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TITLE PAGE

Title: Comparison of Drugs for Active Eosinophilic Oesophagitis: Systematic Review and Network Meta-Analysis

Short running head: Drugs for Active Eosinophilic Oesophagitis: Network Meta-Analysis

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ABBREVIATIONS:

BOS	budesonide oral suspension
BOT	budesonide orally disintegrating tablet
CI	confidence interval
EoE	eosinophilic oesophagitis
FOT	fluticasone orally disintegrating tablet
HPF	high-power field
PPI	proton pump inhibitors
RCT	randomised controlled trial
RR	relative risk

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ABSTRACT

Background: There is currently no recommendation regarding preferred drugs for active eosinophilic oesophagitis (EoE) because their relative efficacy is unclear. We conducted an up-to-date network meta-analysis to compare proton pump inhibitors, off-label and EoE-specific topical steroids, and biologics in EoE.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials from inception to June 2023. We included randomised controlled trials (RCTs) comparing efficacy of all drugs versus each other, or placebo, in adults and adolescents with active EoE. Results were reported as pooled relative risks with 95% confidence intervals to summarise effect of each comparison tested, with drugs ranked according to P-score.

Results: Seventeen RCTs were eligible for systematic review. Of these, 15 studies containing 1813 subjects with EoE reported extractable data for the network meta-analysis. For histological remission defined as ≤6 eosinophils/high-power field (HPF), lirentelimab 1mg/Kg monthly ranked first. For histological remission defined as ≤15 eosinophils/HPF, budesonide orally disintegrating tablet 1mg b.i.d. ranked first. For failure to achieve symptom improvement, budesonide orally disintegrating tablet 1mg b.i.d. and budesonide oral suspension 2mg b.i.d. were significantly more efficacious than placebo. For failure to achieve endoscopic improvement based on the EoE endoscopic reference score, budesonide orally disintegrating tablet 1mg b.i.d. and budesonide oral suspension 1mg b.i.d. or 2mg b.i.d. were significantly more efficacious than placebo.

Conclusions: Although this network meta-analysis supports the efficacy of most available drugs over placebo for EoE treatment, significant heterogeneity in eligibility criteria and outcome measures among available trials hampers the establishment of a solid therapeutic hierarchy.

KEY WORDS: Eosinophilic oesophagitis; treatment; topical steroids; dupilumab; meta-analysis

What is already known on this topic

There is currently no recommendation regarding preferred drugs for active eosinophilic oesophagitis (EoE), or according to different delivery methods of topical steroids, because their relative efficacy is unclear. We performed a systematic review and network meta-analysis to compare efficacy of proton pump inhibitors (PPIs), EoE-specific and off-label topical steroids, and biologics, versus each other, or placebo, in terms of failure to achieve histological remission, symptomatic response, or endoscopic response in active EoE.

What this study adds

For histological remission defined as ≤6 eosinophils/high-power field (HPF), lirentelimab low-dose (1mg/Kg) monthly, BOT 1mg b.i.d., benralizumab 30mg 4-weekly, lirentelimab high-dose (1mg/Kg at month 1 then 3mg/Kg for five monthly doses), FOT 1.5mg b.i.d., FOT 3mg b.i.d., FOT 3mg o.d., dupilumab 300mg weekly, dupilumab 300mg 2-weekly, esomeprazole 40mg o.d., BOS 1mg b.i.d. or 2mg b.i.d., FOT 1.5mg o.d., and aerosolised fluticasone 440mcg b.i.d. or 880mcg b.i.d. were all significantly more efficacious than placebo. Among drugs available outside of clinical trials, BOT 1mg b.i.d. and dupilumab 300mg weekly ranked higher than esomeprazole 40mg o.d. and off-label topical steroids, including aerosolised fluticasone or budesonide. EoE-specific formulations were generally superior to adapted asthma medications in achieving histological remission. For failure to achieve symptom improvement, budesonide orally disintegrating tablet 1mg b.i.d. and budesonide oral suspension 2mg b.i.d. were significantly more efficacious than placebo. For failure to achieve endoscopic improvement based on the EoE endoscopic reference score, budesonide orally disintegrating tablet 1mg b.i.d. and budesonide oral suspension 1mg b.i.d. or 2mg b.i.d. were significantly more efficacious than placebo.

