proteins can be used as a marker of persistent CMA. The successful linkage of these peptides to a commercial matrix should enable the conduct of large prospective studies and simplify future diagnostic approaches.

Kirsten Beyer, MD[a,b]
Kirsi-Marjut Jarvinen, MD, PhD[a]
Ludmilla Bardina, MS[a]
Michelle Mishoe[a]
Kristiina Turjanmaa, MD[c]
Bodo Niggemann, MD[b]
Staffan Ahlstedt, PhD[d,e]
Lennart Venemalm, PhD[e]
Hugh A. Sampson, MD[a]
[a]*Mount Sinai School of Medicine*
New York, NY
[b]*Department of Pediatric Pneumology and Immunology*
University Children's Hospital Charité
Humboldt University
Augustenburger Platz 1
D-13353 Berlin, Germany
[c]*Tampere University Hospital*
Tampere, Finland
[d]*Department of Environmental Medicine and Center for Allergy Research*
Karolinska Institute
Stockholm, Sweden
[e]*Pharmacia Diagnostics AB*
Uppsala, Sweden

Supported by a grant from the National Institutes of Health (AI-44236).
Disclosure of potential conflict of interest: K. Beyer has received grants/research support from Danone. S. Ahlstedt and L. Venemalm are employed by Pharmacia Diagnostics. H. Sampson has a consultant arrangement with Seer, Inc, and has received grants/research support from the National Institutes of Health and Pharmacia Diagnostics (through Mount Sinai School of Medicine).

REFERENCES

1. Sampson HA. Food allergy, part 1: immunopathogenesis and clinical disorders. J Allergy Clin Immunol 1999;103:717-28.
2. Wood RA. The natural history of food allergy. Pediatrics 2003;111:1631-7.
3. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunol 2002;13(suppl 15):23-8.
4. Chatchatee P, Jarvinen KM, Bardina L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on alpha(s1)-casein: differences in patients with persistent and transient cow's milk allergy. J Allergy Clin Immunol 2001;107:379-83.
5. Chatchatee P, Jarvinen KM, Bardina L, Vila L, Beyer K, Sampson HA. Identification of IgE and IgG binding epitopes on beta- and kappa-casein in cow's milk allergic patients. Clin Exp Allergy 2001;31:1256-62.
6. Busse PJ, Jarvinen KM, Vila L, Beyer K, Sampson HA. Identification of sequential IgE-binding epitopes on bovine alpha(s2)-casein in cow's milk allergic patients. Int Arch Allergy Immunol 2002;129:93-6.
7. Jarvinen KM, Chatchatee P, Bardina L, Beyer K, Sampson HA. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. Int Arch Allergy Immunol 2001;126:111-8.
8. Jarvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. J Allergy Clin Immunol 2002;110:293-7.

Available online July 5, 2005.
doi:10.1016/j.jaci.2005.05.007

Topical viscous budesonide suspension for treatment of eosinophilic esophagitis

To the Editor:

Eosinophilic esophagitis (EE) is a clinical entity composed of marked diffuse esophageal eosinophilia and basal zone hyperplasia thought to be provoked, in at least a subset of patients, by food and/or aeroallergen exposure.[1,2] In parallel with other atopic disorders, the incidence of EE appears to be increasing.[3,4] Current treatment options for children are limited, and if steroid therapy is initiated for treatment, we routinely use a fluticasone metered dose inhaler (MDI) puffed into the oropharynx and swallowed as topical esophageal therapy.[5] However, we have encountered 2 patients who failed to respond to elemental formula and were unable, because of developmental problems, to perform the puff and swallow technique. We report here treatment of these 2 patients with an oral suspension of budesonide.

Patient 1 was a 6-year-old boy with a history of abdominal pain, failure to thrive, and vomiting since infancy, and developmental delay with isolated EE diagnosed in 2001. His allergic history was significant for allergic rhinitis secondary to cat, dog, and dust mite exposure as well as positive UniCAP radioallergosorbent testing (Pharmacia, Kalamazoo, Mich) for fish and milk. After upper gastrointestinal endoscopy (EGD) with esophageal biopsies demonstrating a maximum eosinophil count of 60 per high-powered field (HPF at 400× magnification), he was diagnosed with EE and treated with oral corticosteroid (prednisone 0.5 mg/kg daily) for 1 month. This resulted in resolution of esophageal eosinophilia with a maximum of 2 eosinophils per HPF on repeat EGD with biopsy. He was subsequently treated with omeprazole (Prilosec, AstraZeneca, Wilmington, Del) 10 mg twice daily and fluticasone (Flovent, GlaxoSmithKline, Research Triangle Park, NC) 220 mcg twice daily as topical esophageal therapy, but repeat EGD with biopsy after 6 months demonstrated a maximum eosinophil count of 50 per HPF. His therapeutic regimen was changed to elemental formula and fluticasone, but repeat EGD with biopsy demonstrated persistent esophageal eosinophils with a maximum eosinophil count of 74 per HPF accompanied by basal zone hyperplasia. He was referred to the Children's Hospital Eosinophilic Gastrointestinal Disorders clinic for further management of EE recalcitrant to usual therapy. At the time of his referral, he continued to have vomiting and poor weight gain, and his mother reported significant difficulty with the puff and swallow technique. He was placed on a regimen of twice-daily oral budesonide suspension (Pulmicort, AstraZeneca) 500 μg mixed with sucralose (Splenda, McNeils Nutritionals, Washington, Pa), a nonabsorbed sugar, to increase fluid viscosity, to be swallowed twice daily. After 3 months of therapy, repeat EGD showed a normal esophagus, and biopsies demonstrated complete resolution of both esophageal eosinophils and basal zone hyperplasia. In addition, his abdominal pain and vomiting resolved, resulting in increased appetite with documented

Dr. Falk Pharma Ex. 1014
IPR Petition - USP 10,632,069

weight gain. Eight AM cortisol was 13.2 mcg/dL (normal range for age, 3-15 mcg/dL) after 4 months of therapy.

