

Eosinophilic oesophagitis in children: responders and non-responders to swallowed fluticasone

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ABSTRACT

Eosinophilic Oesophagitis (EO) is characterised by large numbers of eosinophils in oesophageal mucosa in response to food or inhaled antigens. Treatment with elimination diet or corticosteroids lead to improvement in some children, but their efficacy is not optimal.

Aim of this study is to identify clinical, endoscopic and/or histological features associated with response to treatment with swallowed fluticasone propionate.

Patients and methods In the last 12 years 34 children (M/F 25/9) with EO were treated with fluticasone propionate spray 250 µg/puff by inhaler without spacer, three puffs three times a day for 6 weeks, and returned for a follow-up endoscopy. At histology 25 of them were found to be responders to therapy (73.5%) and 9 were non-responders. Anthropometric characteristics, symptoms at presentation, endoscopic and histological data at baseline between responders and non-responders were compared.

Results Age, sex, height, duration and type of main symptom at presentation, type of allergy and number of allergens, peripheral eosinophil counts and serum IgE were similar in responders and non-responders. At baseline histology findings responders had a more severe inflammation: median peak eosinophils/high power field was higher (76 vs 44 in non responders $p=0.04$), eosinophilic microabscesses were present in a significantly higher number of responders ($p=0.04$) and peak mast cells/ high power field was significantly higher ($p=0.001$).

Conclusions Clinical characteristics of children with EO at baseline were similar in responders and non-responders, but a more severe inflammation in oesophageal mucosa was associated with a higher response rate to fluticasone treatment.

INTRODUCTION

Eosinophilic oesophagitis (EO) is a disease of the oesophagus with male predominance, becoming increasingly recognised in children and adults over the last decade. It is characterised by a dense oesophageal eosinophilia with severe squamous epithelial hyperplasia in association with upper gastro-intestinal symptoms, primarily oesophageal. In EO, the gastric and duodenal mucosae are normal. The oesophageal abnormalities do not respond to treatment with high-dose proton pump inhibitors.¹ There is evidence that food allergens and aeroallergens contribute to the pathogenesis of EO in children, but efficacy of treatments with elimination diet²⁻³ or corticosteroids⁴ does not exceed 80%.

The aim of our study is to ascertain whether there are any clinical, endoscopic or histological

characteristics at baseline, that could predict the response to topical corticosteroid treatment.

PATIENTS AND METHODS

In the last 12 years we observed 36 children with EO, they were all treated with swallowed fluticasone for 6 weeks and 34 of them (M/F 25/9) returned for a follow-up. We included in the study only the 34 that returned 1 week after the end of treatment for an endoscopic control. They were predominantly males (24 vs 10 females) and their median age was 8.2 years (range 4 months 16 years). Clinical characteristic and family history were collected using a standardised chart. All children had been either non-responders to proton-pump inhibitor (PPI) (22 children) or 24 h pH-monitoring was negative for gastro-oesophageal reflux (12 children). The same day of the first endoscopy (baseline) blood was drawn for determination of peripheral eosinophil counts, serum total IgE and radio allegro sorbent test (RAST) for common food antigens. In a subset of children where RAST was negative, a prick and patch test was also performed, and in those with a suspected allergy to aeroallergens by clinical history, a prick test for aeroallergens was performed.

During upper gastro-intestinal (GI) endoscopy six oesophageal biopsies were taken: two at distal, two at medium and two at proximal oesophagus. Gastric biopsies: two at the fundus and three at the antrum (one for rapid urease test) and duodenal biopsies: one at the bulb and two at the distal duodenum were also taken. Diagnosis of EO was established by histology as peak count of >15 intraepithelial eosinophils per any high power field (HPF at 400×light microscopy) after H&E staining, without any eosinophil infiltration in gastric or duodenal mucosa (<5/HPF) according to recent guidelines.¹ Mast cells/HPF were also counted, after immunostaining with anti-CD117 antibody (Dako, Milan, Italy, dilution 1:100). Presence of oedema and fibrosis in lamina propria were evaluated by a semiquantitative score, as previously proposed.⁵⁻⁶ In four children duodenal biopsy showed coeliac disease. All biopsy specimens were independently evaluated by two pathologists (RB and FM). All children were treated for 6 weeks with fluticasone propionate spray, 250 µg/puff by inhaler without spacer, three puffs three times a day after meals and at bed time, independently of age, height or weight. The children were trained to swallow immediately after the puffs, and were suggested not to eat for at least a couple of hours. They returned for a follow-up endoscopy 1 week after the end of treatment. Fluticasone boxes were examined for evaluating compliance (three of them resulted non-compliant and a second course of treatment was

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Original article

prescribed). Treatment was well tolerated by all the children, no adverse events were seen and none of the children had to stop it for any side effects.

