

IgE and non-IgE-mediated food allergy: treatment in 2007

Mirna Chehade

Purpose of review

Our understanding of the mechanism of food allergy has substantially increased over the past decade. Food allergies can be classified into those that are IgE mediated and those that are non-IgE mediated.

Recent findings

Various advances have been made in treating IgE-mediated food allergies. A phase II clinical trial of a second anti-IgE antibody, omalizumab, was recently initiated in subjects with peanut allergy, but was stopped as a result of safety concerns after severe reactions occurred during initial oral challenges. Oral immunotherapy is showing promise in various studies on patients with IgE-mediated food allergies. Gastrointestinal food allergic disorders involving non-IgE-mediated food allergies have recently received attention, particularly eosinophilic esophagitis. Although amino acid-based formula therapy remains the most successful in controlling inflammation and symptoms in these disorders, other therapeutic options including various dietary elimination protocols and swallowed fluticasone are showing success. Anti-IL-5 therapy may prove to be a promising future therapeutic option for refractory patients.

Summary

Although there are no specific therapeutic recommendations for many IgE-mediated and non-IgE-mediated food allergic disorders besides allergen avoidance, various novel approaches are currently being investigated and may influence treatment approaches in the future.

Keywords

anti-IL-5, dietary therapy, food allergy, immunoglobulin E, immunotherapy

Introduction

Food allergies affect an estimated 6% of young children and 3.7% of adults in the United States [1,2]. During the past decade, our understanding of food allergic diseases and manifestations has substantially increased. We can classify food allergies into those that are IgE mediated and those that are non-IgE mediated.

IgE-mediated reactions develop when food-specific IgE antibodies residing on mast cells and basophils come into contact with and bind circulating food allergens and activate the cells to release potent mediators and cytokines. In non-IgE-mediated food allergic disorders, multiple inflammatory cells and their mediators play a role in immunopathogenesis. Activation of lymphocytes and the recruitment of eosinophils and mast cells are cardinal features of many of these diseases. IgE-mediated reactions are typically rapid in onset, mostly involve the skin, and may lead to anaphylaxis; whereas non-IgE-mediated disorders become evident hours to days after allergen ingestion, and mostly manifest in the gastrointestinal tract. IgE-mediated gastrointestinal disorders include gastrointestinal anaphylaxis and oral allergy syndrome. Non-IgE-mediated gastrointestinal allergic disorders include food protein-induced enterocolitis, proctocolitis and enteropathy. Some gastrointestinal diseases, such as eosinophilic esophagitis and gastroenteritis, involve both IgE and non-IgE-mediated mechanisms [1].

The mainstay of the management of food allergies remains focused on prevention by avoidance of the allergenic foods. Multiple advances in the field have, however, led to various therapies that may eventually complement or even replace food avoidance. The purpose of this summary is to discuss these various treatment modalities, focusing mainly on gastrointestinal food hypersensitivities.

IgE-mediated food allergies

The mainstay of the management of IgE-mediated food allergies still consists of prevention, by avoiding exposure to the offending allergenic foods. This involves extensive education to patients and their caregivers about the proper reading of packaged food labels. New labeling legislation that came into effect during the past year in the United States and Europe has made this task easier, by mandating clear labeling and enforcing ingredient statements on packaged food labels [3•], and declaring information relating to the presence of possible allergenic

Curr Opin Allergy Clin Immunol 7:264–268. © 2007 Lippincott Williams & Wilkins.

Division of Gastroenterology/Nutrition, Division of Allergy/Immunology, Mount Sinai School of Medicine, New York, New York, USA

Correspondence to Mirna Chehade, MD, Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA
Tel: +1 212 241 0830; fax: +1 212 426 1902; e-mail: mirna.chehade@mssm.edu

Current Opinion in Allergy and Clinical Immunology 2007, 7:264–268

© 2007 Lippincott Williams & Wilkins
1528-4050

residues from processing other foods in the same food manufacturing company.

