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The Consequences of Not Having Eosinophils

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Abstract

Several lines of evidence suggest that deficiency of eosinophils is not associated with any characteristic abnormality. Patients lacking eosinophils, in the setting of immunodeficiency or as a consequence of IgG-mediated eosinophil precursor destruction, do not display any distinguishing abnormalities related to eosinophil reduction. The observation that eosinophil-deficient mice do not display any distinctive syndrome or failure of their health is evidence that, under ordinary laboratory conditions, the eosinophil does not play a critical role in the well-being of mammals. Observations that monoclonal antibodies to interleukin-5 (IL-5) are well tolerated appear unsurprising in light of these findings. For example, patients with the hypereosinophilic syndrome have received mepolizumab, an anti-IL-5 monoclonal antibody, for as long as 6 years and have not developed any characteristic set of adverse events. Safety data for reslizumab, another anti-IL-5 monoclonal antibody, and benralizumab, a monoclonal antibody to the IL-5 receptor α -chain, are comparatively limited, especially for benralizumab, although reports of administration of these antibodies to humans suggest that they are well tolerated. Thus, data to the present suggest that reduction of eosinophils appears to have no characteristic ill effects on normal health, and monoclonal antibodies that deplete eosinophils have the potential to be widely employed in the treatment of eosinophil-associated diseases.

Keywords

anti-interleukin 5; deficiency; eosinophil; thymoma

The eosinophilic leukocyte was discovered about 130 years ago and was quickly associated with parasitic and allergic disease, especially bronchial asthma [1]. Later studies showed that eosinophils are recruited into tissues that undergo allergic reactions, and for a time, it seemed that the eosinophil might function as a reparative cell to heal tissues injured during hypersensitivity reactions. However, subsequent investigations of the properties of the cell, and particularly of the granule proteins, revealed that the eosinophil has a striking ability to

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Conflict of Interest: GJG is a consultant to GlaxoSmithKline and receives honoraria, is a board member of the American Partnership for Eosinophilic Diseases (APFED), holds equity in Immune Design Corporation, is a founder of ImmViz, and can receive royalties from Teva/Cephalon; K.M. Leiferman, GJG's wife, is a consultant to Beiersdorf AG and receives honoraria. ADK has no conflicts. JJJ has no conflicts. PFW is consultant to GlaxoSmithKline and receives honoraria.

Author contributions

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cause damage. Eosinophil granule proteins are cationic toxins that are cytotoxic and cytoestimulatory [2]. Further, the eosinophil is significantly more active in its respiratory burst and production of reactive oxygen species than the neutrophil [3]. Recognition of the phlogistic capabilities of the eosinophil has stimulated increased attention to eosinophilic diseases and the mechanisms by which eosinophils damage tissues [2]. In particular, bronchial asthma is frequently associated with eosinophilia, and agents able to reduce eosinophils are presently under evaluation for their effects in asthma. Such medications include a series of monoclonal antibodies that reduce the number of eosinophils in blood and tissues. A question can be raised whether eosinophil depletion has inimical consequences. Here, we discuss information on the consequences of reducing the numbers of eosinophils in animals and in patients. Eosinophil deficiency can be regarded as having several origins: first, as a spontaneous occurrence in human diseases; second, as a result of genetic manipulations in experimental animals; and third, as an effect of pharmacological agents specifically designed to reduce eosinophil numbers. These categories will be discussed with particular attention to the consequences of eosinophil deficiency.

Eosinophil Deficiency in Patients

Patients with eosinophil deficiency fall into several categories: (i) associated with immune deficiencies, especially thymoma, (ii) the combination of eosinophil and basophil deficiency, and (iii) in the setting of common allergic diseases, especially urticaria and asthma. The last patients are remarkable because of the apparent absence of other associated diseases. These cases argue that eosinophil deficiency itself is benign (aside from the associated immune deficiencies and allergic diseases) and that the absence of the eosinophil for long periods of time does not confer any clinically distinctive consequences. However, we do not know whether these patients traveled to tropical climates where they might have been exposed to helminthic diseases.

