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A NEW FORMULATION OF ORAL VISCOUS BUDESONIDE IN TREATING OF PAEDIATRIC EOSINOPHILIC OESOPHAGITIS: A PILOT STUDY.

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ABSTRACT

Background: Oral Viscous Budesonide (OVB) is a recent therapeutic option for Eosinophilic Oesophagitis (EoE) versus dietary restriction and inhaled steroids. This single center, open label, not blinded study aims to evaluate the efficacy and safety of a new, pre-prepared oral viscous budesonide suspension (PVB) in children and adolescents with EoE.

Methods: We treated with PVB 36 children (29 male; median age 12 years) with EoE diagnosed according to ESPGHAN guidelines. Patients <150 cm and >150 cm height received 2 mg and 4 mg PVB daily, respectively, for 12 weeks. Upper GI endoscopy was performed at baseline, after 12 weeks of therapy and 24 weeks after the end of therapy. Baseline and post-treatment scores were

calculated for symptoms, endoscopy and histology. Serum cortisol was performed at baseline, 12, 36 weeks.

Results: At the end of PVB trial, endoscopy showed macroscopic remission in 32 patients (88,9%), while at histology median pre- and post-treatment peak eosinophil count/HPF markedly decreased from 42.2 (range: 15-100) to 2.9 (range: 0-30); moreover, mean symptom and histology scores impressively improved vs baseline ($p<0.01$). At 24 weeks after the end of PVB therapy, endoscopy showed oesophageal relapse in 21 patients (58,3%), whereas 15 (41,7%) were still in remission. Seven children (19,4%) with positive MII-pH were treated also with proton pump inhibitors. No significant difference between pre-/post treatment morning cortisol levels occurred.

Conclusions: the new PVB suspension presented in this study is effective and safe for treating children with proven EoE. Larger placebo controlled clinical trials would provide more information about dosing, efficacy, and long-term safety of this formulation, specifically designed for the oesophagus.

Key words: eosinophilic oesophagitis, oral viscous budesonide, elimination diet, paediatric endoscopy

Abbreviations:

eosinophilic oesophagitis (EoE)

oral viscous budesonide (OVB)

pre-prepared viscous budesonide (PVB)

pH multichannel intraluminal impedance (MII-pH)

WHAT IS KNOWN

- Topical steroids are the mainstay of Eosinophilic Oesophagitis (EoE) treatment in children and adults for many cases.
- There is presently no topical steroid designed for oesophageal drug therapy.
- Oral viscous budesonide (OVB) is actually considered more effective and is usually preferred to nebulized suspension, due to the higher esophageal mucosal contact time.

WHAT IS NEW

- This study showed that a new pre-prepared OVB (PVB) suspension is an effective and safe treatment for children with proven EoE.
- PVB may have advantages over other therapies in that it is palatable, practical to use, and its volume provides pan-oesophageal mucosal coverage.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is defined as a chronic, immune/antigen-mediated oesophageal disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation (1). The exact incidence of EoE is not yet known, however, since 2000 it has become exponentially more prevalent in western countries, with a yearly incidence now considered to be similar to that of Crohn's disease (2-3).

EoE is more commonly seen in male patients and in patients with atopic diseases such as food allergy, asthma, and allergic rhinitis. Clinical symptoms vary according to age, ranging from food refusal and emesis to dysphagia and food impaction (4).

Oral steroids are very effective in quickly resolving the eosinophilic oesophageal inflammation; however, because EoE is most likely a chronic disease, oral steroids are not indicated in daily management and should be reserved only for emergency, such as severe dysphagia, hospitalization, and weight loss (5).

Swallowed inhaled corticosteroids such as swallowed fluticasone or budesonide have low bioavailability, less potential for systemic side effects, and are considered topical agents. They can improve quality of life, decrease inflammation, and induce EoE remission in up to 90% of patients depending on the different studies (6).

Actually, the new clinical guidelines from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend topical corticosteroids and/or elimination diets as first-line pharmacologic treatment (7). However, despite the optimal results of dietary treatment, the latter may be limited by several drawbacks, such as severe food restriction and low compliance. Thus, topical steroids are the mainstay of EoE treatment in children and adults for many cases (8).

