

Anti-TNF, Infliximab, and Adalimumab Can Be Effective in Eosinophilic Bowel Disease

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ABSTRACT

Background: Eosinophilic enterocolitis (EEC) is an emerging distinct inflammatory bowel disease of unknown etiology. There are no published data on the effect of infliximab (IFX) or adalimumab (ADA) for the treatment of refractory cases.

Methods: A report of all pediatric cases with EEC treated with anti-tumor necrosis factor, identified after an open international call.

Results: We describe here the first 8 children with refractory EEC who were treated with IFX (75% boys; mean age at diagnosis 8.6 ± 4.03 [range 1.6–14 years]; mean age at IFX treatment 11.7 ± 4.4 [range 4.2–16 years]). Allergic and infectious causes of EEC were excluded in all cases. Rapid and complete clinical remission was documented in 6 (75%) children following the induction infusions: 3 (38%) with endoscopic remission, 2 (25%) with endoscopic improvement, and 1 unknown. Four of the 6 responders had secondary loss of response and were switched to ADA, 3 of whom with sustained remission using high doses. Overall, the 6 responders were followed for a median of 7 years (range 4–12; interquartile range 6.4–8.8 years) without evidence of developing Crohn disease or ulcerative colitis. The only case with macroscopic findings on endoscopy was a primary nonresponder.

Conclusions: IFX and ADA may be effective in cases of refractory idiopathic EEC; however, because this is an uncontrolled report, further prospective studies are warranted.

Key Words: adalimumab, anti-TNF antibodies, eosinophilic colitis, eosinophilic enteritis, eosinophilic enterocolitis, infliximab

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The incidence of eosinophilic gastrointestinal disorders is rapidly emerging (1–3). These disorders are clinicopathologic in definition and characterized by dense infiltration of eosinophils associated with symptoms related to the affected gastrointestinal part (4). Although our understanding of eosinophilic esophagitis (EoE) is steadily increasing (5), there are extremely sparse data to guide the diagnosis and management of eosinophilic enterocolitis (EEC), a distinct clinical entity of increasing clinical importance (6–8).

EEC cases can be classified as those presenting in early infancy and those presenting later (whether secondary or idiopathic). The former is typically a self-limiting allergic colitis during the first few months of life, whereas the latter is a distinct form of chronic idiopathic inflammatory bowel disease (IBD). Secondary EEC can be seen in various disease states, most notably allergic and drug reactions, parasitic infections, and systemic eosinophilic syndromes (6). The discussion herein is limited to the idiopathic form.

The diagnosis of EEC is that of exclusion; extensive investigations should rule out parasitic infections (eg, ascariasis, *Strongyloides*, enterobiasis, *Toxocara*, *Trichuris*), medication-induced eosinophilia (eg, gold, rifampicin, calcineurin inhibitors), allergic conditions, and primary hypereosinophilic syndromes, which are exceedingly rare in children (3). Classic IBDs can also present with increased mucosal eosinophils, but the number of cells is typically small and lymphocytic infiltration and histologic evidence of chronicity are more typical of IBD (6,9).

Evidence to support treatments of EEC is limited to small case reports. Reported medications, which may be of some effect, include montelukast (10), ketotifen (11), and sodium cromoglycate (12,13). Steroids and budesonide are clearly effective (3,14), but steroid dependency should not be tolerated, especially in children. Thiopurines may be attempted in refractory or steroid-dependent cases, with anecdotal evidence to support their use (3,6,15). Tumor necrosis factor (TNF)- α is an important mediator of mucosal inflammatory response and its role in IBD is well established (16). Evidence shows that TNF- α enhances survival of eosinophils through nuclear factor- κ B-dependent granulocyte macrophage-colony-stimulating factor production, and that anti-TNF blocks this effect (17). TNF- α is upregulated and is highly expressed in the esophageal mucosa of patients with EoE (18,19). Indeed, 1 report described 3 adults with severe steroid-dependent EoE and suggested that infliximab (IFX) can reduce esophageal TNF- α expression, but with limited clinical response (20). No data on anti-TNF therapy are available in EEC. We report here the first 8 cases with refractory EEC who were treated with anti-TNF- α medications, 6 of which seemed clearly successful.

