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A Case Series of Rapid Resolution of Pediatric Eosinophilic Esophagitis with Dupilumab Treatment as Demonstrated by Sedation-Free Transnasal Esophagoscopy (TN-Eso)

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Abstract

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus. Dupilumab, a treatment for EoE, requires an initial endoscopic evaluation no sooner than 12 weeks after initiation. As it is costly and pediatric patients often experience fear and pain associated with the injection, this could lead to non-adherence or premature cessation of therapy. Here, we report a case series, as part of a larger ongoing study, in which subjects demonstrated an earlier response to dupilumab.

Three male subjects and one female subject, aged 13–21 years, with EoE started dupilumab therapy. Clinical symptoms resolved in all patients within two weeks. Each underwent a sedation-free transnasal esophagoscopy at 3–4 weeks and 6–8 weeks. All subjects tolerated the procedures without significant adverse events. Esophageal biopsies demonstrated persistent mucosal healing at both time points. These data suggest that dupilumab may achieve a therapeutic response sooner than previously thought. Further research is needed.

Keywords: Dupilumab, Eosinophilic esophagitis, Transnasal endoscopy

Abbreviations: EoE: Eosinophilic Esophagitis; TN-Eso: Transnasal Esophagoscopy; TNE: Transnasal Endoscopy; EGD: Esophagogastroduodenoscopy; QoL: Quality of Life; FDA: Food and Drug Administration; IL: Interleukin; VR: Virtual Reality; TEF: Tracheoesophageal Fistula; HIV: Human Immunodeficiency Virus; H&E: Hematoxylin and Eosin; Eos/HPF: Eosinophils per High Powered Field

What is Known

- Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus mediated by type 2 immunity and associated with other atopic conditions.
- Dupilumab is an effective subcutaneous treatment for EoE in both children and adults. The most common complaint is pain and fear associated with the injection.
- Efficacy is typically assessed at least 12 weeks after starting therapy.

What is New

- Dupilumab achieved tissue healing of eosinophilia, as demonstrated by mucosal biopsies, as well as symptom resolution in EoE within 3–4 weeks of treatment initiation, with effects persisting at 6–8 weeks.
- Sedation-free transnasal esophagoscopy with biopsies was well-tolerated, effective, and without significant adverse events when used in a research setting to evaluate the mucosal response to dupilumab therapy in EoE.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus mediated by type 2 immunity and is associated with other atopic conditions triggered in most patients by dietary allergens and treated by a variety of modalities [1,2]. It affects both children and adults with a bimodal appearance and an onset of symptoms between 5-10 years of age in children and 20-30 years in adults [1]. Diagnosing EoE requires a clinicopathological diagnosis and the presence of both clinical symptoms and abnormal tissue eosinophilia as noted by [3], 15 eosinophils per high power field (HPF) in the esophageal mucosa [1-3]. Guidelines recommend that initial diagnosis and subsequent monitoring of disease activity occurs via repeated esophagoscopy or esophagogastroduodenoscopy (EGD) with mucosal pinch biopsies under sedation or general anesthesia at no sooner than 6 weeks after initiating therapies [1,3-5]. The presence of EoE and the therapy and monitoring which follow have been reported to also have a negative impact on many patients' quality of life (QoL) [6,7].

Therapies for EoE are diverse and include a recently approved treatment by the Food and Drug Administration (FDA) known as dupilumab for patients who are 1 year of age and older and over 15 kg [8,9]. It is a monoclonal antibody that targets the Interleukin (IL)-4Ra chain which then suppresses IL-4 and IL-13 signaling, hence inducing mucosal healing and decreasing inflammation of the esophagus [10]. Clinical trials in adults and in children with EoE demonstrated great efficacy in controlling symptoms and esophageal tissue inflammation [8,9]. Esophageal eosinophilia during those trials and during clinical therapy was similarly assessed by obtaining mucosal biopsies obtained during sedated oral upper endoscopy. The injection-based therapy of dupilumab itself is generally well tolerated, but pain/discomfort at the injection site is the most common complaint from patients [8,9]. This complaint seems to be more exaggerated in the pediatric population due to the age of the cohort and their ongoing need for injection-based therapy. Based on current clinical guidelines, patients are recommended to receive the injection-based therapy either weekly or biweekly for at least 12 weeks until the first post-treatment endoscopy to assess the efficacy of the treatment [3,8,9]. Due to the repetitive nature of injections that lack a known efficacy of response, and the knowledge that a repeat endoscopy requires anesthesia and an intravenous catheter placement, additional emotional and financial stress can be placed on pediatric patients and their families.

