




## CLINICAL RESEARCH ARTICLE

## Retrospective study of budesonide in children with eosinophilic gastroenteritis

Shengbo Fang <sup>1</sup>, Yanqing Song<sup>1</sup>, Sixi Zhang<sup>1</sup> and Chunyan Li<sup>1</sup>

**BACKGROUND:** The effectiveness of budesonide (BUD), a locally active steroid, on eosinophilic gastroenteritis (EGE) is not well understood. This study is to retrospectively evaluate the efficacy of BUD in children with EGE.

**METHODS:** Forty-four children, diagnosed with EGE, were enrolled from 2013 to 2017 in our center. According to patients' preference, all the patients were treated with dietary elimination (DE) and montelukast therapy, or combined with prednisone (PRED)/BUD. Patients' clinical manifestations, treatments, and outcomes were reviewed from the medical records. Twenty-four patients (7 PRED, 7 BUD, 10 DE) received therapy for  $\geq 8$  weeks, followed by repeat endoscopy and biopsies. Histological response was defined as  $< 20$  eos/hpf (eosinophils per high-power field).

**RESULTS:** Significant number of patients in DE+PRED (6/7, 85.7%) and DE+BUD (6/7, 85.7%) groups achieved histological response than in the DE group (3/10, 30%) ( $p = 0.024$ ). Mean post-treatment peak eos/hpf in the DE+PRED group was  $16.57 \pm 6.85$  vs.  $10.00 \pm 5.07$  in the DE+BUD group vs.  $36.60 \pm 24.57$  in the DE group vs.  $-0.3 \pm 23.95$  in the DE group ( $p = 0.009$ ). Change of eos/hpf from pre- to post-treatment was  $-49.86 \pm 45.02$  vs.  $-34.29 \pm 23.44$  in the BUD group vs.  $-0.3 \pm 23.95$  in the DE group ( $p = 0.011$ ). There were no significant differences between DE+PRED and DE+BUD groups ( $p = 0.470$ ,  $p = 0.363$ , respectively).

**CONCLUSION:** BUD is effective in the treatment of EGE and has similar effectiveness with PRED.

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## INTRODUCTION

Eosinophilic gastroenteritis (EGE), which was first described by Kaijser in 1937, is a rare disorder characterized by eosinophilic infiltration of the bowel wall with various gastrointestinal (GI) manifestations. It is an allergy-associated disease, characterized clinically by abnormal GI symptoms and histologically by eosinophil infiltration into the GI tract epithelium ( $\geq 20$  eosinophils per high-power field (eos/hpf)).<sup>1</sup> Its recent incidence and prevalence are currently estimated to be 28/100,000 and 5.1/100,000 per person.<sup>2,3</sup> The most common symptoms include abdominal pain, diarrhea, hematochezia, and bloating. Other symptoms, such as dysphagia, hypoalbuminemia, iron deficiency anemia, and protein-losing enteropathy, are uncommon but can be seen as well.<sup>4</sup> For children and adolescents, it can present with growth retardation, failure to thrive, delayed puberty, or amenorrhea.<sup>5</sup>

The goals of our therapy are to resolve symptoms, prevent complications from long-standing EGE, and maintain histological remission. Presently, the optimal treatment for EGE is still uncertain because of the lack of prospective controlled clinical trials. Therapeutic options mainly include dietary eliminations (DEs), mast cell inhibitor, leukotriene receptor antagonist, and corticosteroids. Prednisone (PRED), as systematic steroid, has been used to treat EGE. It has been reportedly useful in most cases, especially in severe patients.<sup>2,6,7</sup> However, long-term systemic steroid therapy can induce growth failure, a cushingoid state, and adrenal suppression. Budesonide (BUD) acts locally and can avoid systemic side effects. Case reports have showed great effectiveness in EGE,<sup>8,9</sup> but no systematic study has been reported.

Our aim in this study was to retrospectively evaluate the effectiveness of BUD in EGE.

