

Chronic urticaria and use of statins

To the Editor,

I read with interest the consensus guidelines on chronic urticaria by Steven KW Chow and colleagues [1] but have reservations with the statement that angiotensin converting enzyme inhibitors (ACEIs) should usually be avoided in chronic urticaria with or without angioedema. Although the EAACI/GA²LEN/EDF/WAO position paper does allude to the fact that ACEIs come second to non-steroidal anti-inflammatory drugs in eliciting and aggravating urticaria [2], the level of evidence to support this statement was not provided. Yet another consensus statement on the management of urticaria by Godse KV et al. [3] does not mention ACEIs as a possible trigger for urticaria.

The incidence of urticaria to the ACEI drug enalapril was reported at 0.3% (32 of 12,543 patients) in a 12 months post-marketing surveillance study, but the report also mentioned that this necessitated withdrawal of the drug only in 5 cases and 6 other cases of urticaria were not attributed to enalapril [4]. Dr. Pfeiffer [5] referenced the above paper in a correspondence to a review by Dr. Allen P Kaplan [6] on chronic urticaria and angioedema in *The New England Journal of Medicine*, but that ACEI drugs can elicit urticaria was not entirely accepted by Dr.

Kaplan in his reply [5].

A more commonly prescribed class of drugs that have a higher incidence of urticaria are lipid lowering statins. Manufacturers of statin drugs report the combined incidence of rash and allergic reactions to be 7.7% (data on file; Parke-Davis, USA) that is much higher than that for ACEIs [see Table 1 for published reports; MEDLINE from PubMed, EMBASE, BNI, CINAHL with search terms: 'statin', 'urticaria']. A recently published 10-year study from the French Pharmacovigilance Database reported 7.3% of systemic lupus erythematosus cases associated with statin use [with reporting odds ratio at 1.67 (95% CI 1.02-2.74)] [7]. The mechanisms of statin-induced (autoimmune) urticaria/systemic lupus erythematosus may be related to (1) the proapoptotic nature of the drug (at least the second generation statins) that may release otherwise inaccessible nuclear antigens and subsequent generation of autoantibodies; and (2) statins have been shown to promote a shift from T helper 1 (Th1) to Th2 immune responses that leads to B-cell reactivity and the production of pathogenic autoantibodies [8-10].

With several consensus guidelines from various clinical groups recommending prophylactic statin therapy, clinicians should be aware of all side effects with these widely prescribed medications.

Table 1. Reports of statin use with development of urticaria

| Description of cases | Implicated statin & management | Reference |
|---|--|-------------------------------------|
| 54-year-old man | Lovastatin 20 mg daily ∼ 9 months; rash resolved 7 days after stopping statin (ANA 1:320) | Chest 1999;115:886-9. |
| 49-year-old man | Pravastatin 40 mg daily ∼ 4 years; rash resolved one month after stopping statin (ANA 1:80) | |
| 77-year-old woman | Pravastatin 10 mg daily ∼ 3 years; rash resolved one month after stopping statin (ANA 1:160) | |
| 73-year-old man | Pravastatin 10 mg daily ∼ 3 years; rash resolved 12 days after stopping statin (ANA 1:80) | |
| 40-year-old woman | Atorvastatin 10 mg daily; dermatographism with urticaria after one month; resolved one month after stopping statin and with antihistamines | J Am Board Fam Pract 2001;14:148-51 |
| 59-year-old woman | Atorvastatin 10 mg daily; strong positive drug skin test –at 30 min; urticaria resolved 10 days after stopping statin | Allergy 2002;57:366 |
| Rheumatoid arthritis patients with chronic severe itching | 34 of 104 patients (32.7%) with chronic severe itching; risk factors statin use ($p = 0.018$), NSAID use ($p < 0.001$) | Allergy 2008;63(s88);114 (P713) |

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There is more than sufficient evidence to support the contributory role of ACEIs in urticaria and angioedema. Kindly see references below. ACEIs are among the many medications known to cause isolated angioedema. Our stated position in the issue is consistent with that in many other published consensuses.

Thank you.

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Dr. Chow replies:

To the Editor,

I refer to the letter regarding ACEIs and urticaria with or without angioedema.

My reply is as follows:

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