Patient education also involves teaching to avoid high-risk situations such as buffets, encouraging patients to wear Medic Alert bracelets, teaching to recognize early symptoms of allergic reactions and to manage an anaphylactic reaction, including the use of self-injectable epinephrine and activating emergency services [1,4]. Several educational materials are available through organizations such as the Food Allergy and Anaphylaxis Network in the United States and the Anaphylaxis Campaign in the United Kingdom to assist patients in avoiding food allergens. Despite the above educational efforts, significant reactions continue to occur. Fortunately, various therapies for IgE-mediated allergies are being explored, eventually to be used either in conjunction with allergen avoidance, or to replace it altogether.

Anti-IgE therapy

Humanized monoclonal anti-IgE antibodies have been developed. To date, only one study by Leung *et al.* [5] has examined the role of anti-IgE in food allergy. In their double-blind, placebo-controlled study on patients with peanut allergy, patients were randomly assigned to receive monthly subcutaneous injections of placebo or one of three doses of the anti-IgE TNX-901 (Tanox Biosystems, Houston, Texas, USA), 150, 300 and 450 mg. TNX-901 at a dose of 450 mg increased the threshold for sensitivity to peanut to a level that confers protection against most unintended peanut ingestions in 76% of patients. The drug was well tolerated. Further investigation using this antibody was discontinued after an agreement among pharmaceutical companies that were involved in the development of anti-IgE therapies.

Omalizumab (Genentech, South San Francisco, California, USA) is another monoclonal antibody against IgE, approved for use in patients with moderate to severe persistent allergic asthma, and shown to be effective for use in patients with allergic rhinitis [6,7]. A phase II multicenter clinical trial was recently initiated using this antibody for patients with peanut allergy, but had to be discontinued prematurely because of concerns with the safety of the oral peanut challenges in some study subjects. Insufficient data were obtained to reach any conclusions about the efficacy of omalizumab, but there was a slight trend towards greater peanut tolerability in subjects treated with omalizumab compared with placebo [8].

Anti-IgE therapy may eventually prove to be useful as an adjunct to allergen avoidance, and may prove to be protective against other food allergies in the same individuals. It may, however, have to be administered indefinitely.

Immunotherapy

Given the high incidence of systemic reactions using standard subcutaneous immunotherapy for IgE-mediated peanut allergy [9,10], oral immunotherapy has been investigated as an alternative over the past few years, with variable results. Recent studies have been encouraging, however, demonstrating its safety and efficacy in increasing tolerance to the food allergen. A randomized, double-blind, placebo-controlled study using the sublingual administration of hazelnut extract demonstrated effectiveness with minimal systemic reactions [11]. Similarly, a 24-month egg oral immunotherapy to non-anaphylactic children with egg allergy resulted in increased tolerance to egg upon placebo-controlled oral challenges to levels higher than those found in accidental ingestions, without systemic side effects [12[•]]. Another recent study using the sublingual administration of increasing doses of various food allergens to children with allergy to milk, egg, fish, wheat and apple, resulted in an 86% success rate in those patients who completed the treatment protocol, also with only mild side effects [13].

More randomized studies on oral immunotherapy are needed to determine the optimal starting and maintenance doses, and titration schedules that would provide an efficacious and safe therapy in the shortest period of time. Although oral immunotherapy offers the advantage of being administered at home, a regular intake of the allergenic food seems to be necessary. Long-term efficacy is also still to be determined.

Other immunotherapies using modified allergens are currently being investigated in animal models. Mutated allergen protein immunotherapy was studied in a murine model of peanut anaphylaxis. Mutated recombinant Ara h 1, 2, and 3, administered subcutaneously or rectally with heat-killed *Listeria monocytogenes* or *Escherichia coli*, respectively, demonstrated effectiveness against anaphylaxis, accompanied by a decrease in peanut-specific IgE levels, and decreased systemic T helper type 2 cytokines [14,15].

