Original research

Mepolizumab for treatment of adolescents and adults with eosinophilic oesophagitis: a multicentre, randomised, double-blind, placebo-controlled clinical trial

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2023-330337).

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Received 23 May 2023
Accepted 28 June 2023

To cite: Dellon ES, Peterson KA, Mitlyng BL, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2023-330337

ABSTRACT

Objective We aimed to determine whether mepolizumab, an anti-IL-5 antibody, was more effective than placebo for improving dysphagia symptoms and decreasing oesophageal eosinophil counts in eosinophilic oesophagitis (EoE).

Methods We conducted a multicentre, randomised, double-blind, placebo-controlled, trial. In the first part, patients aged 16–75 with EoE and dysphagia symptoms (per EoE Symptom Activity Index (EEsAI)) were randomised 1:1 to 3 months of mepolizumab 300 mg monthly or placebo. Primary outcome was change in EEsAI from baseline to month 3 (M3). Secondary outcomes included histological, endoscopic and safety metrics. In part 2, patients initially randomised to mepolizumab continued 300 mg monthly for 3 additional months (mepo/mepo), placebo patients started mepolizumab 100 mg monthly (pbo/mepo), and outcomes were reassessed at month 6 (M6).

Results Of 66 patients randomised, 64 completed M3, and 56 completed M6. At M3, EEsAI decreased 15.4±18.1 with mepolizumab and 8.3±18.0 with placebo (p=0.14). Peak eosinophil counts decreased more with mepolizumab (113±77 to 36±43) than placebo (146±94 to 160±133) (p<0.001). With mepolizumab, 42% and 34% achieved histological responses of <15 and ≤6 eos/hpf compared with 3% and 3% with placebo (p<0.001 and 0.02). The change in EoE Endoscopic Reference Score at M3 was also larger with mepolizumab. At M6, EEsAI decreased 18.3±18.1 points for mepo/mepo and 18.6±19.2 for pbo/mepo (p=0.85). The most common adverse events were injection-site reactions.

Conclusions Mepolizumab did not achieve the primary endpoint of improving dysphagia symptoms compared with placebo. While eosinophil counts and endoscopic severity improved with mepolizumab at 3 months, longer treatment did not yield additional improvement.

Trial registration number NCT03656380.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Novel treatment options for eosinophilic oesophagitis (EoE) are needed.
⇒ Mepolizumab is a monoclonal antibody that binds IL-5, which is involved in EoE pathogenesis and is potential therapeutic target.

WHAT THIS STUDY ADDS

⇒ Using a validated patient-reported outcome metric for the primary outcome of symptom improvement, patients randomised to mepolizumab did not have significantly more improvement in dysphagia than those randomised to placebo.
⇒ Eosinophil counts and endoscopic severity were improved with mepolizumab compared with placebo.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Mepolizumab likely does not have clinical utility in the severe and treatment refractory EoE population studied here, but future research should assess mechanisms of continued disease activity in EoE despite reductions in eosinophil counts, as well as a possible role of this treatment in less severe patients.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic, Th2-mediated allergic disease with pathological eosinophilic infiltration of the oesophagus and symptoms of oesophageal dysfunction.[1 2] The condition has been increasing in incidence and prevalence,[3] and progresses from an inflammatory predominant to fibrostenotic phenotype in many, but not all, patients.[4 5] Pharmacological treatments have traditionally included proton pump inhibitors (PPIs) and topical steroids.[6] PPI response ranges from just 30% to 50%,[7] and while topical steroids are more effective,[8] there are still substantial rates of non-response and loss of response over time.[9–13] While one oesophageal-specific topical steroid is approved outside of the USA,[14] within the US patients must still modify steroid preparations indicated for asthma.[15] Dupilumab, a biological that targets the IL-4/IL-13 pathway, is now approved for treatment of EoE in the USA and EU,[16] but its placement in the treatment algorithm remains

under discussion.[17] Therefore, there is still an unmet need for additional EoE treatments.

The cytokine IL-5 has been thought to play a role in EoE pathogenesis.[18 19] In experimental models of EoE, blocking IL-5 attenuates the disease state, whereas overexpression of IL-5 creates an EoE-like phenotype.[19 20] Mepolizumab is a recombinant monoclonal antibody that binds IL-5 and is an FDA-approved treatment for eosinophilic diseases such as hypereosinophilic syndrome,[21] eosinophilic asthma[22] and eosinophilic granulomatosis with polyangiitis.[23] Mepolizumab has also been previously studied for EoE, including in a small clinical trial in 11 adults[24] and a larger trial in 59 children.[25] While oesophageal eosinophil count responses were promising, the symptom benefit was not clear. This discrepancy, though noted in other EoE studies as well,[25 26] was potentially thought due to the use of non-validated symptom metrics, measuring heterogeneous symptoms in paediatric patients, or trial designs that did not require a sufficient symptom threshold for study entry.

Given the strong biological rationale for anti-IL-5 therapy in EoE, increased understanding about trial design for EoE, the development and validation of EoE-specific patient-reported outcomes (PROs), and the need for additional treatment options in this disease, it was important to reassess mepolizumab treatment for EoE. Therefore, we aimed to determine whether mepolizumab was more effective than placebo for improving symptoms of dysphagia and decreasing oesophageal eosinophil counts in adults and adolescents with active EoE.

METHODS

Study design and participants

This was a multicentre, randomised, double blind, parallel-arm, investigator-initiated, placebo controlled trial that was conducted from 2018 to 2022 at University of North Carolina (UNC), MNGI Digestive Health, Northwestern University and University of Utah. After an initial 3-month blinded period comparing mepolizumab to placebo, there was a second 3-month blinded period where all patients received active treatment. During the second 3-month blinded part, subjects initially randomised to placebo received a lower dose while subjects initially randomised to mepolizumab maintained stable dosing (online supplemental figure 1). The study followed the Consolidated Standards of Reporting Trials (CONSORT) statement for all elements of conduct and reporting. All subjects provided informed consent for participation.