## METHODS

We performed a retrospective review of patients with documented EGE, defined endoscopically as  $> 20$  eos/hpf on GI tract biopsies (other diseases that cause eosinophilic hyperplasia excluded), who were treated with DE and montelukast therapy, or combined with PRED/BUD at Pediatric gastroenterology in our center from 2013 to 2017. The clinical form of patients in our study was mucosal type; the other types were not involved in our study. The primary outcome measure was histological response, defined as a decrease in peak eosinophil count to  $< 20$  eos/hpf after a minimum of 8–12 weeks of treatment. Patients were treated with PRED or BUD with age-dependent dosing consistent with current recommendations.<sup>10,11</sup> The secondary outcome was a comparison of clinical symptoms and endoscopic appearance of the three therapies.

## Patient demographics and clinical data

The three treated groups were compared in terms of their demographic, endoscopic, and histological characteristics. Demographic characteristics included age, gender, race, history of birth, height, and weight. Clinical characteristics included history of atopic diseases (asthma, eczema, seasonal or environmental allergies, and allergic rhinitis), and history of medication and food allergies. Characteristics on initial endoscopic evaluation leading to treatment included normal appearance as well as the presence of circular congestion around the swollen lymph follicle, mucous edema, hemorrhagic spot, and occasional ulcerative changes. Under magnifying endoscopy with narrow band imaging, the submucous blood vessels appeared to be thickened and meandering, accompanied by tissue edema. Histological characteristics included peak eos/hpf.

<sup>1</sup>The First Hospital of Jilin University, 130021 Changchun, China  
Correspondence: Chunyan Li (lovelylycy@126.com)

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**Table 1.** Demographic and clinical characteristics of study groups

|                             | PRED                         | BUD                          | DE                          | P value |
|-----------------------------|------------------------------|------------------------------|-----------------------------|---------|
| N                           | 7 (29.17%)                   | 7 (29.17%)                   | 10 (41.67%)                 |         |
| Age (years)                 | 9.43 ± 4.69 (1–14)           | 10.49 ± 4.62 (1.42–14)       | 5.57 ± 4.46 (1–13)          | 0.085   |
| Gender (%male)              | 4 (57.1%)                    | 6 (85.7%)                    | 8 (80%)                     | 0.59    |
| Nourishment state           | −0.68 ± 1.43 (−3.00 to 1.25) | −0.18 ± 2.16 (−3.00 to 2.25) | 0.23 ± 0.91 (−1.25 to 2.25) | 0.49    |
| History of birth (eutocia%) | 4 (57.14%)                   | 3 (42.85%)                   | 3 (30%)                     | 0.523   |
| Allergy history             |                              |                              |                             |         |
| Food allergies              | 1 (14.29%)                   | 1 (14.29%)                   | 4 (40%)                     | 0.427   |
| Environmental allergies     | 1 (14.29)                    | 2 (28.57%)                   | 3 (30%)                     | 0.853   |
| Drug allergies              | 1 (14.29%)                   | 0 (0)                        | 1 (10%)                     | 1.000   |
| Asthma                      | 0 (0)                        | 1 (14.29%)                   | 0 (0)                       | 0.583   |
| Eczema                      | 0 (0)                        | 0 (0)                        | 2 (20%)                     | 0.315   |

DE dietary elimination

#### Inclusion criteria

We reviewed 44 active patients, aged 1–16, with EGE documented by endoscopic biopsy. Patients who were treated with DE, DE+PRED, or DE+BUD between 2013 and 2017 were identified, but only 24 were included in this study. Twenty patients were excluded due to insufficient data. Patients were required to have undergone upper endoscopy with biopsy both prior to treatment initiation as well as at least 8–12 weeks following treatment with DE, DE+PRED, or DE+BUD. The choice of therapy was determined based on patient preference.