Immunotherapy using the intact peanut allergen in conjunction with heat-killed *L. monocytogenes* as an adjuvant, was more recently studied in dogs with various food allergies, with good results [16]. Immunized dogs were clinically much less reactive to an oral allergen challenge, and had lower IgE levels to the allergen.

Traditional Chinese medicine

In 2001, a Chinese herbal formula, food allergy herbal formula 1, containing a mixture of 11 herbs believed to contain anti-allergenic properties, was tested in a murine model of peanut anaphylaxis, and was found to block peanut-induced anaphylaxis and reduce peanut-specific

IgE levels and systemic T helper type 2 cytokines [17]. More recently, a more simplified formula, food allergy herbal formula 2, containing nine of the original 11 herbs was tested in the same murine model, and was found to be equally effective and safe [18]. Clinical trials using this formula in patients with peanut allergy are awaited to test its safety and efficacy in humans.

Non-IgE-mediated food allergies

Similar to IgE-mediated food allergies, the mainstay of therapy for non-IgE-mediated food allergies consists of the avoidance of the allergenic foods, although in this type of allergy, the difficulty lies in the identification of the allergens because of their slow, cell-mediated, non-IgE mechanism of action. This makes prick skin tests and serum measurement of food-specific IgE levels less sensitive in detecting the food allergens. Furthermore, the clinical reactivity to a food upon oral challenge may take up to a few days to develop, which adds to the difficulty in its identification. Most non-IgE-mediated allergic disorders involve more than one food allergen. Therefore, the overall approach to these disorders has been slightly different than that for IgE-mediated allergies.

Among the various disorders that involve non-IgE-mediated food allergies, pediatric eosinophilic esophagitis has been the most studied over the past few years from a therapeutic standpoint. Eosinophilic esophagitis is characterized by esophageal intraepithelial eosinophilic infiltration. In eosinophilic gastroenteritis, tissue eosinophilia is present in the stomach or duodenum, or both. Some patients with this disease have concomitant esophageal eosinophilia. The treatment of food protein-induced enterocolitis and proctocolitis has not changed over the past few years. Below is a summary of the current and potential future therapies for various disorders that include non-IgE-mediated food allergies.

Amino acid-based formula therapy

The amino acid-based formula therapy approach was first described in 1995 in 10 children with eosinophilic esophagitis and associated severe gastroesophageal symptoms. After 6 weeks of therapy with the formula, most children had symptom resolution and a concomitant resolution of esophageal intraepithelial eosinophilia [19]. The effectiveness of the amino acid-based therapy was confirmed a few years later in a larger number of patients by Markowitz *et al.* [20]. In that study of 51 children, all but two patients had complete clinical and histological resolution of their disease after one month of therapy. In both studies mentioned above, the consumption of one or two solid foods with low allergenic potential was allowed [19]. Once disease resolution is achieved, solid food introductions are gradually implemented while monitoring for symptoms [21].

Amino acid-based formula therapy for eosinophilic gastroenteritis has been less well studied. It was, however, shown to be safe and effective in maintaining growth in children with this disease [22], and was recently reported to be the most effective form of therapy for a severe subset of patients with eosinophilic gastroenteritis, that with concomitant protein-losing enteropathy [23[•]]. In that retrospective study, all patients had an excellent clinical response to treatment with an amino acid-based formula, and tolerated the gradual addition of various foods over time.

Although amino acid-based therapy is very effective and safe, its major limitation is its lack of acceptability by older children as a result of its taste, the large volume that needs to be consumed, and the dramatic life-style change imposed on them. At times, gastrostomy tube feeding may be required for its administration [19,20]. Fortunately, more palatable formulae are currently being introduced onto the market, which may make this form of therapy more acceptable to pediatric patients.