Patients were eligible if they were age 16–75, had a confirmed diagnosis of EoE as per consensus guidelines[1] and had previously been PPI non-responsive. PPI non-response was not required for diagnostic purposes, but was required because we were targeting a population that would be more likely to require biological therapy (ie, PPI failures). Additional key inclusion criteria were: active oesophageal eosinophilia with a peak of at least 15 eosinophils per high-power field (eos/hpf); active dysphagia symptoms (defined as >3 episodes over 2 weeks during screening, and an EoE Symptom Activity Index[27] (EEsAI; see below for details) score of ≥27 at baseline. Patients were excluded if they had: an oesophageal dilation within 8 weeks of the screening endoscopy; inability to pass a standard upper endoscope (8–10 mm) due to oesophageal narrowing or stricturing; topical steroids for EoE within 4 weeks or systemic corticosteroids within 8 weeks of the screening endoscopy; or concomitant eosinophilic gastritis/enteritis/colitis, inflammatory bowel disease or coeliac disease. Intranasal/inhaled steroids were allowed, and any PPI use or diet changes at baseline had to be maintained unchanged throughout the study (see online supplemental methods for full inclusion/exclusion criteria, as well as the protocol which is also available as an online supplement).

Masking, randomisation and interventions

At each site, the subjects, investigators, endoscopists, nurses and research staff/study coordinators were masked to allocation as well as to blood and tissue eosinophil count results after the screening visit; at UNC, study statisticians and pathologists were also masked. The only unblinded personnel were the investigational pharmacists at each site who were responsible for allocation of study medication, and an unblinded study monitor based at UNC.

Patients were randomised 1:1 to either mepolizumab or placebo using a blocked randomisation protocol with computer-generated variable block sizes. Randomisation was administered centrally using a web-based system and was stratified by site and by prior steroid response (steroid non-response vs either response or steroid naïve). Steroid non-response was defined as >15 eos/hpf after a 2-month course of a topical steroid at a standard dose (eg, 2 mg/day of budesonide or 1760 μg/day of fluticasone).[9 26]

In the first part of the study, patients randomised to mepolizumab received 300 mg monthly for 3 months, administered as three 100 mg/1 mL subcutaneous injections in syringes marked as 'study drug'. Patients randomised to placebo received 3 1 mL subcutaneous injections of normal saline in matching syringes also marked as 'study drug'. In the second part of the study, those initially randomised to mepolizumab maintained stable dosing for three additional monthly doses. Those initially randomised to placebo received one 100 mg/1 mL subcutaneous dose of mepolizumab monthly for 3 months in addition to two 1 mL subcutaneous injections of normal saline. In this way, every subject had three injections that were masked to allocation each month for the 6-month treatment duration of this study. The doses were chosen based on pharmacological modelling showing that 100–300 mg of mepolizumab, administered SQ on a monthly basis, was sufficient to suppress eosinophil counts in the blood,[28] acknowledging that prior studies in EoE used higher does (750 mg–1500 mg[24]; 2.5–10 mg/kg[25]) and dose-response of mepolizumab for histological response in oesophageal tissue was not known.

Outcomes

The primary outcome was the mean change in dysphagia as measured by the EEsAI score (7-day recall) from baseline to 3-month post-treatment. The EEsAI is a validated PRO that measures dysphagia frequency, dysphagia severity and food avoidance/modification behaviours in patients with EoE.[27 29 30] Responsiveness has been demonstrated in several clinical trials.[14 31] The EEsAI score ranges from 0 to 100, with higher scores indicating more severe symptoms. A decrease of 20 points represents a meaningful clinical response, and scores ≤20 represent clinical remission; both of these parameters were secondary outcomes.

Other prespecified secondary outcomes included the absolute peak eosinophil count (measured in eos/hpf) after 3 months of treatment and levels of histological response after 3 months of treatment including<15, ≤ 6 and ≤1 eos/hpf.[32] Eosinophil counts were determined centrally at UNC by the study pathologists, using a previously validated protocol.[33 34] In brief, four oesophageal biopsies were obtained from both the distal (3 cm above the gastro-oesophageal junction) and proximal (15 cm

above the junction) oesophagus to maximise sensitivity of detecting eosinophils.[35] The overall peak eosinophil count was determined from the field deemed to be most inflamed from all oesophageal levels and all high-power fields, and we also assessed for other histological features including eosinophil microabscesses and degranulation, basal zone hyperplasia, spongiosis and lamina propria fibrosis, as previously described[15]; we were not able to include the EoE Histologic Scoring System[11] as a prespecified outcome when the study was designed. We quantified endoscopic severity using the EoE Endoscopic Reference Score (EREFS; 0–9 score range),[36 37] and used a second method to assess symptoms with the Straumann Dysphagia Index (SDI).[38 39] In addition to these secondary outcomes, we also assessed blood eosinophils, reassessed endpoints for the 6-month time point, and monitored safety and adverse events (see online supplemental methods for full details on outcomes). During the course of the study, oesophageal dilation was not allowed at screening or at month 3, but was allowed during the month 6 endoscopy after the month 6 EEsAI and last SDI were completed.

Statistical analysis

Descriptive statistics were used to characterise the study population. For the primary outcome, the mean change in EEsAI from baseline to 3 months post-treatment was compared between the mepolizumab and placebo groups using analysis of covariance, in a model that accounted for the baseline EEsAI score and the stratification factor of prior steroid non-response. For continuous secondary outcomes, change from baseline was compared between groups with the same methodology, means between groups were compared with two sample t-tests, and means within groups (for pre–post treatment comparisons) were compared with paired t-tests. For categorical secondary outcomes, proportions were compared between groups with χ^2. We also assessed for baseline characteristics that might predict histological response (at the <15 eos/hpf threshold), and performed prespecified subgroup analyses related to change in symptoms. Full details of the statistical approach are in the included study protocol. The analysis population were subjects who were randomised, received study medication, and underwent post-treatment endoscopy for outcome assessment (modified intention-to-treat population).

The study was powered for the primary outcome, the EEsAI score. We estimated that with a sample size of 30 patients in each group we would be able to detect a difference in the mean change in EEsAI score of as little of 17, with a power of 0.9 at an α of 0.05, which would allow us to detect the clinically meaningful difference of a 20 point change. Assuming a 20% drop-out rate, we planned to randomise 36 patients in each group to reach the target sample size.

Data were collected and the database was managed by the investigators, with UNC acting as the coordinating site. All authors had access to the study data and reviewed and approved the final manuscript. All analyses for the primary and prespecified secondary outcomes were performed masked to allocation and prior to breaking the study blind. The study funder had no role in the collection, analysis or interpretation of the data.