Eosinophil deficiency associated with immune deficiency and thymoma

The first report of eosinophil absence by Good and Varco in 1955 described a 58-year-old man with a benign thymoma, consisting of thymocytes and thymic reticulum cells, in association with agammaglobulinemia (as judged by serum protein electrophoresis) [4]. Analyses of the bone marrow and peripheral blood failed to reveal eosinophils; in contrast, the patient had a normal number of blood basophils. He had a normal level of 17-hydroxycorticoids and responded with an appropriate rise in levels after stimulation with adrenocorticotrophic hormone (ACTH). His clinical course was characteristic of patients with agammaglobulinemia with repeated bouts of pneumonia. Eosinophils were present in normal numbers in the blood and bone marrow of six other study patients with agammaglobulinemia. The following year another patient with a benign thymoma, agammaglobulinemia, marked neutropenia, and absence of eosinophils from the bone marrow was reported [5]. Subsequently, Waldmann et al. [6] in 1967 reported in abstract form on 85 patients with thymoma and noted that five of 10 patients with thymoma and hypogammaglobulinemia had complete absence of marrow and circulating eosinophils. Jeunet and Good summarized findings in 20 patients with thymoma and hypogammaglobulinemia and found that four showed eosinopenia or complete absence of eosinophils [7]. The discussion after presentation of these results concluded that the patients lacking eosinophils reported by Jeunet and Good [7] and those reported by Waldmann et al. [6] likely represented the same abnormality. However, in neither case was the mechanism of the eosinophil deficiency explored further. Furthermore, the short observation period reported precluded demonstration of either persistent eosinopenia or characteristic events related to eosinophil deficiency that may occur over time. The possibility that thymoma is a

consequence of eosinophil deficiency seems remote, especially because this association has not occurred in other patients with eosinopenia or in mice devoid of eosinophils.

Eosinophil deficiency and dysgammaglobulinemia

A summary of a patient with absence of eosinophils is presented by Bass and Beeson in their 1977 book on the eosinophil, and the information was given by Dr. Patricia Charache of the Johns Hopkins Hospital [8]. The patient was a 42-year-old woman with complete absence of eosinophils in blood and bone marrow despite repeated examinations. She showed reduced IgG and IgA, and IgM had risen to 1620 mg per 100 ml. The patient had suffered numerous pyogenic infections and had multiple drug allergies, urticaria, anaphylaxis, asthma as well as autoimmune hemolytic anemia and pernicious anemia.

Eosinophil and basophil deficiency

In 1977, Juhlin and Michaelsson reported a patient lacking eosinophils and basophils [9] with a history of severe respiratory infections with sinusitis and otitis. At age 22, he became completely bald and acquired hemolytic anemia. At age 34, tuberculosis was discovered. He also had warts covering most of his hands and forearms as well as large anal condylomas. At age 47, he presented with *Salmonella* gastroenteritis, and despite treatment, bacterial cultures remained positive for 5 years. He developed mumps at age 50 and scabies at age 51. No eosinophil or basophil leukocytes had been reported in differential blood counts from 1950 to 1976; other cell lineages were normal. He was IgA deficient and had an IgE level <1 international unit per milliliter. The Coombs direct test was positive, indicating the presence of an erythrocyte autoantibody. A bone marrow biopsy showed no eosinophil or basophil leukocytes; a normal number of mast cells were present. Blisters induced by cantharidin application failed to show eosinophils or basophils; in healthy subjects, both cells were found. Incubation of the patient's plasma with normal eosinophils and basophils did not result in destruction or decrease in their numbers; however, degranulation was observed. In their discussion, the authors state that the main clinical features were repeated infections, asthma, vasomotor rhinitis, and hemolytic anemia and that all of these had previously been recorded in IgA deficiency.

In 1988, Juhlin and Venge [10] reported a 71-year-old woman with chronic urticaria and vitiligo who lacked eosinophils and basophils in the blood, bone marrow, and skin. Repeated differential leukocyte counts from 1985 until 1987 failed to demonstrate eosinophils or basophils. Blood eosinophils were not detected even after counting several thousand leukocytes using a Technicon cell counter. Serum IgE was undetectable; the other immunoglobulins were normal. Staining of the patient's leukocytes revealed no storage or secreted forms of the eosinophil cationic protein. The mechanisms responsible for the eosinophil deficiency in this case are unclear.

Subsequently, a case of basophil and eosinophil deficiency was discovered in a 55-year-old man with a history of recurrent bacterial and viral infections in association with hypogammaglobulinemia and benign thymoma. This patient lacked eosinophils in both peripheral blood and bone marrow. The authors speculated that abnormal suppressor T-cell function might mediate this patient's findings [11].