Dietary elimination

For eosinophilic esophagitis, various forms of dietary eliminations were described. As food eliminations based on prick skin tests alone proved to be non-efficacious [23[•],24] as a result of the mixed IgE and non-IgE-mediated mechanisms of this disease, investigators have tried to eliminate foods based on the combined results of skin prick and patch testing with a 77% success rate [25]. A major limitation of this therapeutic approach is that patch tests to various foods are not standardized for general use by allergists. In an observational study, Kagalwalla *et al.* [26[•]] empirically removed six foods thought to be highly allergenic from the diet of patients with eosinophilic esophagitis. These included milk, egg, soy, wheat, peanut/tree nuts, and seafood, with a comparable success rate of 74%, demonstrated by an improvement in esophageal eosinophilia.

In conclusion, dietary elimination may need to be considered as an option in the initial management of eosinophilic esophagitis in the pediatric age group, if failure to thrive is not an associated feature of their disease.

In the case of food protein-induced enterocolitis, the cornerstone of therapy remains strict avoidance of the causal food. More commonly, the allergen is cow's milk, and substitution of an extensive milk protein hydrolysate is still recommended [27,28]. For the rare patient reactive to a protein hydrolysate, an amino acid formula may be needed [29]. In those infants with solid food-induced enterocolitis, strict avoidance of these foods remains the treatment of choice [30,31].

During the institution of elimination diets, follow-up by a dietitian is crucial to ensure adequate and balanced caloric intake, as well as the complete absence of the allergenic foods from the patient's diet. In addition, similar to the case of IgE-mediated allergies, education on reading food labels enquiring about issues of cross-contact among foods is crucial, to avoid the inadvertent intake of the allergenic food and the resultant persistence of symptoms or tissue inflammation.

Corticosteroids

Oral corticosteroids have been successfully used in eosinophilic esophagitis and gastroenteritis. Oral methylprednisolone given for 4 weeks to 20 children with eosinophilic esophagitis resulted in a dramatic clinical and histological improvement in the vast majority of patients [32]. Similarly, oral corticosteroids have been proved to be effective in patients with eosinophilic gastroenteritis [33] and eosinophilic gastroenteritis with protein-losing enteropathy [23[•],24,34]. Limitations with the use of systemic corticosteroids include their systemic side effects, and disease relapse upon their discontinuation, whether clinical [23[•]] or histological [35]. This makes them currently less attractive as treatment options, especially in children.

Another form of corticosteroid administration has recently been pursued, 'topical' administration, consisting of swallowed aerosolized fluticasone propionate. In an open label, prospective study by Teitelbaum *et al.* [36] all 13 children who received fluticasone for 8 weeks had clinical resolution of their symptoms. Overall, histological remission was also found. A retrospective study by Liacouras *et al.* [35] demonstrated a lower efficacy of the drug. Approximately half of the children who received fluticasone for 4 weeks demonstrated clinical response; and the resolution of esophageal eosinophilia was only partial. More recently, a randomized, double-blind, placebo-controlled study of fluticasone, given to pediatric patients with eosinophilic esophagitis for 3 months, resulted in 50% histological remission, compared with 9% remission in placebo-treated patients [37^{••}]. Patients with negative skin prick tests to foods and younger patients seemed to have a better response to therapy.

The variability in response rates among the above studies may be related to differences in the duration of therapy and the dosages of fluticasone administered in each study. Topical viscous budesonide was also recently reported to be successful in treating eosinophilic esophagitis in a case series limited to two children [38].

Similar to oral corticosteroids, topical corticosteroids are not without potential side effects. Esophageal candidiasis was reported to occur in 5–15% of cases [35,36,37^{••}] and

systemic absorption is still possible. In addition, disease relapse was seen upon their discontinuation [35].

Although topical corticosteroids may constitute a good alternative for patients who cannot follow a dietary therapy, larger studies establishing optimal doses that show efficacy without major side effects are needed.

