

# Treatment of Allergic Enteropathy in a 7-year-old Girl with Controlled-release Budesonide

TF **TONG**, DKK **NG**, PK **HUI**, WF **LAU**

## Abstract

We reported the use of controlled-release budesonide in the treatment of allergic enteropathy. A 7-year-old girl presented with features of allergic enteropathy complicated by malabsorption and protein losing enteropathy. She initially responded well to an elimination diet and a course of systemic steroid which however resulted in depressed height velocity. In view of unsatisfactory histological response, a course of controlled-release Budesonide (Entocort) was given for 6 months. This resulted in improvement in mucosa histology together with normalisation of height velocity. She was followed up for 6 years with no clinical relapse.

## Key words

Allergy; Budesonide; Child; Diarrhoea; Enteropathy; Gastroenteropathy

## Introduction

Allergic gastroenteropathy is a term that describes an immune-mediated process that can affect any area of intestinal tract from esophagus to the colon.<sup>1</sup> The presentation of allergic gastroenteropathy is highly variable. It includes classic allergic reaction, protein-losing enteropathy, colitis, enterocolitis, malabsorption syndrome and post-enteritis milk protein intolerance.<sup>1</sup> It may be associated with respiratory and cutaneous symptoms which include wheeze, cough, rhinitis, urticaria, angioedema, exacerbation of atopic dermatitis and cutaneous erythroderma.<sup>2</sup> We report here a girl with allergic enteropathy that was controlled with controlled-release budesonide.

Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong, China

TF **TONG** ( 湯子芬 ) MBChB, MRCP, FHKCPaed  
DKK **NG** ( 吳國強 ) M Med Sc, FHKAM(Paed), FHKCPaed  
WF **LAU** ( 劉永暉 ) MBChB, MRCP, FHKCPaed

Department of Pathology, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong, China

PK **HUI** ( 許伯鈞 ) MD

Correspondence to: Dr DKK **NG**

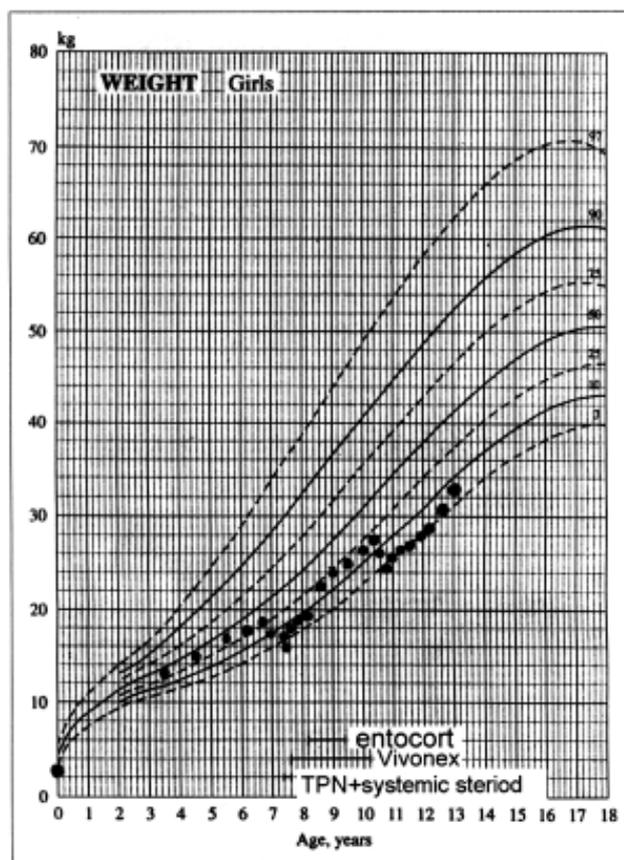
Received August 30, 2002

## Case Report

A 7-year-old Chinese girl presented to us in December 1996 with the complaint of abdominal pain, repeated vomiting, diarrhoea and peripheral oedema. The symptoms began four months ago with gradual progression. She was treated with herbal medicines and a diet restricted to fish and pork only. The girl had history of eczema and had been seen by dermatologist since the age of one-month-old. She had asthma for a few years with infrequent attacks. She also suffered from allergic rhinitis and required ketotifen and budesonide nasal spray. She had no family history of atopy but her elder brother suffered from cow's milk protein intolerance during infancy.

