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EDITORIAL

Climbing New Mountains: How Antibodies Blocking α4β7 Integrins Tamed Eosinophilic Inflammation of the Intestinal Tract

Courtney L. Olbrich[1,2] · Luke Simerly[1,2] · Edwin F. de Zoeten[1,2,3] · Glenn T. Furuta[1,2,3] · Lisa A. Spencer[1,2,3]

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A historical chapter of eosinophilic gastrointestinal diseases (EGIDs) comes full circle in an article published in this month's issue of *Digestive Diseases and Sciences* by Grandinetti et al. [1], who describe their series of EGID patients treated with the novel biologic vedolizumab. In 1993, Dr. Attwood et al. in this journal [2] and Dr. Straumann et al. in another [3] provided the gastrointestinal (GI) community with the first comprehensive descriptions of eosinophilic esophagitis (EoE), a disease that then was a mere curiosity. In their publication, Dr. Straumann et al. used his nascent Swiss EoE Database (SEED) to define clinical features of EoE, and over the next decades defined novel EoE clinical outcome metrics (COMs) and therapeutic approaches. Grandinetti and Biederman et al. used the SEED data to now report a single center's experience with the clinical features of EGID and the use of a novel treatment, vedolizumab with the hope that this will inspire a new generation of EGID investigators, just as its predecessors did for EoE.

Gastrointestinal Eosinophilia—Friend or Foe?

Eosinophils normally reside in the GI tract mucosa at varying density, responding to stimuli within their microenvironment through secretion of mediators, including bioactive lipids, cationic proteins, cytokines, and growth factors. As a consequence, eosinophils likely engage in a myriad of functions that contribute to both health and disease, ranging from immune homeostasis, tissue repair, and antimicrobial responses to cationic protein and reactive oxygen-mediated tissue damage. Although infections, inflammatory bowel diseases (IBD), cancers, and allergic reactions are associated with increased mucosal eosinophil density, what drives their mucosal accumulation and impact on disease pathogenesis (helpful, harmful or neutral) remains uncertain [4]. For example, using IBD mouse models, Hogan et al. [5] showed disease improvement in mice deficient in eosinophil peroxidase, suggesting detrimental effects of eosinophil degranulation. In contrast, Masterson et al. [6] revealed that loss of eosinophils was associated with inferior outcomes due to diminished protectin, an epithelial repair molecule. Thus, gut eosinophils remain enigmatic cells.

Clinical Impact of Eosinophils in Disease

Eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) are uncommon, diverse diseases defined by chronic GI symptoms, increased mucosal eosinophil density, and lack of a recognized underlying cause for mucosal eosinophilia [7]. Patients develop commonplace symptoms ranging from abdominal pain, vomiting, diarrhea, and occult or overt blood loss. Since no reliable biomarker exists, endoscopic and histologic appearances are the only available methods to confirm the diagnosis and to monitor inflammation. To date, it is not certain if or how eosinophils damage the mucosal, muscular or serosal layers in EGIDs although antigen-driven T helper (Th)2-associated responses appear to be involved [4]. Th2 cells and secreted cytokines are involved in eosinophil recruitment and activation; for instance, interleukin (IL)-5 drives expansion of eosinophil-committed bone marrow progenitors, whereas IL-13 induces epithelial cell release of

✉ Lisa A. Spencer
Lisa.Spencer@ucdenver.edu

1 Department of Pediatrics, Gastrointestinal Eosinophilic Diseases Program, Section of Pediatric Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine, 12700 East 19th Avenue, Research 2 P15-6026 Mail Stop: C-226, Aurora, CO 80045, USA

2 Digestive Health Institute, Children's Hospital Colorado, Aurora, CO, USA

3 Department of Medicine, Mucosal Inflammation Program, University of Colorado School of Medicine, Aurora, CO 80045, USA

eotaxin-3, an eosinophil-specific chemokine and activation factor. To date, dietary allergen restriction and systemic or topical steroids effectively diminish mucosal eosinophil density and improve symptoms in most EGIDs. These therapies may achieve suboptimal efficacy and can be accompanied by undesirable adverse effects, highlighting current unmet needs for a better understanding of EGID pathogenesis and natural history, providing the impetus for the identification of biological therapies that target intestinal eosinophils.

Vedolizumab Mechanisms in the GI Tract

One candidate biologic with proposed efficacy in EGIDs is vedolizumab, a humanized mouse monoclonal antibody that targets gut-homing integrin α4β7, preventing binding to its ligand, mucosal addressing cell adhesion molecule-1 (MAdCAM-1), a molecule expressed exclusively on the endothelium of intestinal mucosal venules [8] (Fig. 1). Vedolizumab, FDA approved for use in patients with IBD, is designed to specifically inhibit extravasation of gut-tropic effector T lymphocytes into intestinal tissues. Its major advantage is a high benefit/risk deriving from conformational recognition specifically of the integrin α4β7 heterodimer, with no cross-reactivity with α4 chain alone or with other β chains, thereby avoiding off-target effects such as the systemic immunosuppression encountered with the more broadly reactive α4-targeting antibody natalizumab.