Eosinophil deficiency in allergic diseases

In 1962, Forssman and Korsgren reported a remarkable patient with severe asthma and absence of eosinophils [12]. The patient was 74 years old and had suffered from asthma since age 20. She had a normal leukocyte count, but eosinophils were absent. During a five-month period, 31 analyses of peripheral blood were performed, both while the patient was

well and during asthma attacks, and all failed to show eosinophils. Sputum eosinophils were also absent. The patient died during a prolonged bout of asthma, and autopsy failed to show eosinophils in the spleen and liver or in inflamed areas of the lung. In contrast, neutrophils and plasma cells were present in the inflamed areas. The patient's parents were cousins, and 24 of their descendants were living; 21 were examined for blood eosinophils, and although some had low counts (80, 40, and 20 eosinophils per mm³ in grandchildren of the patient), the others had blood eosinophils in the normal range. The patient also failed to show basophils on two differential blood counts reported, and, although the absence of basophils was not commented on in this report, the patient may have had an absence of both eosinophils and basophils.

A very early report in the Polish literature presents the case of a 28-year-old woman with asthma, who also lacked eosinophils [13]. This patient suffered from urticaria and drug fever, and eosinophils were not detected on repeated examination. Total absence of eosinophils was observed in a 45-year-old woman with a 25-year history of episodic urticaria and rhinitis [14]. Fourteen total eosinophil counts over 2 1/2 years failed to reveal eosinophils. Other than the absence of eosinophils and the occurrence of urticaria, the patient was well. Immunoglobulins and complement proteins were present in normal quantities, and the patient had evidence of IgE antibody to environmental allergens. Eosinophils were not seen in nasal smears during episodes of rhinitis, and a bone marrow biopsy failed to show mature eosinophils or definite eosinophil precursors. The major basic protein was not detected in the patient's serum by immunoassay. The patient's serum caused a 30% reduction of eosinophils from normal individuals associated with release of β -glucuronidase; this reduction was dependent on the presence of fresh serum (a source of complement) and was abolished by treatment of the serum with solid-phase anti-human IgG. The results are consistent with IgG antibody-mediated eosinophil cytotoxicity (presumably leading to the absence of eosinophils). The same research group reported a second patient lacking eosinophils, and this patient suffered from asthma without other maladies [15]. Peripheral blood mononuclear cells from both patients were cultured in the presence of phytohemagglutinin-stimulated leukocyte media and produced eosinophil colonies comparable in number and form to those from control subjects. Transmission electron microscopy suggested the presence of granule cores. When plasma from the patients was included in the cultures, eosinophil colony formation was suppressed by approximately 75% by plasma from patient 1 and by 90% by plasma from patient 2. The authors concluded that these patients are analogous to patients with autoimmune pure red cell aplasia mediated by IgG against erythroid precursors [16].

Yet another association between eosinophil deficiency and allergic disease is a report of a 59-year-old patient who suffered from drug-induced agranulocytosis and, after recovery, showed an absence of eosinophils in blood and bone marrow for the following 8 years [17]. Basophils were present in normal numbers in peripheral blood. Remarkably, bone marrow mononuclear cells formed eosinophil colonies in vitro, and inclusion of the patient's serum in the growth media did not inhibit either total colony or eosinophil colony formation.

Frequency of eosinophil deficiency in patients

Eosinophil deficiency was studied in 24 300 patients at the University of Pittsburgh in the mid 1980s [18]. Differential counts of 100 leukocytes were performed manually, and only patients with normal total leukocytes were included. Patients with reduced eosinophils were reanalyzed on 10 separate occasions, so that a 1000-cell differential was performed. If chemotherapy for cancer was given, the patient was excluded from analysis. Eosinopenia, defined as no more than one eosinophil seen on ten or more differential counts, was present in 24 of the 24 300 patients. Twenty of the 24 patients were receiving glucocorticoids, and

the remaining four suffered from serious organic illness or were receiving other drugs. Overall, the study failed to find any clear-cut case of idiopathic eosinopenia. The authors concluded that in all but one of the patients, administration of glucocorticoids or serious organic illness could explain eosinopenia; the one exception was a severely depressed patient being treated with imipramine.

Animals lacking eosinophils

Eosinophils can be ablated by treatment of guinea pigs with antiserum to eosinophils [19], and for short periods, days to a week or two, the guinea pigs are healthy, and eosinophils are absent from blood and tissues. These animals were not susceptible to enhanced manifestations of hypersensitivity reactions [20] although they did appear to demonstrate increased susceptibility to a helminthic infection [21].

Extensive studies in mice [22] and subsequently in non-human primates [23] using anti-IL-5 monoclonal antibodies to ablate eosinophils showed that the virtual absence of circulating eosinophils had no adverse effects on the health and longevity of these animals, even when the antibody intervention was maintained for extended periods of time up to 6 months [23].

