Efficacy and Safety of Budesonide in the Treatment of Eosinophilic Esophagitis: Updated Systematic Review and Meta-Analysis of Randomized and Non-Randomized Studies

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Published online: 2 November 2018
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Abstract

Background and Objective  Eosinophilic esophagitis (EE) is an immune/antigen-driven inflammation that causes esophageal dysfunction. Budesonide has shown promising effect in the management of EE in multiple studies, and we therefore conducted this systematic review/meta-analysis to assess budesonide efficacy and safety in order to provide more updated and robust evidence.

Methods  In April 2018, we conducted a systematic electronic search through four databases: PubMed, Scopus, Web of Science (ISI), and Cochrane Central. All original studies reporting the efficacy of budesonide in the treatment of EE were included in our meta-analysis. The Cochrane Collaboration tool was employed to assess the risk of bias among included randomized controlled trials, while the Newcastle–Ottawa Scale was used for non-randomized studies.

Results  A total of 12 studies including 555 participants were included in our review. Budesonide showed marked efficacy at the level of histological response compared to placebo [risk ratio (RR) (95% confidence interval (CI)) 11.93 (4.82–29.50); \( p > 0.001 \)]. Analysis of randomized and non-randomized studies revealed considerable reduction in eosinophil count, with a mean difference (MD) (95% CI) of \(- 69.41 \) (\(- 105.31 \) to \(- 33.51 \); \( p < 0.001 \)) and \( 46.85 \) (33.93–59.77; \( p < 0.001 \)), respectively. Similarly, there was a marked improvement in the clinical symptoms via the analysis of randomized and non-randomized studies, with an RR (95% CI) of \( 1.72 \) (1.22–2.41; \( p = 0.002 \)) and MD (95% CI) of \( 2.45 \) (0.76–4.15; \( p = 0.005 \)), respectively.

Conclusion  Budesonide showed significant effect at all treatment endpoints. However, since budesonide carries a risk of candidiasis and our inferences are based only on a small number of included studies, more research is warranted to clarify these results.

Electronic supplementary material  The online version of this article (https://doi.org/10.1007/s40268-018-0253-9) contains supplementary material, which is available to authorized users.

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Eosinophilic esophagitis (EE) is a worldwide chronic immune/antigen-driven inflammation of the esophagus manifested mainly with dysphagia and food impaction and characterized by elevated levels of eosinophils in the histopathological examination of an esophageal biopsy [1]. The clinical features of EE may differ with age; failure to thrive and food rejection are reported in young children, vomiting and food regurgitation occur in older children, while heartburn, food impaction, and dysphagia can be presented in adults [2]. EE is associated with other atopic conditions such as eczema, allergic rhinitis, and asthma [3, 4]. EE is more common in males, and can affect all ages [3]. Based on the consensus guidelines for the diagnosis of EE, a recent study conducted between 2011 and 2016 reported an incidence rate of 24 EE cases per 100,000 children per year, whereas the 5-year prevalence rate was 118 cases per 100,000 children [5]. More recently, another large cross-sectional study showed increasing incidence rates in the past 15 years, in both adults and children [6].

Unfortunately, the exact etiology of EE has not yet been clearly understood; however, most research studies support immune-mediated reactions [4]. Food allergens are considered substantial immunity triggers in the pathophysiology of EE, and the most commonly identified food allergens are dairy, soy, eggs, wheat, peanuts/tree nuts, and fish/seafood. The six food elimination diet (SFED) approach relies on eliminating these specific food allergens [7, 8]. Moreover, environmental allergens have also been involved in the incidence of EE [9], and this has been emphasized by a large, recently conducted cohort study [10, 11]. A recently updated worldwide consensus diagnostic criteria for EE states that EE should be diagnosed when there are symptoms of esophageal dysfunction beside at least 15 eosinophils per high-power field (eos/hpf) on esophageal biopsy and after a thorough assessment of other non-EE disorders that could potentially be attributed to esophageal eosinophilia [12]. Proton pump inhibitors (PPIs), which are commonly used to diagnose EE by ruling out gastroesophageal reflux disease (GERD) [2], are, according to this updated evidence, better classified as a treatment of esophageal eosinophilia that may be due to EE rather than as a diagnostic criterion for EE [12]. The biopsy can detect eosinophils in the superficial epithelium, and more than 15 or 20 eos/hpf is confirmative [13]; recent guidelines report that 15 eos/hpf is the cut-off point of EE diagnosis [12]. Various endoscopic scoring systems are being developed as endoscopic outcome measures to identify individuals with EE and to follow their response to treatment; the Endoscopic Reference Score (ERFS) is a validated system used for initial diagnosis and treatment follow-up of EE [14]. Esophageal diseases, especially EE, can be assessed by the means of patient-related outcome (PRO) and clinician-reported outcome (ClinRO) measures. PRO incorporates various measures of symptom severity, functioning (disability), health status, health-specific quality of life, ‘general’ quality of life, and general health perceptions [15, 16]. Various PRO instruments have been developed and validated for the assessment of EE—especially clinical response to treatment, including the Eosinophilic Esophagitis Activity Index (EesAI) and Dysphagia Symptom Questionnaire (DSQ). Several factors are incorporated in the EesAI tool that assess dysphagia, behavioral adaptation to dysphagia, and pain with swallowing [17], while the DSQ has been shown to be content valid and is currently being further evaluated in a number of trials [16].