Since eosinophils also bear α4β7 integrins and can bind to vascular endothelial MAdCAM-1, vedolizumab may be useful in EGIDs by directly inhibiting eosinophil intestinal homing [9]. Moreover, since Th2-derived cytokines

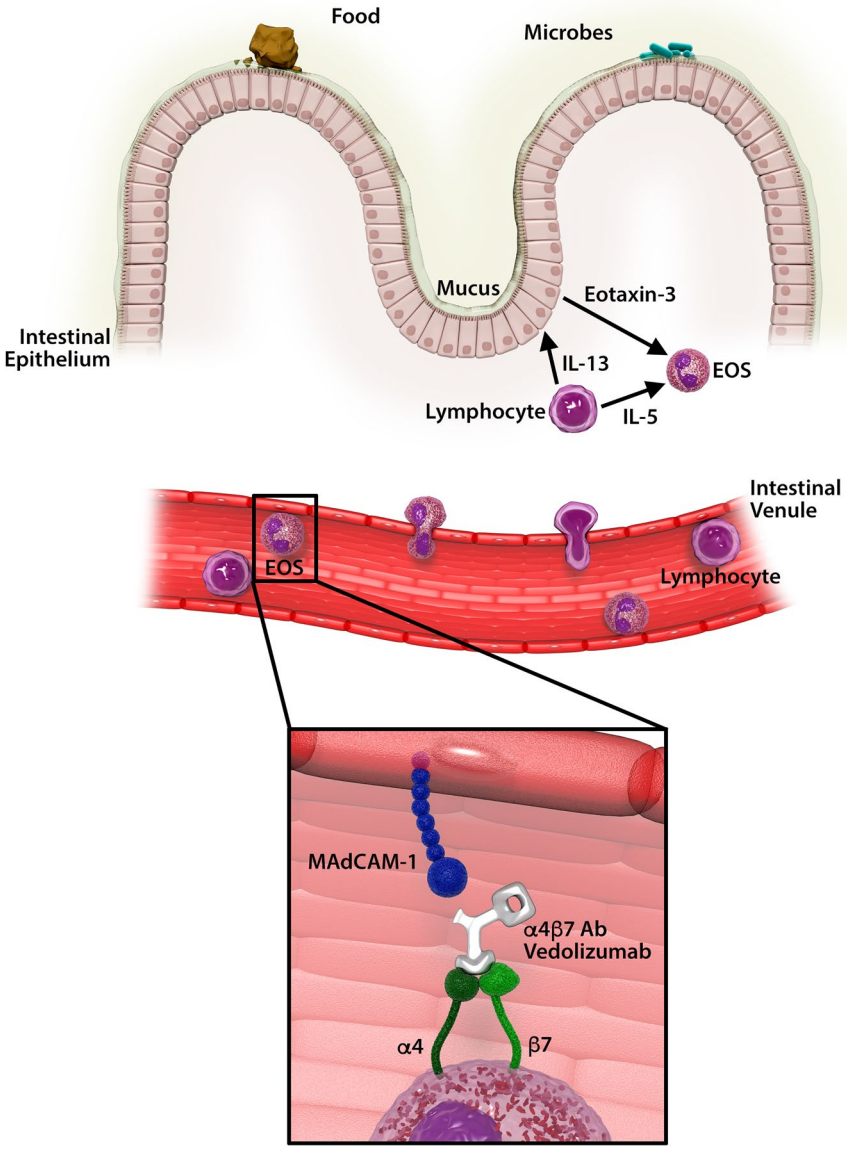

Fig. 1 Vedolizumab impacts leukocyte transmigration. The mucosal density of T lymphocytes and eosinophils increases in eosinophilic gastrointestinal disease inflammation. In the tissue space and upon stimulation, T lymphocytes can release cytokines that directly and indirectly promote eosinophil chemotaxis and activation. Vedolizumab blocks binding of the T lymphocyte-expressed gut-homing integrin α4β7 to its ligand mucosal vascular addressing cell adhesion molecule 1 (MAdCAM-1), specifically expressed on the endothelium of intestinal venules. Therefore, vedolizumab directly prevents the transmigration of T lymphocytes into the intestinal mucosa, indirectly impairing eosinophil recruitment and activation through preventing release of T cell-derived eosinophil-activating cytokines. Moreover, since α4β7 integrin is also expressed on eosinophils, vedolizumab may directly prevent eosinophil transmigration into intestinal tissues

(namely IL-5 and IL-13) promote eosinophil differentiation, recruitment, and activation, vedolizumab might further diminish intestinal eosinophil mucosal accumulation indirectly through blocking effector Th2 cell tissue migration. Finally, vedolizumab inhibits α4β7 interactions with both MAdCAM-1 and fibronectin, an extracellular matrix component. Since eosinophil-expressed α4β7 interactions with fibronectin promote eosinophil survival, one might anticipate vedolizumab has therapeutic effects on EGIDs [10, 11].

