ORIGINAL ARTICLE

Eosinophil Depletion with Benralizumab for Eosinophilic Esophagitis

Marc E. Rothenberg, M.D., Ph.D., Evan S. Dellon, M.D., M.P.H., Margaret H. Collins, M.D., Albert J. Bredenoord, M.D., Ph.D., Ikuo Hirano, M.D., Kathryn A. Peterson, M.D., Laura Brooks, M.Sc., Julie M. Caldwell, Ph.D., Harald Fjällbrant, M.D., Ph.D., Hanna Grindebacke, Ph.D., Calvin N. Ho, Ph.D., Matthew Keith, M.S., Christopher McCrae, Ph.D., Dominic Sinibaldi, Ph.D., Wendy I. White, Ph.D., and Catherine J. Datto, M.D., for the MESSINA Trial Investigators*

ABSTRACT

BACKGROUND

Benralizumab is an eosinophil-depleting anti–interleukin-5 receptor α monoclonal antibody. The efficacy and safety of benralizumab in patients with eosinophilic esophagitis are unclear.

METHODS

In a phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned patients 12 to 65 years of age with symptomatic and histologically active eosinophilic esophagitis in a 1:1 ratio to receive subcutaneous benralizumab (30 mg) or placebo every 4 weeks. The two primary efficacy end points were histologic response (≤6 eosinophils per high-power field) and the change from baseline in the score on the Dysphagia Symptom Questionnaire (DSQ; range, 0 to 84, with higher scores indicating more frequent or severe dysphagia) at week 24.

RESULTS

A total of 211 patients underwent randomization: 104 were assigned to receive benralizumab, and 107 were assigned to receive placebo. At week 24, more patients had a histologic response with benralizumab than with placebo (87.4% vs. 6.5%; difference, 80.8 percentage points; 95% confidence interval [CI], 72.9 to 88.8; P<0.001). However, the change from baseline in the DSQ score did not differ significantly between the two groups (difference in least-squares means, 3.0 points; 95% CI, −1.4 to 7.4; P=0.18). There was no substantial between-group difference in the change from baseline in the Eosinophilic Esophagitis Endoscopic Reference Score, which reflects endoscopic abnormalities. Adverse events were reported in 64.1% of the patients in the benralizumab group and in 61.7% of those in the placebo group. No patients discontinued the trial because of adverse events.

CONCLUSIONS

In this trial involving patients 12 to 65 years of age with eosinophilic esophagitis, a histologic response (≤6 eosinophils per high-power field) occurred in significantly more patients in the benralizumab group than in the placebo group. However, treatment with benralizumab did not result in fewer or less severe dysphagia symptoms than placebo. (Funded by AstraZeneca; MESSINA ClinicalTrials.gov number, NCT04543409.)

The authors' affiliations are listed in the Appendix. Dr. Rothenberg can be contacted at marc.rothenberg@cchmc.org or at Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 7028, Cincinnati, OH 45229-2029.

*A list of the MESSINA trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Rothenberg and Dellon contributed equally to this article.

N Engl J Med 2024;390:2252-63.
DOI: 10.1056/NEJMoa2313318

Eosinophilic esophagitis is a chronic disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation,[1,2] which may progress to fibrostenotic disease.[3] Older children and adults present with solid-food dysphagia and food impaction,[3] substantially affecting mental health and health-related quality of life.[1-5] Eosinophils are proinflammatory cells that are not present in the healthy esophagus, yet they markedly accumulate and degranulate in the esophagus of patients with eosinophilic esophagitis.[6] Therefore, it has been hypothesized that eosinophils are a key pathogenic cellular driver of eosinophilic esophagitis.[1,7]

Current treatments for eosinophilic esophagitis include dietary elimination therapy and medications such as proton-pump inhibitors (PPIs), swallowed topical glucocorticoids, and monoclonal antibodies.[1,7-9] PPIs are used off-label, and only some patients have a histologic response.[7-9] Swallowed topical glucocorticoids have shown limited efficacy and are often used off-label, although formulations have been approved in the past several years.[7,8] Biologic agents that target inflammatory mediators, such as type 2 cytokines, are currently being investigated for eosinophilic esophagitis,[9] and dupilumab has been approved in several countries for this indication.[10] However, responsiveness to dupilumab is not universal, and symptom reduction is seen only with weekly doses, despite an equal reduction in eosinophil counts with weekly administration and administration every 2 weeks.[10] Overall, although some therapies for eosinophilic esophagitis exist, a substantial need for additional treatment options remains.

Benralizumab is an anti–interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and near-complete eosinophil depletion through antibody-dependent cell-mediated cytotoxicity.[11] It is approved as an add-on maintenance therapy for patients 12 years of age or older with severe eosinophilic asthma.[12] In previous studies, benralizumab treatment resulted in near-complete eosinophil depletion in the blood, bone marrow, and lung, stomach, and esophageal tissues,[13-16] findings that make benralizumab an attractive potential therapy for eosinophilic esophagitis. The current phase 3 trial (MESSINA) investigated the efficacy and safety of benralizumab in patients with eosinophilic esophagitis.

Methods

Trial Design and Oversight

We conducted a phase 3, multicenter, double-blind, randomized, placebo-controlled trial involving adults and adolescents with symptomatic and histologically active eosinophilic esophagitis. The trial consisted of four periods (Fig. 1A): a 2-to-8-week run-in period, a 24-week double-blind treatment period, a 28-week open-label benralizumab treatment period, and an optional open-label extension treatment period. Patients at select sites were offered participation in two additional substudies (see the Supplementary Appendix, available with the full text of this article at NEJM.org): an early-time-point substudy (with additional assessments at weeks 4 and 12) and an Endoluminal Functional Lumen Imaging Probe (EndoFLIP)[17] substudy.