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METHODS

An open call was made through the Pediatric Gastrointestinal Internet Bulletin Board (2168 registered pediatric gastroenterologists from 49 countries) to identify children with EEC ever treated with anti-TNF therapy. The inclusion criterion was the presence of gastrointestinal symptoms associated with increased eosinophils in the small or large bowel, for which IFX and/or adalimumab (ADA) were commenced under the presumed diagnosis of EEC, at any time in the past. Those with EoE were excluded. Eight cases with EEC have been identified from Jerusalem, Kansas City, and Glasgow. Slides of biopsies from all patients were sent to a central pathology experienced reader, for disease confirmation (B.N., Toronto). The central reader was blinded to the clinical details and local pathology report.

RESULTS

All cases had an unsuccessful trial of at least 1 month of exclusive elemental diet, exclusion of enteric parasite (by serology, stool, and/or mucosal biopsies), normal serum inflammatory markers, and normal celiac serology. None of the cases had a family history of allergy or IBD. Except for the last case, macroscopic appearance of the bowel wall was normal, and all endoscopic biopsies were without granulomas or evidence of chronicity. IFX was commenced in all cases at a dose of 5 mg/kg using a standard 3-dose induction protocol, followed by a q8 week infusions (unless stated otherwise) (Table 1).

Patient 1

This male infant underwent ileocolonoscopy at the age of 20 months because of diarrhea, low weight, and eosinophilia (4100 eosinophils/ μ L). Histology demonstrated 45 to 50 eosinophils/HPF in the lamina propria of the entire colon, without cryptitis or lymphocytosis. Esophagogastroduodenoscopy (EGD) was completely normal as was skin allergy testing. Anti-*Saccharomyces cerevisiae* antibody/perinuclear anti-neutrophil cytoplasmic antibody were normal. His symptoms improved with prednisone, but he remained steroid dependent. Ileocolonoscopy was repeated 10 months later, revealing 60 to 90 eosinophils/HPF as an isolated finding in the lamina propria of the entire colon and in the terminal ileum. Capsule endoscopy suggested the involvement also of the small bowel by edematous jejunal folds. He remained steroid dependent until 4 years of age. During this period, successive treatments with metronidazole, albendazole, montelukast, ketotifen, mesalazine, 6-mercaptopurine, and subcutaneous methotrexate (all at standard doses) were unsuccessful. IFX was introduced at the age of 4.2 years, with rapid clinical resolution during the induction stage. Steroids were weaned off within 2 months of treatment and catch-up growth was documented. Repeat colonoscopy 2 months later showed a significant improvement, with only 15 to 20 eosinophils/HPF throughout the colon. After 7 months of sustained steroid-free clinical remission, IFX was discontinued, in the hope that remission would continue. The child had a gradual return of diarrhea and severe abdominal pain with a corresponding worsening of findings at colonic biopsies. Prompt clinical remission was noted after a second induction of IFX at 5.3 years of age. After 10 months, the duration of IFX effect gradually shortened requiring dose intensification to 10 mg/kg every month. Serum IFX trough levels were undetectable with a high titer of antibodies to IFX. ADA was started at a dose of 25 mg every other week (23 mg/m²) for 6 months without any clinical effect. He is now 7 years of age and budesonide dependent.