Physical examination on admission revealed abnormal growth parameter with head circumference and height at the third percentile. Her weight started to drop six months ago from twenty-fifth percentile to below third percentile (Figure 1). She was pale and had generalised eczematous rash with excoriation and lichenification. Generalised muscle wasting was noted especially over the buttocks. Mild ankle oedema was present. The abdomen was mildly distended.

Laboratory tests over the course of her hospitalisation revealed hypochromic microcytic anaemia due to iron deficiency. Her haemoglobin level was 9.6 gm/dl and her neutrophil count was normal without eosinophilia. Blood



**Figure 1** Weight chart.

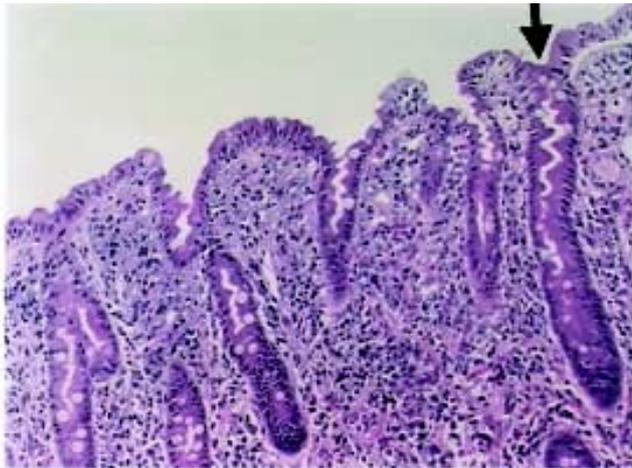
smear showed no acanthocyte. Erythrocyte sedimentation rate was not raised. Blood for zinc, vitamin B12 and folate were normal. There was hypoalbuminaemia with lowest albumin level being 22 gm/l. Stool specimens were negative for pus cell, eosinophil, amoebae, giardia, ova and cyst, bacterial and viral cultures. Five days faecal alpha-1-antitrypsin clearance was 106.6 ml/day (normal <13 ml/day). Xylose absorption test showed low 2- and 5-hour urine xylose output, the 2-hour urine xylose was 0.6 mmol/2-hour (normal 3.2-12.8 mmol/2-hour) and 5-hour urine Xylose was 1.2 mmol/5-hour (normal 8-16 mmol/5-hour). IgA and IgM were normal but IgG level was low, 3.7 gm/l (normal 6-12.3 gm/l). IgE was markedly increased to 2,000 iu/ml. Autoimmune markers including C3, C4 level, ANF, rheumatoid factor, antimitochondrial antibody, anti-smooth muscle antibody, anti-thyroglobulin antibody and thyroid microsomal antibody were negative. Anti-enterocyte antibody was negative. Abdominal X-ray showed mild bowel distension. X-ray of wrist showed marked delay in bone age (four-year) but there were no ricketic changes. Barium meal and follow through showed no evidence of

lymphoma or blind loop. Chromium labelled protein scintiscan confirmed the presence of protein loss in the small bowel. Skin tests to cow milk, cat fur, dog hair, house-dust mite, wool and pollen were positive. RAST tests to nuts, egg white, wheat, Soya bean were positive but negative to fish, shrimp, mussel, tuna and salmon. Upper gastrointestinal endoscopy was done with no visible lesions. Gastric and duodenal biopsies were obtained from upper gastrointestinal endoscopy with advancement of biopsy forcep beyond Ampulla of Vater for the latter. Gastric biopsy showed normal histology whilst duodenal biopsy showed total villous atrophy and infiltration of lymphocytes (Figure 2). Skin biopsy of the eczematous lesion showed subacute dermatitis with no evidence of dermatitis herpetiformis. A bone marrow aspiration did not demonstrate any eosinophilia.