#### Treatment protocols

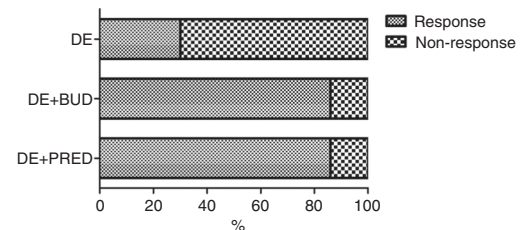
In our center, all the 44 patients accepted montelukast and diet elimination, which include milk, eggs, fish and seafood, soy, nuts, and wheat. Children younger than 2 years were treated with montelukast 2 mg once daily. Children from 2 to 5 years were treated with 4 mg once daily, and 6–14 years were treated with 5 mg once daily. The initial dosage of PRED was 0.5–1 mg/kg/day, with a maximum dose of 40 mg/day. After using PRED for at least 2 weeks, with clinical symptoms relieved, the dosage began to taper at the rate of 2.5–5 mg per 2–3 weeks until a maintenance dosage of 5 mg/day. The dosage of BUD (coated form [Budenofalk®, Entocort®]) was given according to age. Children younger than 1 year were treated with 1 mg twice daily. Children from 1 to 7 years were given 1 mg three times daily, 7–12 years were given 2 mg three times daily, and older than 12 years were given 3 mg three times daily. Budenofalk is a gastro-resistant, pH-modified formulation, while Entocort is a gastro-resistant controlled ileal-release formulation. According to pharmacokinetics, Entocort was used in patients with marked elevation of eosinophils in the stomach and duodenum, and Budenofalk was used in patients with marked elevation of eosinophils in the ileum and colon.

#### Outcomes

The primary outcome was histological response, defined as a decrease in peak eosinophil count to <20 eos/hpf after 8–12 weeks of therapy with DE, DE+PRED, or DE+BUD. Patients who continued to have >20 eos/hpf were considered to be treatment failures. Secondary outcomes included endoscopic visualization and clinical symptoms. Endoscopic improvement was based on resolution of circular congestion around the lymph follicle, mucous edema, and hemorrhagic spot.

#### Statistical analysis

The IBM SPSS Statistics software package (version 20.0; IBM Co., Armonk, NY, USA) was used for statistical analysis. Paired *t* tests,



**Fig. 1** Response rate of prednisone (PRED), budesonide (BUD), and dietary elimination (DE)

one-way analysis of variance, and Fisher’s exact tests were used for analysis. Statistical significance was considered at  $p < 0.05$ .

## RESULTS

### Demographic and clinical features

Forty-four patients aged 1–16 years who had been diagnosed with EGE by endoscopic biopsy were enrolled in our center between 2013 and 2017. All the patients were treated with DE therapy (6-food diet elimination and montelukast). According to patients’ preference, on the basis of DE therapy, 14 patients accepted PRED and 12 patients accepted BUD. Twenty-four patients were eventually included in this study and 20 were excluded due to insufficient data. Patient demographics and clinical characteristics are presented in Table 1. There were no significant differences with respect to demographic characteristics between different study groups.

### Response to treatment

In total, the histological response was seen in 15/24 (62.5%) patients. A significantly greater number of patients responded to DE+PRED (6/7, 85.7%) and DE+BUD (6/7, 85.7%) compared with DE (3/10, 20%) ( $p = 0.024$ ) (Fig. 1). There was no differences of mean pre-treatment peak eos/hpf in the three groups ( $p = 0.142$ ) (Fig. 2a), but there was a significantly greater difference in post-treatment peak eos/hpf in DE+PRED ( $16.57 \pm 6.85$ ) vs. DE+BUD ( $10.00 \pm 5.07$ ) vs. DE ( $36.60 \pm 24.57$ ) ( $p = 0.009$ ) (Fig. 2b). No significant difference was seen between patients in DE+PRED and DE+BUD ( $p = 0.470$ ). In addition, the decrease of peak eosinophil counts after treatment were significant both in the DE+PRED group ( $p = 0.026$ ) and the DE+BUD group ( $p = 0.008$ ), while there was no significant difference in the DE group ( $p = 0.969$ ), with three patients’ peak eosinophil counts increasing (Fig. 2d–f). Finally, change of eos/hpf from pre- to post-treatment was  $-49.86 \pm 45.02$  in the DE+PRED group vs.