A Quick Take is available at NEJM.org

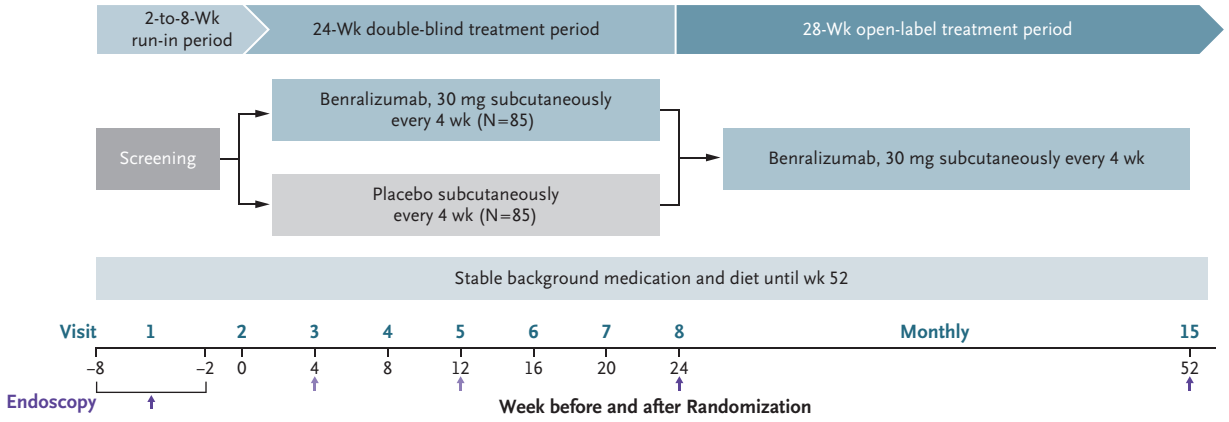
From September 22, 2020, to October 25, 2022, the MESSINA trial was conducted in 78 sites across 12 countries. Independent ethics committees at the trial centers or central institutional review boards approved the trial protocol, available at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation; all the patients provided written informed consent.

The trial sponsor (AstraZeneca) and the academic investigators designed the trial. Data were collected by clinical investigators and analyzed by employees of the sponsor. All the authors had access to the data included in the clinical trial report and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the investigators had confidentiality agreements with the sponsor.

Patients

Eligible patients were 12 to 65 years of age, with eosinophilic esophagitis diagnosed according to consensus guidelines[1,8,9]; at screening endoscopy, patients had at least 15 eosinophils per high-power field in centrally read biopsy samples obtained at two or more esophageal levels. Other medications for eosinophilic esophagitis were permitted, provided the patient had been receiving a stable dose of the medication for at least 4 weeks before the run-in period (≥8 weeks for PPIs) and met histologic and symptomatic inclusion criteria.

A Trial Design



B Patient Disposition

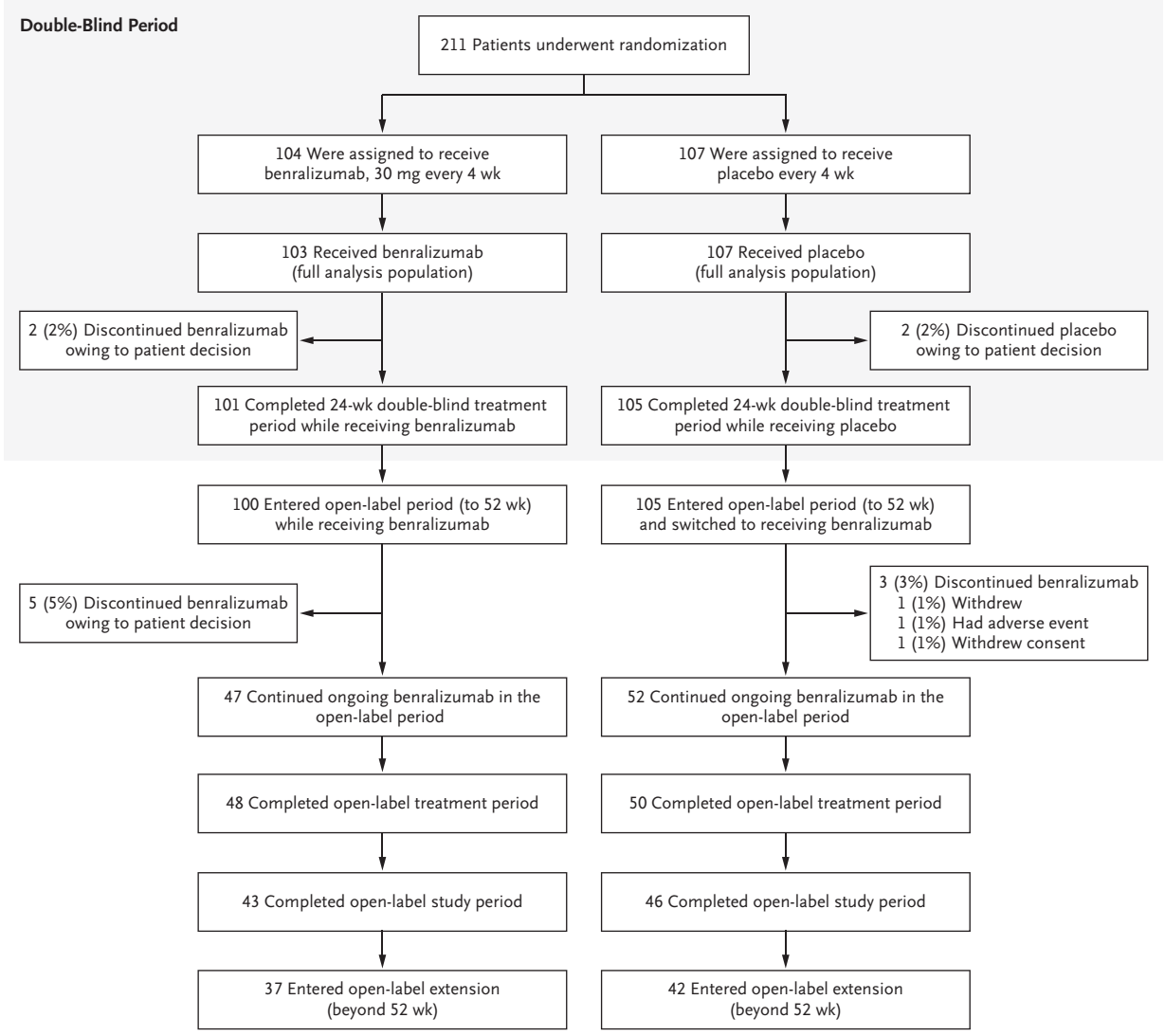


Figure 1 (facing page). Trial Design and Patient Disposition.

