening in all the patients during the 9-month treatment for EoG and 12 months for EoD. EGD done pre- and post-treatment showed significant improvement in tissue eosinophilia, with one of the patients having macroscopic improvement in the preexisting ulcer.

In the second study, the first patient had recurrent gastric ulcers leading to iron deficiency anemia. The patient had minimal responses to steroids and dietary restrictions. However, Dupilumab led to improvement in abdominal pain and iron deficiency anemia with endoscopic and histologic improvements (Table 3 and Table 4). The second patient with further jejunal involvement had symptomatic anemia despite treatment with corticosteroids. However, dupilumab induced endo-

scopic, histologic and symptomatic remission. The third patient with dysphagia due to duodenitis, steroid-responsive, was started on Dupilumab due to side effects and had better improvement on the latter.

Table 3. Symptoms, doses and duration of treatment till treatment improvement.

Symptoms	Dose	Duration of treatment
1. Dysphagia (4 patients), abdominal pain (4 patients), bloating (2 patients), diarrhea (3 patients), constipation (2 patients), nausea/vomiting (4 patients), and heartburn (5 patients)	300 mg of dupilumab every week	Dupilumab treatment course was a median of 36.9 weeks (9 months) for patients with EoG 48.7 weeks (12 months) for patients with EoD
1. Patient 1—Abdominal pain and recurrent GI bleeding from a refractory duodenal ulcer 2. Patient 2—Iron deficiency anemia 3. Patient 3—Dysphagia	1. 200 mg every 2 weeks. 2. 300 mg every 14 days 3. 300 mg every 14 days	Not specified
Abdominal pain	600 mg initially and 300 mg every 2 weeks thereafter.	Not specified
Abdominal pain	Not specified	Not specified

The last two cases had presentations of abdominal pain with gastric and duodenal involvement, both improving on dupilumab with symptom resolution and endoscopic remission.

Table 4. Treatment outcomes.

	Time to repeat EGD while on treatment	Pre-treatment eosinophils/high power field (EoE/hpf)	Post treatment (EoE/hpf)	EGD macroscopic improved
Study 1				
	6 - 7 months	EoG - 80.5 eos/hpf EoD - 38 eos/hpf	EoG - 7.5 eos/hpf EoD - 16.5 eos/hpf	1 patient had a 30-mm gastric ulcer which decreased in size to 10 mm in diameter.
Study 2				
Patient 1	6 weeks	EoG - 150 eos/hpf EoD - 90 eos/hpf	EoG - 15 eos/hpf EoD - 33 eos/hpf	Endoscopy also revealed resolution of his duodenal ulcer
Patient 2	6 months	EoG - 76, EoD - 67, and EoJ - 80 eos/hpf	EoG - 11, EoD - 10, and EoJ - 68 eos/hpf	Resolution of jejunal lesions
Patient 3	Not known	EoD - 150 eos/hpf	EoD - 8 eos/hpf	
Study 3	5 months	EoD - 96 eos/hpf	EoD – 22 eos/hpf	disappearance of the duodenal ulcer
Study 4	43 months	EoG - 96 eos/hpf	EoG - 22 eos/hpf	no signs of gastritis

4. Discussion

The incidence of eosinophilic gastrointestinal disorders is increasing due to in-

creasing awareness despite the lack of diagnostic criteria and the risk of misdiagnosis [12]. It occurs at any age with peak onset between the thirties and fifties with higher female gender and Asian ethnicity predominance possibly linking it to H. pylori infections. Four genes PRDX2, NR3C1, TXN, and AP2B1, are potential biomarkers. Bacterial infections and poor hygiene status may contribute, with individuals who are not exposed during childhood may maintain the ability to mount T-helper type 2 (Th2)-dominant immune responses even in adulthood and, therefore, be at a greater risk of developing various types of allergies.

Eosinophil infiltration that populates in the lamina propria in the stomach and bowel which normally increases in numbers toward the distal segments of the gastrointestinal tract is a key histopathological characteristic of EGE. Many cytokines and chemokines, including interleukin-3 (IL-3), IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been shown to mediate this Th2-mediated immune process. A newer model to explain the relation between peripheral blood and tissue eosinophilia, includes a balance between the eotaxin-1 level and the IL-5 level, where they accumulate in blood when the IL-5 level is higher than the eotaxin-1 level and vice versa.