Unfortunately, there is presently no topical steroid designed for oesophageal drug therapy, and options are limited to off-label administering of swallowed aerosolized or nebulized corticosteroid formulations that are designed for asthma. Budesonide is much easier to administer and was first used in children (9). The compound is bitter and often mixed with a sweetener, such as sucralose,

chocolate syrup, honey, to make a slurry called "oral viscous budesonide" (OVB). Despite, families are often exhausted of the use of artificial sweetener in high doses for their children (10), OVB is actually considered more effective and is usually preferred to nebulized suspension, due to the higher esophageal mucosal contact time (11). The suggested dose in children is 1 mg/day, and 2 mg/day in divided doses for adults, but the optimal dosage has not formally assessed (12).

Since there is not yet available any specific suspension of OVB, this pilot, single center, open label, not blinded study aims at evaluating the efficacy and safety of a new, proprietary, pre-prepared suspension of OVB (PVB), made by ITC Farma (Pomezia, Italy) in children and adolescents with proven EoE.

PATIENTS AND METHODS

Patients. Eligible patients were recruited at the Paediatric Gastroenterology and Liver Unit of the Sapienza University of Rome during 12 months (between January 2014 and February 2015). This Unit is a tertiary referral paediatric center for eosinophilic disorders. We prospectively enrolled 36 consecutive paediatric subjects with a new or established diagnosis of EoE. Inclusion criteria were: age < 18 years; diagnosis of EoE with > 15 eosinophils/HPF in oesophageal biopsies after a PPI trial of at least 8 weeks (7); requesting alternatives to diet for new diagnosis, or a different pharmacologic treatment during an histological flare (in case of previous diet treatment and/or nebulized or systemic steroids). Exclusion criteria were: presence of non-EoE gastrointestinal diseases (eosinophilic gastroenteritis/colitis, IBD, or celiac disease); oesophageal stricture on baseline endoscopy that precluded passage of an upper scope; use of steroids (topical or systemic) within 4 weeks of the baseline endoscopy; change in dosing regimen of PPIs, diet, allergy medications, or inhaled steroids during the study period. Written informed consent was obtained from parents of all children; children over 12 years of age signed a statement of assent.

An allergy assessment (through skin prick test, atopy patch test and specific IgE tests) was performed in all patients before the enrolment. A 24 hours pH multichannel intraluminal impedance

(MII-pH) was also executed during the screening period (or before an 8-week PPI therapy for new diagnosis) in order to minimize the potential for GERD to be the cause of oesophageal eosinophilia in case of positive results. According to the ESPGHAN guidelines, the following pH-MII variables were analyzed: occurrence both of acid (defined as a drop in pH < 4.0), and non-acid (defined as a drop in pH > 7.0) GER events; total exposure acid time (% of GER); the total number of acid and non-acid GER events; the long-lasting number of acid GER events; the symptomatic index (SI), that is the percentage of symptoms attributable both to acid (SI-A) and non-acid (SI-NA) GER. An exam was considered positive only if at least ≥ 3 of variables reported above were positive. Patients with a positive MII-pH continued a concurrent therapy with PPI (after the PPI test of 8 weeks) at dose of 1.0 mg/kg/day along the study. All authors have accessed to the study data, and have reviewed and approved the final manuscript. The study protocol was defined in accordance with the Declaration of Helsinki and approved by the ethical committee of the University Hospital Umberto I in Rome.

Treatment. PVB is a galenic, pre-prepared formulation of budesonide, mainly mixed with xylitol, at concentration of 0.2 mg/mL, made by ITC Farma Srl (Pomezia, Italy), who provided the entire drug supply. Study participants were divided according to their height. Patients <150 cm and >150 cm height received 1mg/5ml bid (2 mg/daily) and 2mg/10ml (4 mg/daily), respectively, for 12 weeks. Morning and evening doses were administered after breakfast and at bedtime, respectively. The appropriate dose has been provided by using a capacity syringe. After the administration the bottle could be conserved at room temperature (no > 35°C or < 4°C). Subjects were instructed not to eat, drink, rinse their mouth, or brush their teeth for 30 minutes after taking study medication. Patients were clinically monitored at 6-week intervals and had access to a physician throughout their participation in the study to assist with any issues regarding the trial. Study medication adherence were also evaluated at each study visit by assessing the volume of medication remaining in each bottle to determine the approximate amount that has been taken since the prior visit. Adherence was calculated by dividing the amount of medication taken by the amount that should

have been taken, multiplied by 100. Subjects were considered adherent if they have received between 80% and 120% of the expected amount of medication.