The trial was designed to enroll approximately 170 patients (Panel A). All the patients underwent endoscopy at week –8 to week –2 before randomization, week 24, and week 52 (dark purple arrows); patients in the early-time-point substudy also underwent endoscopy at weeks 4 and 12. The final full analysis population (Panel B) was larger than the originally planned 170 patients because a large number of patients were undergoing screening at the time that recruitment was completed; these patients then became eligible for randomization. The data-cutoff date occurred when all the patients had completed the 24-week double-blind period. Of the 211 randomly assigned patients, 210 were included in the full analysis population and the safety analysis population; 1 patient in the benralizumab group did not receive at least one dose of the drug and was excluded. Because all the patients in the full analysis population received the investigational product assigned to them, the full analysis population and the safety analysis population were identical.

A full list of inclusion and exclusion criteria is provided in the Supplementary Appendix.

INTERVENTIONS AND PROCEDURES

Patients were randomly assigned (in a 1:1 ratio) to receive subcutaneous benralizumab (30 mg) or placebo every 4 weeks. Randomization for adults was stratified according to global region (North America vs. the rest of the world) and the use or nonuse of swallowed glucocorticoids at baseline. Adolescents underwent randomization in a separate stratum. From week 24, all the patients were treated with unblinded subcutaneous benralizumab (30 mg) every 4 weeks until week 52 or discontinuation of the investigational product.

END POINTS

The efficacy end points (assessed at weeks 24 and 52) are described in detail in the Supplementary Appendix. The two primary efficacy end points at week 24 were a histologic response, defined as a peak esophageal intraepithelial eosinophil count of no more than six eosinophils per high-power field, and the change from baseline in the daily score on the Dysphagia Symptom Questionnaire (DSQ; range, 0 to 84, with higher scores indicating more frequent or severe dysphagia).[18,19] Key secondary end points included in a hierarchical plan to adjust for multiple testing were the percentage change from baseline in the tissue eosinophil count, the change from baseline in the total grade and stage scores (centrally read) on the Eosinophilic Esophagitis Histology Scoring System (EoE-HSS; both scores range from 0 to 1, with higher scores indicating greater severity of histologic changes or greater extent of abnormal tissue, respectively[20]), the change from baseline in the centrally read Eosinophilic Esophagitis Endoscopic Reference Score (EREFS; range, 0 to 9, with higher scores indicating more endoscopic abnormalities[21]), and treatment response, defined as a composite of histologic response and a clinically meaningful (≥30%) improvement from baseline in the DSQ score.[18,19,21,22]

Other secondary end points were tissue eosinophil counts, dysphagia-related items captured by the DSQ, abdominal pain and nausea as captured by the Eosinophilic Esophagitis Daily Dysphagia Diary (EoE-3D),[23] and the change from baseline in scores on the Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS)[24]; the Adult Eosinophilic Esophagitis Quality-of-Life Questionnaire; the Short-Form 36-Item Health Survey, version 2; the Patient Global Impression of Severity (PGI-S); and the Patient Global Impression of Change (PGI-C). EndoFLIP measurements[18] and the 94-gene Eosinophilic Esophagitis Diagnostic Panel[25] were assessed as exploratory end points (see the Supplementary Appendix). Table S1 in the Supplementary Appendix provides a full list of all the end points prespecified in the trial protocol.

STATISTICAL ANALYSIS

Detailed statistical methods, including how missing data were handled, are provided in the Supplementary Appendix. Primary efficacy analyses were based on the first 24 weeks and performed according to the intention-to-treat principle in the full analysis population. A composite estimand strategy was used for all the end points that were analyzed statistically. The proportion of patients who had a histologic response at week 24 was compared between benralizumab and placebo with the use of Cochran–Mantel–Haenszel testing; the number and percentage of patients with a histologic response were summarized according to trial group. Results for treatment effects are presented as differences for ease of interpretation, with 95% confidence intervals

and two-sided P values. The change from baseline in the DSQ score at week 24 was compared between the trial groups with the use of an analysis of covariance model. To account for multiplicity testing for the two primary and five key secondary end points, a hierarchical fixed-sequence testing strategy was used to control the overall type I error rate at the 0.05 level (Table S2). P values are not reported for end points in the hierarchy after a nonsignificant result. Confidence intervals were not adjusted for multiple testing and should not be used in place of hypothesis testing.

RESULTS

PATIENTS

A total of 211 patients underwent randomization, with 104 assigned to receive benralizumab and 107 to receive placebo (Fig. 1B); 207 patients (98.1%) completed the 24-week double-blind period. A total of 25 patients (11 in the benralizumab group and 14 in the placebo group) participated in the early-time-point substudy; 16 patients (9 in the benralizumab group and 7 in the placebo group) participated in the EndoFLIP substudy. Of the 211 patients who underwent randomization, 206 (97.6%) completed the double-blind period while receiving benralizumab or placebo; 205 (97.2%) were enrolled in the open-label period and received benralizumab. A total of 89 patients (42.2%) completed the open-label period (week 52), 8 (3.8%) discontinued benralizumab in the open-label period, and 3 (1.4%) withdrew from the trial during the open-label period. At the start of the open-label period (week 24), 105 patients switched from placebo to benralizumab. The open-label period was discontinued early because the between-group difference for one of the two primary end points was not significant.