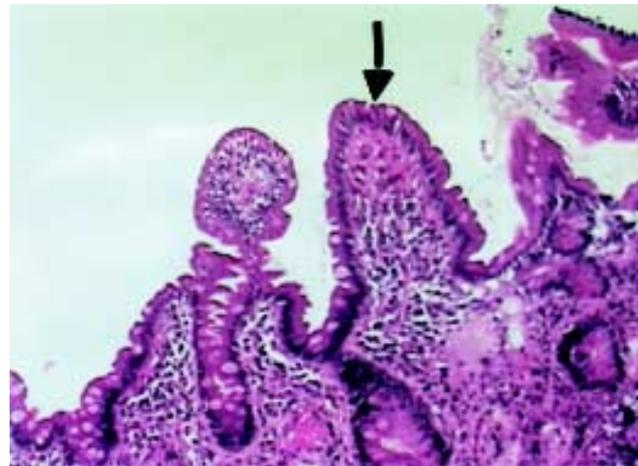
As her symptoms persisted despite a restrictive diet with plain rice and chicken, intravenous hyperalimentation was started via a Hickmann catheter and supplementary semi-elemental formula, Pepti-Junior™ (Nutricia, Holland) and polycal was given. Second duodenal biopsy three weeks later showed no improvement of total villous atrophy. Oral feeding was stopped and this resulted in marked improvement of her eczema. A course of prednisolone was started with 2 mg/kg/day and it was then gradually tapered off in five weeks. Third duodenal biopsy was performed three weeks after starting systemic steroid. It showed improvement with only partial villous atrophy and a decrease in lymphocyte infiltration. She developed hirsutism while on systemic steroid but the problem resolved gradually. Vivonex (Novartis, USA), a complete elemental enteral nutrition, was tried and parenteral nutrition was slowly weaned off after six weeks. Diarrhoea and abdominal distension gradually settled and there was no evidence of fat malabsorption or gut protein loss. The patient was then discharged.

Food items were gradually added one by one every two months, initially with rice followed by chicken, lamb, and pork. She had no gastrointestinal symptom. Her body weight climbed up to tenth percentile (Figure 1). Repeated biopsy still showed persistent partial villous atrophy. In view of the persistent mucosal changes, controlled-release budesonide (Entocort) capsule 9 mg daily was added as an alternative to systemic steroid at this stage. Subsequent endoscopy and biopsy were performed two months after budesonide was started (Figure 4 and Table 1). It showed improvement in villous architecture and significant reduction in lymphocytes population. Budesonide was gradually tapered over 6 months and finally discontinued.

She developed cushingnoid features, hirsutism and adrenal suppression while she was receiving budesonide. Short synacthen test showed depressed adrenal response with cortisol production of 50 nmol/l, 113 nmol/l and 146 nmol/l at 0 min, 30 min and 60 min respectively. But these

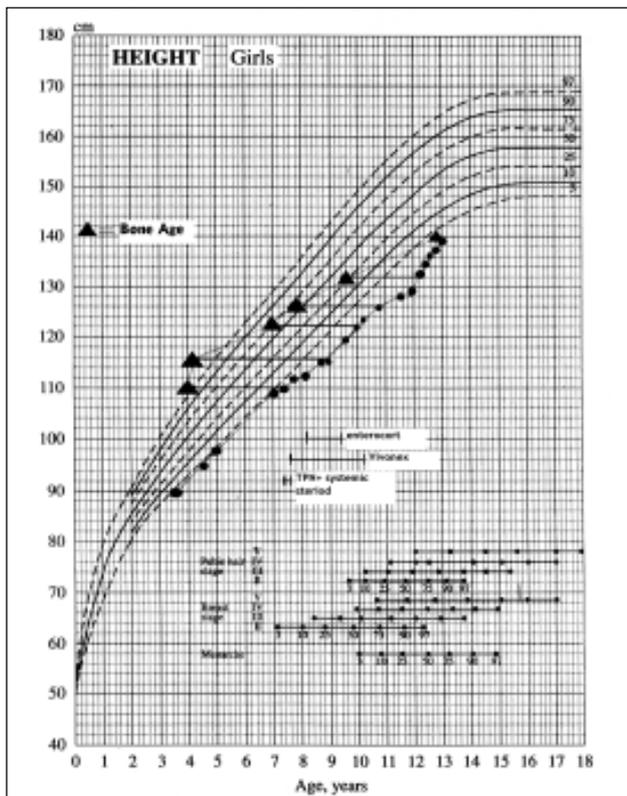


**Figure 2** Duodenal biopsy showed total villous atrophy and elongation of the crypts. (↓)There were increased lymphocytes in the lamina propria. (H&E Stain x125)