Sedation-free transnasal esophagoscopy (TN-Eso) with virtual reality (VR) distraction and dissociation has been reported as a novel endoscopic technique that does not require general anesthesia or any sedation [3,5,11-16]. The newly released 2025 ACG guideline recommends it as the preferred pediatric form of endoscopy to monitor EoE activity [3]. It has been adopted across the United States and has been shown to be safe and well-tolerated in children and adults [3,17]. It enables pediatric and/or adult gastroenterologists to monitor EoE disease activity without the risks, costs, fear, or time associated with sedation or general anesthesia. Due to this change in care paradigm, TN-Eso also offers the opportunity to systemically study the kinetics of tissue eosinophilia in EoE when initiating dupilumab treatment or other treatments [4]. A study recently showed this concept and further studies reconfirmed that the technique demonstrates adequate tissue biopsy specimens, further confirming the adequacy of the technique in a clinical setting [4,13,18].

Massachusetts General Hospital initiated a study to evaluate therapeutic kinetics and molecular changes in EoE by using the TN-Eso approach and utilized the newly released, FDA cleared for pediatrics, EvoEndo Model LE ultra-slim gastroscope (EvoEndo, Inc, Centennial, Colorado) to perform the procedure in EoE subjects who started various therapies. As part of this study, we are reporting early case-series data prior to completion of the entire study to benefit the larger clinical population. We hereby share the first ever report of early response to dupilumab in the literature, which may provide beneficial kinetic and therapeutic response information to clinicians as they are considering treatment plans for their patients.

Methods

Subjects, aged 8-40 years, with active recently confirmed EoE by previous conventional oral, sedated EGD, within 3 months of the enrollment, were eligible and recruited for the study. Exclusion criteria included subjects <30 kg or with any of the following medical conditions: planned treatment with proton pump inhibitor (PPI); hyper eosinophilic disorder, eosinophilic gastrointestinal disorder other than EoE, eosinophilic granulomatosis with polyangiitis vasculitis, Inflammatory Bowel Disease (IBD), celiac disease, tracheoesophageal fistula (TEF), anatomical GI obstructions, infections including human immunodeficiency virus (HIV), Hepatitis B and C and other bacterial and parasitic infections, previous major nose surgical procedures, history of choanal atresia, serious cardio-pulmonary disorders, severe and poorly managed major anxiety disorder or panic disorder, females who are pregnant, and suspicion for drug abuse or alcohol abuse within the past 6 months. This study was approved by the MassGeneral Brigham (MGB) Institutional Review Board (#2023P002300). Written informed consent was obtained from all participating subjects and their parent (for subjects <18 years) as required by the study protocol. Subjects underwent a sedation-free TN-Eso at 3-4 weeks and 6-8 weeks after initiating therapy for EoE. TN-Eso utilizing topical analgesia with 4% lidocaine was performed as previously described utilizing the EvoEndo Model LE 110 cm gastroscope (Centennial, CO) [5,11,14,16]. All endoscopies and biopsies were performed by an expert

endoscopist new to sedation-free TN-Eso. Mucosal biopsies were obtained from the distal, mid, and proximal esophagus using a pediatric gastrointestinal forceps device (Boston Scientific, Boston, MA). They were subsequently evaluated by a board-certified pathologist using hematoxylin and eosin (H&E) staining. Histologic findings were reported, including the presence of lamina propria (LP) and eosinophils per high powered field (eos/HPF). Symptoms associated with EoE were queried via survey, and visual findings and tolerance of the procedure were also recorded as TNEase Score by the endoscopist [12]. Adverse events were collected. Specific to this early case-series all patients reported were initiated on dupilumab therapy.

Results

Four consecutive subjects aged 13-21 years, with endoscopically confirmed, active EoE were started on dupilumab 300 mg weekly subcutaneous injection and underwent TN-Eso at week 3–4 and 6–8 from start of therapy initiation **(Figure 1)**. Three subjects were male, and one subject was female. All four subjects reported clinical symptom improvement after 2 weeks of therapy, and complete resolution of symptoms after 3–4 weeks of treatment. TN-Eso was well tolerated by 4/4 subjects with TNEase Score and scored as 1-2 by all subjects. No significant adverse events occurred [16]. The pathologic review of biopsies found <5 eos/HPF in all four patients with the first TNE at 3–4 weeks and a persistent response confirmed with the second TNE at 6–8 weeks post initiating dupilumab treatment **(Table 1)**. Additionally, LP was identified in 3/4 subjects during baseline oral sedated endoscopy, 0/4 at TNE #1, and in 3/4 at TNE #2. Subject 1 who did not have LP identified during baseline EGD biopsy was noted to have LP without fibrosis in TNE #2. Subject 2 who had no LP fibrosis at baseline endoscopy, did not have identifiable LP at any subsequent TNE. Of the remaining subjects, subject 3 had no LP fibrosis at baseline endoscopy but had LP fibrosis at TNE #2. Subject 4 had LP fibrosis identified at baseline endoscopy and at TNE #2.