Repeat endoscopy was performed and six biopsy specimens were taken from the oesophagus as in the baseline endoscopy, and re-evaluated by the same pathologists. Children where the eosinophils/HPF in oesophageal mucosa was ≤ 6 were considered responders, whereas where eosinophils/HPF were >20 were considered non-responders, and where eosinophils/HPF were between 7 and 20 were considered borderline⁴ Compliance to treatment was measured on a dose count. At the time of endoscopy signed informed consent was obtained for each participant, for the anonymous use of their data for the present study.

Statistical analysis was performed using STATISTICA software V.6.1 (Statsoft Inc, Tulsa, Oklahoma, USA). Comparison between groups was performed using the Kruskal-Wallis analysis of variance test and the Mann-Whitney U test, and differences between rates were analysed by the χ^2 test or Fisher's exact test when appropriate.

RESULTS

In 25 children peak eosinophil/HPF was ≤ 6 (median 0, range 0–6) and they were considered responders (25/34=73.6%, 95% CI 55 to 87) in nine children peak eosinophil/HPF was >20 (median 34, range 22–80) and they were considered non-responders. In none of the children peak eosinophil/HPF was borderline. Anthropometric and clinical characteristics were similar at baseline in responders and non-responders (table 1). At baseline endoscopic findings were similar in the two groups. However, histological findings showed that responders had a more severe inflammation: median peak eosinophils/HPF was higher ($p=0.04$). Eosinophilic microabscesses were present in a significantly higher number of responders ($p=0.04$) and peak mast cells/HPF was significantly higher ($p=0.001$). The scores of fibrosis and oedema were similar in the two groups (table 2).

All children presented symptomatic improvement or disappearance of symptoms irrespective of histological results. Of the four children with coeliac disease three were responders and one was a non-responder.

DISCUSSION

Treatment of EO is still a matter of debate. When a clear history of food allergy is present an elimination diet with restriction of specific foods is recommended² but dietary elimination can be difficult because children are typically sensitized to multiple foods. Different strategies have been tried, from an elementary diet (amino acid-based formula)⁷ to a six-food elimination diet³ but results have not been consistent and elemental diet is often necessary though not well tolerated or accepted. So anti-inflammatory treatment has been proposed with either topical⁴ or systemic corticosteroids. Topical treatment given as inhaled corticosteroids⁸ is usually well accepted and tolerated, but its efficacy is variable.

In our study efficacy of inhaled fluticasone was 73.5%, and when analysing data of responders and non-responders we did not find any clinical variable influencing response to treatment. Although girls tended to respond better than boys, and children with no history of allergy by history and tests tended to respond better, the same was true for children with alimentary and aero-allergen allergy. However, due to the low numerical consistency of the series these differences did not reach a statistical significance.

On the other hand, we found that children with a more severe inflammation (ie, presence of eosinophilic microabscesses, higher number of eosinophils/HPF and higher number of mast cells/HPF) showed a higher response rate to treatment. The number of mast cells infiltrating the oesophageal mucosa at baseline was the most significant difference we found between responders and non-responders. Mast cells are known to play a central role in orchestrating inflammation⁹ and their

Table 1 Clinical characteristics at baseline of responders and non-responders to fluticasone

	Responders (N=25)	Non-responders (N=9)	p Value
M/F	17/8	7/2	.16
Age at diagnosis* (years) (range)	7.2 (0.4–15.4)	9.4 (0.6–16.2)	.83
Height * (cm) (range)	126 (0.65–181)	144 (0.68–175)	0.34
Duration of symptoms *(years) (range)	2.7 (0.3–9)	2 (0.2–9)	0.50
Age at initial symptoms* (years) (range)	7 (0.4–15.4)	9.3 (0.4–16.2)	0.65
Allergy (by history and/or tests)†			
No allergy	5	–	
Foods and aeroallergens	9	1	
Foods only	5	4	
Aeroallergens only	5	4	
Total number of allergens/child* (range)	3 (0–10)	2 (1–11)	
Main symptom at presentation			
Failure to thrive	8	–	
Abdominal pain	7	2	
GI Bleeding	1	2	
Dysphagia	4	2	
Food impaction	3	2	
Asthma or chronic cough	2	–	
Blood tests			
Peripheral eosinophil counts/ μ l* (range)	562 (108–1779)	485 (284–1029)	0.74
Serum IgE* (range)	205 (64–2000)	660 (103–1624)	0.13

*Data are presented as median.

