

Does Eosinophil Depletion in Gastroenteric Diseases Associated With the Hypereosinophilic Syndrome Teach Us Whether Normal Humans Need Eosinophils in 2022?



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The introduction of mAbs into medical care has resulted in remarkable advances both benefiting patients and adding to our understanding of pathophysiology,^{1,2} including diseases associated with eosinophilia. For example, the discovery of IL-5 was succeeded by utilization of neutralizing mAbs that benefited patients with eosinophilic asthma and other eosinophil-related diseases and established the importance of IL-5 as an eosinophil provocation.³ However, it remained for another eosinophil-directed mAb, benralizumab, targeting the IL-5 receptor alpha,^{4,6} to take us further. Benralizumab ablates eosinophils by marking them for antibody-dependent cell-mediated cytotoxic destruction.⁷ In contrast to the IL-5–neutralizing antibodies, benralizumab appears to markedly, essentially totally, deplete eosinophils from treated patients with asthma, as judged by eosinopenia,^{8,9} sputum analyses,⁹ bronchial biopsies,⁹ and bone marrow aspirates.⁹ Presently, benralizumab is approved for treatment of severe asthma.

Because of the potent ability that benralizumab has to reduce eosinophils in blood and tissues, Kuang et al¹⁰ conducted a phase

2 clinical study of its effectiveness in the hypereosinophilic syndromes (HESs). Although a relatively small trial (20 patients with this rare syndrome), the results met the primary end point, a reduction of at least 50% in the absolute blood eosinophil count at week 12. Following the double-blind phase, the open-label phase in 19 patients showed continued suppression of eosinophilia in bone marrow and other tissues. Biopsy specimens from patients obtained at week 24 during the open-label phase showed nearly complete eosinophil depletion by light microscopy and by immunohistochemical localization of eosinophil peroxidase; specimens included 52 gastrointestinal tissues, bronchoalveolar lavage from 1 patient, and repeated skin biopsies from 2 patients.

The present publication by Kuang et al¹¹ describes clinical and histopathologic features in 7 patients with HESs from the previous study who suffered from gastrointestinal disease and presented with various and wide-ranging gastrointestinal symptoms, including dysphagia, odynophagia, abdominal pain, constipation, diarrhea, nausea, easy satiety, and weight loss. The diagnosis of HESs in the patients was based on peripheral blood hypereosinophilia and increased numbers of eosinophils in biopsy specimens from esophagus, stomach, duodenum, and colon. The patients symptomatically improved with benralizumab treatment at a dose of 30 mg every 4 weeks over 24 to 52 weeks; some were able to reduce or stop medications previously used for therapy, and many were able to expand the varieties of food consumed in their diets. However, at 1 year, most of the patients had partial return of symptoms, some related to food reintroductions. One patient relapsed with return of peripheral blood hypereosinophilia and gastrointestinal symptoms, indicating unresponsiveness to benralizumab. Endoscopy at week 24 showed improvement in the appearance of the esophagus and the duodenum, albeit slight in some, with a return to normality in the endoscopic appearance of the colon. Histopathologic examinations at week 24 did not identify tissue eosinophils. At 1 year of benralizumab treatment in 3 subjects, eosinophils remained undetectable. Analyses of serum cytokines showed increases in IL-5 and IL-4 levels.

What does this report teach us? First, patients were benefited both symptomatically and on endoscopic inspection but not uniformly. Moreover, the relatively short duration of the study precludes judgment of the potential for long-term benefit or long-term detriment from benralizumab treatment. Nonetheless, the findings are encouraging and highlight the need for further studies in a larger number of patients using comparable methodology. Second, the benefit to patients was not robust. Some patients had apparent reactions to foods or recurrence of symptoms without clear-cut stimuli. Remarkably, there appeared to be