Patients were generally representative of the overall population with eosinophilic esophagitis (Table S3). Most patients were White (193 of 207 [93.2%]) and male (157 of 210 [74.8%]) (Table 1 and Table S4). The median age was 33.7 years (range, 12 to 62); 28 patients (13.3%) were younger than 18 years of age. Baseline demographic characteristics, previous disease-related treatments, and concomitant medications for eosinophilic esophagitis (Table S5) were generally balanced between the two groups. More patients in the placebo group than in the benralizumab group had strictures present at baseline (59.8% vs. 47.6%). Most patients had previously received swallowed glucocorticoids and PPIs, with more than 40% having no response with respect to symptoms or histologic features.

EFFICACY

Primary End Points

The percentage of patients who had a histologic response at week 24 was higher in the benralizumab group than in the placebo (87.4% vs. 6.5%; difference, 80.8 percentage points; 95% confidence interval [CI], 72.9 to 88.8; P<0.001) (Fig. 2A). The change from baseline in the DSQ score at week 24 did not differ significantly between the two groups (difference in least-squares means, 3.0 points; 95% CI, −1.4 to 7.4; P=0.18) (Fig. 2B). No prespecified subgroups were identified that appeared to benefit symptomatically from benralizumab (Fig. S1). Week 52 data were similar to week 24 data for histologic response (benralizumab, 83%; placebo switching to benralizumab, 89%) and change from baseline in the DSQ score (Fig. S2). Sensitivity analyses confirmed that point estimates for treatment effect were not appreciably affected by between-group differences in baseline characteristics (Table S6).

Secondary End Points

Key secondary end points are presented in Table 2. Because the between-group difference in the second of the two primary end points was not significant, no formal hypothesis testing was conducted for the five key secondary end points included in the hierarchical testing plan. At week 24, the change from baseline in the esophageal intraepithelial eosinophil count in the benralizumab group was −94.8%, as compared with 1.4% in the placebo group (difference, −96.2 percentage points; 95% CI, −114.5 to −77.9). Differences in tissue eosinophil counts and histologic response between the two groups were already present at week 4 and were maintained through weeks 12 and 24 (Fig. S3). Near-complete depletion of blood eosinophils was observed in the benralizumab group starting from the first post-baseline assessment at week 8; this depletion was maintained through week 52 (Fig. S4).

Changes from baseline to week 24 in the EoE-HSS total grade and stage scores in the benralizumab group were −0.26 and −0.20 points,

Table 1. Selected Characteristics of the Patients at Baseline (Full Analysis Population).*

Characteristic	Benralizumab (N=103)	Placebo (N=107)	Total (N=210)
Age — yr	33.9±13.5	33.6±12.7	33.7±13.1
Sex — no. (%)			
Male	72 (69.9)	85 (79.4)	157 (74.8)
Female	31 (30.1)	22 (20.6)	53 (25.2)
Peak esophageal intraepithelial eosinophil count — eosinophils/high-power field	83.8±42.2	82.5±43.5	83.2±42.8
Median blood eosinophil count (IQR) — cells/μl	280 (180–390)	320 (215–450)	310 (190–410)
Time since diagnosis of eosinophilic esophagitis — yr	5.1±4.1	4.7±4.6	4.9±4.4
Current use of swallowed topical glucocorticoid — no. (%)†	12 (11.7)	14 (13.1)	26 (12.4)
Previous use of swallowed glucocorticoid — no. (%)	57 (55.3)	62 (57.9)	119 (56.7)
Symptom nonresponse — no./total no. (%)	21/42 (50)	22/51 (43)	43/93 (46)
Histologic nonresponse — no./total no. (%)	20/42 (48)	20/51 (39)	40/93 (43)
Refractory to swallowed glucocorticoid — no. (%)‡	22 (21.4)	23 (21.5)	45 (21.4)
Current use of PPI — no. (%)†	45 (43.7)	51 (47.7)	96 (45.7)
Previous use of PPI — no. (%)	95 (92.2)	88 (82.2)	183 (87.1)
Symptom nonresponse — no./total no. (%)	53/95 (56)	48/88 (55)	101/183 (55)
Histologic nonresponse — no./total no. (%)	50/95 (53)	52/88 (59)	102/183 (56)
Previous esophageal stricture — no. (%)	36 (35.0)	29 (27.1)	65 (31.0)
Previous esophageal dilation — no. (%)	26 (25.2)	25 (23.4)	51 (24.3)
DSQ score§	35.9±12.1	34.1±11.3	—
Centrally read EREFS¶	5.2±1.6	5.1±1.7	—
EoE-HSS grade score‖	0.5±0.2	0.5±0.1	—
EoE-HSS stage score‖	0.4±0.1	0.5±0.1	—
Median IgE — IU/ml	0.3	0.4	—

* Plus–minus values are means ±SD. Patients were randomly assigned to receive benralizumab (30 mg) or placebo every 4 weeks. PPI denotes proton-pump inhibitor.
† Current use refers to the use of these medications for background treatment of eosinophilic esophagitis.
‡ "Refractory" refers to patients who had tried a glucocorticoid for at least 8 weeks without any reduction in symptoms.
§ Scores on the Dysphagia Symptom Questionnaire (DSQ) range from 0 to 84, with higher scores indicating more frequent or severe dysphagia.
¶ The Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) is a macroscopic measure of esophageal pathologic features that reflects the presence and severity of edema, rings, exudates, furrows, and strictures. Total scores range from 0 to 9, with higher scores indicating more endoscopic abnormalities.
‖ Each Histologic Scoring System (HSS) feature (eosinophilic inflammation, basal zone hyperplasia, eosinophil abscess, eosinophil surface layering, dilated intracellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis) was scored separately for grade (severity) and stage (extent) of abnormality with the use of a 4-point scale (from 0 [normal] to 3 [most severe or extensive]). The maximum total score possible was 24 (maximum grade or stage score of 3×8 features=24), representing the most severe grade or stage for each esophageal-biopsy sample collected if all 8 features were evaluated. The overall scores were then converted to scores ranging from 0 (representing 0 of 24 points) to 1 (representing 24 of 24 points).

respectively, as compared with −0.09 and −0.12 points, respectively, in the placebo group (Table 2 and Fig. S5). These changes were driven predominantly by eosinophil-related components (eosinophil inflammation, abscess, and surface layering).