†Number of children with allergy.

Table 2 Endoscopy and histology findings at baseline in responders and non-responders

	Responders (N=25)	Non-responders (N=9)	p Value
Endoscopy findings			
Rings	5	5	0.14
Erosions/ulcer	9	1	0.43
Nodularity	4	2	0.57
Hyperaemia	4	0	0.23
Normal	3	1	0.65
Histology findings			
Peak eosinophil/HPF* (range)	76 (30–174)	44 (16–80)	0.04
Peak mast cells/HPF* (range)	9 (1–22)	3 (1–9)	0.001
Presence of eosinophilic microabscesses†	15	1	0.01
Oedema score (range)	2 (0–3)	2 (2–3)	0.75
Fibrosis score (range)	2 (0–3)	3 (2–3)	0.52

*Data are presented as median.

†Number of children with the finding.

HPF, high power field.

participation in the physiopathology of EO has been suggested for their interaction with T lymphocytes and eosinophils. Our data seem to indicate that mast cells also play a role in determining response to topical corticosteroid treatment. We suggest the use of anti-CD 117 antibody in the standard evaluation of oesophageal biopsies in children with suspected EO, in order to disclose and count the mast cells that are not easily found with routine staining.

Efficacy of fluticasone treatment in our series gave better results than in a recent series of 21 children from USA¹⁰ where only 50% of fluticasone treated children showed histological remission, and where younger age, shorter height and lighter weight favoured response to treatment. Our data did not confirm theirs, but we observed a more favourable effect of treatment in non-allergic children (ie, all five non-allergic children were responders) as reported in children treated with oral viscous budesonide.⁴

The better response to fluticasone in children with a more severe inflammation may seem counter-intuitive. However, a more severe inflammation may induce the secretion of higher levels of interleukin 8, another proinflammatory cytokine and angiogenesis promoter, as are reported in EO.¹¹ The consequent increased blood flow may favour better diffusion of the antibiotics. There are other examples of infectious diseases, such as *Helicobacter pylori* gastritis, meningitis and prostatitis, for which this is the case.

Data on long term history of these children are only rarely reported and we do not know whether short term response is in

any way influencing the disease prognosis, and particularly preventing oesophageal thickening and stricture formation. However, a good relationship between decrease of oesophageal eosinophil infiltration and resolution of oesophageal remodelling in response to topical corticosteroids has been recently reported.⁶ But whether this phenomenon is associated with a decreased risk for developing extensive remodelling and stricture formation is still to be studied.

Many of these children will probably experience a relapse. Twenty weeks after a 4-week treatment with topical or systemic corticosteroids 45% of 68 children were reported to experience symptom relapse.¹² Long term follow-up is therefore needed to ascertain whether responders to swallowed fluticasone may have a better prognosis than non-responders, and in particular how many of them—to maintain symptomatic control—will need the leukotriene receptor antagonist, montelukast,¹³ which however does not have any influence on eosinophils' infiltration nor in resolution of remodelling, and so possibly not on preventing oesophageal strictures.

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Contributors RB and GO designed the study and wrote the manuscript. GO performed the endoscopy, took the oesophageal biopsy specimens and clinically followed the children. RB and FM evaluated the histological examinations of all mucosal biopsies. All Authors contributed to the discussion of the results and agreed to the manuscript content.

Competing interests None.

Patient consent Obtained.

Ethics approval Azienda Ospedaliera Maggiore della Carità, Novara.

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Take home message

What is currently known

- Eosinophilic oesophagitis is becoming increasingly recognised in children and adults over the last decade.
- Efficacy of treatments with elimination diet or corticosteroids is unsatisfactory.

What is new here

- A more severe inflammation in oesophageal mucosa may predict a higher response rate to fluticasone treatment.

Original article

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