The current approaches to the management of EE comprise dietary elimination, endoscopy, and corticosteroids [18]. Although specific food elimination may be safe and efficacious, patient compliance is an issue [2]. While both approaches (pharmacological and food elimination diet) seem promising in managing EE, a recent meta-analysis concluded that both approaches have the same magnitude of histologic and symptomatic response [19]; however, the effectiveness of food elimination should be tempered by the absence of a randomized study and the potential challenges of adherence to such diets [20, 21]. It has also been reported that a food elimination diet is expensive, not palatable, and associated with marked weight loss, and thus results in high rates of dropout and non-compliance [22]. In 2002, a study revealed the ability of skin prick testing and patch testing to identify potential causative foods that might attribute to the pathogenesis of EE [23]. Later, it was reported that dietary management can benefit EE patients without the need for skin tests [24]. More recently, the use of skin-patch testing in food-related allergic disease per se has been questioned, and it was reported that such tests—disliked by both patients and clinicians—should not be used in EE [25]. In some cases, it may be necessary to remove the impacted food and dilate the esophagus via endoscopy; however, this...
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Budesonide in Eosinophilic Esophagitis carries the risk of perforation [3]. Thus, medical treatment with PPIs, which are effective remedies with few risks and low costs, should be considered first. Also, corticosteroids, specifically budesonide and fluticasone, which can inhibit maturation and activation of eosinophils through suppression of the release of their stimulating cytokines, have been proven effective in managing EE [26]. A network meta-analysis in 2016 deduced no statistically significant difference between PPIs and corticosteroids; however, their inferences were limited by the risk of bias and the small number of study participants [27]. In the same year, a meta-analysis of randomized controlled trials (RCTs) reported corticosteroids as having a promising role in histological remission of EE, but not a comparable role in relieving the clinical complaints [28]. However, there are contradictory results from recent RCTs, in which budesonide induced improvement of clinical symptoms as well as significant histological remission [29, 30]. Moreover, the previous systematic reviews and meta-analysis [27, 28] did not include non-randomized studies and only pooled the RCTs as a well-designed study, whereas it has been recommended that these studies not be excluded from meta-analysis [31]. Therefore, we aimed to conduct an updated large-scale systematic review and meta-analysis of randomized and non-randomized studies to assess the efficacy and safety of budesonide in the treatment of EE in both adults and children.

2 Methods

2.1 Search Strategy and Selection Criteria

Based on the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [32], we conducted a systematic review of literature with the aim of meta-analyzing all relevant data. We performed an electronic search using four databases—PubMed, Scopus, Web of Science (ISI), and Cochrane Central—to retrieve all potentially relevant articles. The following integrated search terms were used to gather all related articles: (Budesonide OR Pulmicort) AND (Eosinophilic esophagitis OR eosinophilic oesophagitis OR allergic oesophagitis). MeSH (Medical Subject Headings) terms used were “Budesonide” and “Eosinophilic Esophagitis”. In addition, manual searching of reference lists of included trials was carried out. There was no search filtering applied with regard to language, year, and design. Three reviewers blindly screened titles and abstracts for eligibility according to our inclusion and exclusion criteria. Inclusion criteria were as follows: (1) original articles reporting the use of budesonide in EE; (2) articles reporting data on humans; and (3) no restriction was made with respect to language, sex, age, and area. Exclusion criteria were as follows: (1) case reports, case series, letters, comments, and review articles; (2) data cannot be extracted; (3) overlapped dataset; (4) abstract-only papers; (5) animal or in vitro studies; and (6) duplication and irrelevant data.