Vedolizumab as a Biologic to Treat EGIDs

Grandinetti [1] et al. expand on the clinical description of EGIDs, report on its natural history, and describe the efficacy of treating four steroid-refractory or steroid-dependent EGID patients with vedolizumab. This report is significant for several reasons: First, this work provides a comprehensive description of EGIDs. Since 1991, Dr. Straumann has meticulously recorded EGID patients in SEED, a unique resource. In his work, he describes the novel clinical and endoscopic EGID score that he applied to all the described patients. Since he performed all assessments, observer variability was minimized. The authors of the current paper report that in contrast to EoE, EGE is not a male-predominant disease (8/22 male), can be ulcerating (1/22), is often associated with a normal-appearing mucosa, and may not be responsive to elimination diets. Second, this study provides valuable data regarding the natural history of these waxing and waning diseases. Their EGID patients followed a chronic course with 70% continuing to exhibit symptoms. Patients with more proximal disease were more symptomatic and had histologically contiguous inflammation, whereas those with EGE and EC had intermittent symptoms and more focal inflammation. Although most EGID patients respond to topical or systemic steroids, the authors document that some do not. Steroid-refractory or steroid-dependent EGID patient treatments are limited to immunosuppressive drugs such as azathioprine and 6-mercaptopurine, medications that may or may not be safer than biologics. Third, they expand the understanding of the use of vedolizumab for the treatment of EGIDs. To date, only six other EGID patients have been reported to have received this treatment, with 50% of these patients demonstrating clinical and histological improvement. Kim et al. reported vedolizumab treatment in five severely ill adult (2 female) EG/EGE patients with treatment-refractory disease. Two experienced symptom improvement and tissue normalization and were able to be weaned from steroids. One improved clinically, and two showed no improvement [12]. Nhu et al. [13] reported a 43-year-old male with complicated Crohn's disease and esophageal eosinophilia with symptoms consistent with EoE who had symptomatic, endoscopic, and histologic improvement with vedolizumab. Grandinetti and Biederman et al. expand these data reporting the clinical impact of vedolizumab as an alternative therapy in four treatment-refractory/steroid-dependent EGID patients exhibiting diverse patterns of eosinophilia, with three of the four patients responding. Of note, the non-responder had serosal disease, perhaps representing an alternative form of EGID. Long-term use of up to one year showed that three of the four patients reported improvement of patient global assessment scores and had reduced histological eosinophil density. One patient developed peripheral eosinophilia and elevated serum eosinophil cationic protein levels following vedolizumab treatment, suggesting that assessment of systemic degranulation may not be a viable approach to monitor disease. No obvious adverse effects or complications have been reported.

What Does the Future Hold for EGID Treatments?

Future studies will benefit from the establishment of uniform EGID diagnostic criteria, development of COMs, identification of reliable biomarkers, creation of innovative methods to detect inflammation, and completion of mechanistic studies to determine novel therapeutic targets. Drs. Biederman and Straumann's efforts here, as well as in their work with the Consortium for Eosinophilic GI Researchers (CEGIR), are beginning to address these areas. Are EG and EGE separate diseases or do they represent a spectrum of GI eosinophilia linked by a common mechanistic pathway? As with the more "mature" EoE field, determination of EG, EGE, and EC endotypes will be essential going forward in order to enable the development of novel interventions [14]. Finally, pathologists' efforts will be essential to help develop relevant and implementable diagnostic criteria for EGID patients that can be used as endpoints for clinical care and therapeutic trials. Eosinophil enumeration alone has served the EoE community to date, but due to the variability inherent when enumerating eosinophil density, there is no accepted normal mucosal eosinophil density in other GI tract locations, necessitating other approaches for differentiating diseased mucosae from normal. Collins et al. [15] developed a novel EoE histological scoring system that uses not only eosinophil density, but an eosinophil degranulation and epithelial feature score. One can imagine that the gastric, small intestinal, and colonic mucosal surfaces will be scored not only by characterizing resident eosinophils but also by the state of the epithelium, villi, crypts, and underlying lamina propria.

In summary, vedolizumab shows promise as a novel means of reducing symptoms and improving tissue inflammation in EGIDs patients. Its activity as an α4β7-integrin

inhibitor allows for a targeted approach to blocking eosinophil accumulation within intestinal tissues. The experiences in the IBD literature suggest that vedolizumab is effective and has limited impact on systemic immune tolerance. Larger-scale trials are needed to determine vedolizumab's mechanisms of action and efficacy as an EGID therapeutic.

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