RESULTS

Patient flow and baseline characteristics

Of 87 patients screened, 21 were excluded (did not meet inclusion criteria or declined to participate), 66 were randomised, and 64 were included in the month 3 analysis, 33 in the placebo group and 31 in the mepolizumab group. Then, 62 subjects moved into part 2, and 28 in each group were analysed for month 6 outcomes (online supplemental figure 2).

Baseline characteristics were generally well balanced between the two study groups (table 1). The mean age of study subjects was mid-30s, >80% had a concomitant atopic condition, symptoms persisted 6–7 years on average prior to EoE diagnosis, and EoE diagnosis was 6–7 years prior to study entry. By definition, all patients had failed PPI therapy. In addition, >80% had been previously treated with topical steroids, and half the study population were steroid non-responders. Approximately three-quarters had previously undergone oesophageal dilation, with an average number of dilations of >6, while >60% had an

Table 1 Baseline characteristics of randomised subjects

	Placebo (n=34)	Mepolizumab (n=32)
Age (mean years±SD)	33.1±9.8	38.1±12.0
Male (n, %)	18 (53)	21 (66)
White (n, %)	33 (97)	30 (94)
BMI (mean kg/m^2±SD)	27.8±5.7	27.5±4.6
Any atopic condition (n, %)	29 (85)	27 (84)
Asthma	15 (44)	10 (31)
Food allergy	16 (47)	16 (50)
Atopic dermatitis	11 (32)	10 (31)
Allergic rhinitis	27 (79)	20 (63)
Pollen food-allergy syndrome	8 (24)	5 (16)
EoE history characteristics		
Symptom length prior to diagnosis (mean years±SD)	5.8±6.5	7.4±9.0
EoE duration from diagnosis to enrolment (mean years±SD)	6.4±5.1	7.3±4.2
Prior EoE treatments (n, %)		
PPI (all non-responders)	34 (100)	32 (100)
Topical steroids	30 (88)	26 (81)
Prior non-response	17 (50)	16 (50)
Diet elimination	21 (62)	22 (69)
Montelukast	6 (18)	6 (19)
Biologics (prior clinical trial use)	3 (9)	7 (22)
Dilation	23 (68)	25 (78)
No of prior dilations (mean±SD)	6.8±6.1	6.0±5.4
Time since last dilation (mean years±SD)	1.2±1.6	1.8±2.3
Baseline EEsAI score (mean±SD)	52.3±14.8	55.6±15.8
Endoscopic findings (n, %)		
Normal	0 (0)	0 (0)
Exudates	30 (88)	25 (78)
Rings	28 (82)	26 (81)
Oedema	32 (94)	28 (88)
Furrows	32 (94)	31 (97)
Stricture	20 (59)	22 (69)
Diameter (mean mm±SD)	14.4±2.1	13.3±1.9
EREFS score (worst mean±SD)	5.3±1.5	5.0±1.6
Baseline peak oesophageal eosinophil counts (mean eos/hpf±SD)	147.1±92.3	112.5±75.7
Peripheral blood eosinophil count (mean 10^9 cells/L±SD)	0.4±0.3	0.4±0.2

BMI, body mass index; EEsAI, Eosinophilic Esophagitis Symptom Activity Index; EoE, eosinophilic oesophagitis; EREFS, EoE Endoscopic Reference Score; PPI, proton pump inhibitor.

Table 2 Primary and secondary study outcomes for month 3 in the modified intention-to-treat population

	Placebo (n=33)	Mepolizumab (n=31)	P value*
Symptom scores (mean±SD)			
EEsAI score			
Baseline	52.6±14.9	54.7±15.3	0.38
Post-treatment	44.2±14.6	39.3±17.3	0.22
P value (within groups)	0.01	<0.001	
Change in score from baseline†	8.3±18.0	15.4±18.1	0.14
Score ≤20‡ (clinical remission; n, %)	2 (6)	2 (6)	0.95
Decrease in score ≥20‡ (clinical response; n, %)	7 (21)	11 (35)	0.20
SDI			
Baseline	5.5±1.6	5.6±1.6	0.75
Post-treatment	2.8±1.9	2.3±2.2	0.33
P value (within groups)	<0.001	<0.001	
Change in score from baseline‡	2.7±2.2	2.4±1.7	0.44
Endoscopic severity scores (mean±SD)			
Overall EREFS			
Baseline	5.4±1.5	5.0±1.6	0.36
Post-treatment	5.0±1.9	4.0±1.7	0.03
P value (within groups)	0.11	<0.001	
Change in score from baseline‡	0.4±1.3	1.0±1.1	0.03
Inflammatory			
Baseline	3.6±1.0	3.2±1.1	0.09
Post-treatment	3.4±1.1	2.5±1.2	0.004
P value (within groups)	0.31	0.001	
Fibrostenotic			
Baseline	1.8±1.0	1.8±0.9	0.94
Post-treatment	1.6±1.0	1.5±1.0	0.46
P value (within groups)	0.10	0.03	
Stricture diameter (mean mm±SD)			
Baseline	14.3±2.1	13.3±1.9	0.09
Post-treatment	14.3±2.1	13.5±1.9	0.19
P value (within groups)	0.99	0.70	
Peak eosinophil counts (mean eos/hpf±SD)			
Overall peak‡			
Baseline	146.3±93.6	113.3±76.9	0.13
Post-treatment	163.0±133.1	35.7±43.0	<0.001
P value (within groups)	0.37	<0.001	
Absolute change from baseline	+16.7±104.6	−77.5±73.4	<0.001
Percent change from baseline	+41.7±136.0	−64.4±34.9	<0.001
Histological response (n, %)‡			
<15 eos/hpf	1 (3)	13 (42)	<0.001
≤6 eos/hpf	1 (3)	7 (34)	0.02
≤1 eos/hpf	1 (3)	3 (10)	0.27
Other histological findings (n, %)§			
Eosinophil degranulation			
Baseline	30 (91)	27 (87)	0.63
Post-treatment	29 (94)	23 (74)	0.04
P value (within groups)	0.65	0.10	
Eosinophil microabscesses			
Baseline	30 (91)	22 (73)	0.07
Post-treatment	27 (90)	9 (32)	<0.001
P value (within groups)	0.65	<0.001	
Basal zone hyperplasia			
Baseline	30 (94)	25 (86)	0.32
Post-treatment	27 (84)	25 (89)	0.58
P value (within groups)	0.08	1.0	
Spongiosis			
Baseline	33 (100)	31 (100)	--
Post-treatment	32 (97)	29 (94)	0.52
P value (within groups)	0.32	0.16	
Lamina propria fibrosis			
Baseline	20 (80)	18 (86)	0.61
Post-treatment	27 (90)	15 (60)	0.009
P value (within groups)	0.32	0.05	