At baseline, the mean total EREFS was 5.2 in the benralizumab group and 5.1 in the placebo group (Table 2). There were no apparent differences between the two groups in the total EREFS at weeks 24 and 52 (Table 2 and Fig. S6). The change from baseline in the score for exu-

dates (range, 0 to 2, with higher scores indicating the presence of lesions covering more of the esophageal mucosa) at week 24 was −0.43 points for benralizumab and −0.10 points for placebo. There were no apparent differences for other EREFS components. At week 24, the percentage of patients who were considered to have had a response differed between the trial groups by 39.0 percentage points (95% CI, 28.6 to 49.4) (Table 2).

Symptoms and Health-Related Quality of Life

There were no apparent differences between the two groups in changes in DSQ dysphagia-related items, EoE-3D–measured abdominal pain and nausea severity, and PGI-S and PGI-C scores at weeks 24 and 52 (Table S7). In pediatric patients, the severity of eosinophilic esophagitis symptoms as assessed by the PEESS was similar in the two groups. There were no apparent between-group differences in health-related quality of life as assessed by the Adult Eosinophilic Esophagitis Quality-of-Life Questionnaire and Short-Form 36-Item Health Survey, version 2.

EndoFLIP Measurements

The mean (±SD) distensibility plateau at baseline was 18.65±3.01 mm in the benralizumab group (nine patients) and 16.60±1.79 mm in the placebo group (seven patients). The difference in mean change from baseline to week 24 between the benralizumab and placebo groups was 3.62 mm (95% CI, 0.22 to 7.01) and was driven by an outlier in the placebo group. In a sensitivity analysis in which the patient with the outlying values was excluded, the between-group difference was only 0.83 mm (95% CI, −0.65 to 2.31) (Fig. S7).

Eosinophilic Esophagitis Diagnostic Panel

At week 24, few changes in the expression of genes associated with eosinophilic esophagitis were observed relative to baseline in the patients who received benralizumab as compared with those who received placebo (Fig. S8). The largest apparent decreases after benralizumab treatment were in the expression of Charcot–Leyden crystal galectin (*CLC*) and C-C motif chemokine receptor 3 (*CCR3*), both highly expressed in eosinophils.

SAFETY

The percentage of patients with adverse events was similar in the two trial groups (Table 3 and Table S8). The most common adverse events included coronavirus disease 2019 (13 patients [12.6%] in the benralizumab group and 13 patients [12.1%] in the placebo group), headache (9 [8.7%] and 11 [10.3%], respectively), and naso-

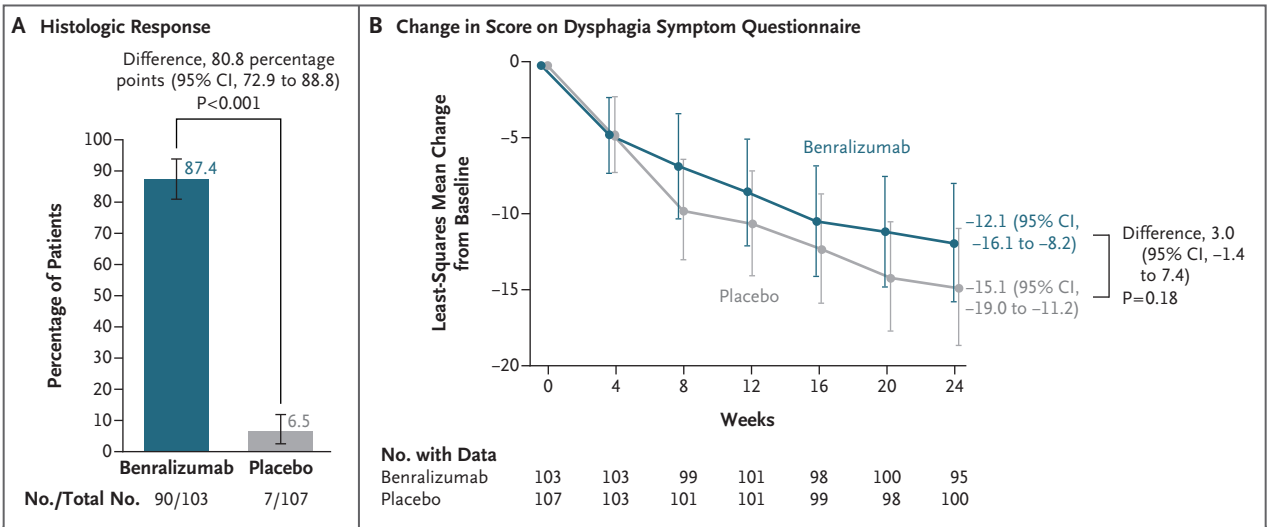


Figure 2. Primary End Points — Histologic Response and Change from Baseline in DSQ Score at Week 24.

A histologic response was defined as a peak esophageal intraepithelial eosinophil count of no more than six eosinophils per high-power field. Scores on the Dysphagia Symptom Questionnaire (DSQ) range from 0 to 84, with higher scores indicating more frequent or severe dysphagia. I bars indicate 95% confidence intervals.

Table 2. Key Secondary End Points at Weeks 24 and 52.