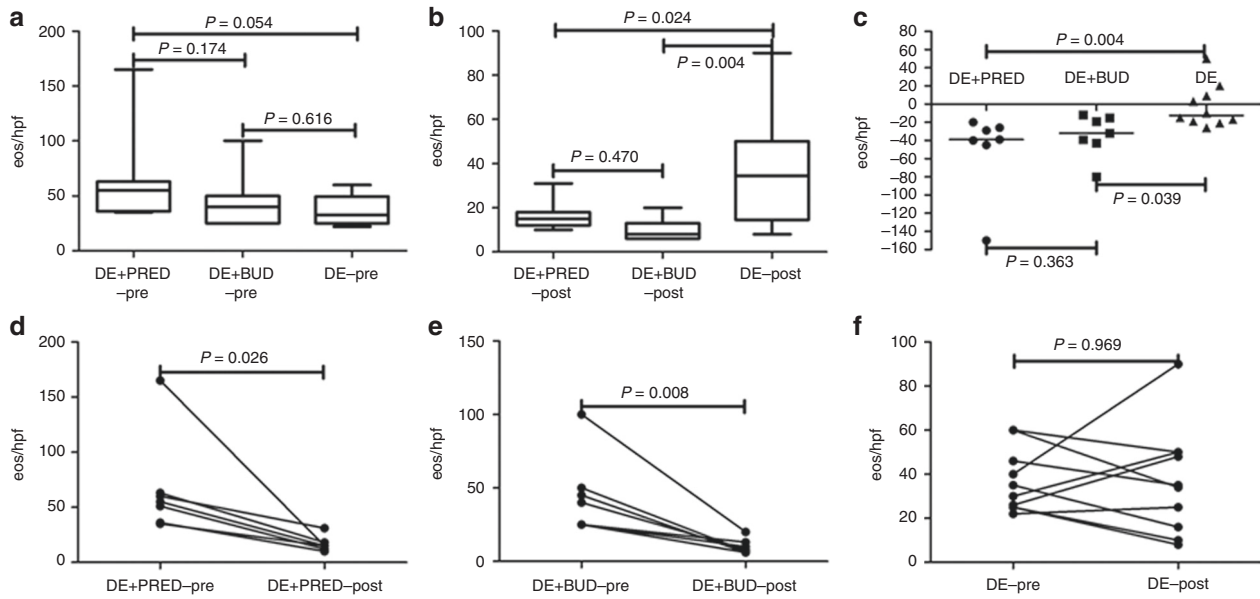
−34.29 ± 23.44 in the DE+BUD group vs. −0.3 ± 23.95 in the DE group ( $p = 0.011$ ). There was no significant difference between DE+PRED and DE+BUD ( $p = 0.363$ ) (Fig. 2c).

Improvements of clinical symptoms were summarized in Table 2. Overall, there was a significant improvement of abdominal pain, diarrhea, and hematochezia after treatment ( $p < 0.0001$ ,  $p = 0.023$ ,  $p = 0.004$ , respectively). There was a more robust resolution of abdominal pain in the DE+PRED and DE+BUD groups compared to the DE group ( $p = 0.021$ ,  $p = 0.005$ ,  $p = 0.582$ , respectively).

Endoscopic findings are shown in Table 3. In total, there was a significant resolution of circular congestion around the swollen lymph follicle and mucous edema after treatment ( $p = 0.036$ ,  $p = 0.019$ , respectively). However, there were no significant differences in the three study groups.

**DISCUSSION**

EGE is a rare GI disorder described as a pathologic eosinophilic infiltration of the GI tract. Clinical treatments include diet



**Fig. 2** Comparison of pre- and post-treatment peak eosinophil counts. **a** prednisone (PRED) vs. budesonide (BUD) vs. dietary elimination (DE) pre-treatment eos/hpf (eosinophils per high-power field); **b** PRED vs. BUD vs. DE post-treatment eos/hpf; **c** Change in peak eos/hpf from pre- to post-treatment; **d** PRED pre- vs. post-treatment peak eos/hpf; **e** BUD pre- vs. post-treatment peak eos/hpf; **f** DE pre- vs. post-treatment peak eos/hpf

