

Correspondence

Basophil secretion in chronic urticaria: Autoantibody-dependent or not?

To the Editor:

A recent study by Vonakis et al¹ presents new, interesting data to indicate that patients with chronic urticaria can be divided into 2 groups based on normal versus diminished responsiveness to anti-IgE. Further search for an explanation revealed abnormalities in Src-homology 2-containing inositol phosphatases (SHIPs) with decreased SHIP1 in anti-IgE responders and increased SHIP2 (and possibly SHIP1) in anti-IgE nonresponders. There was no apparent association of either subgroup with autoimmunity; thus, hyporesponsiveness was not a result of *in vivo* desensitization caused by the presence of a circulating autoantibody. However, neither abnormality explains why hives occur. I would like to call attention to other studies not referenced by the authors that deal with abnormalities in signal transduction. Confino-Cohen et al² found increased expression of the P21 Ras pathway in blood mononuclear cells of patients with chronic urticaria along with diminished expression of the regulatory protein Son of Sevenless (HSOS1). Luquin et al³ also found hyporesponsiveness of basophils to anti-IgE but did not sort out the 2 subgroups found by Vonakis et al.¹ They also found the same basophils to be hyperresponsive to a factor present in serum. That is, sera stimulated basophil histamine release not seen with basophils of normal controls or atopic subjects. Thus, the nature and breadth of abnormality in signal transduction needs further work, but finding abnormalities in so-called *idiopathic urticaria* are on the horizon.

The authors also digress to point out inconsistencies in methodology used to distinguish the subgroups of patients with chronic urticaria now designated idiopathic versus autoimmune, and we would like to clarify this as well. The authors include immunoblot as an assay for antibody to FcεRI in some patients and found no relation to basophil histamine release using patient serum (histamine-releasing activity). We feel it important to note that we have previously reported such immunoblot analysis does not discriminate who does or does not have chronic urticaria and has no utility.^{4,5} RAST assay even with purified IgG anti FcεRI similarly has no validity.⁵ Much of this is a result of IgG₂ anti-FcεRIα that is not functional.⁵ We suspect that the α-subunit bound to a solid matrix cross-reacts with IgG antibody directed to other antigens or to carbohydrates. Thus, the suggestion that anti-FcεRIα occurs with a frequency in “pemphigus vulgaris” (39%), dermatomyositis (36%), bullous pemphigoid (13%), and systemic lupus erythematosus (20%)” similar to that seen in chronic urticaria is not meaningful because these are all figures based on immunoblot analysis.⁶ In fact, the next figure in the article by Fiebiger et al⁶ indicates that the same patients are negative by histamine release assay, whereas a major fraction of the patients with chronic urticaria is positive.

In our hands, normal or atopic subjects are rarely positive in the functional assay. Although the authors

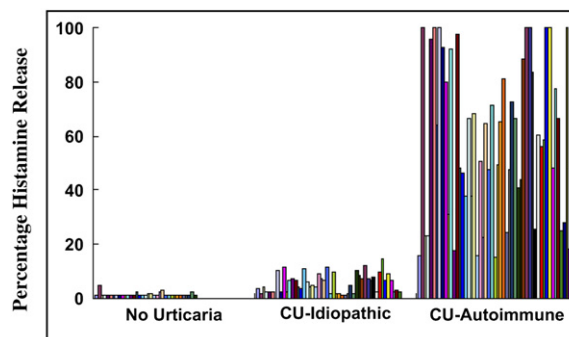


FIG 1. Basophil histamine release in allergic subjects without urticaria and 2-subpopulations of patients with hives. *cu*, Chronic urticaria.

report 4 of 7 positives in normal subjects, we have had no positives in the last 20 control sera we assayed. Further, when we remove the IgG from positive sera, all the basophil-releasing reactivity is in the IgG fraction, and the IgG-depleted serum is then negative. We have not performed such a comparison with the autologous skin test, but there is recent controversy regarding the use of serum versus plasma that will need to be resolved.⁷ Nevertheless, we will shortly report an improved method for assessment of the autologous skin test using serum that has a close relationship to the basophil histamine release assay. The result of the histamine release assay of 35 additional sera with a variety of allergic diagnoses (rhinitis, asthma, insect sting allergy) but not urticaria is shown (Fig 1). A positive test requires at least 15% histamine release. The number of positives is 0 of 35 with mean histamine release of 0.47%. Our last series of chronic urticaria sera had 54 positives of 104 sequentially obtained samples. They are divided into chronic idiopathic urticaria (mean histamine release, 5.63%) and chronic autoimmune urticaria (mean histamine release, 59.26%). A weak histamine-releasing agent may be present in the idiopathic group, which is 10-fold higher than the nonurticaria group and 10-fold less than the autoimmune group.

Allen P. Kaplan, MD^a
Kusumam Joseph, PhD^b

From the Department of Medicine, Divisions of ^aPulmonary, Critical Care, Allergy and Immunology, and ^bRheumatology and Clinical Immunology, Medical University of South Carolina, Charleston. E-mail: kaplana@musc.edu.

Supported by Novartis Pharmaceuticals Corp.

Disclosure of potential conflict of interest: A. P. Kaplan and K. Joseph have received grant support from Novartis Pharmaceuticals.

Editor's note: There is no accompanying reply to this correspondence.

REFERENCES

1. Vonakis BM, Vasagar K, Gibbons SP Jr, Gober L, Sterba PM, Chang H, et al. Basophil FcεRI histamine release parallels expression of Src-homology 2-containing inositol phosphatases in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2007;119:441-8.
2. Confino-Cohen R, Aharoni D, Goldberg A, Gurevitch I, Buchs A, Weiss M, et al. Evidence for aberrant regulation of the p21 Ras pathway in

- PBMCs of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002;109:349-56.
3. Luquin E, Kaplan A, Ferrer M. Increased responsiveness of basophils of patients with chronic urticaria to sera but hyporesponsiveness to other stimuli. *Clin Exp Allergy* 2005;35:456-60.
 4. Kikuchi T, Kaplan A. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001;107:1056-62.
 5. Soundararajan S, Kikuchi Y, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005;115:815-21.
 6. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-Fc epsilon RI alpha autoantibodies in autoimmune-mediated disorders: identification of a structure-function relationship. *J Clin Invest* 1998;101:243-51.
 7. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol* 2006;117:1113-7.

doi:10.1016/j.jaci.2007.05.008