End Point	Week 24		Week 52	
	Benralizumab (N=103)	Placebo (N=107)	Benralizumab (N=46)	Placebo→Benralizumab (N=47)*
Least-squares mean percentage change from baseline in peak esophageal intraepithelial eosinophil count (95% CI)†	−94.8 (−100.0 to −82.5)	1.4 (−11.8 to 14.6)	−85.0 (−100.0 to −62.5)	−88.6 (−100.0 to −73.7)
Difference vs. placebo (95% CI) — percentage points	−96.2 (−114.5 to −77.9)	—	—	—
Least-squares mean change from baseline in EoE-HSS total grade score (95% CI)†	−0.3 (−0.3 to −0.2)	−0.1 (−0.1 to −0.1)	−0.2 (−0.3 to −0.2)	−0.2 (−0.3 to −0.2)
Difference vs. placebo (95% CI)	−0.2 (−0.2 to −0.1)	—	—	—
Least-squares mean change from baseline in EoE-HSS total stage score (95% CI)†	−0.2 (−0.2 to −0.2)	−0.1 (−0.1 to −0.0)	−0.2 (−0.2 to −0.1)	−0.1 (−0.2 to −0.1)
Difference vs. placebo (95% CI)	−0.1 (−0.2 to −0.1)	—	—	—
Least-squares mean change from baseline in centrally read EREFS (95% CI)‡	−0.5 (−0.9 to −0.1)	−0.4 (−0.9 to −0.0)	−0.3 (−0.9 to 0.3)	−0.7 (−1.4 to −0.1)
Difference vs. placebo (95% CI)	−0.1 (−0.5 to 0.4)	—	—	—
Treatment response — no. (%)§	45 (43.7)	5 (4.7)	29 (63.0)	31 (66.0)
Difference vs. placebo (95% CI) — percentage points	39.0 (28.6 to 49.4)	—	—	—

* Shown are data for patients randomly assigned to receive placebo during the double-blind period who switched to benralizumab during the open-label period.
† The number of patients with data for this end point (including patients with imputed values after intercurrent events) was as follows: at week 24, a total of 97 with benralizumab and 100 with placebo; at week 52, at total of 46 with benralizumab and 47 with placebo switching to benralizumab.
‡ The number of patients evaluated was as follows: at week 24, a total of 85 with benralizumab and 84 with placebo; at week 52, a total of 41 with benralizumab and 41 with placebo switching to benralizumab.
§ A treatment response was defined as a peak esophageal intraepithelial eosinophil count of no more than six eosinophils per high-power field across all available esophageal levels and a clinically meaningful improvement (≥30%) from baseline in the DSQ score.

Table 3. Adverse Events during the 24-Week Double-Blind Treatment Period.

Event	Benralizumab (N=103)	Placebo (N=107)
	no. of patients (%)	
Any adverse event	66 (64.1)	66 (61.7)
Any adverse event leading to trial discontinuation	0	0
Any adverse event with outcome of death	0	0
Serious adverse event	2 (1.9)	1 (0.9)
Asthma	0	1 (0.9)
Bronchospasm	1 (1.0)	0
Pneumonia, bacterial	1 (1.0)	0
Adverse events occurring in ≥3% of the patients in either group*		
Coronavirus disease 2019	13 (12.6)	13 (12.1)
Headache	9 (8.7)	11 (10.3)
Nasopharyngitis	8 (7.8)	6 (5.6)
Asthma	4 (3.9)	4 (3.7)
Upper respiratory tract infection	2 (1.9)	5 (4.7)
Oropharyngeal pain	4 (3.9)	1 (0.9)
Abdominal pain	0	4 (3.7)

* These adverse events were coded with the use of the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.0.

pharyngitis (8 [7.8%] and 6 [5.6%], respectively). There were no adverse events leading to trial discontinuation. Serious adverse events were infrequent (2 [1.9%] in the benralizumab group and 1 [0.9%] in the placebo group); all resolved, and none were considered by the investigator to be related to the investigational product.

DISCUSSION

In the MESSINA trial, benralizumab substantially reduced esophageal eosinophil counts by 4 weeks and maintained this reduction to 24 and 52 weeks but did not reduce dysphagia symptoms as compared with placebo. There was no apparent improvement in endoscopic findings associated with benralizumab treatment. Whereas benralizumab depleted both tissue and blood eosinophils, as expected, and heterogeneity may exist among patients with eosinophilic esophagitis, we were unable to identify a subgroup of patients who appeared to benefit symptomatically. Week 52 data did not support that prolonged treatment with benralizumab increased efficacy in reducing dysphagia symptoms. The safety profile was similar to that in previous trials of benralizumab, with no new safety signals.[26]

Despite apparent improvements in eosinophil-related components of the EoE-HSS in patients who received benralizumab, the lack of change in basal zone hyperplasia[27] and other measures of eosinophilic esophagitis–associated epithelial pathologic features suggests ongoing disease activity despite substantial eosinophil depletion in blood and esophageal tissue. Conclusions cannot be made regarding the link between lamina propria fibrosis and symptoms of eosinophilic esophagitis, including dysphagia, given the small number of samples with lamina propria fibrosis that were present and could be evaluated, which is common in endoscopic mucosal biopsies. On the EREFS, there may have been a modest decrease in severity with respect to exudates, which are associated with the presence of eosinophils,[28] but no apparent decrease in severity with respect to edema, furrows, rings, or strictures, which suggests that eosinophil depletion did not affect other inflammatory features or remodeling aspects of eosinophilic esophagitis–associated endoscopic activity[26] and that a decrease in severity with respect to exudates was not associated with clinical response.

Molecular profiling showed that the main effects of benralizumab were limited to a major decrease in expression of the eosinophil marker genes *CLC* and *CCR3*. The expression of epithelial-specific genes as well as C-C motif chemokine ligand 26 (*CCL26*) was similar in the two groups. There was no improvement in cardinal pathways involved in the pathogenesis of eosinophilic esophagitis; rather, there was a paradoxical increase in expression of the genes encoding the type 2 cytokines interleukin-5 and interleukin-13, the latter of which has been shown to mediate eosinophilic esophagitis symptoms and pathologic processes by targeting cells that are likely to be broadly involved in disease pathogenesis, such as epithelial cells.[6,29,30] Whether these increases in gene expression are sufficient to mediate the observed persistent disease activity warrants future investigation.