Mice congenitally lacking eosinophils over their life span have provided us with unprecedented opportunities to determine the eosinophil's contributions to normal health and to biological phenomena. Two strains of mice lacking eosinophils have been developed. One strain was engineered by deletion of a high-affinity GATA-binding site in the GATA-1 promoter. The GATA-1 transcription factor programs immature myeloid cells to three different hematopoietic lineages, namely erythroid cells, megakaryocytes, and eosinophils [24]. Deletion of the GATA-binding site within the gene's promoter led to selective loss of the eosinophil lineage, and these mice have been used to determine the role of the eosinophil in disease models, including asthma [25]. A second strain was created by engineering expression of a cytotoxic protein with a promoter fragment from the gene for eosinophil peroxidase [26]. A transgene, including the diphtheria toxin A chain open-reading frame (that interferes with protein synthesis), was constructed to induce disruption of eosinophil production. The resulting transgenic mouse strain, referred to as PHIL, lacks eosinophils, but all other hematopoietic lines are intact. The eosinophil deficiency is profound (only one eosinophil was identified in surveys of peripheral blood of 20 animals) and lifelong.

These mouse strains provide an opportunity to determine the contribution of the eosinophil to normal health in a mammal. They have been investigated for almost a decade, and, although the mice have been lodged in animal quarters and thus not in the wild, they have been exposed to varying degrees of cleanliness (i.e., random exposures to numerous mouse infectious agents, including helminthic infections). Yet, they have not displayed significant differences in pathogen-mediated responses relative to wild-type mice. Even defined studies infecting these eosinophil-less mice with *Schistosoma mansoni* [27], *Strongyloides stercoralis* [28], and *Trichinella spiralis* [29] have failed to suggest a defect in the animal's host defense. Indeed, no differences were observed in the infective cycle of these parasites (i.e., worm burden) relative to wild type. Interestingly, the studies of *Trichinella* did reveal that eosinophils appeared necessary to limit the inflammation occurring when this parasite attempts to take up residence in the skeletal muscle. Surprisingly, host defense eosinophil activities evidently are exploited by the parasite to continue its life cycle! The eosinophil-less strains of mice also display only nominal changes in immune and physiological responses compared to wild-type mice. For example, perturbations in allergen-mediated responses [25, 26, 30, 31], bone marrow plasma cell accumulation [32], and adipose tissue glucose metabolism [33] have been reported, but these small changes have had limited impact on the animal's biochemistry/physiology at homeostatic baseline. In addition,

eosinophil-less mice have not spontaneously developed carcinomas or other malignant tumors (J. J. Lee, unpublished). Studies of the role of eosinophils in tumor genesis support both antitumorigenic effects [34] and protumorigenic effects [35]. Therefore, presently the role of the eosinophil in tumor genesis is controversial. Overall, the eosinophil-deficient mice appear to display no overt changes in health, fecundity, ability to nurse, and vitality relative to eosinophil-sufficient wild-type animals with the exception of not having this lineage as a product of the bone marrow. Furthermore, these observations suggest that while eosinophils appear to have contributory roles to a wide range of processes, they alone are not required for the maintenance of homeostasis and that eosinophil-independent pathways of these key physiological events exist that are both overlapping and redundant.

Drugs reducing eosinophils

Since their introduction, glucocorticoids have been known to deplete eosinophils, presumably by interfering with eosinophil-active cytokines at the bone marrow level and by increasing the eosinophils' passage into apoptosis. Administration of high doses of glucocorticoids to patients will essentially abolish eosinophils from both the blood and the tissues. However, the consequences of this reduction are masked by the disease process for which glucocorticoids are administered and by their manifold pharmacological effects. Therefore, whether eosinophil ablation by administration of glucocorticoids produces any distinctive syndrome as a result of eosinophil reduction is unknown.

The discovery that commitment of bone marrow cells to the eosinophil lineage was mediated by IL-5 was an important advance [36–38]. A series of investigations showed that IL-5 is elevated in the blood and in tissues of patients suffering from eosinophil-associated diseases [39–42] and is able to activate eosinophils alone and in concert with other agonists [43] (Fig. 1). These discoveries established IL-5 as an attractive pharmacological target and stimulated testing of monoclonal antibodies to IL-5 that reduce the numbers of eosinophils in the body.