Discussion

EoE is a chronic, life-long disease managed by a variety of therapies to heal esophageal inflammation and potentially prevent long term complications such as fibrosis [1]. Therapies can include dietary elimination, swallowed steroids, elemental diet, and most recently, biologic therapies [1,2,7,8]. Recently a monoclonal antibody-based therapy known as dupilumab was released and clinical trials, guidelines, and clinical recommendations suggested dosing and follow-up evaluation to confirm response at 12 weeks after initiation [3,8,19]. During an ongoing study evaluating kinetics of EoE therapies and molecular, mucosal changes in EoE, our novel finding suggesting earlier clinical response to dupilumab occurred. We felt it imperative to hence report the first series of cases demonstrating rapid resolution of clinical symptoms and tissue eosinophilia of EoE within 3–4 weeks and maintained at 6–8 weeks after starting dupilumab therapy. In the case series that findings are extrapolated, and the study results are repeatable at a larger scale, this could improve the QoL of patients or improve the therapeutic planning for clinicians. QoL in pediatric patients could be improved by assuring that injection-based therapy is only given with appropriate clinical response and additionally avoids the fear associated with an injection-based therapy if not needed. Improved therapeutic planning may occur when associated with earlier knowledge of medication response and could also allow for lower costs of care. This is possible by having the earlier knowledge of

Figure 1. A schematic diagram of the procedures during study. (TNE: Transnasal Endoscopy; EGD: Esophagogastroduodenoscopy).

Table 1. Rapid Histological Resolution With Dupilumab Treatment for EoE.

Age (years)	Sex	Baseline Eosinophil Count (Eos/HPF)			TNE 1 Eosinophil Count (Eos/HPF)			TNE 2 Eosinophil Count (Eos/HPF)		
		D	M	P	D	M	P	D	M	P
14	M	>40	>40	>40	0	0	0	5	0	3
13	M	>40	8	10	0	4	0	3	3	0
18	M	33	14	9	0	0	0	<3	0	0
21	F	>40	35	30	4	4	0	0	5	0

D: Distal Esophagus; M: Mid Esophagus; P: Proximal Esophagus; Eos/HPF: Eosinophils/High Power Field; TNE: Transnasal Endoscopy

lack of medication response at 3–4 or 6–8 weeks as compared to previous clinical trial recommended 12 weeks and allows the provider to avoid a longer course of treatment when it is ineffective.

Additionally, findings in this case series around the use of TN-Eso also demonstrated the potential that sedation-free technology with a newly released ultra-slim endoscopic device had in clinical and research-based care. It showed the opportunity for safer, quicker, and earlier evaluation of response to therapies. This occurred by eliminating the higher cost of administering anesthesia, decreasing the risk of anesthesia, decreasing research costs, and improving throughput and efficiency of endoscopy [4,14]. In all patients, similar to previous research using bronchoscopes for a TN-Eso trial by Friedlander *et al.*, TN-Eso was well tolerated [4]. As in the previous study and in this one, all subjects underwent the second TN-Eso and the biopsies were all adequate for evaluation including similar acquisition rates of LP discovered on histology [4,12]. Also, no significant adverse events during serial TN-Eso occurred. The difference in this case series is that a physician new to the sedation-free TN-Eso was utilized, and he used a new FDA-cleared device specific for this procedure. This is all new and novel data presented here.

The weaknesses of this study are that it represents a small cohort of subjects, and TNEs were performed by a newly trained sedation-free endoscopist. It is possible that earlier responses to dupilumab seen in these four subjects may not continue to be seen with a larger cohort. Further research is needed to evaluate further and is planned in the larger forthcoming study. The results are reported early here because of its potential clinical impact. Skewed data could have also been introduced due to the procedure being performed by a newly trained sedation-free endoscopist. This, however, is unlikely to be significant, as other studies have shown similar rates of adequate tissue acquisition and similar TNEase scores [12,16].

Conclusion

In conclusion, this study demonstrated that evaluation of the esophagus with sedation-free TN-Eso, done by a newly-trained sedation-free endoscopist performing the TN-Eso with a newly released endoscopic device, showed an earlier response to dupilumab for the first time. This TN-Eso was well tolerated for serial evaluation of response to therapies in EoE, and biopsy specimens in TN-Eso were adequate for evaluation. Further research is needed and is planned.

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Conflict of Interest Statement

Joel Friedlander DO, MA-Bioethics is Chief Medical and Innovation Officer of EvoEndo, Inc. He is an employee, board member, stockholder, and is listed as co-inventor on several patents related to endoscopic technology, methods, and virtual reality technology.

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