*Means between groups compared with two sample t-tests; means within groups (pre–post treatment) compared with paired t-tests; change form baseline p value calculated by ANCOVA with least square change method; proportion between groups compared with $\chi 2$; proportions within groups (pre–post treatment) compared with McNemar's test.
†Primary study outcome.
‡Secondary study outcomes.
§For post-treatment histological response data, for degranulation, n=31 in group A; for microabscess, n=30 in group A and n=28 in group B; for BZH, n=32 in group A and 28 in group B (and for BZH pretreatment, n=32 in group A and n=29 in group B); and for LPF, n=30 in group A and 25 in group B (and for LPF pretreatment, n=25 in group A and 21 in group B).
ANCOVA, analysis of covariance; BZH, basal zone hyperplasia; EEsAI, Eosinophilic Esophagitis Symptom Activity Index; EREFS, EoE Endoscopic Reference Score; LPF, lamina propria fibrosis; SDI, Straumann Dysphagia Index.

oesophageal stricture present at their baseline endoscopy (with an average diameter of 13–14 mm).

Symptom outcomes

The baseline EEsAI was 54.7 in the mepolizumab group and 52.6 in placebo, with post-treatment EEsAIs of 39.4 and 44.2 at month 3, respectively (table 2). For the primary study outcome, the change from baseline was an improvement of 15.4±18.1 (95% CI 8.8 to 22.0) points with mepolizumab and 8.3±18.0 (95% CI 1.9 to 14.7) points with placebo (p=0.14; figure 1A). These average decreases were below the clinically meaningful EEsAI response of 20 points. While 6% in each group had a month 3 EEsAI score≤20 (p=0.95), 35% on mepolizumab had an EEsAI score decrease ≥20 vs 21% with placebo (p=0.20). The change in SDI was also similar between the groups (2.4±1.7 vs 2.7±2.2 for mepolizumab vs placebo; p=0.44).

The change in EEsAI from baseline to month 6 was 18.3±18.1 (95% CI 11.3 to 25.3) in the group that continued mepolizumab 300 mg monthly, compared with 18.6±19.2 (95% CI 11.2 to 26.1) in the placebo to mepolizumab 100 mg monthly group (p=0.85) (table 3). After 6 months of treatment, the same proportion in each group had an EEsAI≤20 (18%) and an EEsAI score decrease ≥20 (46%). Symptom scores over the study timeframe for EEsAI and SDI are shown in figure 2.

Histological outcomes

At month 3, the peak eosinophil count decreased with mepolizumab treatment (113.3±76.9–35.7±43.0) and increased (146.3±93.6–163.0±133.1) with placebo, a significant change from baseline for the between group comparison (p<0.001; figure 1B). After 3 months of mepolizumab, 42% and 34% achieved histological responses of <15 and ≤6 eos/hpf, respectively, compared with 3% and 3% respectively, with placebo (p<0.001 and p=0.02; figure 1C). There were also fewer subjects with eosinophil degranulation and microabscesses with mepolizumab compared with placebo, but basal zone hyperplasia, spongiosis and lamina propria fibrosis were similar (table 2).

From study baseline to month 6, the peak eosinophil count decreased to 50.2±42.2 eos/hpf with the placebo to mepolizumab 100 mg group, and 26.0±19.7 with the group that remained on mepolizumab 300 mg (p=0.008 for post-treatment comparison) (table 3). However, the absolute change from baseline to month 6 was slightly larger in the placebo to mepolizumab group (−102.4±82.5 vs −87.9±76.6; p=0.04). At month 6,