How this study might affect research, practice or policy

This network meta-analysis supports the efficacy of most available drugs over placebo for the treatment of EoE. However, the significant heterogeneity in the eligibility criteria and outcome measures hampers the establishment of a solid therapeutic hierarchy in the setting of EoE based on available trials.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic, progressive, immune-mediated disease restricted to the oesophagus and characterised by symptoms of oesophageal dysfunction and increased oesophageal intra-epithelial eosinophils.[1] Typical symptoms in adults and adolescents include dysphagia, intermittent food bolus impaction, and chest pain,[1] which are often present for years before a conclusive diagnosis is made.[2] Burden of disease studies report incidence estimates of around 20 per 100,000 individuals per year, similar to that of inflammatory bowel disease,[3, 4] and a prevalence of more than 1 in 1000 individuals in Western Countries.[5] In addition, although the economic burden of EoE already exceeds that of inflammatory bowel disease and celiac disease,[6, 7] because of increasing incidence, costs of the disease are expected to increase further.[8]

Drug options for EoE recommended by current clinical guidelines include proton pump inhibitors (PPIs) and topical steroids.[9-12] In this regard, evidence on topical steroid treatment in EoE comes mostly from studies using medications designed for the treatment of asthma, rather than formulations designed specifically for EoE. However, more data on novel EoE-specific steroid formulations are becoming available,[13] so a comparison with the efficacy of off-label steroids is needed. In addition, current guidelines do not recommend the use of monoclonal antibodies outside of randomised controlled trials (RCT) because data were lacking at the time of their development.[10-12] However, the clinical trial literature for the treatment of EoE has expanded considerably recently, and more data on monoclonal antibodies are now available.[13] In addition, current guidelines advocate use of either PPIs or topical steroids as first-line treatment for active EoE, with no recommendation regarding preference between these drugs because their relative efficacy is still unclear.[10-12]

Although two network meta-analyses have investigated the efficacy of various drugs for EoE,[14, 15] and another compared PPIs with topical steroids,[16] these have major limitations. None included RCTs of dupilumab, the only approved drug for EoE in the US, nor newer agents such as lirentelimab or benralizumab. In addition, one did not include any RCTs of budesonide orally

disintegrating tablet (BOT), the only approved drug for EoE in Europe, or any RCTs of PPIs, nor could it compare off-label topical steroids with those designed specifically for EoE.[14] In addition, the three previous network meta-analyses did not investigate the comparative efficacy of drugs on endoscopic improvement based on the validated EoE endoscopic reference score (EREFS),[14-17] and one only assessed efficacy in terms of histological outcomes, rather than symptom improvement,[14] despite the fact that EoE treatment endpoints require a reduction in eosinophil count to <15 eosinophils per high power field (HPF), improvement of symptoms, and improvement in endoscopic abnormalities, as recently highlighted by an interdisciplinary consensus.[18, 19]

We, therefore, performed a network meta-analysis to evaluate efficacy and safety of all drugs tested in EoE, compared with each other or with placebo, in terms of induction of histological remission, symptomatic response, and endoscopic response in active EoE. To inform EoE treatment based on recent evidence, in our network meta-analysis, we analysed efficacy of novel topical steroids designed specifically for the treatment of EoE separately to off-label topical steroids designed for the treatment of asthma.

METHODS

Search Strategy and Study Selection

For this systematic review and network meta-analysis, we searched MEDLINE (1946 to 4th June 2023), EMBASE and EMBASE classic (1947 to 4th June 2023), and the Cochrane central register of controlled trials (from 2005 to 4th June 2023). We also hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2006 and 2023 to identify studies published only in abstract form.

RCTs examining the efficacy of topical steroids, PPIs, or biologic drugs versus each other, or versus a placebo, in adults and adolescents ≥12 years with active EoE were eligible for inclusion (Table 1). Duration of therapy had to be at least 6 weeks. Trials using any dose or combination of topical steroids, PPIs, or biologics were eligible. Studies had to report either an assessment of failure to achieve histological remission, clinical response or endoscopic response in patients with active EoE. Histological remission was defined as a reduction in oesophageal eosinophilic infiltrate to ≤15 eosinophils per HPF and to ≤6 eosinophils per HPF, clinical response was defined according to the symptom endpoints used in each trial, and endoscopic response was defined as a 50% improvement in the EREFS score compared with baseline. We did not include trials studying the maintenance of remission in EoE. Ethical approval for this evidence synthesis was not required.