**Figure 4** Duodenal biopsy showed improvement after treatment with Budesonide. (↓)There was presence of villous but they were shorter than normal. Lymphocytes cells were decreased. (H&E Stain x 250)

problems settled after discontinuation of treatment for 2 months. The patient's symptom abated completely with satisfactory growth for nearly 3 year. Serial albumin level remained normal (Table 1). Repeated Xylose absorption test was also normal. Her body weight moved from the tenth to the twenty-fifth percentile (Figure 1). Her height velocity during the use of Budesonide was 6 cm/year, compare to 4 cm/year whilst on systemic steroid and zero cm/year before steroid treatment (Figures 3 & 5). Her height age and bone age was summarised in Table 2. At the time of writing, she enjoyed a near-normal diet, she tolerated rice, wheat, pork, chicken, lamb, freshwater fish and many different kinds of fruit and vegetable. She only needed to avoid diary product, beef, soy-based product and egg as she developed abdominal discomfort, decreased appetite with increased eczema after ingestion of these products. Repeated small bowel biopsy was refused. She is being followed up regularly in the gastroenterology clinic of this department.



**Figure 3** Height chart.

### Discussion

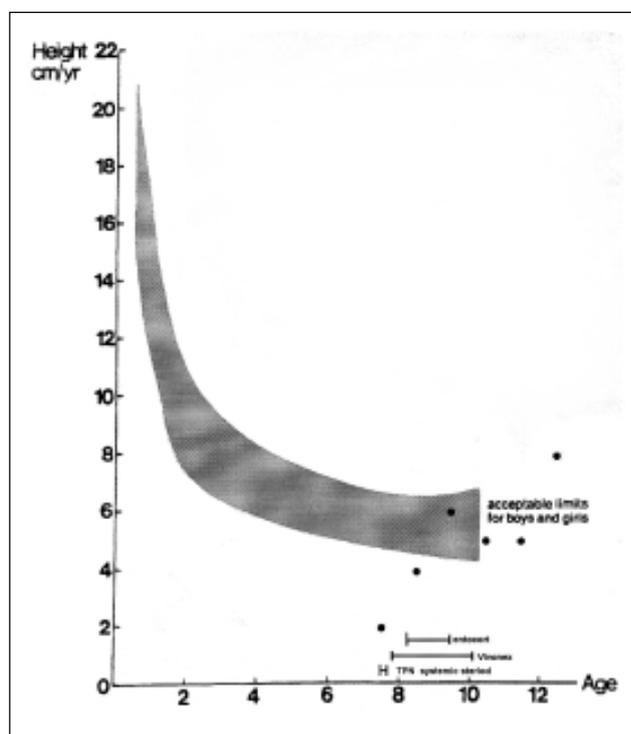
Allergic reactions to food component affecting the gastrointestinal tract have been reported since ancient times.<sup>1,2</sup> Food allergy can cause a wide range of symptom including anaphylactic shock, asthma, rhinitis, urticaria, eczema, gastrointestinal disturbance, malabsorption and protein-losing enteropathy. In 1967, Waldmann et al

**Table 1** Summary of albumin level and biopsy results

| Date     | Action  | Albumin level (gm/l) | Biopsy   |
|----------|---|----------------------|--|
| Jan 1997 | TPN for 6 weeks   | 22-31                | Total villous atrophy, lymphocyte                              |
| Feb 1997 | Systemic steroid for 6 weeks                              | 22-33                |  |
| Mar 1997 | Solely on elemental formula for 2 months                  | 48                   | Partial villous atrophy, lower lymphocyte                      |
| Apr 1997 |   | 36                   |  |
| Nov 1997 | Budesonide for 12 months<br>(i.e. 9 mg Q.D. for 4 months) | 44                   | Improvement in villous height & further decrease in lymphocyte |
| Jul 1998 |   | 48                   |  |
| Dec 2000 |   | 41                   |  |

**Table 2** Summary of bone and height age

| Year              | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 |
|-------------------|------|------|------|------|------|------|
| Chronological age | 7    | 8    | 9    | 10   | 11   | 12   |
| Bone age          | 4    | 4    | 7    | 8    | 9.5  | 12   |
| Height age        | 5.5  | 5.8  | 6.4  | 7.5  | 8.2  | 9.5  |