Patient 2

A 4-year-old boy presented with abdominal pain, vomiting, occasional hematemesis, and nonbloody diarrhea, without peripheral eosinophilia (300 eosinophils/ μ L). He underwent EGD, which was normal except for 30 to 35 eosinophils/HPF in the esophagus. Symptoms persisted despite prednisone and omeprazole treatment. Repeated EGD, 6 months later, showed complete resolution of the esophagitis but also duodenal eosinophilia (25–30/HPF) in the mucosa and the lamina propria without evidence of lymphocytic infiltrate or villous atrophy. During the following 6 months, the patient failed to respond to montelukast, hydroxyzine, sodium cromoglycate, and budesonide. EGD was repeated after 4 months with similar duodenal findings. At the age of 6 years, complete clinical and endoscopic remission followed 4 months of bowel rest and total parenteral nutrition (TPN). Attempts to reintroduce elemental formula resulted in severe pain and diarrhea associated with recurrence of isolated duodenal eosinophilia on repeated EGD. At the age of 7 years, IFX was introduced with significant clinical improvement after the second dose. The patient was weaned off TPN to an unrestricted diet and repeat EGD with initial colonoscopy was completely normal. After approximately 1 year of remission, his symptoms gradually increased despite infusions every 4 weeks and he was transitioned to ADA at 10 years of age. He has done well since with only occasional mild symptoms. He has been maintained on a dose of 80 mg (42 mg/m²) every 2 weeks; attempts to decrease to 40 mg have resulted in increased pain and loose stools. The patient has been followed for a total of 7 years receiving anti-TNF without showing any evidence of IBD.

Patient 3

A boy presented at 9 years of age with abdominal pain, vomiting, heartburn, and early satiety, without peripheral eosinophilia (400 eosinophils/ μ L). Esophageal biopsies showed occasional eosinophils, but duodenal biopsies showed 25 eosinophils/HPF involving the epithelium and lamina propria, mild lymphoplasmacytosis in the lamina propria, and no villous atrophy. The patient failed to respond to omeprazole, montelukast, hydroxyzine, and sodium cromoglycate, and thus EGD and colonoscopy were repeated. Duodenal histology was unchanged except for the presence of mild villous atrophy. Ileocolonoscopy was normal with the exception of the rectosigmoid, revealing 20 eosinophils/HPF without cryptitis. Bowel rest and TPN at the age of 10 years led to clinical remission. Because attempts to introduce an elemental formula or solid foods resulted in severe pain, nausea, and diarrhea, he was commenced on IFX. Within 1 month, symptoms abated and food was successfully reintroduced. Because symptoms recurred 6 weeks after infusions, infusions were administered at this interval. Repeat EGD while receiving IFX demonstrated complete resolution of eosinophilia, and because he was no longer having diarrhea, colonoscopy was not performed. He remains essentially symptom-free with only occasional mild symptoms after 6 years of receiving IFX.

Patient 4

A girl presented at the age of 10 years with abdominal pain, nausea, and diarrhea, without peripheral eosinophilia (200 eosinophils/ μ L). On EGD, esophagus and stomach were microscopically normal but the duodenum revealed 25 eosinophils/HPF involving the epithelium and lamina propria without villous atrophy or lymphocytosis. Over time, the patient failed to respond to montelukast, hydroxyzine, sodium cromoglycate, budesonide,