Studies were identified with the terms: *eosinophilic esophagitis*, *eosinophilic oesophagitis*, *EoE*, *oesophageal eosinophilia*, or *oesophageal eosinophilia* (all as medical subject headings and as free text terms). These were combined using the set operator AND with studies identified with the terms: *proton pump inhibitor*, *fluticasone*, *orodispersibile fluticasone*, *budesonide*, *orodispersible budesonide*, *oral viscous budesonide*, *oral budesonide suspension*, *budesonide orodispersible tablet*, *anti-IL4*, *anti-IL5*, *anti-IL13*, *mepolizumab*, *reslizumab*, *QAX576*, *RPC4046*, *omalizumab*, *benralizumab*, *dupilumab*, *infliximab*, *vedolizumab*, *AK001*, *AK002*, *tezepelumab*, *etrasimod*, *anti-*

SIGLEC-8, lirentelimab, montelukast, CRTH2-antagonists, or OC000459. There were no language restrictions. We screened the titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant to examine them in more detail. We performed a recursive search, using the bibliographies of all eligible articles. We planned to translate foreign language articles, where required. If a study appeared potentially eligible, but did not report the data required, we planned to contact authors to obtain supplementary information. We performed eligibility assessment independently. This was done by two investigators (PV and BB), using pre-designed eligibility forms. We resolved any disagreements by consensus and measured the degree of agreement with a kappa statistic.

Outcome Assessment

The primary outcome assessed was the efficacy of topical steroids, PPIs, or biologics versus each other, or placebo, in terms of failure to achieve histological remission, clinical response, or endoscopic response in adult and adolescent patients with EoE. The secondary outcome was treatment-related adverse events.

Data Extraction

Data were extracted independently by two investigators (PV, BB) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) as dichotomous outcomes (histological remission or no histological remission, clinical response or no clinical response, and endoscopic response or no endoscopic response). Results of data extraction were compared and any disagreements resolved by consensus. We extracted the following clinical data for each trial, where available: year of publication, country of origin, number of centres, sample size, endpoint(s) of the study, type, dosage, and duration of drug, and number of individuals incurring any of the adverse events. Wherever trial reporting allowed, we extracted data as intention-to-treat analyses, with all dropouts assumed to be treatment failures (i.e., failed to achieve histological remission, clinical response, or

endoscopic response). If the number of dropouts was not clear from the original article, we extracted data only for patients with reported evaluable data. Individual trials reported different cut-offs of eosinophils per HPF for the definition of histological remission, but we standardised this by extracting two cut-offs, as reported in the individual trials themselves, of either ≤15 eosinophils per HPF or ≤6 eosinophils per HPF. These cut-offs are those set in the recently interdisciplinary consensus aimed to develop a core outcome set for therapeutic studies in EoE (COREOS).[19]

Quality Assessment and Risk of Bias

We used the Cochrane Risk of Bias tool to assess the quality of studies.[20] Two investigators (PV, BB) assessed study quality independently, with disagreements resolved by discussion. For all RCTs we recorded the method used to generate the randomization schedule and conceal treatment allocation, whether participants, personnel, and outcome assessors were blinded, whether there was evidence of incomplete patient outcome data, and whether there was evidence of selective reporting of patient outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using the frequentist model with the statistical package netmeta (version 0.9-0), in R (version 3.4.6) to compare (directly and indirectly) the efficacy and safety of each of the drugs of interest across studies. We reported this according to the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses,[21] to explore direct and indirect treatment comparisons on the efficacy and safety of each intervention. Network meta-analysis usually give a more precise estimate of the relative efficacy and safety than results from standard pairwise analyses,[22, 23] and can rank interventions to inform clinical decisions.[24] We examined the symmetry and geometry of the data by producing a network plot with node sizes corresponding to number of study participants, and connection sizes corresponding to number of studies for each drug. We also generated comparison-adjusted funnel

plots to evaluate publication bias and small study effects for all available treatment comparisons, using R studio (version 3.4.6), where there were sufficient studies (≥10 studies).[25] These are scatterplots of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias or small-study effects.[26] For each drug, we generated a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested using a random effects model as a conservative estimate. We used the RR of failure to achieve histological remission, clinical response, or endoscopic response at the last time point of assessment in the trial, whereby if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of one drug over another, or over placebo. This approach is more stable, compared with RR of improvement, or using the OR, for some meta-analyses.[27]