Clinical symptom score. Patients were clinically evaluated at 6-week intervals in our unit. Clinical presentation was evaluated at baseline, 12 and 36 weeks, with a clinical score that considered seven variables: regurgitation/heartburn**,** abdominal pain, nausea/vomiting, anorexia/early satiety, dysphagia/food impaction, symptom induced nocturnal wakening, gastrointestinal bleeding; each symptom category were scored from 0 to 2 for intensity and frequency (13), for a total score from 0 to 14 (Table 1).

Endoscopy and histology. Endoscopy was performed at baseline, 12 and 36 weeks (6 months after the end of treatment) by the same board-certified gastroenterologist (SO), using conscious sedation, deep sedation or general anaesthesia (according with the different ages) (Figure 1). Endoscopic alterations were evaluated with an endoscopic score that considered presence of five characteristics: mucosal pallor, linear furrows/mucosal thickening, white plaques, friability and concentric rings or strictures; endoscopic score ranged from 0 to 5 for each oesophageal segment (maximum total score 15 pts) (13). At the inclusion/T0 endoscopy, all subjects received oesophageal, gastric, and duodenal biopsies. At least 2 mucosal pinch biopsies were obtained from the proximal, mid, and distal oesophagus. Subjects with peak intraepithelial eosinophil counts of ≥15/HPF and no significant gastric or duodenal pathology were histologically eligible for the study. At the end of study endoscopy, at least 2 biopsies from all 3 oesophageal levels were performed in all subjects, while gastric and duodenal biopsies were performed at the physician's discretion. Proximal, mid, and distal oesophageal biopsies, taken before and after treatment, were processed routinely and evaluated using light microscopy by an expert pathologist (AT). Two biopsies per level (proximal, mid and distal) yielded between 15 and 20 evaluable hps. A peak eosinophil count/HPF was obtained for each esophageal level by counting the number of eosinophils in the most inflamed area by using a Nikon Eclipse E400 (Nikon, Tokyo, Japan) light microscope at x 400 magnification (0.3

mm 2 HPF). Histological findings were scored with values of peak intraepithelial eosinophils count and other mucosal alterations characteristics of EoE (13); with a totally score from 0 to 18.

Outcomes measures. The primary outcome measure was the improvement of oesophageal eosinophilia. The response to therapy was determined by comparing baseline and final treatment peak/counts/hpf under light microscopy (x400). Patients were categorized into responders (0-6 eos/hpf), partial responders (7-19 eos/hpf), and non-responders (≥20 eos/hpf) based on final treatment biopsy results. Secondary outcomes included response in symptom, endoscopy and histology scores at the end of treatment.

Safety assessment. Safety assessment included adverse event monitoring during the treatment; physical examination; height; weight; vital signs (heart rate, blood pressure); and laboratory tests (complete blood count with differential, serum glucose, morning serum cortisol). Clinical evaluations were assessed at baseline, at 6 and 12 weeks of treatment, while laboratory tests at baseline and 12 weeks only (Figure 1). Baseline and post-treatment morning cortisol levels were measured to estimate adrenal suppression of the PVB suspension. The cortisol was measured during other laboratory tests.

Statistical analysis. All statistical analysis was carried out using the SPSS (SPSS 17.0 Chicago, USA). Two-tailed *P* values were calculated using paired *t*-tests to compare the means of patient values for eos/hpf, endoscopy, histology and symptom scores before and after budesonide therapy. Two-tailed unpaired *t*-tests were utilized in order to compare variables grouped by responders versus non-responders. Correlation between symptoms, endoscopy score, and peak eosinophil count were calculated using Spearman correlation coefficient. Results with *P* values <0.05 were considered statistically significant. Both mean and median statistics were generated, both were equivalent, and mean statistics are presented. Data were given as mean±SD and as median (and ranges).

RESULTS

During the study period, 51 patients were screened. Five were excluded because of one or more exclusion criteria, while 10 had a positive response to the 8-week PPI therapy and were considered as PPI-REE.