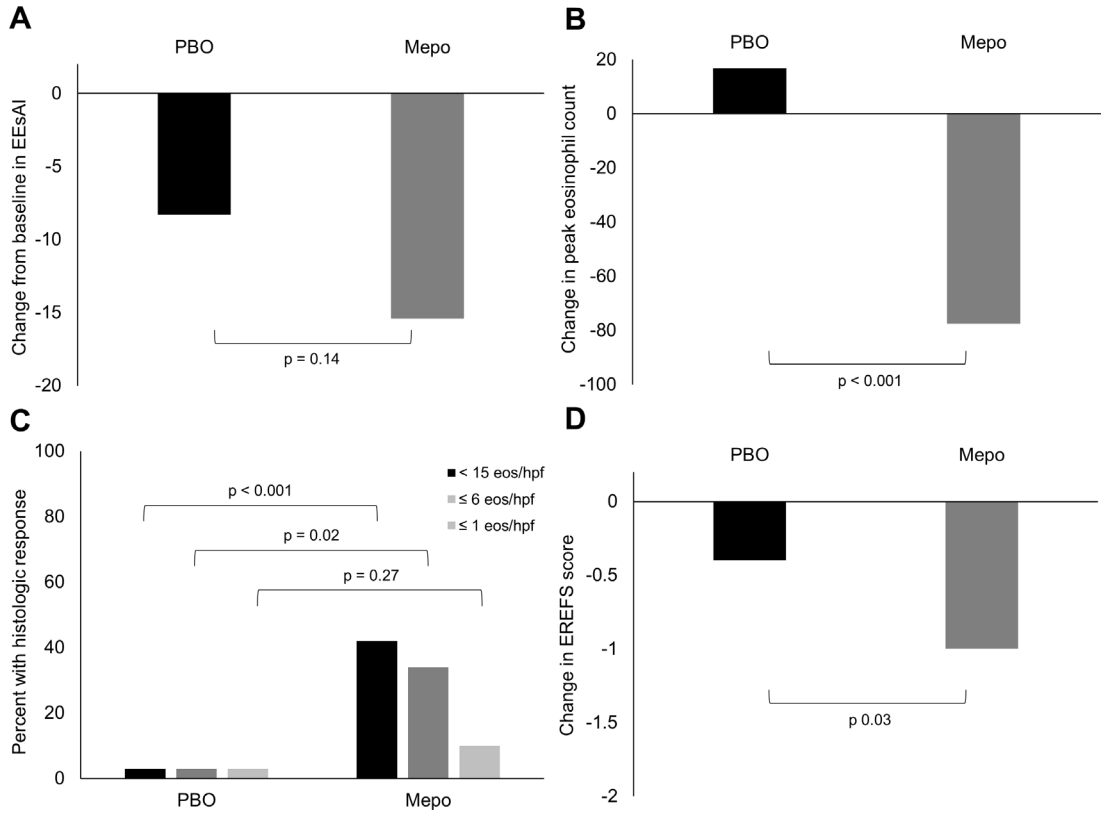

Figure 1 Primary and key secondary study outcomes at month 3. (A) Change in dysphagia symptoms as measured by the EEsAI score from baseline to month 3 in the placebo (PBO) (black bar) and mepolizumab (grey bar) groups. (B) Change in the absolute peak oesophageal eosinophil count (eos/hpf) from baseline to month 3. (C) Proportion of subjects with histological response at month 3 at the <15 eos/hpf (black bars), ≤6 eos/hpf (medium grey bars) and <1 eos/hpf (light grey bars) levels. (D) Change in endoscopic severity as measured by EREFS from baseline to month 3. EEsAI, Eosinophilic Esophagitis Symptom Activity Index; EREFS, EoE Endoscopic Reference Score.

histological responses of <15 eos/hpf were seen in 21% of the placebo to mepolizumab group and 32% of those who remained on mepolizumab (p=0.37), though there was less lamina propria fibrosis in this group; table 3).

Blood eosinophil counts were also examined and decreased substantially in the mepolizumab group by month 1, remained unchanged with placebo at month 3, and were suppressed at month 4 in the subjects who were originally assigned placebo and began mepolizumab at month 3 (online supplemental figure 3).

Endoscopic outcomes

The change in EREFS from baseline to month 3 was larger with mepolizumab than with placebo (1.0±1.1 vs 0.4±1.3; p=0.03; figure 1D), though this was mostly accounted for by change in the inflammatory features (table 2). The change in EREFS by month 6 was similar for those who started on placebo and changed to mepolizumab and those who remained on mepolizumab (0.9±1.1 vs 0.5±1.5; p=0.26) (table 3), and dilation rates at month 6 were also similar (61% and 57%, respectively; p=0.79).

Predictors and subgroup analyses

For the subjects who received mepolizumab 300 mg monthly, we did not identify any baseline characteristics that predicted histological response (<15 eos/hpf) at month 3 (online supplemental table 1). For example, while histological responders were 6.9 years older, the 95% CIs of this difference (−1.7 to 29.1) crossed zero. Similarly, while odds of dilation were six times higher in histological responders, the 95% CIs (0.6 to 57.7) crossed 1. There was also no difference in baseline blood eosinophil counts by response status.

When we examined the differences in change in EEsAI scores at month 3 among study subgroups, overall there were no major differences (online supplemental table 2). However, the change in EEsAI was greater for mepolizumab than placebo for those with <6 years since EoE diagnosis (15.6±6.0 vs 1.5±6.5) and for those with <5 prior oesophageal dilations (14.4±7.9 vs 2.7±6.6), though these differences did not exceed the meaningful symptom reduction of 20 points with the EEsAI.

Safety

Overall, mepolizumab was generally well tolerated, with no medication-related serious adverse events (SAEs) (table 4). The overall rate of AEs was 47% for mepolizumab and 71% for placebo in part 1, and 79% for the placebo to mepolizumab group and 64% for the group continued on mepolizumab in part 2. The most common AEs were injection site reactions, occurring in 28% in mepolizumab and 12% in placebo in part 1, and in similar proportions in part 2. There were five SAEs reported for four patients in this study, all of which were in the mepolizumab group and all of which were deemed unrelated to the study medication. These events were acute appendicitis, cervical spine fracture from a fall requiring surgery, worsening of pre-existing lumbar degenerative disc disease that required surgery, and both corrective jaw surgery and corrective wrist surgery in the same patient for pre-existing conditions. There was one case

Table 3 Month 6 treatment outcome responses for patients initially randomised to mepolizumab (6 months of 300 mg monthly) compared with patients initial randomised to placebo who then received mepolizumab (3 months of 100 mg monthly)

	Placebo → mepo 100 mg monthly (n=28)	Mepo 300 mg monthly for six mos (n=28)	P value*
EEsAI scores (mean±SD)			
Baseline	52.6±14.3	54.4±15.4	0.66
Month 3	44.0±14.8	39.1±17.6	0.27
Month 6	33.9±16.0	36.0±20.1	0.67
P (within groups—BL–M3)	0.02	<0.001	
P (within groups—M3–M6)	0.008	0.32	
P (within groups—BL–M6)	<0.001	<0.001	
Change in score from BL to M3	8.6±18.9	15.2±18.5	0.14
Change in score from M3 to M6	10.1±18.4	3.1±16.2	0.37
Change in score from BL to M6	18.6±19.2	18.3±18.1	0.85
Score ≤20 at M6 (clinical remission; n, %)	5 (18)	5 (18)	1.0
Decrease in score ≥20 at M6 (clinical response; n, %)	13 (46)	13 (46)	1.0
SDI scores (mean±SD)			
Baseline	5.7±1.5	5.7±1.6	1.0
Month 3	2.7±2.0	3.4±2.2	0.26
Month 6	2.2±2.1	2.6±2.2	0.50
P (within groups—BL–M3)	<0.001	<0.001	
P (within groups—M3–M6)	0.38	0.04	
P (within groups—BL–M6)	<0.001	<0.001	
Change in score from BL to M3	2.9±2.3	2.3±1.8	0.44
Change in score from M3 to M6	0.4±2.2	0.7±1.6	0.97
Change in score from BL to M6	3.4±2.7	3.0±1.9	0.55
Overall EREFS (mean±SD)			
Baseline	5.4±1.5	5.1±1.6	0.51
Month 3	5.1±1.8	4.0±1.7	0.02
Month 6	4.5±1.8	4.6±1.8	0.88
P (within groups—BL–M3)	0.22	<0.001	
P (within groups—M3–M6)	0.01	0.05	
P (within groups—BL–M6)	<0.001	<0.001	
Change in score from BL to M3	0.3±1.2	1.1±1.0	0.03
Change in score from M3 to M6	0.6±1.1	−0.6±1.6	0.01
Change in score from BL to M6	0.9±1.1	0.5±1.4	0.26
Peak eosinophil counts (mean eos/hpf±SD)			
Baseline	152.6±96.9	113.8±75.3	0.10
Month 3	179.2±138.4	37.0±44.9	<0.001
Month 6	50.2±42.2	26.0±19.7	0.008
P (within groups—BL–M3)	0.20	<0.001	
P (within groups—M3–M6)	<0.001	0.19	
P (within groups—BL–M6)	<0.001	<0.001	
Absolute change from BL to M3	+26.6±106.2	−76.8±72.2	<0.001
Absolute change from M3 to M6	−129.0±120.5	−11.0±43.0	<0.001
Absolute change from BL to M6	−102.4±82.5	−87.9±76.6	0.04
Histological response (n, %)			
<15 eos/hpf	6 (21)	9 (32)	0.37
≤6 eos/hpf	3 (11)	3 (11)	1.0
≤1 eos/hpf	1 (4)	1 (4)	1.0