2.2 Data Extraction

The authors of this meta-analysis independently extracted relevant data. Firstly, a pilot data extraction was undertaken for three articles to determine the data reported. After that, a standardized data extraction form was constructed and any disagreement was resolved through discussion and consensus between the reviewers. Retrieved data comprised baseline characteristics of study subjects and outcomes such as histological response, eosinophil count, and clinical response.

2.3 Statistical Analysis

All data were analyzed using R statistical software version 3.4.4 [33]. First, we calculated the effect size [risk ratio (RR) or mean difference (MD)] and associated standard errors [34] for drug versus control or pre- versus post-treatment groups, and then all data were pooled with the help of the ‘meta’ package for R [35]. A fixed-effect model [36] was used when there was no evidence of heterogeneity between studies; otherwise, a random-effects model was chosen. Heterogeneity between studies was evaluated using the $Q$ statistic and $I^2$ test, which describes the percentage of variability in the effect estimates [37, 38].

3 Results

3.1 Literature Search

The electronic search yielded 297 references from the four databases. After excluding duplicates and title/abstract screening, we had 20 relevant papers for full-text screening. Of those, seven non-randomized [30, 39–44] and five randomized [29, 45–48] studies were eligible for meta-analysis. The manual search of references did not find any additional papers (Fig. 1).

3.2 Baseline Characteristics of Randomized and Observational Studies Eligible for Meta-Analysis

Five RCTs [29, 45–48] including 300 cases with a mean age ranging from 7.8 to 46.5 years were included and meta-analyzed. Most participants were males (78.33%) and the follow-up varied from 2 to 12 weeks. Detailed data on the baseline characteristics of the included participants are shown in Table 1. Quality assessment of the included RCTs
was carried out using the Cochrane Collaboration’s quality assessment tool [49]. Each domain was evaluated as having a low, high, or unclear risk of bias. Results of the quality assessment for RCTs are summarized in Electronic Supplementary Material Table 1A. In addition, seven non-randomized studies [30, 39–44] including 255 participants were included, most of whom were males [190 (74.5%)]. The age of participants, intervention, and follow-up in these studies are summarized in Table 2. Quality of evidence has been assessed using the Newcastle–Ottawa Scale for quality assessment of non-randomized studies [50]. The assessment of each domain was categorized as good, fair, and poor using a scoring system from 0 to 4 stars; this is discussed in detail in Electronic Supplementary Material Table 1B.

### 3.3 Therapeutic Efficacy and Safety

#### 3.3.1 Histological Response and Eosinophil Count

Through a meta-analysis of five RCTs including 245 patients, our results showed marked efficacy of budesonide

| First author/year | Sample size (n) | Age (years) [mean (SD)] | Males [n (%)] | Route/dose | Histologic diagnostic criteria: (eos/hpf) | Follow-up (weeks) |
|-------------------|-----------------|--------------------------|---------------|------------|----------------------------------------|------------------|
| Dellon/2016 [29]  | 51 42           | 22.3 (7.9) 20.8 (7.5) 35 (69) 29 (69) | Oral suspension/2 mg twice daily | ≥ 15 | 12 |
| Gupta/2015 [45]   | 17 18           | 8.6 (6.18) 9.8 (4.3) 14 (82.4) 13 (72.2) | Oral suspension/low dose (0.35 mg) | ≥ 20 | 12 |
|                   | 19              | 10.2 (4.89) 17 (89.5) | Oral suspension/medium dose (1.4 mg) | | |
|                   | 17              | 7.9 (4.39) 13 (76.5) | Oral suspension/high dose (2.8 mg) | | |
| Miehlke/2015 [46] | 19 19           | 38.9 (12.6) 36.3 (9.9) 17 (89.5) 16 (84.2) | Orodispersible/BET2 (1 mg/day) | ≥ 20 | 2 |
|                   | 19              | 37.2 (13.9) 16 (84.2) | Orodispersible/BET2 (2 mg twice daily) | | |
|                   | 19              | 46.5 (14.1) 14 (73.7) | Oral viscous suspension/BVS 2 (5 mL/day) | | |
| Straumann/2010 [47]| 18 18           | 33.1 (13.1) 38.2 (12.4) 17 (94.44) 14 (77.78) | Oral suspension/1 mg twice daily | ≥ 20 | 2 |
| Dohil/2010 [48]   | 15 9           | (1–17)a  (2–16)a 12 (80) 8 (88.89) | Oral viscous/OVB 2 mg in those ≥ 5 feet tall and 1 mg in those < 5 feet | ≥ 20 | 12 |