Thirty-six patients were enrolled (21 males, 15 females, age 12.3±7.3; disease duration: 16.8±11.4), 17 (47%) were diagnosed in the latest 3 months prior the enrolment, while 19 (53%) had an established diagnosis with different previous treatments. Of these nineteen with an established diagnosis, 16 have been previously treated with fluticasone for 3 months, but only 10 have had a complete histological response. All clinical information are summarized in Table 2.

The PVB suspension significantly reduced the median peak eosinophil count/HPF from baseline (42.2; range: 15-100) to 12 weeks (2.9; range: 0-30) ($p<0.01$). Thirty-two patients (88,9%) had a complete histological response and were considered as "responders", while 2 as "partial responders". Only two patients (5,5%) were non-responders, presenting more than 20 eosinophils/hpf as well as an incomplete reduction of symptoms after OVB treatment. Of these two patients, one had received a specific elimination diet and the other systemic steroids. Seven of 36 children (19,4%) had a positive MII-pH and were also treated with proton pump inhibitors.

All patients stopped PVB therapy after 12-week period, but 2 non-responders continued PVB combined with other treatment (diet and/or short courses of systemic steroids), due to the presence of severe symptoms. After 24 weeks of follow-up, the median value of peak eosinophil count/HPF was 20.8 (range: 0-70), with a significant increase from 12-week value ($p<0.05$). Only 15 patients of 32 responders maintained a peak intraepithelial eosinophils count below 6 (46.7%) (9 completely eosinophil-free, 25%), while 13 showed a significant increase, and the remaining 4 a partial increase (Figures 2, 3). The two non-responders showed a mild improvement in symptoms but not in the eosinophil count. In the majority of our patients (9) the relapse started from the distal part of the esophagus, but there was no statistically significant difference from those with a relapse in the mid or proximal part.

Only 21 patients were positive at RAST/SPT tests. Seventeen were either positive at RAST and SPT, while 4 had only RAST positivity. The most common antigen was cow's milk 8/21 (38%), followed by egg 6/21 (33%), fish 4/21 (19%), soy 4/21 (19%) and wheat 3/21 (14%). Fifteen (71%) had also a sensitization to environmental allergens. No correlation was found between response to budesonide, tendency to relapse, and positivity at RAST/SPT.

The new PVB suspension was able to evidently improve the clinical symptom score from 3.25 (range: 0-9) to 1.53 (range: 0-7) after 12 weeks of therapy ($p<0.01$). This statistical improvement was roughly unaltered after the treatment free period (1.72; range: 0-8) with no significant difference from the 12-week value (Figure 4-A). Interestingly, at baseline 11 of 36 patients were completely asymptomatic (clinical symptoms score=0), despite evidence of active disease at histology, as well as 10 patients at the end of study. Symptoms poorly correlated with peak eosinophil count and disease activity throughout the study ($r < 0.5$).

The endoscopy score significantly decreased from 4.94 (range: 0-9) to 1.22 (range: 0-6) after 12 weeks ($p<0.01$), but noticeably increased to 2.67 (range: 0-9) ($p<0.05$) at the end of study (Figure 4-B). At the enrolment, 3 patients had no clear lesions at endoscopic examination, as well as 4 at the end of study. The endoscopic appearance weakly correlated with values of peak eosinophil count ($0,1< r < 0,67$).

Finally, the histology score changed from 10.28 (range: 4-16) to 1.31 (range: 0-14) and to 6.03 (range: 0-18), at 12 and 36 weeks respectively ($p<0.01$) (Figure 4-C). A complete histologic remission (histology score = 0) was observed in 28 patients after the OVB treatment, but only in 9 at the end of study.

No patient reported serious adverse events. A suspected oral candida occurring in one patient was not confirmed at the follow-up. Oesophageal candida was not detected at the endoscopy follow-ups in any patient.

There was no significant difference between pre-/post treatment morning cortisol levels, 12.3 ug/dl (range: 4.2–22) and 10.3 ug/dl (range: 4.4 –16), respectively as well as at the end of the study 11.3

ug/dl (range 4.1-18). There were no clinically significant drug-related effects on values for heart rate or temperature, or clinically important differences or trends for changes in mean height or weight. All patients were considered completely adherent at the end of treatment, with 97% (range 95-105) of the expected amount of medication consumed during the 12 weeks.