This trial is not the first to suggest a discordance between histologic and symptom response

in patients with eosinophilic esophagitis.[31-38] Earlier trials of the anti–interleukin-5 biologics mepolizumab and reslizumab showed histologic improvement without symptom reduction in patients with eosinophilic esophagitis.[35-38] Despite promising results in a phase 2 clinical trial of lirentelimab, an anti–Siglec-8 antibody,[39] a subsequent phase 3 trial showed reduced eosinophil counts but no reduction in symptoms in patients with eosinophilic gastritis, eosinophilic duodenitis, and eosinophilic esophagitis.[40] A phase 2 clinical trial of benralizumab involving patients with eosinophilic gastritis showed sustained clinical symptoms, endoscopic abnormalities, non–eosinophil-associated histopathological findings, and unresolved gastric transcriptomic changes, including increased levels of type 2 cytokines.[16] Dupilumab, which targets the cytokines interleukin-4 and interleukin-13, has been shown to reduce symptoms of eosinophilic esophagitis only with weekly dose administration.[11,41] Studies have highlighted the pathological role of adaptive T-cell immunity in eosinophilic esophagitis[42] and have also described variants of eosinophilic esophagitis–like disease without eosinophils.[43] By contrast, topical glucocorticoids such as orodispersible budesonide have a broad mechanism of action and act at multiple inflammatory targets in addition to eosinophils, which probably explains their documented efficacy.[44,45] It is noteworthy that eosinophilic esophagitis differs from asthma, for which both targeting of type 2 inflammation and eosinophil depletion are effective.[11,46] These findings support the need for biomarkers other than peak esophageal eosinophil count as an objective end point for therapy for eosinophilic esophagitis.[47]

Strengths of the trial include the relatively large sample, a multicenter design, a long-term extension study, the use of validated clinical outcome metrics, few discontinuations and protocol deviations, a trial population with a long duration of disease burden, and a trial design that permitted continuation of background therapy for eosinophilic esophagitis, reflecting real-world clinical disease management. A limitation was the lack of a placebo-control group during the open-label period; however, there were no apparent differences between patients who received benralizumab for 52 weeks and those who were initially assigned to receive placebo before receiving benralizumab in the open-label period.

In this trial, benralizumab resulted in a higher incidence of histologic response than placebo but did not result in a greater reduction in dysphagia symptoms. This trial calls into question the clinical relevance of monitoring eosinophilic esophagitis for treatment effect solely on the basis of the degree of eosinophilic inflammation. Future therapeutic strategies may involve broader targets or those higher upstream in pathogenic pathways.

Supported by AstraZeneca.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers, as well as the site investigators and staff, who participated in this trial; Justin Kwiatek, Xiao Xu, and Rohit Katial (AstraZeneca) for their contributions to discussions of the design and interpretation of the trial; Sean O'Quinn and Erik Bark (AstraZeneca) for contributions to aspects of the trial design related to patient-reported outcomes; Christopher Nazaroff (AstraZeneca) for support with biomarker analyses; Margaret Melville (AstraZeneca) for leadership and inspiration; Rama Empati, Yasa Reddy, and Peter Barker (AstraZeneca) for statistical programming support; Jing Wang and Sarah Cohen (ClinChoice) for statistical programming support; Cezary Dmochowski and Eileen Babcock (AstraZeneca) for support with the conduct of the trial; and Sara N. Fischer and Dan Jackson (Citrus Health Group) for medical writing support with earlier versions of the manuscript, provided in accordance with Good Publication Practice (GPP 2022) guidelines and funded by AstraZeneca.

APPENDIX

The authors' affiliations are as follows: the Divisions of Allergy and Immunology (M.E.R., J.M.C.) and Pathology and Laboratory Medicine (M.H.C.), Department of Pediatrics, and the Department of Pathology and Laboratory Medicine (M.H.C.), University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati; the Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill (E.S.D.); the Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam (A.J.B.); the Kenneth C. Griffin Esophageal Center, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago (I.H.); the Division of Gastroenterology, Department of Internal Medicine, University of Utah, Salt Lake City (K.A.P.); Late-Stage Respiratory and Immunology, BioPharmaceuticals Research and Development, AstraZeneca, Cambridge, United Kingdom (L.B.); Late-Stage Respiratory and Immunology, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden (H.F., H.G.); and Patient Centered Science, BioPharmaceuticals Medical Evidence (C.N.H.), Late-stage Respiratory and Immunology (M.K., C.J.D.) and Translational Science and Experimental Medicine, Early Respiratory and Immunology (C.M.), BioPharmaceuticals Research and Development, and Data Sciences and AI (D.S.) and Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences (W.I.W.), Research and Development, AstraZeneca, Gaithersburg, MD.