We assessed global statistical heterogeneity across all comparisons using the I^2 measure with the netmeta statistical package. The I^2 measure ranges from 0% to 100% with a value of 25% to 49% indicating low study heterogeneity, 50% to 74% moderate heterogeneity, and ≥75% high heterogeneity.[28] Moreover, we ranked drugs according to the P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the extent of certainty that one drug is better than another, according to any given endpoint, as an average over all other competing drugs.[29] The higher the P-score, the greater the probability of the drug being ranked as best,[29] but magnitude of the P-score should also be considered. As the mean value is always 0.5, if individual drugs cluster around this value, they are likely to have similar efficacies. However, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.[30]

RESULTS

Systematic Literature Review

The literature search identified 3319 citations, of which 3259 were excluded on review of the title and abstract (Figure 1). Therefore, 60 articles appeared relevant to the study question. Forty-three studies were excluded because they involved a paediatric or a mixed population of paediatric and adult patients, were dual publications, or did not involve patients with EoE, but other eosinophilic gastrointestinal disorders. In total, 17 studies were eligible for the systematic review. Among these, two other potentially eligible studies could not be included in the network meta-analysis because they did not report extractable data,[31] or because the duration of the study was shorter than 6 weeks.[32] In one of these studies, OC000459 was superior to placebo in terms of histological and clinical improvement after eight weeks of treatment.[31] In the other study, a 2-week treatment with either effervescent or viscous budesonide was superior to placebo in terms of induction of histological remission defined as a reduction in oesophageal eosinophilic infiltrate to ≤15 eosinophils per HPF and endoscopic improvement, but was comparable to placebo in terms of symptoms response.[32] A full list of excluded papers, with reasons for exclusion, is provided in Supplementary Table 1.

In total, 15 studies, containing 1813 subjects with active EoE, fulfilled all eligibility criteria for the network meta-analysis. Detailed characteristics of all included studies are provided in Supplementary Table 2. Among the studies eligible for the meta-analysis, there was significant heterogeneity in inclusion and exclusion criteria, as well as outcome measures. In terms of the enrolled population, studies on biologics included a proportion of patients that had already tried or failed topical steroids.[33-36] In contrast, studies on topical steroids only included PPI-refractory patients. For the assessment of symptoms, few studies used validated patient-reported outcomes,[35-41] with most using non-validated instruments.[33, 34, 42-45] In addition, the size of high-power fields varied from 0.19mm^2 to 0.53mm^2 across included studies and was not reported in two studies (Supplementary Table 2).[35, 44] Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.92). Overall, 1221 patients received active drug and 592 received

placebo. Eleven trials studied the efficacy of active drug versus only placebo,[33-37, 39-41, 43, 46, 47] and four compared active drugs.[38, 42, 44, 45] Five trials investigated EoE-specific steroid formulations,[37, 39-41, 44] and five investigated off-label swallowed steroid formulations adapted from the treatment of asthma.[38, 42-45] Patients were allocated to active therapy or placebo as described in Supplementary Table 3. Risk of bias for all included trials is reported in Supplementary Table 4; nine studies were at low risk of bias across all domains.[33-39, 41, 43]

Failure to Achieve Histological Remission in Active EoE

Failure to Achieve a Reduction in Oesophageal Eosinophilic Infiltrate to ≤6 Eosinophils per HPF

All fifteen RCTs, containing 1813 patients, reported data concerning efficacy of topical steroids, esomeprazole, or biologics in terms of failure to achieve histological remission as a reduction in oesophageal eosinophilic infiltrate to ≤6 eosinophils per HPF.[33-47] The network plot is provided in Supplementary Figure 1A. Pooled analysis revealed moderate statistical heterogeneity (I^2 = 60.2%). Low-dose lirentelimab (1mg/Kg monthly for 6 months), BOT 1mg b.i.d., benralizumab 30mg 4-weekly, high-dose lirentelimab (1mg/Kg at month 1 then 3mg/Kg for five monthly doses), FOT 1.5mg b.i.d., FOT 3mg b.i.d., FOT 3mg o.d., dupilumab 300mg weekly, dupilumab 300mg 2-weekly, esomeprazole 40mg o.d., BOS 1mg b.i.d. or 2mg b.i.d., FOT 1.5mg o.d., and aerosolised fluticasone 440mcg b.i.d. or 880mcg b.i.d. were all significantly more efficacious than placebo, but low-dose lirentelimab (RR of failure to achieve histological remission as a reduction in oesophageal eosinophilic infiltrate to ≤6 eosinophils per HPF = 0.08, 95% CI 0.04 to 0.19, P score 0.94) ranked first (Figure 2A). This means the probability of low-dose lirentelimab being the most efficacious when all drugs, including placebo, were compared with each other was 94%. BOT 1mg b.i.d. ranked second (RR = 0.08, 95% CI 0.03 to 0.21, P score 0.94), and benralizumab 30mg 4-weekly ranked third (RR = 0.14, 95% CI 0.07 to 0.25, P score 0.85). After indirect comparison of active drugs, low-dose lirentelimab was superior to all drugs except BOT 1mg b.i.d., benralizumab 30mg 4-weekly, high-dose lirentelimab, FOT 1.5mg b.i.d., and FOT 3mg b.i.d. (Figure 2B).