*Means between groups compared with two sample t-tests; means within groups (pre–post treatment) compared with paired t-tests; change form baseline p value calculated by ANCOVA with least square change method; proportion between groups compared with $\chi 2$; proportions within groups (pre–post treatment) compared with McNemar's test.
ANCOVA, analysis of covariance; BL, baseline; EEsAI, Eosinophilic Esophagitis Symptom Activity Index; EREFS, EoE Endoscopic Reference Score; M3, month 3; SDI, Straumann Dysphagia Index.

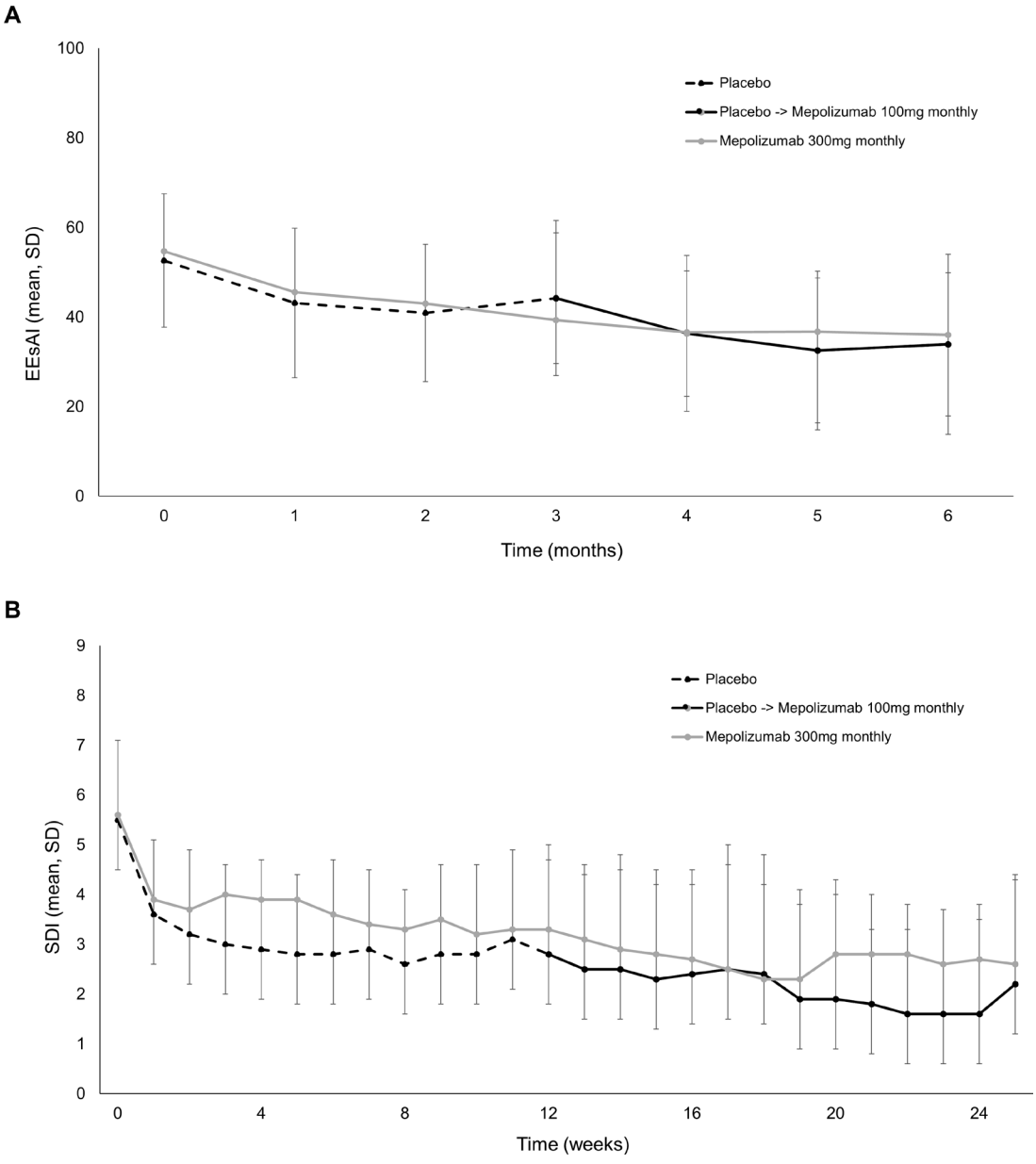

Figure 2 Symptom scores (±SDs) over the study timeframe for mepolizumab (grey solid line) and placebo (black dotted line). (A) Monthly EEsAI scores. (B) Weekly SDI scores. EEsAI, Eosinophilic Esophagitis Symptom Activity Index; SDI, Straumann Dysphagia Index.

of oral herpes simplex infection which occurred in the placebo group during the first study period.

