Are Eosinophils Needed for Normal Health?

To the Editor: The recent state-of-the-art review on eosinophils in health and disease by Wechsler et al1 is a comprehensive statement of current thought. In their summary, the authors conclude that eosinophils may be involved in numerous homeostatic functions, including metabolism, tissue remodeling and development, neuronal regulation, epithelial and microbiome regulation, and immunoregulation, implicating a critical role for eosinophils in human health. This conclusion, however, would appear open to challenge because the monoclonal antibody, benralizumab, directed to the interleukin 5 receptor, totally abolishes eosinophils from the body. Studies have found that biopsy specimens of patients receiving benralizumab are devoid of eosinophils.2,3 Presently, benralizumab is used widely for the treatment of eosinophilic asthma, and, therefore, many patients with this disease are testing whether eosinophil depletion results in abnormalities. Note that a double-blind study of the safety of benralizumab failed to find any consequences of long-term, 2-year eosinophil depletion.4 Furthermore, a patient has been described who had the hypereosinophilic syndrome, was benefited by benralizumab, and became pregnant while taking the drug.5 She completed her pregnancy while remaining on benralizumab and delivered a healthy baby girl who failed to show eosinophils in her blood until about 7 months of age. At approximately 2 years, both mother and daughter appear fine (personal communication, A. Klion November 7, 2021). Surely, if eosinophils have these manifold homeostatic properties, some consequences would be observed in their absence. However, current treatment outcomes have not disclosed such abnormalities. In addition, a prior review of the consequences of not having eosinophils also failed to find any characteristic effect of eosinophil depletion in humans.6 Because much of the data supporting the homeostatic properties of the eosinophils is derived from in vitro experiments and from murine studies, one can question whether the authors’ conclusions are correct in humans.

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In Reply—Are Eosinophils Needed for Normal Health?

To the Editor: We thank Drs Gleich and Leiferman for their letter in response to our state-of-the-art review on eosinophils in health and disease.1 They question the concluding summary, that eosinophils may be involved in numerous homeostatic mechanisms, including metabolism, tissue remodeling and development, neuronal regulation, epithelial and microbiome regulation, and immunoregulation, implicating a role for eosinophils in human health. They raise this point as the anti—interleukin (IL)—5Rz monoclonal antibody benralizu- mab, which abolishes circulating eosinophils through induction of antibody-dependent cytotoxicity, has not been associated with an adverse effect profile. Indeed, an open label study of 5 years’ experience provides some reassurance,2 although this publication included only 48 participants who have safety data exceeding 5 years, a number that is far too small to be conclusive. Furthermore, there is lack of insight as to whether the licensed dose of benralizumab, which depletes blood eosinophils, also depletes tissue eosinophils—an important unknown, as the metabolic and immunoregulatory roles of eosinophils in human health are tissue related, and the extrapolation from blood eosinophil depletion to the suggestion that eosinophils play no role in human health overlooks this specificity.


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Drs Gleich and Leiferman also quote the case report of the pregnancy outcome in a mother administered benralizumab during pregnancy. This led to undetectable blood eosinophils in the infant when born, who took 7 months to recover, without any apparent detriment to growth or development during this period. However, it has been demonstrated that eosinophil-deficient mice develop an altered gastrointestinal microflora compared with wild-type litter mates. Such a change is not apparent from assessment of external appearance. Should this murine dysbiosis also apply to the human benralizumab-induced equivalent, it is unknown what the subsequent consequences might be. Gastrointestinal dysbiosis is increasingly appreciated to be linked to long-term risk of disease. Such a long-term perspective is also of relevance when one considers the tissue roles of eosinophils. Eosinophils are present in human adipose tissue, and as their numbers decrease at this site with age, there is a concomitant unlocking of adipocyte regulation and an increase in adipose gene expression of inflammatory cytokines such as IL-6. Increased circulating levels of IL-6 are associated with metabolic syndrome and the likelihood of type 2 diabetes mellitus in asthma. It is noteworthy that benralizumab therapy is also associated with an increase in serum IL-6, although whether this relates to depletion of adipose eosinophils is undefined. Recent publications also highlight the protective relevance of tissue eosinophils in humans, to ischemic damage in coronary artery disease, abdominal aortic aneurysm progression, and gastrointestinal cancer survival. These are all situations in which eosinophil depletion may adversely influence outcome, and there is a need for much more substantial epidemiologic data than are now available to be able to state that this is not the case.

We thus do not accept that benralizumab data are conclusive evidence for a redundant role for eosinophils in human health as there is no knowledge of its tissue impact at sites relevant to metabolic, immunomodulatory, and microbiome homeostasis; there are no specific studies focusing on the impact of disordered regulation that could arise with tissue eosinophil depletion; and there are inadequate long-term data with assessment of relevant outcomes. The weight of evidence is thus very much with our concluding statement in the review article, and whereas some may still consider the jury out, it is pertinent to remember the medical dictum *primum non nocere*, first do no harm, when a treatment that completely depletes eosinophils has no indirect or direct formal trial evidence of clinical advantage over strategies that reduce eosinophils but retain them within the normal range.

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