Failure to Achieve a Reduction in Oesophageal Eosinophilic Infiltrate to ≤15 Eosinophils per HPF

Eleven RCTs reported extractable data concerning efficacy of topical steroids, esomeprazole, or biologics in terms of failure to achieve histological remission defined as a reduction in oesophageal eosinophilic infiltrate to ≤15 eosinophils per HPF.[33-42, 44] In total, 1306 patients were recruited of whom 1005 received active drug. The network plot is provided in Supplementary Figure 2A. Pooled analysis revealed high statistical heterogeneity (I^2 = 82.0%). BOT 1mg b.i.d., fluticasone orally disintegrating tablet (FOT) 1.5mg b.i.d., FOT 3mg b.i.d., dupilumab 300mg weekly, FOT 3mg o.d., FOT 1.5 o.d., budesonide oral suspension (BOS) 1mg b.i.d. or 2mg b.i.d., and RPC4046 180mg or 360mg weekly were all significantly more efficacious than placebo, but BOT 1mg b.i.d. (RR of failure to achieve histological remission as a reduction in oesophageal eosinophilic infiltrate to ≤15 eosinophils per HPF = 0.07, 95% CI 0.02 to 0.20, P score 0.96) ranked first (Figure 3A). FOT 1.5mg b.i.d. ranked second (RR = 0.09, 95% CI 0.02 to 0.37, P score 0.92), while FOT 3mg b.i.d. ranked third (RR = 0.19, 95% CI 0.07 to 0.55, P score 0.78). After indirect comparison of active drugs, BOT 1 mg b.i.d. was superior to all other drugs except for FOT 1.5mg b.i.d. and FOT 3mg b.i.d. (Figure 3B). Four other trials did not report data on histological remission defined as a reduction in oesophageal eosinophilic infiltrate to ≤15 eosinophils per HPF.[43, 45-47]

Failure to Achieve Symptom Improvement in Active EoE

Eight RCTs reported extractable data concerning efficacy of topical steroids, esomeprazole, and biologics in terms of failure to achieve symptom improvement.[34, 36, 37, 39-43] In total, 760 patients were recruited of whom 511 received active drug. The network plot is provided in Supplementary Figure 3. Pooled analysis revealed moderate statistical heterogeneity (I^2 = 58.9%). Only BOT 1mg b.i.d. and BOS 2mg b.i.d. were significantly more efficacious than placebo, ranking first (RR of failure to achieve symptom improvement = 0.47, 95% CI 0.28 to 0.79, P score 0.93) and second (RR = 0.68, 95% CI 0.48 to 0.96, P score 0.71), respectively (Figure 4A). Again, after indirect

comparison of active drugs, BOT 1mg b.i.d. was also superior to FOT 1.5mg b.i.d. (Figure 4B). Seven other studies provided data on symptom outcomes, but these could not be pooled with other studies due to way in which the endpoints were reported.[33, 35, 38, 44-47] In these studies, dupilumab[35] and RPC4046 360mg[33] were both superior to placebo, and esomeprazole was superior to fluticasone in terms of symptom improvement.[45] Oral viscous budesonide, inhaled budesonide or fluticasone were all compared with each other and improved symptoms comparably.[38, 44] In contrast, lirentelimab[46] and benralizumab[47] were not superior to placebo in terms of symptoms improvement.