DISCUSSION

With the increasing burden of disease related to EoE and with limited approved therapies, there is a need to investigate additional treatment options. Based on the presumed mechanistic role of IL-5 in EoE pathogenesis[2 18–20] and prior treatment data,[24 25 40] we performed a multicentre, randomised, double-blind, placebo-controlled clinical trial of mepolizumab for treatment of adults and adolescents with active EoE. We found that while symptoms of dysphagia decreased somewhat more in the mepolizumab group at 3 months, the change was not significant and the study did not meet the primary endpoint, and symptoms were similar between the two groups at 6 months regardless of mepolizumab dosing or frequency (100 mg for 3 months or 300 mg for 6 months). However, we also found that oesophageal eosinophil counts significantly improved, histological response was significantly higher with mepolizumab compared with placebo, and the effect was stronger with the higher mepolizumab dose, though this was balanced by lack of response in other histological features such as basal zone hyperplasia. There was a modest but significant improvement in endoscopic severity with mepolizumab, particularly for inflammatory features, and the medication was generally well tolerated with no new safety signals detected. Notably, these results were observed in an EoE patient population that could be classified as severe.[41] Patients had long-standing disease, were treatment experienced (all patients were PPI non-responders, half were steroid non-responders, about one in six had received a biologic in a prior clinical trial), and were largely fibrostenotic (three quarters had prior oesophageal dilations). Based on this, mepolizumab is likely not clinically beneficial in this severe group, but could be explored in the future in a less severe population

Table 4 Adverse events and safety

Event (n, %)	Part 1 (screening to month 3)		Part 2 (month 3 to end of study)	
	Placebo (n=34)	Mepolizumab 300 mg monthly (n=32)	Placebo → Mepo 100 mg monthly (n=28)	Mepo 300 mg monthly continued (n=28)
Death	0	0	0	0
Any adverse event	24 (71)	15 (47)	22 (79)	18 (64)
Serious adverse event (SAE)*	0	2 (6)	0	2 (7)
Adverse event leading to discontinuation†	0	1 (3)	1 (4)	0
Adverse event occurring in ≥5% of patients‡				
Injection site reaction	4 (12)	9 (28)	5 (18)	8 (29)
Injection site bruise	3 (9)	1 (3)	4 (14)	2 (7)
Headache	3 (9)	2 (6)	3 (11)	0
Fatigue	2 (6)	3 (9)	1 (4)	1 (4)
COVID-19	4 (12)	0	3 (11)	0
Abdominal pain	2 (6)	2 (6)	1 (4)	0
Flu-like symptoms	3 (9)	1 (3)	1 (4)	0
Upper respiratory infection	1 (3)	1 (3)	2 (7)	1 (4)
Sore throat	2 (6)	1 (3)	1 (4)	0
Oesophageal pain	2 (6)	0	1 (4)	1 (4)
Vomiting	1 (3)	1 (3)	2 (7)	0
Dysphagia	2 (6)	0	1 (4)	0
Nausea	1 (3)	1 (3)	1 (4)	0
Sinusitis	2 (6)	0	0	1 (4)

*None of the SAEs assessed were considered by the trial investigators to be related to the study medication. SAEs included acute appendicitis, cervical spine fracture from a fall requiring surgery, worsening of pre-existing lumbar degenerative disc disease that required surgery, and both corrective jaw surgery and corrective wrist surgery in the same patient for pre-existing conditions.
†One subject withdrew for back surgery and one withdrew for COVID-19. Neither event was deemed related to the study medication.
‡Adverse events were reported according to the Common Terminology Criteria for Adverse Events V.5.0.

as earlier therapy, as part of combination therapy, or as maintenance therapy.

The first report of use of mepolizumab in EoE was by Stein *et al* where four adults with EoE were given 750 mg intravenously (open-label) monthly for 3 months.[40] All patients had a substantial decrease in oesophageal eosinophilia, and a general improvement in symptoms and endoscopic findings. Straumann *et al* then performed a randomised clinical trial in 11 adults, with 2 intravenous doses of 750 mg, with additional dosing of 1500 mg allowed for those in whom histological remission (<5 eos/hpf) was not achieved.[24] They showed a good histological effect (55% decrease in mean tissue eosinophil levels with mepolizumab vs 7% decrease with placebo at week 13), but variable symptom response. A larger randomised trial examining three dosing regimens in 59 children also showed a good histological effect (peak eosinophil count decreased from 118 eos/hpf to 24 eos/hpf in the 2.5 mg/kg arm) with overall histological response (<20 eos/hpf) of 32%, but symptoms were relatively mild at baseline and there was no clear overall trend towards symptom improvement.[25] Of note, similar results were also observed in a clinical trial of children treated with a different anti-IL-5 antibody (reslizumab),[42] though those who initially responded maintained long-term remission.[43] Overall, these results are generally consistent with our own, with moderate levels of histological response in the absence of clear symptom improvement, though it is somewhat difficult to compare the clinical characteristics of the prior study populations to our more fibrostenotic adult/adolescent population. We also note that our results, including for symptoms, histology and endoscopic severity, are more modest that has been previously noted either with the budesonide orodispersible tablet or with dupilumab.[14 39]

These results raise the question of why the symptom response was not stronger in the patients on active therapy compared with placebo in our study. It is now well understood that there can be discordance between histologic and symptom severity in EoE,[30] and previous trials have found histological improvement without symptom improvement.[25 42 44] Moreover, if fixed fibrosis is present, symptoms may not improve even if inflammatory activity subsides.[26] If oesophageal dilation is performed, then symptoms improve regardless of biological disease activity, which has been noted in some trials as well as cross-sectional studies,[45–47] but has not been seen in other trials.[16] Our study design attempted to guard against this by using a validated PRO, requiring a symptom threshold for entry, excluding patients with severe strictures or narrowing that precluded passage of a standard adult upper endoscope, and excluding patients with dilation within 8 weeks of their screening endoscopy. This resulted in a study population with high baseline EEsAI scores (>50), an average of >1 year since last dilation and strictures (present in >60%) with an average diameter of 13–14 mm. While we did not appreciate substantial symptom improvement overall, on subgroup analysis there was a suggestion that a larger change in symptoms was seen in the patients with shorter EoE duration (<6 years since diagnosis) and fewer overall dilations (<5). These results suggest earlier intervention in less treatment-experienced patients may be worth examining in future studies.