**Figure 5** Height velocity chart.

described five infants with anaemia, protein-losing enteropathy and other manifestations of allergy such as asthma, eczema and allergic rhinitis. All infants responded to an elimination diet or corticosteroid. The allergen was found to be cow's milk and the disease was subsequently designated as "allergic gastroenteropathy".<sup>3</sup>

Over the past 30 years, there were numerous cases reports or case series published on the discussion of allergic gastroenteropathy. The term 'eosinophilic gastroenteropathy' was used interchangeably with allergic gastroenteropathy.<sup>4-7</sup> Recently, some authors considered eosinophilic gastroenteropathy as one of the manifestation of allergic gastroenteropathy,<sup>1</sup> whereas others considered them as different disease entities.<sup>2</sup> The presence of peripheral blood, tissue and bone marrow eosinophilia favoured the diagnosis of eosinophilic gastroenteropathy. Neither allergy nor hypersensitivity symptoms is required for the diagnosis of eosinophilic gastroenteropathy. Conversely, allergic symptom is typically associated with allergic gastroenteropathy.<sup>2</sup>

Allergic gastroenteropathy is more common in infants but may occur at any age. Patients who have a later age of onset are more likely to have a positive allergy history and more varied symptoms. Moreover, they are usually sensitive to multiple allergens compared to younger children, who are usually allergic to milk protein or soy protein alone.

Older children also experienced frequent relapse and required intermittent steroid therapy. A delay in diagnosis is often observed in older patients, due to a lack of suspicion for the condition. Another reason might be attributed to false negative small bowel biopsy resulting from the focal nature of the disease.<sup>4</sup>

The cornerstone for diagnosis of allergic gastroenteropathy is compatible history, physical findings, food challenge and the exclusion of other gastrointestinal disorder. The presence of antigen-specific IgE and the response to corticosteroid treatment may also support the diagnosis.<sup>2</sup> Our patient had a strong history of atopy, which was compatible with allergic enteropathy. The absence of eosinophilia in peripheral blood and the bone marrow biopsy together with presence of lymphocytes in the intestinal biopsies would rule out the diagnosis of eosinophilic enteropathy. The other possible differential diagnosis for malabsorption syndrome, total villous atrophy and protein-losing enteropathy was autoimmune enteropathy. The absence of autoimmune markers including anti-enterocyte antibody together with the presence of positive results of skin prick test and RAST test added weight to the diagnosis of allergic enteropathy. The constellation of findings together with duodenal and gastric biopsy results led to the diagnosis of allergic enteropathy. The mainstay of treatment in allergic gastroenteropathy is the elimination of offending allergens.<sup>1,2</sup> Since skin tests and RAST test yield high incidence of false positive results, they may not be used to accurately identify a single offending agent.<sup>2,6</sup> If no specific offending antigen can be identified, a trial of complete exclusion of all normal food and drink becomes essential. Total parenteral nutrition or elemental formula such as Vivonex can be used to provide nutrition, thereafter single food item is introduced one by one.<sup>7</sup> Goldman and Proujansky recommended that the challenge protocol should be symptom specific.<sup>4</sup> One should look for gastrointestinal disturbance as a reaction to food reintroduction for those patients who had gastrointestinal symptoms initially. These symptoms may recur immediately or may take several days to develop. For those patients who presented initially with protein-losing enteropathy without other significant gastrointestinal symptoms, one needs to use additional diagnostic techniques, like pre- and post-challenge fecal alpha-1-antitrypsin level, to document a positive challenge before the patient becomes symptomatic.<sup>6</sup> In our case, monitoring of pre- and post-challenge alpha-1-antitrypsin excretion could not be done while our patient was receiving the low residual diet. She passed stool once every four to

five days thus rendering stool collection impossible. Therefore our patient was monitored with repeated endoscopy and biopsy for food challenge. The fact that she developed specific symptoms, abdominal pain and eczema, within a few days of offending food helps the monitoring. Other monitoring method such as intestinal permeability test is mainly experimental and not available in Hong Kong.