DISCUSSION

This pilot study confirms the efficacy of a new PVB suspension in treating children with active EoE for 12 weeks. This PVB formulation was successful in inducing symptomatic, endoscopic and histologic remission in children with proven EoE.

According to the current ESPGHAN guidelines, histologic remission is one of the treatment end points in EoE. Indeed, our primary end point was a decrease in the peak eosinophil count to less than 20 cells/hpf, which is consistent with the widely agreed definition of histologic treatment end point (7). We were able to reach an excellent histologic remission in 89% of children treated with our PVB formulation; furthermore, including also the two partially responders subjects, oesophageal eosinophilia was found to improve in 94% of cases. Of the 2 non-responders, one showed a 50% reduction in oesophageal eosinophil count, while the remaining did not show any eosinophilic reduction and received systemic steroids in addition to topical therapy afterwards. This confirms that not all patients respond to steroids and this may be somewhat genetic rather than due to noncompliance. Indeed, Butz at al found that nonresponders had genetic evidence of steroid resistance with genetic transcript patterns predictive of unresponsiveness (14).

It is worth noting that at the 24-week follow up after stopping PVB, only 46,7% and 11,1% remained in complete or partial histologic remission, respectively. These data are similar to those previously described (15). In EoE patients responding to the induction phase, eosinophilic recurrence is seen frequently after discontinuation of therapy and maintenance therapy may be needed. Indeed, since EoE is comparable to asthma of the upper gastrointestinal tract – it is

conceivable that patients with EoE may need a maintenance low dose steroid therapy following the induction (16).

Interestingly, PVB promoted marked reduction in intensity and severity of symptoms that remained in a high proportion of our patients after 36 weeks. Regrettably, the correlation between symptoms and oesophageal eosinophilia seemed to be poor ($r < 0,5$) and some patients with high eosinophil counts may be entirely asymptomatic at diagnosis and/or after treatment. Eleven children were asymptomatic before budesonide therapy despite persisting esophageal eosinophilic infiltration, as well as 10 patients at the end of therapy. As previously reported, our data confirm that endoscopic or histologic remission can be hardly identified on symptoms alone (17): this suggests that assessment of disease severity should not rely on symptoms, while untreated subclinical eosinophilic inflammation can lead to stricture formation (18).

Endoscopy was able to accurately identify disease activity in the majority of our children, in few cases it did not reveal abnormal features, despite presence of oesophageal eosinophilia. This study confirmed that endoscopy is not yet completely sufficient to accurately evaluate oesophageal eosinophilia ($0,1< r < 0,67$), thus making histology always mandatory (19). Indeed, it is known that children with EoE may exhibit more commonly than adults either a normal-appearing oesophagus or findings of plaques or edema (20).

The histology score was also improved on PVB therapy. Despite the oesophageal epithelium is the main parameter of EoE activity, it is always important to consider the concurrent improvement of other histopathologic findings (eosinophilic degranulation, eosinophil microabscesses, basal layer hyperplasia dilated intracellular spaces or spongiosis, and *lamina propria* fibrosis) in order to have more information about histologic remission. Indeed, when the peak eosinophilic count is normal or borderline, only a complete histological examination might be able to evaluate disease activity improvements (21).

Notably, the use of this PVB, which is ready-to-use, without any specific request before the administration and specifically designed for oesophageal therapy increased adherence (>97% in this

study) and feasibility of topical steroids, and it may expand the availability of this type of drug with a specific focus on EoE. Indeed, because no corticosteroids expressly developed for EoE have been approved by the European Regulatory Agency for drugs, current options are limited to swallowing aerosolized or nebulizer corticosteroid formulations. Usually, budesonide inhalation suspension either is mixed with sucralose to create a viscous preparation (11,13,22) or is nebulized and swallowed (11,23). As mentioned, OVB formulation is usually preferred due to higher efficacy; however, parents are often reluctant to a large consumption of sweeteners such as sucralose, maltodextrin and glucose. Although, the latter are generally considered as harmless products, a toxicology study in animals suggested that they could increase levels of cytochrome CYP3A4 and CYP2D, increase the fecal pH, cause mild depletion of goblet cells, and decrease colonic colonization of anaerobes (24). Despite these results have been disputed (25,26), and no clear evidence is yet available about the harmfulness of sucralose in humans, the development of new pre-prepared suspension of OVB, like the product used in this trial, is urgently warranted.

