Half-life of IgE in serum and skin: Consequences for anti-IgE therapy in patients with allergic disease

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We present results from clinical studies on plasma infusion done in the late 1970s in patients with hypogammaglobulinemia in which we documented the short half-life of both total and allergen-specific IgE in serum. The development of specific allergic sensitization in the skin of those patients followed by the gradual decrease in sensitization over 50 days was also documented. The data are included here along with a discussion of the existing literature about the half-life of IgE in both the circulation and skin. This rostrum reinterprets the earlier clinical studies in light of new insights and mechanisms that could explain the rapid removal of IgE from the circulation. These mechanisms have clinical implications that relate to the increasing use of anti-IgE mAbs for the treatment of allergic disease. (J Allergy Clin Immunol 2017;139:422-8.)

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It is generally recognized that the half-life of IgE in serum is short (ie, 2-3 days), whereas the half-life of IgG is much longer (23 days).[1] This long half-life of IgG is attributed to the protection of IgG from catabolism by binding to the neonatal Fc receptor (FcRn).[2,3] However, the reason for the shorter half-life of IgE in comparison with other serum immunoglobulins, which also are not protected by FcRn (5-6 days for IgM and IgA), is not clear. Certainly none of our textbooks includes a coherent explanation of the reasons for the rapid removal of IgE from the circulation.[1,4-7]

The original studies on the half-life of IgE were carried out in the early 1970s with radiolabeled IgE.[1] In those experiments it was difficult to exclude the possibility that the labeling procedure influenced IgE metabolism, although similar results were seen with unlabeled and C^{14}-labeled IgE in individual experiments. In addition, the lack of known specificity of myeloma IgE used in the original studies meant that the presence of IgE could not be detected or monitored by using skin testing.

Abbreviations used
FcRn: Neonatal Fc receptor
Gal: Galectin
PK: Prausnitz-Küstner

Here we present results from clinical studies on plasma infusion done in the late 1970s in patients with hypogammaglobulinemia, in whom we documented the short half-life of both total and allergen-specific IgE in serum. The development of specific allergic sensitization in the skin of those patients followed by the gradual decrease in sensitization over 50 days was also documented. These results were only reported in abstract form because we could not adequately explain where the serum IgE went or how it was catabolized. The data are included here along with a discussion of the existing literature about the half-life of IgE in both the circulation and the skin.[8]

This rostrum reinterprets the earlier clinical studies in light of newer developments in the field that could explain the rapid removal of IgE from the circulation. Understanding these mechanisms is of importance given the increasing use of anti-IgE mAbs for the treatment of allergic disease and might have clinical implications related to their use.

PLASMA INFUSIONS FROM ALLERGIC DONORS IN PATIENTS WITH HYPOGAMMAGLOBULINEMIA AND A HEALTHY CONTROL SUBJECT

Studies were performed in 1976 and 1977 on 3 patients with hypogammaglobulinemia and 1 healthy nonallergic control subject.[8,9] At that time, intravenous immunoglobulin had not been developed, and plasma infusions from healthy donors were occasionally used to treat patients with hypogammaglobulinemia.[10] Because the plasma from allergic donors contained IgE and the patients with hypogammaglobulinemia did not have detectable levels of serum IgE at baseline, this allowed the half-life of transferred IgE in the patients' sera to be monitored. Each subject received 1 or 2 units of plasma containing high levels of both total and specific IgE to the grass pollen allergen Lo1 p 1 or the dust mite allergen Der p 1. This allowed specific IgE and IgG antibodies in the circulation to be monitored and the end point sensitivity to these allergens in the skin to be assessed. For detailed methods, see the Methods section in this article's Online Repository at www.jacionline.org.

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In the patients with hypogammaglobulinemia who lacked detectable total IgE, antigen-specific IgE, and antigen-specific IgG at baseline, levels of total IgE and specific IgE antibody, as well as levels of specific IgG in serum, increased and then decreased rapidly after plasma infusion (Fig 1, *A*,[11] and see Table E1 in this article's Online Repository at www.jacionline.org). Total IgE levels decreased in parallel with specific IgE levels, with a half-life of 2 days. In the control subject, who also initially lacked detectable antigen-specific IgE or IgG and had a baseline total IgE level of 120 U/mL, total IgE levels initially increased and then decreased to preinfusion levels within 4 days (Fig 1, *B*, and see Table E1), suggesting that endogenous IgE production was unperturbed and that the infused IgE had been rapidly cleared from the circulation. Serum specific IgG antibodies to these allergens were also followed and decreased with the expected half-life of IgG (Fig 1 and see Table E1).