Failure to Achieve Endoscopic Improvement in Active EoE Based on the EREFS score

Four RCTs reported extractable data concerning efficacy of topical steroids and biologics in terms of failure to achieve endoscopic improvement based on the EREFS score.[33, 37-39] In total, 443 patients were recruited of whom 304 received active drug. The network plot is provided in Supplementary Figure 4. Pooled analysis revealed no statistical heterogeneity ($I^2 = 0\%$). Only BOT 1mg b.i.d. and BOS 1mg b.i.d. or 2mg b.i.d. were significantly more efficacious than placebo, ranking first (RR of failure to achieve endoscopic improvement = 0.33, 95% CI 0.22 to 0.49, P score 1.00) and second (RR = 0.61, 95% CI 0.45 to 0.83, P score 0.69), respectively (Figure 5A). After indirect comparison of active drugs, only BOT 1mg b.i.d. and BOS were significantly superior to placebo. Moreover, BOT 1mg b.i.d. was superior to all other drugs, including BOS, RCP 4046 360mg weekly, RCP 4046 180mg weekly, and aerosolised fluticasone 440mcg b.i.d. or 800mcg b.i.d. (Figure 5B). Five other studies provided data on endoscopic outcomes according to the EREFS score but could not be pooled with other studies due reporting of data.[35, 36, 40, 41, 47] Dupilumab,[35, 36] FOT,[41] and BOS[40] were superior to placebo, but benralizumab was not superior to placebo in terms of EREFS improvement.[47] Finally, the other six studies did not report endoscopic findings according to the EREFS score.[34, 42-46]

Adverse Events in Active EoE

Total numbers of adverse events were reported by twelve RCTs containing 1319 patients.[33-41, 43-45] There were 921 patients randomised to active treatment. The network plot is provided in Supplementary Figure 5A. Pooled analysis revealed no statistical heterogeneity (I^2= 0%) and no evidence of funnel plot asymmetry (Supplementary Figure 5B). None of the active treatments were more likely to lead to adverse events, compared with placebo (Supplementary Figure 5C), but aerosolised budesonide 1mg b.i.d. ranked first for safety (P-score 0.77). There were twelve RCTs that provided adverse events leading to withdrawal of therapy recruiting 672 patients,[33-38, 40, 41, 43-45] 274 of whom were randomised to active treatment. The network plot is provided in Supplementary Figure 6A. When data were pooled, there was no statistical heterogeneity (I^2= 0%) and no evidence of funnel plot asymmetry (Supplementary Figure 6B). BOS 1mg or 2mg b.i.d. was less likely to lead to withdrawal due to adverse events, compared with placebo (Supplementary Figure 6C), although esomeprazole 40mg o.d. ranked first (P-score 0.82). Three other studies did not report extractable data regarding adverse events.[42, 46, 47]

DISCUSSION

There is currently no recommendation regarding preference between PPIs and topical steroids, or according to different delivery methods of topical steroids in EoE, because their relative efficacy is still unclear.[10-12] In addition, biologics are not currently recommended outside of RCTs.[11, 48] A significant body of literature has been recently published with the potential of changing our current management of EoE. In this systematic review and network meta-analysis, we compared efficacy of esomeprazole, EoE-specific and off-label topical steroids, and biologics, versus each other, or placebo, in terms of failure to achieve histological remission, symptomatic or endoscopic response in active EoE. In our analysis, for histological remission in active EoE, defined as a reduction in oesophageal eosinophilic infiltrate to ≤6 eosinophils per HPF, low-dose lirentelimab, BOT 1mg b.i.d., and benralizumab 30mg 4-weekly ranked first, second, and third, respectively. However, among drugs available outside of clinical trials, BOT 1mg b.i.d. and dupilumab 300mg weekly ranked higher than esomeprazole 40mg o.d. and off-label topical steroids, including aerosolised fluticasone or budesonide. With regards to symptoms improvement, BOT 1mg b.i.d. and BOS 2mg b.i.d. were significantly more efficacious than placebo. However, other drugs, including dupilumab, FOT, and BOS, which showed superiority compared to placebo in terms of symptoms improvement could not be included in the analysis because of a lack of extractable data. Similarly, two included studies on lirentelimab and benralizumab were only available as conference papers, and the full details of non-histological outcomes were not available or extractable for the network meta-analysis. For failure to achieve a >50% improvement in endoscopic EREFS score, BOT 1mg b.i.d. and BOS 1mg b.i.d. or 2mg b.i.d. were significantly more efficacious than placebo, and ranked first, and second, respectively. In terms of safety, none of the active treatments were more likely to lead to adverse events compared with placebo, and BOS 1mg b.i.d. or 2mg b.i.d. was less likely than placebo to lead to withdrawal due to adverse events.