Our study confirms previous results of placebo-controlled trials on EoE treatment with topical corticosteroids (13,23,27-29). However, we used a higher dosage than previous reported as suggested by the current guidelines. Only one paediatric study evaluated the efficacy and safety of a high dose of OVB in EoE, showing a marked both histologic and symptom response compared to placebo (12). However, the optimal dose of OVB in children with EoE has not been formally assessed (7). In this pilot study we tested a higher dose also on the basis of the manufacturer's instruction with the objective to cover the entire oesophageal surface. Obviously, in the next future it will be of critical interest to evaluate the efficacy of this new preparation at lower dosage and to find the minimal effective dose. Moreover, since the role of a concomitant reflux disease has not been defined in depth, all patients with positive results at MII-pH evaluation before the enrolment have received concomitant PPI therapy, in order to reduce the potential effect of GERD on oesophageal eosinophila.

Remarkably, no significant changes in cortisol levels were reported in this study, even with this greater dosage. However, due to the controversial data on the adrenal function suppression, we would suggest monitoring both for adrenal suppression and other corticosteroid-associated side effects when treating EoE children with topical corticosteroids, especially if therapeutic program includes longer duration and higher dosages than traditional regimens (30-32).

Undoubtedly, this study has several limitations. We did not design the study in a randomized fashion and a placebo arm was not included, differently from the majority of previous studies on topical steroids in adults and children (11-14). However, while OVB formulation has repeatedly shown to be superior to placebo, this was a pilot study based on a novel PVB formulation. Moreover, different concerns are currently rising in the scientific community about the use of placebo in paediatric chronic diseases. Indeed, recently, 4 organizations provided a joint statement on the role of placebo in paediatric inflammatory bowel disease trials, declaring that it should be avoided when the active treatment has been proven to be effective in prior large trials in adults, supported by clinical experience in children (33). This statement might also be accepted for EoE, due to similar behaviours and the risk of complications in untreated patients.

Another limitation was a lack of a standardized validated symptom score to evaluate clinical response, however this concerns several others randomized, placebo-controlled studies in children and adults (12-13, 23-26).

Moreover, neither histology nor endoscopy score were blinded. Nevertheless, it is also true that one single operator performed all the endoscopies and a single pathologist evaluated all the histological examinations (pre- and post- treatment). This reduced as much as possible the variability in the evaluations. Obviously, future studies will require a blinded evaluation with an inter-observer agreement calculation.

In conclusion, this study showed that this new pre-prepared OVB suspension is an effective and safe treatment for children with proven EoE. It may have advantages over other therapies in that it

is palatable, practical to use, and its volume (5– 10 mL) provides pan-oesophageal mucosal coverage. Obviously, larger controlled clinical trials would provide more information about dosing, efficacy, and long-term safety of this new formulation designed specifically for the oesophagus.