*BET* budesonide effervescent tablet for orodispersible use, *BVS* budesonide viscous suspension, *eos/hpf* eosinophils per high-powered field, *OVB* oral viscous budesonide, *SD* standard deviation

*RANGE R*
at the level of histological response compared to placebo [RR (95% CI) 11.93 (4.82–29.50); p < 0.001]. No significant heterogeneity was found among the included RCTs (I² = 0%; p = 0.776) (Fig. 2a). In addition, biopsies revealed that patients taking budesonide (n = 82) had considerable reduction in their eosinophil count compared with those taking placebo (n = 65), with an MD (95% CI) of −69.41 (−105.31 to −33.51; p < 0.001). However, significant heterogeneity was found between the studies (I² = 75%; p = 0.017) (Fig. 2b). In the same context, six non-randomized studies including 187 patients showed a significant decline in the mean eosinophilic count in patients who received budesonide compared with before treatment [MD (95% CI) 46.85 (33.93–59.77); p < 0.001]. Significant heterogeneity between studies was noticed (I² = 84%; p < 0.001) (Fig. 2c).

### 3.3.3 Endoscopic Changes

The results from four non-randomized studies showed a significant decrease in endoscopic abnormalities for patients (n = 156) who underwent treatment with budesonide compared with before treatment [RR (95% CI) 1.61 (1.41–1.84); p < 0.001]. The highest reduction was in esophageal furrows (RR = 2.23) followed by white specks/plaques/exudates (RR = 1.67) (Fig. 4a). In the same context, mean esophageal scores were also reduced in patients treated with budesonide compared with pre-treatment scores [MD (95% CI) 2.24 (0.59–3.90); p = 0.008] (Fig. 4b).

### 3.3.4 Incidence of Candidiasis

A meta-analysis conducted using four RCTs including 227 subjects showed an increased risk of candidiasis with the use of budesonide compared with placebo (RR [95% CI] 3.29 [0.74–14.70]; p = 0.119); however, this finding is insignificant. No significant heterogeneity was found between results (I² = 0%; p = 0.914) (Fig. 5).

### 4 Discussion

EE is a clinical condition characterized clinically by esophageal dysfunction and histologically by a high eosinophil count per high-power field. Patients with EE have used topical corticosteroids as a first-line remedy after PPI resistance [51]. However, there are an increasing number of

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**Table 2** Baseline characteristics of non-randomized studies

| First author/year | Sample size | Age (years) [mean (SD)] | Males [n (%)] | Route/dose | Histologic diagnostic criteria (eos/hpf) | Follow-up |
|-------------------|-------------|-------------------------|--------------|------------|----------------------------------------|-----------|
| Reed/2018 [39]    | 48          | 33.6 (16.1)             | 33 (69)      | Compounded viscous budesonide suspension/1 mg/8 mL | > 15      | Mean = 13.2 months                   |
| Rubinstein/2017 [40] | 8         | 10 (4)                  | 8 (100)      | OVB/patients < 10 years received 1 mg/day and those > 10 years received 2 mg/day | > 15      | 10 weeks                             |
| Fable/2017 [41]   | 68          | 11 (5)                  | 55 (81)      | Inhalation/20 patients on FP 110–220 µg/puff Oral/45 patients on OVB 0.5–1 mg/2 mL (twice daily) | > 15      | 8–12 weeks                           |
| Oliva/2016 [30]   | 36          | 12 (5–18)a              | 21 (58.33)   | Pre-prepared OVB suspension/0.2 mg/mL, patients took 2–4 mg/day morning and evening doses, based on height | > 15      | 36 weeks                             |
| Nennstiel/2016 [43] | 20        | 34 (11)                 | 19 (95)      | Liquid budesonide suspension/1 mg/2 mL twice daily | ≥ 15      | 8 weeks                              |
| Aceves/2007 [44]  | 20          | 5.5                     | 17 (85)      | OVB/1–2 mg daily based on age | ≥ 24      | 3–4 months                           |

eos/hpf: eosinophils per high-powered field, FP: fluticasone propionate, OVB: oral viscous budesonide, SD: standard deviation

aMedian (range)
randomized and non-randomized research studies reporting the efficacy of budesonide in the management of EE. To the best of our knowledge, this is the first systematic review and meta-analysis aimed at shedding light on the potential role of budesonide in patients with EE through analysis of all of the published original studies on this topic. Our results show that budesonide has considerable effects in terms of histological remission and improvement of clinical symptoms. Moreover, the eosinophil count has been reduced markedly with budesonide treatment. However, patients taking budesonide had an increased risk of candidiasis.