We used accepted and reproducible methodology for this network meta-analysis, which allowed us to make indirect comparisons between 1813 patients across various drugs, dose regimens, and drug delivery methods. For the analysis on histological remission, defined as a reduction in

infiltrate to ≤15 eosinophils per HPF, we pooled the doses of RPC4046 because the two regimens had comparable efficacy. In addition, for the analysis of histological remission and of endoscopic improvement based on the EREFS score, we pooled the doses of BOS to overcome a closed loop in the analysis and avoid the exclusion of aerosolised fluticasone, aerosolised budesonide, and esomeprazole from the network. Similarly, we pooled the doses of aerosolised fluticasone to include esomeprazole in the network.

Limitations of this study include the use of different thresholds to define histological remission and varying sizes of high-power fields in included studies. However, we standardised this as much as possible in our analyses by extracting data at only two cut-offs, either ≤15 or ≤6 eosinophils per HPF, which represent the two main histological outcomes of interest in studies on EoE to date.[19] Nevertheless, recent trials[46, 47] have questioned the peak eosinophil count as the optimal endpoint for establishing superiority of therapy for EoE. In this regard, lirentelimab and benralizumab, the first and third highest ranking drugs for failure to induce histological remission defined as eosinophils ≤6 per HPF in this study, failed to provide symptomatic or endoscopic improvement compared to placebo. In addition, most studies used non-validated instruments to assess symptom response.[33, 34, 42-45] Therefore, the efficacy of these drugs in terms of symptomatic improvement may have been overestimated. Another criticism that could be levelled at this study is that we calculated endoscopic response based on a >50% improvement in the EREFS score, rather than the recently proposed definition of EREFS ≤2.[19, 49] However, the included RCTs did not provide extractable data for this endpoint. We were unable to include data for montelukast, CRTH2-antagonists, or some anti-IL5 drugs, due to a paucity of eligible trials in active EoE. Additionally, some published RCTs of budesonide formulations were ineligible due to a short duration of treatment or the fact that they studied maintenance of remission of EoE.[50, 51] Finally, although we provided estimates of the likelihood of failure to induce histologic, endoscopic, and symptomatic remission with different treatments and provided a ranking, due to significant heterogeneity between available trials in some of our analyses, more homogenous data are required to establish a solid hierarchy to

inform a therapeutic algorithm for active EoE. In this regard, it must be acknowledged that studies on biologics included higher proportions of steroid-refractory patients compared to trials on steroids. Accordingly, studies on biologics are likely to have included more difficult to treat patients and, therefore, the use of heterogenous eligibility criteria might have biased the ranking of drugs in terms of histological remission. In addition, the heterogeneity in the assessment of symptom response might have biased the ranking of drugs.

In contrast to prior work, our network meta-analysis provides updated evidence on the efficacy of treatments for EoE based on specific, well-established, and clinically relevant histological endpoints and endoscopic findings.[19] Overall, our findings are consistent with previous studies showing that BOT was superior to other drugs for the induction of histological response in EoE,[15] and that esomeprazole ranked higher than off-label topical steroids.[14-16] In addition, our study also assessed the efficacy of dupilumab, which ranked higher than both off-label steroids and esomeprazole, in terms of failure to achieve histological remission and symptom response in active EoE.

Historically, nebulised/swallowed topical steroids adapted from the treatment of asthma have been used for the treatment of EoE with good results.[52] However, novel drug delivery systems have been developed recently to improve the mucosal contact time of topical steroids.[13] Through indirect comparison, we were able to demonstrate that EoE-specific formulations were generally superior to adapted asthma medications. In particular, BOT 1mg b.i.d., FOT 1.5mg b.i.d. and FOT 3mg b.i.d. were superior to aerosolised budesonide 1mg b.i.d. in terms of failure to induce histological remission, and BOT 1mg b.i.d. was superior to aerosolised fluticasone in terms of failure to induce endoscopic response based on the EREFS score.

In this network meta-analysis, only BOT 1mg b.i.d. and BOS 2mg b.i.d. were superior to placebo in terms of symptom improvement. Our results are consistent with previous meta-analyses showing that most available treatments for EoE have suboptimal efficacy for symptoms,[52-54] possibly because of concomitant participant factors, such as co-existence of gastro-oesophageal

reflux disease,[55, 56] oesophageal dysmotility,[57, 58] anxiety, or hypervigilance,[59] which are not considered routinely as confounders in RCTs investigating drugs for EoE.[13]