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Figure Legend

Figure 1. The flow-chart of the study

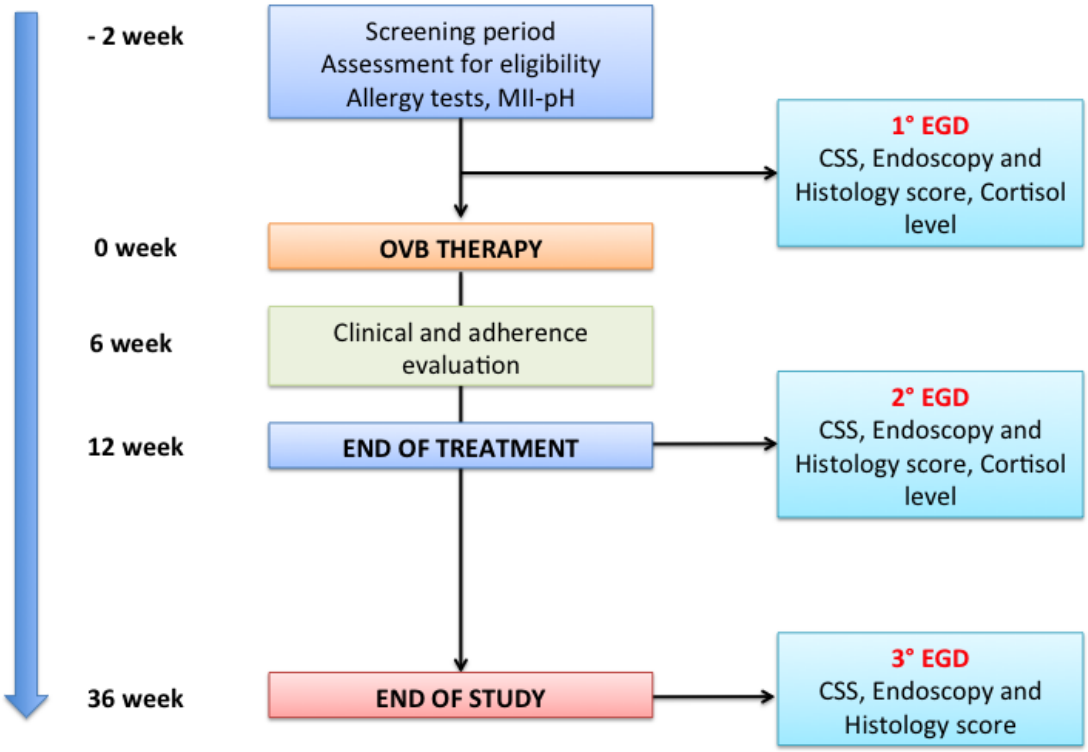

Figure 2. Comparison of peak eosinophil count pre- and post- treatment with the new suspension of oral viscous budesonide.

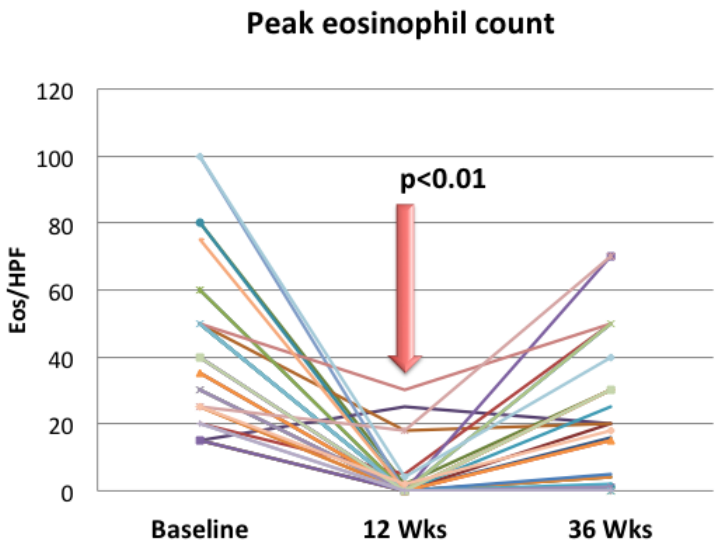

Figure 3. Percentage of responders after 12-week treatment and at 36-week follow-up.

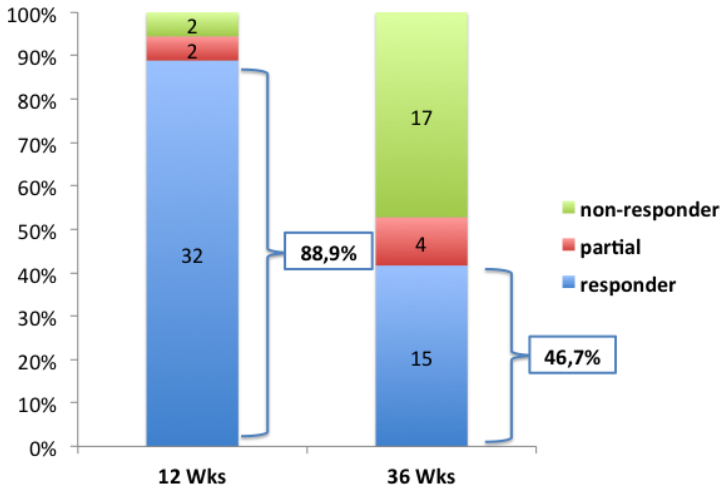

Figure 4. Median values and IQR of symptom score (A), endoscopy score (B) and histology score (C) during the study period, *p<0.01.