TABLE 1. Patients' characteristics

Patient no.	Age*/sex	Clinical presentation	Endoscopic appearance	Previous meds†	Age at anti-TNF and dose	Outcome
1	20 mo/male	Nonbloody diarrhea, weight loss, irritability, abdominal pain	Eosinophilic pancolitis (macroscopically normal)	1, 4–5, 7–8, 10–11	IFX: 4.2 y; 5 $\geq$ 10 mg/kg every 4 wk; ADA: 6.5 y; 23 mg/m ² EOW	Clinical remission on prednisone and budesonide but steroid dependent. Clinical remission with IFX, and endoscopic improvement. Lost response to IFX and switched to ADA. No response to ADA, now budesonide dependent.
2	4 y/male	Abdominal pain, vomiting, hematemesis, and nonbloody diarrhea	Eosinophilic duodenitis (macroscopically normal), normal colon	1–5	IFX: 7 y; 5 mg/kg every 4 wk; ADA: 10 y; 80 mg EOW	Complete clinical and endoscopic remission with IFX. Lost response to IFX and switched to ADA. Complete remission also with ADA; now 4-y sustained remission on ADA; unsuccessful attempts to reduce ADA dose.
3	9 y/male	Abdominal pain, vomiting, heartburn, and early satiety	Eosinophilic duodenitis and rectosigmoiditis (macroscopically normal)	1–4	IFX: 10 y; 5 mg/kg every 6 wk	Complete clinical and endoscopic remission during 6 y of follow-up on IFX
4	10 y/female	Abdominal pain, nausea, nonbloody diarrhea, and flushing	Eosinophilic duodenitis (macroscopically normal), normal colon	1–6 paroxetine, gabapentin	IFX: 14 y; 5 mg/kg every 4 weeks; ADA: 15.5 y; 80 mg EOW	Complete clinical and endoscopic remission with IFX; because of loss of response, switched successfully to ADA with a 5-year sustained remission on anti-TNF
5	8 y/male	Abdominal pain, heartburn, early satiety, and depression	Eosinophilic duodenitis and colitis (in ascending colon) with cryptitis (macroscopically normal)	1–6	IFX: 11 y; 5 mg/kg every 4 wk; ADA: 12 y 80 mg EOW	Partial and temporary response on elemental diet. Prompt and complete clinical remission on IFX with complete resolution of colonic eosinophilia but persistence of duodenal eosinophilia; lost response and successful switch to ADA with a 4-y sustained remission on anti-TNF.
6	10 y/male	Epigastric and chest pain	Eosinophilic duodenitis and rectosigmoiditis (macroscopically normal)	1–3, 8 cetirizine;	IFX: 16 y; 5 mg/kg every 4 wk	Symptom improved initially and only transiently on IFX; the symptoms probably were unrelated to EEC; clinical remission obtained with psychotherapy for PTSD
7	12 y/male	Vomiting and feeding intolerance	Eosinophilic duodenitis (macroscopically normal) no colonoscopy	1, 3–4 cetirizine, anti-IgE	IFX: 15 y; 5 $\geq$ 10 mg/kg every 4 wk	Complete clinical remission on IFX; recurrence after 2 y but with escalated dose; sustained 4-y remission on IFX

Patient no.	Age*/sex	Clinical presentation	Endoscopic appearance	Previous meds†	Age at anti-TNF and dose	Outcome
8	14 y/female	Bloody diarrhea, weight loss, abdominal pain	Eosinophilic colitis with some chronicity and neutrophils (severe pancolitis macroscopically)	1, 3, 4, 7, 10, 11	IFX: 16 y; 5 mg/kg combined with methotrexate	No clinical or endoscopic response to 3 infusions of IFX; underwent colectomy and developed eosinophilic pouchitis

None of patients 2 to 7 had a trial of methotrexate or thiopurines. Patient no. 8 was the only one with macroscopic inflammation (colitis). Patient no. 2, 3, 4, and 6 had symptom relief while on bowel rest and prolonged TPN but no resolution of symptoms with elemental diet. ADA = adalimumab; EEC = eosinophilic enterocolitis; EOW = every other week; IFX = infliximab; PTSD = posttraumatic stress disorder.

* At presentation of the EEC.

† Medications: 1) montelukast; 2) hydroxyzine; 3) sodium cromoglycate; 4) elemental diet; 5) budesonide; 6) amitriptyline; 7) prednisone; 8) ketotifen; 9) cyproheptadine; 10) thiopurines; 11) methotrexate.

paroxetine, amitriptyline, and gabapentin. EGD at the age of 11 years was unchanged, and accompanying ileocolonoscopy was normal. Symptoms completely resolved on bowel rest with home TPN, for a total of 12 months. Symptoms recurred upon reintroduction of formula food, and thus IFX was introduced at the age of 14 years. Complete clinical and histological remission was achieved within 1 month and regular diet was successfully introduced. The symptom-free interval gradually shortened to 3 to 4 weeks, despite infusion frequency every 4 weeks, and after 18 months, treatment was switched to ADA at a dose of 80 mg (34 mg/m²) every 2 weeks. Symptoms recurred after an attempt to reduce the dose to 40 mg. The patient is now symptom-free after a total of 5 years receiving anti-TNF therapy without developing any evidence of IBD.