Another possibility is that targeting the IL-5 pathway alone, while effective for decreasing eosinophil counts, may not be effective for fully controlling all aspects of EoE. Recent studies of more potent eosinophil depleting medications such as lirentelimab (anti-siglec-8) and benralizumab (anti-IL-5R) showed a marked histological response with no overall symptom benefit

compared with placebo.[48 49] This suggests that though eosinophils are a biomarker for diagnosis of EoE and key effector cells,[1 2] they may not be solely responsible for driving EoE pathogenesis. As a T-cell-mediated disease, there are multiple other cytokines and cell types involved,[2] and elimination of a single element in the pathway may not give as broad of a treatment effect compared with steroids or biologics that target more elements.[11 14 16] For example, our data show persistent basal zone hyperplasia and spongiosis, and no change in the EREFS fibrostenotic subscore, which could be reflective of ongoing proliferative, epithelial barrier and fibrosis-related changes. However, this would be in contrast to other data showing that mepolizumab may have broader effects, including reduction in the level of mast cells and IL-9.[50] Elucidating these mechanisms further will be a goal of future research.

There are potential limitations of this study. First, the patient population was on the severe spectrum for EoE, treatment experienced and refractory to a number of prior therapies. While this is a reasonable target population for a biologic and not a limitation in itself, because this is among the most severe populations yet enrolled in an EoE clinical trial we are unable to assess how mepolizumab would work in a less severe population. Second, while we enrolled adults and adolescents, the majority of our patients were above 18 years of age, so results cannot be extended to children. Third, while the second part of the study was blinded to dose, patients knew they were receiving active medication so symptom outcomes at month 6 should be interpreted with caution. As a multicentre, double blind, placebo-controlled, randomised clinical trial, there are many strengths including the rigorous design, data collection protocols, validated outcome metrics, and enrolment sites that spanned both academic and community practices. Further, we stratified randomisation by steroid non-response, which had a strict definition applied to all subjects, and we precluded dilation at baseline and during the month 3 endoscopy to minimise confounding of symptoms.

In conclusion, in this population of previously difficult to treat EoE patients, mepolizumab 300 mg given subcutaneously monthly as stand-alone therapy for 3 months did not meet the primary endpoint of a statistically significant improvement in dysphagia symptoms compared with placebo. However, mepolizumab yielded significant improvements in oesophageal eosinophil counts and endoscopic severity. Extending the use of mepolizumab to a total of 6 months did not lead to additional symptom, endoscopic or histological improvement compared with 3 months of use, but responses were generally maintained. Subjects who initially received placebo but who then received mepolizumab 100 mg monthly for 3 months generally had similar improvements to those receiving the higher dose. The mediation was well-tolerated overall. Future studies could investigate mepolizumab efficacy in less severe populations or as longer-term maintenance, determine whether this medication could be positioned in EoE treatment algorithms, and elucidate other pathogenic mechanisms that may lead to persistent disease activity despite targeting IL-5 and eosinophil-specific pathways.

Contributors All authors approved the final manuscript. ESD: project conception, study design, data collection, data analysis/interpretation, manuscript drafting, critical revision, obtained funding, guarantor. KAP, BLM and IH: data collection, data interpretation, critical revision. AI, CB and JTW: data collection, study pathologist, data interpretation, critical revision. LMC, KBW, TSG, SJM, BAC and SEM: data collection and management, monitoring, critical revision. JAG: study design, data analysis/interpretation; critical revision. SE: data collection, data interpretation, monitoring, critical revision.

Funding This study was supported by an investigator-initiated research grant from GlakoSmithKline (GSK ISS 209033), and used resources from UNC Center for GI Biology and Disease (NIH P30 DK034987), NC TraCS, which is funded by the National Center for Advancing Translational Sciences (NCATS) Clinical and Translation Science Award (UM1TR004406), and the UNC Pathology Services Core, which is supported in part by an NCI Center Core Support Grant (P30 CA016086), and the North Carolina Translational and Clinical Sciences Institute which is supported by the National Center for Advancing Translational Sciences (NCATS; NIH UL1TR002489).

Disclaimer The study sponsor did not have any role in the study design or in the collection, analysis, or interpretation of the data.

Competing interests ESD has received research funding from Adare/Ellodi, Allakos, Arena, AstraZeneca, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/BMS, Regeneron, Revolo, Shire/Takeda; consulting fees from Abbott, Abbvie, Adare/Ellodi, Aimmune, Akesobio, Alfasigma, ALK, Allakos, Amgen, Aqilion, Arena/Pfizer, Aslan, AstraZeneca, Avir, Biorasi, Calypso, Celgene/Receptos/BMS, Celldex, Eli Lilly, EsoCap, Eupraxia, Ferring, GSK, Gossamer Bio, Holoclara, Invea, Landos, LucidDx, Morphic, Nexstone Immunology, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Salix, Sanofi, Shire/Takeda, Target RWE, Upstream Bio; and educational grants from Allakos, Holoclara, Invea. IH has received research funding from Adare/Ellodi, Allakos, Arena, AstraZeneca, Meritage, Celgene/Receptos/BMS, Regeneron, Shire/Takeda; consulting fees from Adare/ Ellodi, Allakos, Amgen, Arena/Pfizer, Aslan, AstraZeneca, Celgene/Receptos/BMS, Celldex, EsoCap, Gossamer Bio, Nexstone Immunology, Parexel/Calyx, Phathom, Regeneron, Sanofi, Shire/Takeda. KAP has received research funding from AstraZeneca, Allakos, Adare, Regeneron-Sanofi, Revolo,; Speaker: AGA, Regeneron, Peerview, Takeda, Allakos, WebMD; unrestricted grant support from Allakos, Chobani; consulting or advisory board fees from AGA, Alladapt, AstraZeneca, Allakos, Bristol Meyers Squibb, Ellodi, Invea, Lucid, Nexstone, WebMD, Peerview, Regeneron, Revolo, Takeda, WebMD; and has equity in Nexeos Bio. The other authors report no relevant disclosures.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by University of North Carolina IRB #18-0431. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data may be shared after all planned analyses have been completed, and with required approvals in place.

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