**Table 2.** Clinical symptoms pre- and post-treatment with PRED vs. BUD vs. DE

|                       | PRED (n = 7) |       |         | BUD (n = 7) |       |         | DE (n = 10) |         |         | Total (n = 24) |           |         |
|-----------------------|--------------|-------|---------|-------------|-------|---------|-------------|---------|---------|----------------|-----------|---------|
|                       | Pre-         | Post- | P value | Pre-        | Post- | P value | Pre-        | Post-   | P value | Pre-           | Post-     | P value |
| Abdominal pain (n, %) | 5 (71.43%)   | 0 (0) | 0.021   | 6 (85.71%)  | 0 (0) | 0.005   | 3 (30%)     | 1 (10%) | 0.582   | 14 (58.33%)    | 1 (4.17%) | <0.0001 |
| Diarrhea (n, %)       | 3 (42.86%)   | 0 (0) | 0.192   | 1 (14.29%)  | 0 (0) | 1.000   | 4 (40%)     | 1 (10%) | 0.303   | 8 (33.33%)     | 1 (4.17%) | 0.023   |
| Hematochezia (n, %)   | 2 (28.57%)   | 0 (0) | 0.462   | 1 (14.29%)  | 0 (0) | 1.000   | 5 (50%)     | 0 (0)   | 0.033   | 8 (33.33%)     | 0 (0)     | 0.004   |
| Bloating (n, %)       | 1 (14.29%)   | 0 (0) | 1.000   | 2 (28.57%)  | 0 (0) | 0.462   | 1 (10%)     | 0 (0)   | 1.000   | 4 (16.67%)     | 0 (0)     | 0.109   |

DE dietary elimination

**Table 3.** Endoscopic findings pre- and post-treatment with PRED vs. BUD vs. DE

|                            | PRED (n = 7) |            |         | BUD (n = 7) |            |         | DE (n = 10) |         |         | Total (n = 24) |             |         |
|----------------------------|--------------|------------|---------|-------------|------------|---------|-------------|---------|---------|----------------|-------------|---------|
|                            | Pre-         | Post-      | P value | Pre-        | Post-      | P value | Pre-        | Post-   | P value | Pre-           | Post-       | P value |
| Circular congestion (n, %) | 6 (85.71%)   | 2 (28.57%) | 0.103   | 6 (85.71%)  | 2 (28.57%) | 0.103   | 7 (70%)     | 7 (70%) | 1.000   | 19 (79.17%)    | 11 (45.83%) | 0.036   |
| Mucous edema (n, %)        | 5 (71.43%)   | 1 (14.29%) | 0.103   | 4 (57.14%)  | 1 (14.29%) | 0.266   | 6 (60%)     | 4 (40%) | 1.000   | 15 (62.5%)     | 6 (25%)     | 0.019   |
| Hemorrhagic spot (n, %)    | 4 (57.14%)   | 0 (0)      | 0.070   | 0 (0)       | 0 (0)      | –       | 2 (20%)     | 1 (10%) | 1.000   | 6 (25%)        | 1 (4.17%)   | 0.097   |

DE dietary elimination

therapy, drug therapy, and surgical therapy. Corticosteroids, mast cell stabilizer, leukotriene receptor antagonist, immunosuppressants, and interleukin-5 monoclonal antibodies are choices for treatment of EGE. Montelukast, representative of leukotriene receptor antagonist, has been widely used in clinical practice due to its low side effects, but it has not reached the effective clinical expectation.<sup>12–15</sup> Compared with leukotriene, glucocorticoid is considered as an effective drug for the treatment of EGE, which in about 90% of patients could cause response.<sup>16</sup> PRED, as a systemic glucocorticoid, has been shown to be effective therapeutically, but can cause Cushing syndrome, infectious, hypertension, and adrenal suppression in long-term use. Thus, alternative treatments are needed. BUD, which is a second-generation topical glucocorticoid, undergoes a 90% first-pass metabolism to form 6 $\beta$ -hydroxybudesonide and 16 $\alpha$ -hydroxyprednisolone, both of which have <1% of the parent compound's corticosteroid activity. By minimizing systemic exposure, BUD offers an improved safety profile compared with PRED. Presently, BUD has been used for treating Crohn's disease, ulcerative colitis, microscopic colitis, eosinophilic esophagitis, and autoimmune hepatitis.<sup>17,18</sup> As for EGE, there is no large-scale randomized controlled trial of BUD in the treatment of EGE, but its efficacy and safety have been reported in many cases.<sup>8,9,19–22</sup> However, most studies reported clinical symptoms relief without endoscopic and histopathological improvement. Our study retrospectively analyzed 24 EGE patients with complete data, including 7 in the DE+PRED group, 7 in the DE+BUD group, and 10 in the DE group. Results showed that diet elimination and montelukast alone had no significant effect on histopathological improvement, while glucocorticoids had a significant improvement in histopathology, and the therapeutic effect of BUD is comparable to that of PRED. Siewert et al.<sup>22</sup> reported a successful case of EGE with severe protein-losing enteropathy treated with BUD. Eosinophils were no longer detected by histopathology after 9 months.