Patient 5

A boy presented at 8 years of age with abdominal pain, heartburn, early satiety, and depression. Duodenal biopsies showed 30 eosinophils/HPF in the epithelium and lamina propria without lymphocytosis. The patient failed to respond to montelukast, hydroxyzine, sodium cromoglycate, budesonide, and amitriptyline. Repeated EGD along with ileocolonoscopy at the age of 10 years showed continued duodenal eosinophilia (45 eosinophils/HPF) and increased eosinophils (80 eosinophils/HPF) in the ascending colon involving the epithelium and lamina propria, including eosinophilic cryptitis; biopsies from the ileum and other parts of the colon and upper gastrointestinal tract were normal. Prometheus IBD serology was normal. Duodenal and colonic findings were unchanged at repeated endoscopic evaluations, performed at the age of 11 years for persistent symptoms. Partial clinical improvement followed a trial of elemental diet but symptoms recurred after 1 month. IFX was then introduced with complete resolution of symptoms after the second infusion. Repeated endoscopy while receiving IFX showed complete resolution of colonic eosinophilia but persistence of duodenal eosinophilia (50 eosinophils/HPF). Gradually, symptoms recurred in decreasing intervals despite every 4-week infusion protocol. After 9 months, the patient was switched to ADA at a dose of 80 mg (35 mg/m²) every 2 weeks with improvement in symptoms. Attempts to decrease to 40 mg in this patient have resulted in increased abdominal pain. The patient has been followed for a total of 7 years, including 4 years of receiving anti-TNF therapy, without developing any evidence of IBD.

Patient 6

A boy presented at the age of 10 years with epigastric pain with normal EGD, without peripheral eosinophilia (300 eosinophils/ μ L). He failed to respond to omeprazole and gabapentin. Under the assumption of functional syndrome, the pain was unsuccessfully managed symptomatically for 18 months with acetaminophen, codeine, oxycodone, alprazolam, fentanyl patch, alprazolam, gabapentin, amitriptyline, cognitive therapy, and relaxation techniques. He established a pattern of pain for 4 to 5 months annually, beginning in the fall. While receiving gabapentin, amitriptyline, and tramadol for 3 days, EGD was repeated at the age of 15 years. The duodenum showed 30 eosinophils/HPF in the epithelium and lamina propria with a slight increase in lymphocytes in the lamina propria. Bowel rest and TPN were then introduced with significant decrease in pain, but symptoms recurred with attempts to reintroduce elemental formula or a regular diet within 1 month. Again, symptoms resolved after the expected 5-month period. At age 16 years, IFX was introduced with decrease in symptoms after 2 weeks. After 1 month, EGD with

ileocolonoscopy was performed. Histology revealed occasional intraepithelial eosinophils with basal cell hyperplasia and papillary elongation in the esophagus, a normal stomach, duodenum, and terminal ileum, with mild rectosigmoid eosinophilia (20 eosinophils/HPF) without other inflammatory infiltrates. Despite IFX maintenance, however, symptoms recurred the following year consistent with his previous pattern, and IFX was discontinued. During this bout, some unfortunate past events became evident and he was diagnosed as having posttraumatic stress disorder. He underwent psychotherapy and has gone 2 years without recurrence of symptoms.