Two monoclonal antibodies to IL-5, mepolizumab [44] and reslizumab [45], are presently in clinical efficacy trials for the treatment of eosinophil-associated diseases. Mepolizumab has been shown to be effective in treatment of patients with PDGFRA-negative, corticosteroid-responsive hypereosinophilic syndrome (HES) [46] and in patients with asthma [47–49]. The spectrum of adverse events observed during treatment of HES did not differ appreciably from those in the placebo arm. Subsequent to the controlled trial [46], mepolizumab was used in an open-label extension trial to determine long-term safety and efficacy, including the effects of prolonged eosinophil depletion, in 78 patients with HES [50]. The mean duration of mepolizumab treatment in patients who received more than one infusion (including prior exposure during the placebo-controlled trial) was 251 weeks (range 4–302 weeks). Although nearly all subjects in the study developed at least one adverse event (AE) during the >5 years of the study, these events were similar in nature and severity to those observed in the placebo-controlled trial. Furthermore, the incidence of AEs adjusted per subject-year declined over the course of the study despite continued suppression of eosinophilia. Three subjects developed serious adverse events that were felt by the investigator to be possibly related to mepolizumab, including one death due to angioimmunoblastic T-cell lymphoma with dysproteinemia (AILD) in a patient known to have a T-cell clone prior to enrollment in the trial. Seven patients developed neoplasms: prostate cancer and basal cell carcinoma in two subjects each, mycosis fungoides, multiple myeloma, and AILD in one patient each. Five patients developed nonallergic immune-mediated disorders: rheumatoid arthritis, polymyalgia rheumatica, temporal arteritis, lichen planus, and autoimmune thrombocytopenia. Glucocorticoid tapering resulted in the development of severe adrenal insufficiency in two subjects. One patient became pregnant

twice during the study. The first pregnancy was electively terminated, and the second resulted in the birth of a healthy neonate.

Overall, the reported adverse effects in the mepolizumab open-label extension trial likely reflect the long duration of this study, preexisting end-organ damage by eosinophils, and the reduction (and discontinuation) of prednisone. However, because of the absence of a control group of comparably selected placebo-treated HES patients, it is impossible to completely exclude the possibility that reduced eosinophil numbers contributed to the observed adverse effects. Furthermore, because anti-IL-5 antibody therapy profoundly reduces the numbers of blood and tissue eosinophils, but does not deplete them completely, treatment with these agents is not entirely comparable to the mouse models and patients described above. Although larger studies will be necessary to confirm the lack of excess risk of neoplastic, autoimmune or infectious diseases in patients treated with these agents, the results to date do not suggest a major safety concern.

Reslizumab® has been employed in fewer clinical studies, and therefore, less information is available [51]. Nonetheless, our current information suggests that it is not associated with any remarkable adverse events.

The last monoclonal antibody being tested for the treatment of eosinophil-associated diseases is benralizumab [52]. This antibody is directed against the alpha chain of the interleukin-5 receptor (CD125). Presently, our information about this drug is limited. Both eosinophils and basophils possess CD125, and benralizumab depletes both cells. Preliminary information of the adverse effects of this monoclonal antibody [53] is insufficient to determine whether any distinctive adverse events are associated with its use.

Conclusions

The information summarized above suggests that absence of eosinophils from mammals is not associated with any distinctive syndrome or spectrum of adverse events. However, this conclusion must be tempered by the paucity of patients lacking eosinophils and the failure to identify such patients since the 1980s in spite of the use of automated cell counters that perform leukocyte differential counts. The observation that eosinophil-deficient mice do not display any characteristic syndrome or failure of their health is strong evidence that under usual laboratory conditions the eosinophil does not play a critical role in maintenance of well-being of mammals. This conclusion contrasts with neutrophil deficiency, that is typically associated with bacterial infection [54]. Therefore, based on the information from the patients lacking eosinophils and from mice rendered eosinophil deficient, the observations that the monoclonal antibodies to IL-5 are well tolerated appear unsurprising. In particular, the HES patients who have received mepolizumab for as long as 6 years and who have not developed any characteristic set of adverse events attest to the safety of this drug. Furthermore, in many cases, mepolizumab administration to these patients has eliminated their dependence on glucocorticoids and permitted them to live normal lives. Our knowledge concerning the safety of reslizumab and benralizumab is comparatively limited, although the reports of reslizumab treatment of patients with asthma and the hypereosinophilic syndrome suggest that it too is well tolerated [51]. Thus, whereas longer-term data from clinical trials of agents that more potently reduce eosinophil numbers are needed to confirm the lack of effect of eosinophil depletion on neoplasia, infection, and autoimmunity in humans, data to date suggests that current therapies that specifically target eosinophils are safe and have the potential to be widely employed in the treatment of eosinophil-associated diseases.

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Figure 1. Effects of IL-5 on eosinophilopoiesis and eosinophil function

Monoclonal antibodies to IL-5 block all of these functions and thus reduce levels of eosinophils and their activation.