REFERENCES

1. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679-92.
2. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373:1640-8.
3. Dhar A, Haboubi HN, Attwood SE, et al. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. Gut 2022;71:1459-87.
4. Reed CC, Corder SR, Kim E, et al. Psychiatric comorbidities and psychiatric medication use are highly prevalent in patients with eosinophilic esophagitis and associate with clinical presentation. Am J Gastroenterol 2020;115:853-8.
5. Taft TH, Carlson DA, Simons M, et al. Esophageal hypervigilance and symptom-specific anxiety in patients with eosinophilic esophagitis. Gastroenterology 2021;161:1133-44.
6. Jackson DJ, Akuthota P, Roufosse F. Eosinophils and eosinophilic immune dysfunction in health and disease. Eur Respir Rev 2022;31:210150.
7. Tourlamain G, Garcia-Puig R, Gutiérrez-Junquera C, et al. Differences in management of eosinophilic esophagitis in Europe: an assessment of current practice. J Pediatr Gastroenterol Nutr 2020;71:83-90.
8. Papadopoulou A, Amil-Dias J, Auth MK, et al. Joint ESPGHAN/NASPGHAN guidelines on childhood eosinophilic gastrointestinal disorders beyond eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2024;78:122-52.
9. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. Gastroenterology 2018;155:1022-1033.e10.
10. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. N Engl J Med 2022;387:2317-30.
11. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010;125:1344-1353.e2.
12. AstraZeneca. Fasenra prescribing information. 2024 (https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/3647bed4-ce91-4fe7-9bc5-32dbee73f80a/3647bed4-ce91-4fe7-9bc5-32dbee73f80a_viewable_rendition__v.pdf).
13. Pham T-H, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respir Med 2016;111:21-9.
14. Kuang FL, Legrand F, Makiya M, et al. Benralizumab for *PDGFRA*-negative hypereosinophilic syndrome. N Engl J Med 2019;380:1336-46.
15. Kuang FL, De Melo MS, Makiya M, et al. Benralizumab completely depletes gastrointestinal tissue eosinophils and improves symptoms in eosinophilic gastrointestinal disease. J Allergy Clin Immunol Pract 2022;10:1598-1605.e2.
16. Kliewer KL, Murray-Petzold C, Collins MH, et al. Benralizumab for eosinophilic gastritis: a single-site, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol 2023;8:803-15.
17. Hirano I, Pandolfino JE, Boeckxstaens GE. Functional lumen imaging probe for the management of esophageal disorders: expert review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol 2017;15:325-34.
18. Dellon ES, Irani A-M, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:634-42.
19. Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. J Patient Rep Outcomes 2017;1:3.
20. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2017;30:1-8.
21. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489-95.
22. Hirano I, Collins MH, Katzka DA, et al. Budesonide oral suspension improves outcomes in patients with eosinophilic esophagitis: results from a phase 3 trial. Clin Gastroenterol Hepatol 2022;20:525-534.e10.
23. O'Quinn S, Ho CN, Griffiths P, et al. Development of the eosinophilic esophagitis daily dysphagia diary: a patient-reported outcome assessment to measure frequency and severity of dysphagia episodes in eosinophilic esophagitis. United European Gastroenterol J 2022;10:Suppl 8:466-7.
24. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol 2015;135:1519-28.e8.
25. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. Gastroenterology 2013;145:1289-99.
26. Korn S, Bourdin A, Chupp G, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. J Allergy Clin Immunol Pract 2021;9:4381-4392.e4.
27. Whelan KA, Godwin BC, Wilkins B, et al. Persistent basal cell hyperplasia is associated with clinical and endoscopic findings in patients with histologically inactive eosinophilic esophagitis. Clin Gastroenterol Hepatol 2020;18:1475-1482.e1.
28. Rodríguez-Sánchez J, Barrio-Andrés J, Nantes Castillejo O, et al. The Endoscopic Reference Score shows modest accuracy to predict either clinical or histological activity in adult patients with eosinophilic oesophagitis. Aliment Pharmacol Ther 2017;45:300-9.
29. Zuo L, Fulkerson PC, Finkelman FD, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. J Immunol 2010;185:660-9.
30. Rothenberg ME. Scientific journey to the first FDA-approved drug for eosinophilic esophagitis. J Allergy Clin Immunol 2022;150:1325-32.
31. Attwood SE. Multiple inflammatory mechanisms in eosinophilic oesophagitis make it unlikely that single pathway inhibition by monoclonal biological therapies would succeed. Gut 2023;72:1806-7.
32. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526-1537, 1537.e1.
33. Safroneeva E, Straumann A, Schoepfer AM. Latest insights on the relationship between symptoms and biologic findings in adults with eosinophilic esophagitis. Gastrointest Endosc Clin N Am 2018;28:35-45.
34. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012;10:742-749.e1.
35. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011;141:1593-604.
36. Moran AM, Ramakrishnan S, Borg CA, et al. Blood eosinophil depletion with mepolizumab, benralizumab, and prednisolone in eosinophilic asthma. Am J Respir Crit Care Med 2020;202:1314-6.
37. Dellon ES, Peterson KA, Mitlyng BL,

et al. Mepolizumab for treatment of adolescents and adults with eosinophilic oesophagitis: a multicentre, randomised, double-blind, placebo-controlled clinical trial. Gut 2023;72:1828-37.
38. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012;129(2):456-463, 463.e1-463.e3.
39. Dellon ES, Peterson KA, Murray JA, et al. Anti–siglec-8 antibody for eosinophilic gastritis and duodenitis. N Engl J Med 2020;383:1624-34.
40. Dellon ES, Chehade M, Genta RM, et al. Results from KRYPTOS, a phase 2/3 study of lirentelimab (AK002) in adults and adolescents with EoE. Am J Gastroenterol 2022;117:Suppl 10:e316-e317.
41. Rothenberg ME, Dellon ES, Collins MH, et al. Efficacy and safety of dupilumab up to 52 weeks in adults and adolescents with eosinophilic oesophagitis (LIBERTY EoE TREET study): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2023;8:990-1004.
42. Morgan DM, Ruiter B, Smith NP, et al. Clonally expanded, GPR15-expressing pathogenic effector T_H2 cells are associated with eosinophilic esophagitis. Sci Immunol 2021;6:eabi5586.
43. Straumann A, Blanchard C, Radonjic-Hoesli S, et al. A new eosinophilic esophagitis (EoE)-like disease without tissue eosinophilia found in EoE families. Allergy 2016;71:889-900.
44. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomized placebo-controlled trial. Gastroenterology 2019;157:74-86.e15.
45. Straumann A, Lucendo AJ, Miehlke S, et al. Budesonide orodispersible tablets maintain remission in a randomized, placebo-controlled trial of patients with eosinophilic esophagitis. Gastroenterology 2020;159:1672-1685.e5.
46. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.
47. Hirano I, Dellon ES, Falk GW, et al. Ascending to new heights for novel therapeutics for eosinophilic esophagitis. Gastroenterology 2024;166:1-10.