Patient 7

A male with a history of cerebral palsy and shunted hydrocephalus presented at 12 years of age with vomiting and feeding intolerance, associated with delayed gastric emptying, without peripheral eosinophilia (500 eosinophils/ μ L). EGD was normal. Skin prick test was positive to corn, which caused itchy eyes and nasal congestion, but its elimination did not improve his gastrointestinal symptoms. He failed to respond to ranitidine, cetirizine, montelukast, sodium cromoglycate, and cyproheptadine. At 15 years of age, he complained of multiple daily vomiting. Repeated EGD demonstrated normal esophagus, mild lymphoplasmacytosis in the antrum, and duodenal eosinophilia (30 eosinophils/HPF) involving the epithelium and lamina propria without lymphocytosis. Owing to distressing symptoms, IFX was then introduced, leading to complete resolution of symptoms after the second dose. Following 2 years of clinical remission, his vomiting recurred and thus IFX dose was escalated to 10 mg/kg every 4 weeks. Symptoms resolved after the first increased dose. He has done well now for 2 further years on the increased dose. He did not have colonoscopy or repeat endoscopy while receiving IFX.

Patient 8

A girl presented at 14 years of age with bloody diarrhea, without peripheral eosinophilia (500 eosinophils/ μ L). Colonoscopy demonstrated uniform macroscopic pancolitis with nonerosive confluent erythema, granularity, and friability. Biopsies were consistent with severe active eosinophilic colitis, showing 60 to 100 eosinophils/HPF in the mucosa and lamina propria and eosinophilic cryptitis, without lymphocytosis or granulomas, but occasional neutrophils and plasma cells in the lamina propria. There was a variable crypt irregularity and goblet cell depletion, consistent with mild chronicity. EGD and terminal ileum were completely normal. Magnetic resonance enterography and capsule endoscopy were normal. Radioallergosorbent testing was positive only to house dust mite. She failed to have a significant response to any treatments tried including steroids (oral and intravenous), sodium cromoglycate, montelukast, azathioprine, and methotrexate. IFX was given at the age of 16 years in combination with methotrexate, but without clinical response after 3-dose induction protocol. Calprotectin pre- and post-IFX was 1000 and 1740, respectively, and repeat ileocolonoscopy showed unchanged findings. She then underwent a colectomy with symptomatic remission. A pouch was constructed at the age of 17 and she soon developed eosinophilic pouchitis. At the age of 18 years, her symptoms are controlled with steroids, enemas, and loperamide.

DISCUSSION

To the best of our knowledge, this is the first report in the literature of treating EEC with anti-TNF therapy. Eosinophilic

disorders of the gastrointestinal tract are rapidly emerging. Although EoE has been reasonably characterized as an allergic condition, the etiology underlying EEC is elusive and it remains at present a diagnosis of exclusion. The main 3 disorders to be excluded are parasitic infection, allergic enterocolitis, and IBDs; all 3 conditions were convincingly excluded in the 8 reported cases, although the last case deserves special attention. Although the first 7 cases had macroscopically normal-appearing mucosa on repeated endoscopic evaluations and no evidence of chronicity, case no. 8 had refractory severe macroscopic colitis, otherwise compatible with UC, and mild chronicity; however, the large number of eosinophils, the lack of lymphocytic infiltrate, and the recurrence of eosinophilic pouchitis after colectomy lend support to the diagnosis of EEC, or at least as recently published, an overlap syndrome of IBD with EEC (9). It is interesting to note that this outlier case had absolutely no response to IFX. The second nonresponder (case no. 6) is also different from the rest; the positive biopsy findings of this child are probably incidental findings unrelated to the irritable bowel syndrome–like symptoms, which resolved after psychotherapy.

The other 6 cases were clearly responsive, with occasional typical gradual loss of response to IFX as seen in IBD, supporting our conclusion that IFX was biologically effective. Further support comes from the endoscopic improvement or remission after initiating IFX. The high ADA dose required here for remission may be incidental but merits further evaluation in future studies. It is possible that case no. 1 did not respond to ADA after losing response to IFX, because of the lower dose received, compared with the other 4 cases. The possibility of using other biological treatments, most notably anti-IL-5 (21,22), may also be a therapeutic possibility, although their lack of success in EoE warrants careful evaluation in EEC.