Skin sensitization was also monitored after infusion by using quantitative intradermal testing with purified Lol p 1 or Der p 1 serially diluted from 10^{-1} to 10^{-5} μg/mL. Each recipient showed a progressive decrease in skin sensitivity, such that it required approximately 10-fold more Lol p 1 or Der p 1 to produce an 8-mm wheal at each 16-day interval (Table I and see Table E2 in this article's Online Repository at www.jacionline.org). Positive skin test results were demonstrated as late as 50 days after plasma infusion. Prausnitz-Küstner (PK) testing was then performed on the control subject using intradermal injections of serial 2-fold dilutions of donor serum from 1:25 to 1:1600. This method was used to load IgE directly onto skin mast cells and thus does not rely on the diffusion of IgE from the plasma into the skin, as in previous experiments. The subject was tested at 24 hours after injection with serial dilutions of Lol p 1 ranging between 10^{-1} and 10^{-4} μg/mL. Results suggested that a 2-fold decrease in the concentration of IgE antibody injected into the skin increased the quantity of allergen needed to produce an 8-mm wheal by 10-fold (see Table E3 in this article's Online Repository at www.jacionline.org). Thus in combination with the results of the previous plasma infusion experiments, the half-life of IgE in the skin was calculated to be approximately 16 to 20 days.

Plasma infusion studies confirmed the dramatic difference in the half-life of IgE (2 days) and IgG (18-23 days) in the circulation (Table I). Persistence of IgE in the skin for at least 50 days occurred in both immunodeficient patients who previously lacked IgE and in a healthy nonallergic subject. This is consistent with other studies, which have reported persistence of passive sensitization up to 56 days in an IgE-deficient mouse model and up to 70 days after treatment with anti-IgE in patients with allergic rhinitis.[12-14]

DISTRIBUTION OF IgE IN THE BODY

Understanding the distribution of IgE in the body at steady state is of central importance to explain the observed difference in the kinetics of infused IgE in the circulation and skin. Although lymph nodes and bone marrow are thought to be the major sites of IgE antibody production, allergic sensitization is present in all parts of the skin, respiratory tract (nose and lungs), and conjunctivae, as well as in the gastrointestinal tract. This phenomenon reflects normal passage of IgE into the circulation (the vascular compartment), extravasation into the primary and secondary lymphoid tissue and interstitial space (the extravascular compartment), and binding to tissue-resident mast cells distributed throughout the body (the cellular compartment). It is important to note that recent evidence suggests that perivascular mast cells can actively acquire IgE directly from the blood and that this process is not solely dependent on passive diffusion.[15] IgE is also found on the surfaces of circulating basophils, dendritic cells, and Langerhans cells through binding to the high-affinity IgE receptor FcεRI. Although IgE is bound to the low-affinity IgE receptor FcεRII on B cells, monocytes, Langerhans cells, dendritic cells, and eosinophils,[16] these cells likely account for only a fraction of cell-bound IgE because of their low receptor density and lower receptor affinity for IgE.

To address whether the cellular compartment is sufficient to serve as a "sink" for infused IgE, a principal question becomes calculating its capacity for binding molecules of IgE. Circulating basophils capture IgE through binding to FcεRI expressed at the cell surface. There are extensive published data about the numbers of IgE molecules and high-affinity IgE receptors on basophils in the circulation. The number of IgE receptors expressed on basophils varies widely between 6,000 and 900,000 molecules per basophil and correlates with the serum IgE level.[16-18] However, the latest estimates are that the median number of FcεRI receptors is 150,000 per basophil for subjects with a normal serum IgE level.[19] Based on the calculated number of circulating basophils in peripheral blood being 3.1×10^8 cells (see the Methods section in this article's Online Repository for detailed methods), with 150,000 FcεRI receptors per basophil, the number of FcεRI receptors on basophils as a whole is 4.5×10^{13}. Circulating basophils display increasing FcεRI occupancy (from 21% to 95%), which also correlates with the serum IgE level, with a reported 80% to 95% occupancy at a normal serum IgE level of 100 to 200 ng/mL; therefore an estimated 2 to 9×10^{12} unoccupied receptors are found on circulating basophils at steady state.[18]

Surprisingly, there do not appear to have been many serious estimates of the number of mast cells in the body since Paul Ehrlich described these cells in 1878.[20] Ehrlich estimated that there were enough mast cells in the body to make up "an organ the size of the spleen" (approximately 150-200 g). More recent estimates have estimated the mast cells in the body to be "the size of a child's fist."[21] Based on the surface area of the skin, mast cell numbers in the dermis, and average tissue weight and tissue density, it is possible to estimate the total number of mast cells in the human body as approximately 3×10^{11} cells; this is likely an overestimate because of the assumptions used in the calculation (see the Methods section in this article's Online Repository for detailed methods).[22-24]

In contrast to basophils (median diameter, 12 μm), mast cells display a high degree of size heterogeneity (diameter, 8-20 μm),[25] indicating the potential to express lower or higher numbers of FcεRI receptors on the surface (10,000 to 420,000 per mast cell) compared with basophils if the same receptor density is maintained.[26] Unlike basophils, tissue mast cells are not bathed in a milieu rich in IgE. Thus the FcεRI occupancy on mast cells is likely to be lower than in basophils. It is clear that mast cell FcεRI receptors are not fully saturated with IgE and thus have the ability to bind additional IgE molecules, even in allergic subjects. As evidence of this, it is possible to elicit a positive