Patient 2 was a 5-year-old girl with a history of developmental delay, abdominal pain, and RAST positivity for milk, egg, and wheat. EGD showed a normal esophagus, but histopathology of biopsies demonstrated maximal eosinophil counts of 40 per HPF and basal zone hyperplasia. She was placed on a hydrolyzed formula containing milk protein (Peptamen Jr, Nestlé, Glendale, Calif), omeprazole 10 mg twice daily, and oral cromolyn (Gastrocrom, Celltech Pharmaceuticals, Rochester, NY) 100 mg 4 times daily. After 12 months of therapy, repeat EGD demonstrated a pale, furrowed esophagus with maximum eosinophil counts of 94, 65, and 90 per HPF and diffuse basal zone hyperplasia in the distal, mid, and proximal esophagus, respectively. She was referred to the Children's Hospital Eosinophilic Gastrointestinal Disorders clinic for further treatment. Subsequent skin prick testing showed a positive response to her hydrolyzed milk protein–containing formula, and her diet was changed to elemental formula. After 2 months of elemental formula and oral cromolyn sodium, EGD was unchanged, with a pale, furrowed esophagus and maximal eosinophil counts of 100, 90, and 70 per HPF in the distal, mid, and proximal esophagus with diffuse basal zone hyperplasia. Her developmental delay precluded the use of a fluticasone inhaler device with puff and swallow technique. As an alternative, she received oral budesonide 500 μg (Pulmicort) mixed with sucralose (Splenda) twice daily as topical esophageal therapy. After 3 months of budesonide, she had improvement in her abdominal pain, and EGD revealed a normal-appearing esophagus with improved maximum eosinophil counts of 28, 20, and 5 per HPF in the distal, mid, and proximal esophagus and decreased basal zone hyperplasia.

Because long-term systemic steroid therapy can result in significant secondary side effects on growth and bone development, we opted for a topical steroid formulation that is easier to use in young or developmentally delayed children and does not require the use of a MDI inhaler. In one series, 15% of patients with EE had concurrent developmental delay.[6] Although treatment with anti–IL-5 mAb has been reported to be successful, this therapy is currently not approved for use in children.[7] In our experience, a viscous oral suspension of budesonide improved symptoms, resolved endoscopic abnormalities, and markedly reduced or eliminated esophageal eosinophils in 2 patients unable to use a MDI inhaler with a puff and swallow technique. As such, oral budesonide suspension warrants further investigation for the treatment of patients with EE.

Seema S. Aceves, MD, PhD[a,b]
Ranjan Dohil, MD[c]
Robert O. Newbury, MD[d]
John F. Bastian, MD[a,b]
[a]*Division of Allergy, Immunology*
Children's Hospital, San Diego
3020 Children's Way MC-5114
San Diego, Calif 92123
[b]*Department of Pediatrics*
University of California, San Diego
La Jolla, Calif
[c]*Division of Pediatric Gastroenterology*
University of California
San Diego, Calif
[d]*Division of Pathology*
Children's Hospital, San Diego
San Diego, Calif

Disclosure of potential conflict of interest: None disclosed.

REFERENCES

1. Rothenberg ME. Eosinophilic gastrointestinal disorders. J Allergy Clin Immunol 2004;113:11-28.
2. Fogg MJ, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol 2003;112:796-7.
3. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med 2004;351:940-1.
4. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? J Allergy Clin Immunol 2005;115:418-9.
5. Teitelbaum JE, Fox VL, Twarog FJ, Nurko S, Ntonioli D, Gleich G, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology 2002;122:1216-25.
6. Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME. Eosinophil-associated gastrointestinal disorders: a World-Wide Web based registry. J Pediatr 2002;141:576-81.
7. Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 2004;113:115-9.

Available online June 30, 2005.
doi:10.1016/j.jaci.2005.05.011

The cradle of IgE autoreactivity in atopic eczema lies in early infancy

To the Editor:

Patients with atopic eczema (AE) are frequently sensitized against a multitude of exogenous allergens and mount high levels of total serum IgE. A great variety of factors, among them cutaneous and gastrointestinal allergen exposure or bacterial and viral superinfections, are associated and are able to induce exacerbations of AE. AE and food allergy belong to those allergic manifestations that occur very early in childhood and frequently proceed to respiratory symptoms of allergy.[1] However, in many cases, it is not possible to identify clearly exogenous or endogenous factors that trigger the chronicity of the disease.

The idea that mechanisms of autoimmunity could also play a role in the pathogenesis of AE gained support by the observation that patients with AE display IgE reactivity to a variety of human protein antigens, of which several have been characterized at a molecular level.[2] The spectrum of IgE-reactive autoantigens seems to be very broad and includes proteins with structural similarities to exogenous allergens such as plant profilins, dog serum albumin, mold-derived manganese, superoxide dismutase, and genuine autoantigens.[2-6] The presence of autoreactivity seems to be associated with the severity of the disease