In summary, this network meta-analysis supports the efficacy of most available drugs over placebo for the treatment of EoE. All EoE-specific steroid formulations and dupilumab ranked higher than off-label topical steroids for the induction of histological remission in active EoE, and most EoE-specific steroid formulations and dupilumab ranked higher than esomeprazole, despite having comparable safety. Refractoriness to treatment in EoE leads to oesophageal remodelling with fibrosis and stricture formation,[60, 61] which may require endoscopic or surgical interventions and subsequent possible complications.[62, 63] Accordingly, the achievement of histological remission is necessary to prevent disease progression and represents a primary endpoint in EoE treatment trials.[13] Of note, in this network meta-analysis, most drugs were superior to placebo for achieving histological remission, although only BOT 1mg b.i.d. and BOS 2mg b.i.d. led to a significant improvement in symptoms. However, it is well known that there may be a discrepancy between histological activity and symptoms in patients with EoE.[64, 65] Therefore, these results prompt further research to better understand the mechanisms underlying symptom generation in EoE, to target their cause and achieve better outcomes. To improve the ability to compare treatments for EoE, future RCTs should investigate efficacy using recognised and standardised endpoints with validated outcome measures on which there is international agreement,[19] and should include patients with comparable previous treatment history. In addition, now that approved drugs are available, head-to-head comparisons of one drug versus another may help establish a therapeutic algorithm in patients with active EoE, without the need for placebo-controlled trials in the future. However, it must be acknowledged that heterogeneity in both eligibility criteria and outcome measures hampers the establishment of a solid therapeutic hierarchy in EoE, based on the available trials.

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FIGURES AND TABLES LEGENDS

Table 1. Eligibility criteria

Figure 1. Flow Diagram of Assessment of Studies Identified in the Network Meta-analysis.

Figure 2A. Network Meta-analysis of Likelihood of Failure to Achieve Histological Remission as a Reduction in Oesophageal Eosinophilic Infiltrate to ≤6 Eosinophils per HPF in Patients

with Active EoE.

Figure 3B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Histological Remission as a Reduction in Oesophageal Eosinophilic Infiltrate to ≤6 Eosinophils per HPF in Patients with Active EoE.

Caption of figure 2B:

League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve histological remission as a reduction in oesophageal eosinophilic infiltrate to ≤6 eos/hpf. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons. *aerosolised 440mcg b.i.d. or 880mcg b.i.d.; **750mg weeks 0 – week 1 then 1500mg week 5 – week 9; ***aerosolised 1mg b.i.d. HD, high-dose (i.e., 1mg/kg for 1 dose then 3mg/Kg x5 doses); LD, low-dose (i.e., 1mg/Kg).

Figure 3A. Network Meta-analysis of Likelihood of Failure to Achieve Histological Remission as a Reduction in Oesophageal Eosinophilic Infiltrate to ≤15 Eosinophils per HPF in Patients with Active EoE.

Figure 3B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Histological Remission as a Reduction in Oesophageal Eosinophilic Infiltrate to ≤15 Eosinophils per HPF in Patients with Active EoE.

Caption of figure 3B:

League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve histological remission as a reduction in oesophageal eosinophilic infiltrate to ≤15 eos/hpf. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons. *aerosolised 440mcg b.i.d. or 880mcg b.i.d.; **750mg week 0 – week 1 then 1500mg week 5 – week 9; ***aerosolised 1mg b.i.d.;

Figure 4A. Network Meta-analysis of Likelihood of Failure to Achieve Symptom Improvement in Patients with Active EoE.

Figure 4B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Symptom Improvement in Patients with Active EoE.

Caption of figure 4B:

League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve symptoms improvement . Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons; *aerosolised 440mcg b.i.d. or 880mcg b.i.d.; **750mg w0-w1 then 1500mg w5-w9

Figure 5A. Network Meta-analysis of Likelihood of Failure to Achieve Endoscopic Improvement Based on EREFS score in Patients with Active EoE.

Figure 5B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Endoscopic Improvement Based on EREFS score in Patients with Active EoE.

Caption of figure 5B:

League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve endoscopic improvement based on the EREFS score. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparison; *aerosolised 440mcg b.i.d. or 880mcg b.i.d.

Table 1. Eligibility criteria

Randomised controlled trials.
Adults and adolescents ≥12 years of age with active eosinophilic oesophagitis.
Compared oral corticosteroids, proton pump inhibitors, or biological drugs with each other, or with placebo.
Minimum duration of therapy of 6 weeks.
Assessment of failure of clinical response or histological remission, at the last time point of assessment in the trial.