The natural history of adverse food reaction depends on the particular food involved. Patients with food hypersensitivity reaction to soy and wheat tend to outgrow their sensitivity within the first few years after diagnosis. Those who react to milk, eggs and fish tend not to lose the sensitivity over time.<sup>2</sup> Our patient tolerated food with low allergenicity well. Those foods with high allergenicity such as beef and milk are still omitted at the present moment and extra caution must be taken if these foods are to be introduced. MacLean et al suggested that the introduction of food items should be slow because rapid advancement of the diet often results in acute exacerbation of diarrhoea secondary to malabsorption.<sup>8</sup>

When the response to antigen elimination is sub-optimal or the offending food antigen cannot be identified, medications may be useful. Use of systemic steroid usually results in remission.<sup>1,2</sup> Use of oral sodium cromoglycate and ketotifen is controversial.<sup>9,10</sup> Montelukast was reported to be useful in treating one case of eosinophilic gastroenteritis.<sup>11</sup> It would be interesting to see its effect on allergic gastroenteropathy. Although our patient responded well to systemic steroid but her weight gain was not satisfactory upon its withdrawal. It therefore necessitated the consideration of the use of second course of steroid. Trial of controlled-release budesonide showed good clinical response with her body weight returning to twenty-fifth percentile. The use of topical intestinal formulation of budesonide in treating Crohn's disease has been found effective in inducing remission. It is also found to be associated with fewer side effects and less suppression of the pituitary-adrenal function.<sup>12</sup> The controlled release gelatin capsule of budesonide is coated with a layer of methacrylic acid copolymer that dissolves at a pH above 5.5. Without significant acid suppression, e.g. a proton pump inhibitor, budesonide is unlikely to be effective to treat the gastric part of allergic gastroenteropathy. It would, however, be effective in our case which had no gastric involvement. Once absorbed into systemic circulation, it is rapidly metabolized by cytochrome P450 enzyme in the liver. The controlled-release budesonide acted locally on the damaged small bowel mucosa. We adopted the

budesonide treatment regime for Crohn's disease and applied it to our patient. The patient improved clinically as evidenced by the satisfactory gain in weight and height. Although she developed transient Cushing syndrome with the use of systemic steroid and controlled-release budesonide, her height velocity was much better while she was receiving controlled-release budesonide than on systemic steroid. Here we report the first case of using controlled-release budesonide in treating allergic enteropathy and the result was encouraging. For patients with allergic enteropathy, it is worthwhile to try controlled-release budesonide before considering a systemic steroid treatment. However, further control study is warranted for the use of controlled-release budesonide in treatment of allergic enteropathy.

## References

1. Moon A, Kleinman RE. Allergic gastroenteropathy in children. *Ann Allergy Asthma Immunol* 1995;74:5-16.
2. Burks AW. Allergic gastroenteropathy. In: Wyllie R, Hyams J (eds). *Pediatric gastrointestinal disease; pathophysiology, diagnosis, management*. WB Saunders, Philadelphia 1993;535-65.
3. Waldmann TA, Wochner RD, Laster L, Gordon RS Jr. Allergic gastroenteropathy. A cause of excessive gastrointestinal protein loss. *N Engl J Med* 1967;276:761-9.
4. Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 1986;10:75-86.
5. David TJ. Diagnosis of food intolerance. *Current Paediatrics* 1993;3:180-5.
6. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984;59:983-6.
7. Steffen RM, Wyllie R, Petras RE, et al. The spectrum of eosinophilic gastroenteritis. Report of six pediatric cases and review of the literature. *Clin Pediatr (Phila)* 1991;30:404-11.
8. MacLean WC Jr, Lopez de Romana G, Massa E, Graham GG. Nutritional management of chronic diarrhea and malnutrition: primary reliance on oral feeding. *J Pediatr* 1980;2:316-23.
9. Watson JB, Timmins J. Food allergy: response to treatment with sodium cromoglycate. *Arch of Dis Child* 1979;54:77-9.
10. Kingsley PJ. Letter: Oral sodium cromoglycate in gastrointestinal allergy. *Lancet* 1974;2:1011.
11. Schwartz DA, Pardi DS, Murray JA. Use of montelukast as steroid-sparing agent for recurrent eosinophilic gastroenteritis. *Dig Dis Sci* 2001;46:1787-90.
12. Rutgeerts P, Lofberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 1994;331:842-5.