Mast cell stabilizers and leukotriene inhibitors

No controlled trials have been performed using these drugs, and they seem to have limited effectiveness in treating non-IgE-mediated disorders. Cromolyn sodium was reported to be effective in one adult with eosinophilic gastroenteritis with protein-losing enteropathy [39]. The use of montelukast demonstrated limited effectiveness in treating adults with eosinophilic esophagitis [40], and its use in children with various gastrointestinal eosinophilic diseases is limited to a case series reporting clinical improvement but lacking histological follow-up [41].

Anti-IL-5 therapy

Anti-IL-5 is emerging as a promising biological therapeutic option for eosinophilic esophagitis. Human IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils [42].

The humanized monoclonal anti-IL-5 SCH55700 (Shering-Plough, Kenilworth, New Jersey, USA) was first used in a pilot trial on four patients with eosinophilic gastroenteritis and food allergy as a single intravenous dose [43]. Following therapy, peripheral eosinophil counts and tissue eosinophilia decreased, but no clinical improvement was seen. This may indicate that additional mediators may be required to suppress the clinical manifestations of eosinophilic gastroenteritis completely.

In eosinophilic esophagitis, preliminary studies using the anti-IL-5 mepolizumab (GlaxoSmithKline, Research Triangle Park, North Carolina, USA) seem to be more promising. In an open-label phase I/II safety and efficacy study conducted in four adult patients with eosinophilic esophagitis and long-standing dysphagia [44^{••}], mepolizumab given as 3-monthly intravenous infusions resulted in a marked decrease in peripheral blood and esophageal eosinophilia and improved symptoms. The drug was generally well tolerated. A phase I/II multicenter clinical trial to assess its safety and tolerability in children with eosinophilic esophagitis is currently being conducted.

Conclusion

Although the mainstay of therapy for both IgE and non-IgE-mediated food allergies remains based on the avoidance of the offending foods, the past few years were marked by major research advancements into other ther-

apies that may eventually serve as useful adjuncts, if not even substitutes for allergen avoidance, and may soon influence our treatment approach for food allergic patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 291).