Alfadda et al (6) recently summarized 196 heterogeneous published EEC reports of approximately 300 reported cases (7,8). EEC is defined as dense isolated eosinophilic infiltrates of the bowel wall, at times with crypt abscesses and deep cellular invasion (6). Mild eosinophilic colitis was associated with at least 10 eosinophils/HPF and marked as >20 eosinophils/HPF with decreasing gradient distally (23). Although there are no clear definitions for diagnosing EEC, the aforementioned criteria qualify our cases. In EEC, the stomach is involved in 26% to 81% of cases and the small bowel in 28% to 100% (7). Patients may present with abdominal pain (most common symptom in children), diarrhea (seldom bloody), vomiting, malabsorption, and protein losing enteropathy (3,6,23–25). Hyperemia, nodularity, and ulcerations may be present on endoscopic evaluation (7) but, as seen in 7 of 8 of our cases, normal-appearing mucosa is not uncommon (6). Consistent with our finding, overt ulcerations or hemorrhage were not noted in any of 33 children with eosinophilic colitis (23). Peripheral eosinophilia is reported to be present in 70% to 80% of cases (7,26), and its degree is correlated with the number of mucosal eosinophils (23). In contrast, however, most of our cases did not show peripheral eosinophilia.

The evidence to date suggest that eosinophilic disease of the columnar epithelium (ie, enteritis and colitis) differs from EoE in pathogenesis, clinicopathological features, and treatment (27). Most EoE cases can be attributed to allergen exposure (28). Aside from its infantile form, response to a hypoallergenic exclusion diet is much less common in EEC, as are family and personal history of atopic conditions, asthma, and eczema. In 22 children with eosinophilic colitis, elevated IgE was present in $<50\%$ of patients and allergy history was negative in all (23). Nonetheless, it is possible that aeroallergens have a pathogenetic role in EEC (27,29).

A possible etiologic factor of EEC is an aberrant immune response to ingested material and dysbiosis associated with the

“hygiene hypothesis” and altered Th2 immune response (27). Indeed, eosinophilic colitis may precede the diagnosis of IBD by years (30). Although we cannot completely exclude the possibility that some of our children were “pre-IBD” cases, this seems unlikely given the long median follow-up period of our cases (7 years [range 4–12; interquartile range 6.4–8.8 years]) and that the clinical presentation is not typical of IBD. It could be argued that classic IBD was not evident because the anti-TNF therapy altered the natural history of disease; however, the fact that no IBD feature has developed in any of the 8 cases for 7 years makes this possibility less likely. Another limitation of our report is its retrospective nature with all the associated inherent biases; however, we took extra care to minimize these biases by central blinded and independent reading of the biopsies and by meticulous chart review by senior pediatric gastroenterologists, well experienced with managing IBD. Lastly, publication bias may account for the apparent high success rate of anti-TNF in our series; however, this bias was minimized by posting an open call on the large international Pediatric GI Bulletin Board, and all cases of EEC identified in that call are included herein.

Translational studies linking immunohistochemical analysis with clinical phenotypes have been recently identified as a burning research topic in eosinophilic disorders by the eosinophilic gastrointestinal disorders working group (31). We have technically failed to stain the biopsies for several cytokines, mainly because of the long time elapsed since the biopsies were obtained. Future studies should ensure in vitro assays of TNF, interleukin-5, and eotaxin expression in the intestinal mucosa. Eosinophilic recruitment into the colon after mucosal injury is mediated through the β_2 -integrin/intercellular adhesion molecule-1 pathway, unique to the colon (32).

In summary, EEC is an emerging intestinal disorder with unknown etiology and lack of data to guide its management. We report here 8 pediatric cases of refractory EEC who were treated with anti-TNF medications, 6 of whom clearly responded. The 1 case with macroscopic changes did not respond, and before embarking on such a therapy, other etiologies for the symptoms must be excluded (such as irritable bowel syndrome diagnosed eventually in case no. 6). It is possible that when using ADA, higher doses than practiced in IBD should be used. Although the applicability of these cases is still limited by the retrospective description and small uncontrolled sample size, the results are encouraging and warrant further evaluation.

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