

Basophil Phenotypes in Chronic Idiopathic Urticaria in Relation to Disease Activity and Autoantibodies

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TO THE EDITOR

The paper by Eckman *et al.* (2008) offers new insights into the behavior of circulating basophils in chronic “idiopathic” urticaria. The authors detected autoantibodies against the high-affinity immunoglobulin E (IgE) receptor (FcεRI) or IgE in the majority of patients and healthy controls by a sensitive immunoenzymatic assay. They showed that the levels remained steady during follow-up and did not fall significantly after disease remission. They conclude that unknown serological factors or primary basophil abnormalities may be important in the pathogenesis of the disease. They imply this provides further evidence that anti-FcεRI and anti-IgE autoantibodies are not pathogenic. However, there is a large and increasing body of clinical and laboratory evidence in favor of an autoimmune subset of patients with chronic urticaria who would previously have been labeled idiopathic. The term autoimmune urticaria has been in use for almost a decade (Grattan and Francis, 1999). Functional autoantibodies that release histamine from healthy donor basophils have been demonstrated in at least 30% of chronic “idiopathic” urticaria patients since 1991 (Grattan *et al.*, 1991). Unfortunately, the histamine releasing activity of sera was not assessed by Eckman *et al.*, so it is not possible to compare their results directly with those of others who have reported functional autoantibodies using basophil or mast cell assays. The limitations of serum-induced basophil histamine release are well recognized but superiority of the immunoenzymatic assay has not been shown in parallel studies. Use of both tests would clarify whether they define the same population of chronic urticaria patients or not.

Using the etiological term “idiopathic” implies that none of the patients had an autoimmune etiology and this is at variance with current international opinion. The alternative term ordinary urticaria (Grattan and Humphreys, 2007) makes no such assumptions about etiology as it describes a clinical pattern of disease presenting with continuous spontaneous weals, with or without angioedema but it does exclude physical urticarias, angioedema without weals, urticarial vasculitis, contact urticaria, and auto-inflammatory syndromes presenting with urticaria for which there is currently no evidence of an autoimmune etiology.

The key to understanding the etiology of urticaria is what stimulates degranulation of cutaneous mast cells, rather than circulating basophils, as they are widely acknowledged to be the primary effector cell in almost all clinical patterns of urticaria. Local events at the level of the mast cell rather than in the blood may provide answers. Histamine releasing activity of chronic urticaria sera on mast cells from newborn foreskin has been demonstrated (Niimi *et al.*, 1996; Ferrer and Kinet, 1998). The same sera released histamine from healthy donor basophils. Studies of the delayed phase response of IgE-mediated hypersensitivity reactions have shown that basophils are important in the development of chronic allergic inflammation in a murine model (Mukai *et al.*, 2005). The presence of basophils has been shown in cutaneous infiltrates in urticarial wheals (Ying *et al.*, 2002) but their role is less clear. It is therefore unconvincing to ascribe a basophil functional abnormality as “a primary

feature of the pathogenesis associated with chronic urticaria”.

Anti-IgE autoantibodies were detected by immunoassay in chronic urticaria, atopic dermatitis, and healthy controls (Quinti *et al.*, 1986) several years before they were shown to have *in vitro* functional properties in chronic urticaria (Grattan *et al.*, 1991) so it was perhaps unsurprising that anti-FcεRIα autoantibodies have been found in healthy controls (Horn *et al.*, 1999) and other autoimmune disorders (Fiebiger *et al.*, 1998). Current evidence strongly suggests that the functionality of these autoantibodies depends on additional factors including co-activation of mast cells by complement (Ferrer and Nakazawa, 1999) and the subclass of IgG (Soundararajan *et al.*, 2005). Neither of these were examined by Eckman *et al.* A hypothesis of conditional autoimmunity (Horn *et al.*, 2001) proposes that functionality of anti-FcεRIα autoantibodies depends on skin mast cell receptor occupancy by IgE under the control of local environmental influences, with the implication that degranulation depends both on the soil (the cutaneous mast cell) and the seed (the presence of autoantibodies, with or without relevant cofactors).

The local tissue concentration of autoantibody rather than circulating plasma concentrations may determine whether sufficient receptors can be cross-linked or not to initiate degranulation.

The subjects in the study of Eckman *et al.* with profound basopenia who were labeled CIU-unclassified because there were insufficient basophils to assess anti-IgE responsiveness probably correspond to the subgroup of chronic urticaria patients with functional histamine releasing autoantibodies and

Abbreviation: IEMA, immunoenzymatic assay

absent circulating basophils identified previously (Grattan et al., 1997). It is therefore of interest that the mean level of anti-FcεRIα detected by immunoenzymatic assay was substantially and significantly higher than other chronic urticaria patients with enough circulating basophils to assess responsiveness to anti-IgE. This would support the possibility that the level of autoantibody may be a factor in determining functionality. Testing chronic urticaria basophil responsiveness to a monoclonal anti-FcεRIα in addition to anti-IgE would seem appropriate in the context of defining basophil phenotypes in a disease that is believed to be caused by both. Debate about the importance of autoantibodies in urticaria pathogenesis will no doubt continue but it is important not to be side-lined from the autoimmune hypothesis on the strength of work that only shows part of a much wider portfolio of clinical and laboratory evidence supporting the concept.

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Response to Grattan et al.

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TO THE EDITOR

We appreciate the comments by Dr Grattan and Dr Brozova to our article (Eckman et al., 2008) concerning blood basophil phenotypes and their relationship to autoantibodies in patients with chronic idiopathic urticaria (CIU). However, we would like to respond to their comments.

Grattan stated, “Unfortunately the histamine releasing activity of sera was not assessed by Eckman et al...” We have three main concerns with histamine-releasing activity (HRA). First, the reliance on a normal basophil donor is

a major concern given the literature's demonstration of significant differences in HRA results depending on who is chosen as the basophil donor (Grattan et al., 1991; Kikuchi and Kaplan, 2001). Second, the reagents and methods are not standardized, and they differ with regard to the basophil isolation method, the ratio of CIU sera to donor basophils, the use of IL-3 as a basophil enhancer, and the interpretation and variability (poor replication) of a positive results (Vonakis and Saini, 2005). Furthermore, verification of HRA's specificity for autoantibodies by preincubating a CIU

patients sera with soluble FcεRIα and observing a reduction in HRA are sparse and shown for only selected datasets. HRA's specificity is shown by preincubating the IgG fraction of CIU patients sera with soluble FcεRIα and then showing a subsequent reduction in HRA in comparison to a sham control. Hide et al. only show this inhibition in 4/17 patients, Kikuchi and Kaplan only show inhibition in 7/111 patients, and Fiebiger et al. in 9/50 patients (complete sera; IgG fraction not isolated; Hide et al., 1993; Fiebiger et al., 1998; Kikuchi and Kaplan, 2001). The inhibition profiles in these studies are significantly different. In addition, Fiebiger showed 9 HRA-negative/

Abbreviation: CIU, chronic idiopathic urticaria; CIU R, CIU responder; CIU NR, CIU non-responder; HRA, histamine releasing activity