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Conflicts of interest: G. J. Gleich is employed by the University of Utah; is Chief Science Officer of NexEosBio; his spouse is employed by the University of Utah, is Co-Director, Immunodermatology Laboratory, and is Medical Director, Immunodermatology at ARUP Laboratories; has a royalty sharing agreement with Teva; reports consultancy for AstraZeneca, GlaxoSmithKline, Genentech, and Knopp Biosciences; receives royalties from Mayo Foundation (spouse and self); spouse receives royalties from UpToDate; is co-founder with spouse of NexEosBio; reports grants from NIH; spouse has grant from Regeneron; reports grants and consultancies from/with AstraZeneca and GlaxoSmithKline; is on the Board of Directors for American Partnership for Eosinophilic Disorders (APFED); reports that he and his spouse hold patents in methods for diagnosing, monitoring, and treating eosinophil-related diseases. K. M. Leiferman is employed by the University of Utah; is Co-Director of Immunodermatology Laboratory; is Medical Director of Immunodermatology at ARUP Laboratories; her spouse is employed by the University of Utah, is Chief Science Officer at NexEosBio, has a royalty sharing agreement with Teva, reports consultancies from GlaxoSmithKline, Genentech, AstraZeneca, and Knopp Biosciences, and reports grants from NIH, GlaxoSmithKline, and AstraZeneca; reports consultancy for AstraZeneca; her and her spouse receive royalties from Mayo Foundation and UpToDate; is co-founder with her spouse of NexEosBio; reports grants from Regeneron; holds patents with spouse in methods for diagnosing, monitoring, and treating eosinophil-related diseases.

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differences among the different segments of the gastrointestinal tract with notable improvement of colonic involvement in contrast to more variable results in the esophagus. Third, measurements of other likely interacting factors, including mast cells and cytokines, were not informative, with the possible exception of increased serum IL-4 levels; this argues that medications to block IL-4 might have enhanced value, and several studies have supported the benefit of dupilumab in eosinophilic esophagitis.¹² Lastly and importantly, despite the complete ablation of eosinophils from the gastrointestinal tract, no pattern of adverse effects occurred. Among normal human organs and tissues, appreciable eosinophil infiltration consistently occurs only in the gut.¹³ If eosinophils are critically important in normal homeostasis of the gastrointestinal tract, the absence of adverse reactions would seem unexpected. Of note, the study was limited timewise, and data tracking over longer time periods will be important. Also, although Kuang et al¹¹ studied considerable portions of the gastrointestinal tract, the jejunum and the ileum were not evaluated, and, therefore, a substantial part of the gastrointestinal tract was not analyzed.

With the evident total ablation of eosinophils from the gastrointestinal tract and, likely, from all organs and tissues in the human body over an extended period up to 1 year, the absence of increased susceptibility to infection or any other adverse event pattern is notable. These findings are consistent with other studies reporting on the use of a lower dose of benralizumab, 30 mg every 2 months to treat bronchial asthma, in which no clear-cut pattern of adverse reactions was evident.^{14,15} One of the patients in the initial HES study¹⁰ became pregnant while in the open-label phase.¹⁶ Treatment with benralizumab was continued throughout the pregnancy, and the patient delivered a healthy baby girl by cesarean section at 38 weeks of gestation. No eosinophils were present in the peripheral blood of the infant. At age 2 years, the child and the mother are fine (A. Klion, personal communication through phone call, 2021). Pregnant cynomolgus monkeys treated with benralizumab, at doses up to 30 mg per kg every 14 days beginning at gestational day 20, showed normal growth and fetal development throughout gestation, with the only benralizumab-related effect being eosinophil depletion. These observations demonstrate that eosinophil depletion is not associated with discernible abnormalities, and prompt questioning whether the results from numerous studies showing important homeostatic functions of eosinophils,¹⁷ particularly in murine models, are applicable in humans. Is it possible that human primates no longer need eosinophils for normal health and that their presence in humans largely is in response to or in association with disease? Previous reviews of this subject have argued that the absence of eosinophils does not critically affect normal health, and the results with benralizumab appear to strengthen that view.¹⁸ Thus, although the conclusions from the studies of Kuang and his associates are limited, their findings open a tantalizing view of the effects on disease and normal health. "For now we see through a glass, darkly," (I Corinthians

13:12 [KJV]) but, hopefully, later studies will reveal fully the contributions of the eosinophil to diseases of the gastrointestinal tract, specifically, and to human health, generally.

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