In previous studies, diarrhea is reported as the most common clinical manifestations of EGE followed by abdominal pain.<sup>2,7,12,23</sup> However, in our study, more cases presented with abdominal pain, as Ko et al.<sup>24</sup> reported. Studies have shown that the clinical symptom relief rate can reach 60% after treatment.<sup>25</sup> We compared different treatment regimens, namely, DE+PRED, DE+BUD, and DE before and after treatment for abdominal pain, diarrhea, blood in the stool, and bloating symptoms. Results showed that only the DE+PRED and DE+BUD groups had statistics on the relief of abdominal pain ( $p = 0.021$ ,  $p = 0.005$ ). Nevertheless, the number of patients with discomfort decreased in any treatment group.

The most common endoscopic findings are hyperemic mucosa followed by erosions, ulcers, and whitish lesions. However, studies by Wong et al.<sup>16</sup> and Hui and Hui<sup>2</sup> showed that endoscopic findings in adults are not completely consistent with histopathological findings. More than half of patients can present with normal looking mucosa under endoscopy but with eosinophilic infiltration. In our study, we found that endoscopic findings were consistent with histopathological changes in children. Most of the children diagnosed with EGE showed circular congestion around the lymph follicle and mucosal edema. After treatment, circular congestion and mucosal edema have been significantly relieved ( $p = 0.036$ ,  $p = 0.019$ ). However, there are three limitations. First, this study is a retrospective study. We failed to grade patients' age and disease severity. In addition, the time of reviewing endoscopic examinations was not completely unified and we did not carry on long-term follow-up of these children. Second, with insufficient data, the sample size is small, which might be a possible limitation factor in generalized BUD use in EGE. There were limited cases included with many cases of shedding, because without permission of children's parents, many cases did not perform endoscopic examinations again after symptom relief. Third, there is lack of standard for the

histological definition of EGE in children. We defined 20 eosinophils/hpf as cutoff in our study, but 30 eosinophils/hpf as cutoff was identified in a recent study by Walker et al.<sup>26</sup> For one thing, the subjects were different. Walker et al.<sup>26</sup> studied adults, while we studied children. In our unfinished study, we found that the intestinal immune system and mucosal barrier became closer in adults with aging. The younger the patients are, the more vulnerable GI function is to pathological damage. In another study, we observed that setting 20 eos/hpf as the cutoff was sufficient to cause GI dysfunction in the children. Nevertheless, this provides a direction for our future research on the comparison between 20 and 30 eos/hpf as the cutoff of diagnosis.

In conclusion, the best choice for EGE is still controversial, but glucocorticoids are still first-line treatments. BUD, as a novel topical glucocorticoid, has the advantage of few side effects than systematic glucocorticoid. This study preliminarily demonstrated that BUD is effective in the treatment of EGE. In the future, well-designed, larger and prospective randomized controlled studies are needed to validate the efficacy of BUD in the treatment of EGE.

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## AUTHOR CONTRIBUTIONS

S.F. designed the study, collected and interpreted data, drafted the initial manuscript, and reviewed and revised the manuscript. C.L., Y.S. and S.Z. designed the study and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## ADDITIONAL INFORMATION

The online version of this article (<https://doi.org/10.1038/s41390-019-0444-2>) contains supplementary material, which is available to authorized users.

**Competing interests:** The authors declare no competing interests.

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