

Correspondence

Basophil histamine release in patients with chronic spontaneous urticaria: Optimize or minimize

To the Editor:

A recent article by Dr MacGlashan¹ concludes that the “true” incidence of IgE receptor antibody in patients with chronic spontaneous urticaria is less than 10%.¹ Although most studies report an incidence of 25% to 45% positive basophil histamine release, constraints were added to the analysis, including dependence of basophil histamine release of SYK, Bruton tyrosine kinase, and phosphoinositide 3-kinase, which are linked to IgE receptor activation, plus successful desensitization using aggregated IgE. The initial histamine release value of 41% was then decreased to 7%.

There are at least 2 confounding issues with this analysis. Serum levels of purified IgG from patients’ sera yields 2- to 3-fold less histamine release compared with whole serum because of complement activation² during the course of the reaction with release of C5a.³ C5a will not fulfill the constraining criteria, yet the complement activation is IgG dependent² and is prevented when pathogenic IgG is added to C2- or C5-deficient serum. The process was inhibitable by incubation with the α subunit of the IgE receptor,^{2,4,5} IgG-depleted sera were negative, and addition of myeloma IgE to saturate IgE receptors sterically blocks histamine release⁶ by anti-Fc ϵ RI α .

Then there is an issue of sensitivity. Sera were used at a 1:4 dilution or less, whereas we and others assay sera undiluted or at 1:2 dilution. Our incidence of 40% to 45% uses basophils of 2 particular subjects chosen for high releasability and low stable baseline values. Values beyond 15% release were considered positive to avoid potential confounding effects of serum enzymes, histamine in serum (chronic urticaria), bradykinin in serum (produced by clotting), and histamine-releasing cytokines. Pre-dilution of sera plus dilution with reagents might substantially lower the percentage of positive values, even when controlled internally.

Assessment of the activity in sera has gone beyond phenomenology. Histamine-releasing activity was predominantly IgG₁ and IgG₃, which activate complement. No positive result has been obtained with IgG₂ (but one was IgG₄),⁵ and IgA, positive for binding to the IgE receptor by immunoblotting, does not cause

histamine release when purified. Thus binding assays are unreliable^{5,7} as a predictor of function.

The study by MacGlashan¹ further dissects one aspect of the problem, namely the features guiding basophil responsiveness and criteria to assume action through the IgE receptor. This approach is an important addition. However, the studies referenced above are also the only ones that have analyzed serum determinants behind the observed basophil activation. Both approaches are needed to best delineate the role of autoimmune phenomena in patients with chronic spontaneous urticaria, even though cutaneous mast cells would be preferable. Thus although the incidence of histamine-releasing sera could vary from a low of 7% to a high of 45% (or zero using “nonreleasing” basophils), it is my opinion that the histamine release ought to be optimized and not minimized. Specificity might be diminished; however, in our laboratory this has been minimal, and it is well known that most autoantibodies have a low percentage of positive results in healthy subjects.

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