- 1 Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004; 113:805–819.
- 2 Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004; 114:159–165.
- 3 Taylor SL, Hefle SL. Food allergen labeling in the USA and Europe. *Curr Opin Allergy Clin Immunol* 2006; 6:186–190.
- A good overview and discussion of the new food labeling legislation that came into effect in the United States and Europe.
- 4 Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2006; 117 (2 Suppl):S470–S475.
- 5 Leung DY, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
- 6 Mankad VS, Burks AW. Omalizumab: other indications and unanswered questions. *Clin Rev Allergy Immunol* 2005; 29:17–30.
- 7 Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int* 2006; 55:379–386.
- 8 Sampson HA. A phase II, randomized, double-blind, parallel-group, placebo-controlled, oral food challenge trial of Xolair (omalizumab) in peanut allergy (TOPS). *J Allergy Clin Immunol* 2007; 119 (Suppl 1):S117.
- 9 Oppenheimer JJ, Nelson HS, Bock SA, *et al.* Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; 90:256–262.
- 10 Nelson HS, Lahr J, Rule R, *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997; 99:744–751.
- 11 Enrique E, Pineda F, Malek T, *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005; 116:1073–1079.
- 12 Buchanan AD, Green TD, Jones SM, *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; 119:199–205.
- A recent study demonstrating the effectiveness of oral immunotherapy in egg allergic patients.
- 13 Patriarca G, Nucera E, Pollastrini E, *et al.* Oral specific desensitization in food-allergic children. *Dig Dis Sci* 2007; In press.
- 14 Li XM, Srivastava K, Grishin A, *et al.* Persistent protective effect of heat-killed *Escherichia coli* producing “engineered” recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 2003; 112:159–167.
- 15 Li XM, Srivastava K, Huleatt JW, *et al.* Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J Immunol* 2003; 170:3289–3295.
- 16 Frick OL, Teuber SS, Buchanan BB, *et al.* Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 2005; 60:243–250.
- 17 Li XM, Zhang TF, Huang CK, *et al.* Food allergy herbal formula-1 (FAHF-1) blocks peanut-induced anaphylaxis in a murine model. *J Allergy Clin Immunol* 2001; 108:639–646.
- 18 Srivastava KD, Kattan JD, Zou ZM, *et al.* The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005; 115:171–178.
- 19 Kelly KJ, Lazenby AJ, Rowe PC, *et al.* Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995; 109:1503–1512.
- 20 Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003; 98:777–782.
- 21 Liacouras CA. Eosinophilic esophagitis: treatment in 2005. *Curr Opin Gastroenterol* 2006; 22:147–152.
- 22 Sicherer SH, Noone SA, Koerner CB, *et al.* Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities. *J Pediatr* 2001; 138:688–693.
- 23 Chehade M, Magid MS, Mofidi S, *et al.* Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr* 2006; 42:516–521.
- A study listing the success of different treatment options for patients with eosinophilic gastroenteritis and protein-losing enteropathy; the first study to report on long-term follow-up in these patients.
- 24 Katz AJ, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984; 74:72–78.
- 25 Spergel JM, Andrews T, Brown-Whitehorn TF, *et al.* Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005; 95:336–343.
- 26 Kagalwalla AF, Sentongo TA, Ritz S, *et al.* Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006; 4:1097–1102.
- An interesting study highlighting the success rate of a simple empiric food elimination therapy.
- 27 Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr* 1978; 93:553–560.
- 28 Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998; 133:214–219.
- 29 Kelso JM, Sampson HA. Food protein-induced enterocolitis to casein hydrolylate formulas. *J Allergy Clin Immunol* 1993; 92:909–910.
- 30 Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; 111:829–835.
- 31 Levy Y, Danon YL. Food protein-induced enterocolitis syndrome – not only due to cow's milk and soy. *Pediatr Allergy Immunol* 2003; 14:325–329.
- 32 Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998; 26:380–385.
- 33 Lee CM, Changchien CS, Chen PC, *et al.* Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 1993; 88:70–74.
- 34 Waldmann TA, Wochner RD, Laster L, Gordon RS. Allergic gastroenteropathy. A cause of excessive gastrointestinal protein loss. *N Engl J Med* 1967; 276:762–769.
- 35 Liacouras CA, Spergel JM, Ruchelli E, *et al.* Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005; 3:1198–1206.
- 36 Teitelbaum JE, Fox VL, Twarog FJ, *et al.* Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002; 122:1216–1225.
- 37 Konikoff MR, Noel RJ, Blanchard C, *et al.* A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006; 131:1381–1391.
- The first randomized, placebo-controlled study using fluticasone in children with eosinophilic esophagitis.
- 38 Aceves SS, Dohil R, Newbury RO, Bastian JF. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005; 116:705–706.
- 39 Van Dellen RG, Lewis JC. Oral administration of cromolyn in a patient with protein-losing enteropathy, food allergy, and eosinophilic gastroenteritis. *Mayo Clin Proc* 1994; 69:441–444.
- 40 Attwood SE, Lewis CJ, Brondor CS, *et al.* Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003; 52:181–185.
- 41 Vanderhoof JA, Young RJ, Hanner TL, Kettlehut B. Montelukast: use in pediatric patients with eosinophilic gastrointestinal disease. *J Pediatr Gastroenterol Nutr* 2003; 36:293–294.
- 42 Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004; 113:11–28.
- 43 Prussin C, James SP, Huber MM, *et al.* Pilot study of anti-IL-5 in eosinophilic gastroenteritis. *J Allergy Clin Immunol* 2003; 111 (Suppl 2):S275.
- 44 Stein ML, Collins MH, Villanueva JM, *et al.* Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006; 118:1312–1319.
- The first open label phase I/II study on the use of mepolizumab for patients with eosinophilic esophagitis.