Upon recruitment, eosinophils release four major cationic proteins, other mediators, such as leukotrienes, and interleukins which enhance inflammatory responses. Some patients displayed non-atopic-like responses, instead of Th2 responses to food, implying the existence of another T-cell-independent pathogenesis. IL-4 plays a dominant role in the differentiation of Th2 cells, whereas IL-4 and IL-13 are essential for immunoglobulin E (IgE) class switching and expression. IL-13 can upregulate eotaxin-3 thereby potentiating allergic inflammation.

Per current literature, EoG includes redness and congestion often progressing to erosions, ulcers, and rarely strictures. Patients with enteritis and colitis have demonstrated flattened villi, as well as similar erosions, ulcers, ulceration, nodules, and strictures. Normal values have been estimated as follows: stomach (5 - 10 eosinophils/high-power field [eos/hpf], duodenum (10 - 25 eos/hpf), and terminal ileum and cecum (likely > 50 eos/hpf), with a decreasing number in the distal colon [11]. Thresholds for diagnosis have been proposed at 30 eos/hpf, 40 - 50 eos/hpf, 100 eos/hpf, 85 eos/hpf, 65 eos/hpf in the stomach, duodenum and ascending descending colon, and the sigmoid colon [5].

In these cases, no particular guidelines were used to diagnose the disease or clarify remission. Loosely, abdominal symptoms with eosinophilia in lamina propria, coexisting atopic conditions including but not limited to asthma, eczema, and EoE, with no alternate explanation for infiltration, with or without elevated serum IgE or eosinophils were used to define non-EoE EGID. For remission, a significant decline in eosinophils corresponding to endoscopic healing and symptom improvement can be used.

Dupilumab is a human monoclonal G4 subclass antibody designed to inhibit downstream of the JAK-STAT pathway by blocking interleukin-4. As an IL-4R antagonist, it inhibits pro-inflammatory cytokines, or interleukins, that induce responses in eczema, asthma, allergic reactions, and rhinosinusitis.

Dupilumab is currently approved for atopic dermatitis, eczema, and EoE. Per the above criteria, the patients showed clinical improvement. Limitations include unclear ideal dosages with varying dosages from 300 mg weekly to two weekly, total duration of treatment for symptom relief, endoscopic changes, and histological decline in eos/hpf. Clinical studies for the use of Dupilumab are limited. These cases indicate symptomatic improvement and corresponding endoscopic healing as well. On average, 300 mg every other week was used, and the average time to endoscopy was 6 months. The most common presenting symptom that shows improvement was abdominal pain followed by tolerance to trigger foods and then iron deficiency anemia.

Currently, Dupilumab is in phase 3 trial for use in non-EoE EGID. Other biologics include Mepolizumab, an IL-5 antibody, which has been efficacious in case reports. Further, Benralizumab another IL-5 alpha antagonist is in phase 3 trials for non-EoE EGID. Omalizumab has not been seen to be efficacious in previous studies.

Eosinophilic disorders not included in the review are eosinophilic pancreatitis and hepatitis, which are extremely rare and might not share the same pathophysiology, given that no direct contact with food-borne antigens is present Eosinophilic pancreatitis is characterized by elevated immunoglobulin E (IgE) levels, hypereosinophilia, and eosinophilic infiltrates in other organs [13]. It is a rare disorder, with only 16 case reports in 40 years [13]. Hepatitis with eosinophils is further rare and a part of Idiopathic hypereosinophilic syndrome [14]. Eosinophilic cholangitis (EC) is a further rare causing dense eosinophilic infiltration causing fibrosis, structuring, and obstruction causing eosinophilic cholecystitis and eosinophilic cholangitis [15]. Dupilumab has not been studied in these populations.

5. Conclusions

Dupilumab shows efficacy in improving both endoscopic and histologic findings in patients with eosinophilic gastrointestinal disorders (non-EoE-EGID), including eosinophilic gastritis, duodenitis, and other forms of eosinophilic enteritis.

The treatment leads to a significant reduction in eosinophil counts and noticeable endoscopic healing. The current data is limited, and more extensive clinical trials are needed.

Declarations

All authors have read and agreed to the published version of the manuscript.

This article is a revised and expanded version of a poster presentation entitled Dupilumab and Non-EOE GI Disorders, which was presented at the American College of Gastroenterology conference in Philadelphia on October 28, 2024 [12].

Conflicts of Interest

The authors declare no conflicts of interest.

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