The treatment endpoints may vary between clinicians and patients. For instance, patients are mostly concerned with relieving the clinical complaints and improving their quality of life, while clinicians seek good histological response and lessening endoscopic abnormalities [52]. However, eosinophil count remains one of the most important treatment endpoints. Fortunately, our meta-analysis revealed that patients in the budesonide-treated group compared with placebo controls and who received pre-treatment compared with post-treatment with budesonide experienced considerable reduction in the eosinophil count. However, it is worth mentioning that there are factors against approving the eosinophil count as a sole standard treatment endpoint, one of which is the different histologic diagnostic cutoff values used in the included studies. However, most of the included studies used the reduction in eosinophils to less than 15 eos/hpf as the main treatment endpoint, which is consistent with the guidelines from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and American Society of Gastroenterology (ACG) [53, 54]. Another issue is how the researchers count...
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the eosinophils; a systematic review of the literature found that some studies used the peak eosinophil count while other researchers prefer to use a mean count from multiple fields [55]. Moreover, the eosinophil count may vary with different locations of the esophageal biopsy, which is why researchers have recommended utilizing multiple biopsy locations for proper diagnosis [56].

Improvement of clinical symptoms is also considered a substantial treatment endpoint, especially from a patient’s perspectives. Our meta-analysis of randomized and non-randomized studies revealed significant improvement in clinical symptoms after receiving budesonide, and significant heterogeneity was found with the non-randomized studies. Different questionnaires have been implemented to evaluate the clinical response but only the EEsAI and DSQ were validated [57, 58]. The authors of the two analyzed RCTs used the DSQ questionnaire [29, 45]. Nevertheless, clinicians cannot assume histological remission or resolution of endoscopic abnormalities based on symptoms relief. Such dissociation between clinical features and histological and endoscopic findings has been reported in both adults and pediatric patients with EE [59, 60].

In addition to good clinical response, our analysis showed a significant improvement of endoscopic abnormalities (furrows, rings, edema, structure, and white specks/plaques/exudates), which is also an important treatment endpoint. One of the methods to assess the endoscopic abnormalities and monitor treatment effect is the EREFS, which has been tested by a prospective study as a scoring system for such abnormalities [61]. More than one study contributed to the analysis of esophageal furrows, rings, and stricture, but only one study reported a decrease in the esophageal narrowing [39]. It has been reported that the optimal diameter of esophageal lumen is about 15 and 18 mm to smoothly ingest regular modified food and full meal, respectively.

The main strength of our study is that it is the first meta-analysis, to our knowledge, to assess the efficacy and safety of budesonide in the treatment of EE. Another strength of our meta-analysis is that we included more studies and analyzed more outcomes than the previous meta-analysis. We believe that budesonide is worth examining further via large-population randomized studies. Nevertheless, our study has several limitations. One important limitation is the small number of included studies and participants, which precludes the standardization of budesonide for all patients with EE in clinical practice. Another limitation is the significant heterogeneity between the different studies regarding the outcomes of eosinophil count and clinical response. Moreover, different values for histologic diagnostic criteria were noticed between studies, which in turn alters the definition of responders between studies. The variation in the follow-up duration between included studies may also manipulate the results. Our study pooled both adults and children in one analysis and we could not perform meta-regression of age or of other factors such as sex and publication year due to the small number of included studies. Future well-designed randomized studies including adequate populations should consider these limitations.
Fig. 4 Forest plot meta-analysis for endoscopic abnormalities [39, 41–43] (a) and mean esophageal scores [30, 42–44] (b) pre- and post-budesonide treatment. CI confidence interval, MD mean difference, RR risk ratio, SD standard deviation
5 Conclusion

Budesonide may have promise in lessening the eosinophilic count and inducing histological remission in patients with EE. Furthermore, budesonide can reduce the endoscopic abnormalities and improve the clinical status of those patients. Since it carries the risk for candidiasis and our inferences are based on a small number of studies, these findings should be interpreted with caution. Future large-scale randomized studies are desired before we can make conclusive inferences and construct a standard treatment protocol.

Author Contributions P.R. participated in the design of the study. All authors participated in the screening of articles, extraction of data, analysis, writing, and approval of the manuscript.

Funding This work was not supported by any funder.

Compliance with Ethical Standards

Conflict of Interest Prashanth Rawla, Tagore Sunkara, Krishna Chaitanya Thandra, and Vinaya Gaduputi declare no conflict of interest.

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