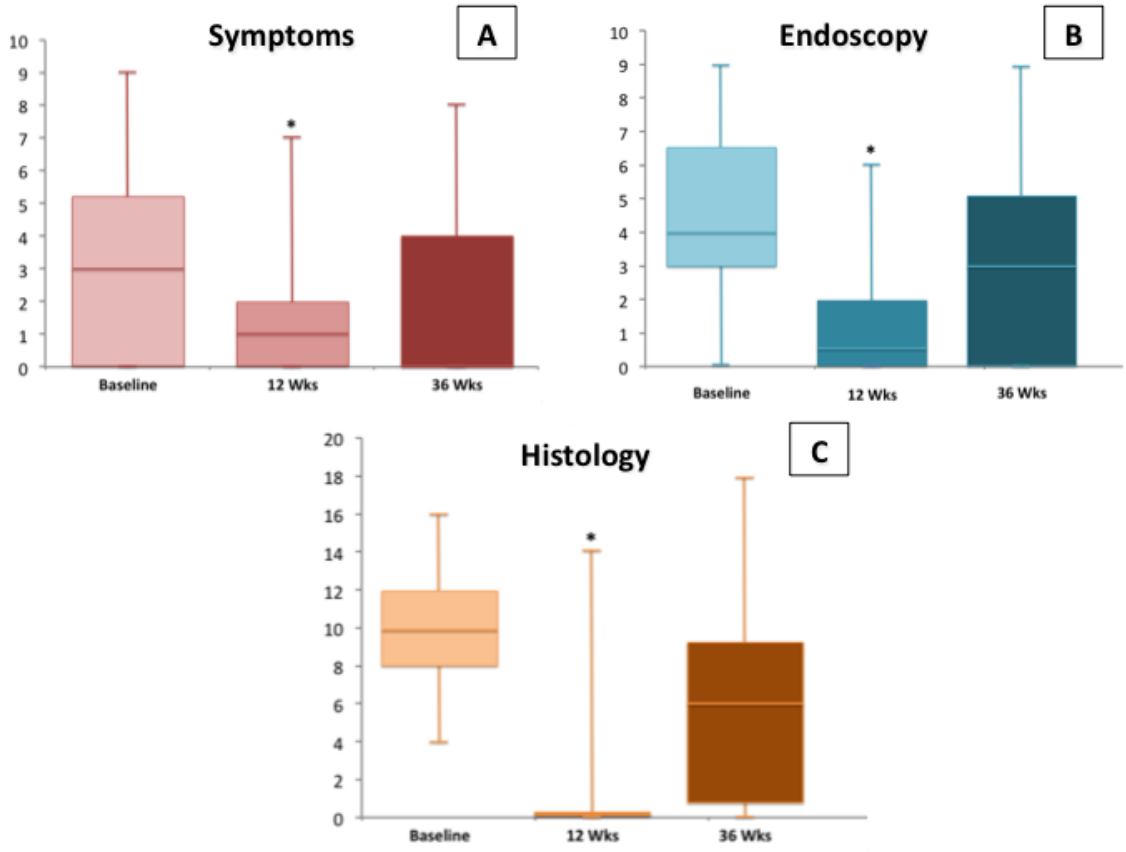

Table 1. Clinical symptom score

SYMPTOMS	**SCORE (0-14)**		
	0 = Absent	**1 = Mild symptoms** (Intermittent or not interrupt daily activities)	**2 = Severe symptoms** (every day or interrupted daily activities)
Regurgitation/heartburn			
Abdominal pain			
Nausea/vomiting			
Anorexia/early satiety			
Dysphagia			
Symptom induced nocturnal wakening			
Gastrointestinal bleeding			

Table 2. Patients demographics and clinical information

PATIENTS	N=36
Median age, y (range)	12 (5 – 18)
Gender (M, F)	21, 15
Height	
• < 150 cm	16 (46%)
• ≥ 150 cm	20 (56%)
New diagnosis	17 (47%)
Disease duration, m, median (ranges)	14.3 (1 – 36)
Age at diagnosis, y, median (ranges)	10.8 (4 – 17)
Previous medications, n (%)	
Corticosteroids (any)	16 (44%)
Antihistamines	11 (31%)
Leukotriene antagonists	12 (33%)
Diet	14 (39%)
Allergy, n (%)	
Family history	16 (44%)
RAST/Skin Prick test	21 (50%)
Patch Atopy test	4 (11%)