

CORRESPONDENCE



Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose

TO THE EDITOR: Chung and colleagues (March 13 issue)¹ found IgE antibodies to galactose- α -1,3-galactose in pretreatment serum samples from 17 of 25 patients who had hypersensitivity reactions to cetuximab, whereas IgE antibodies were found in only 1 of 51 patients who did not have a hypersensitivity reaction. If, as suggested, the presence of such antibodies in pretreatment samples is predictive of anaphylaxis, pretreatment testing would help in minimizing the risk of anaphylaxis associated with cetuximab. It would be important to know whether skin testing was done in the study patients, and if so, whether the results were concordant with the presence of IgE antibodies to cetuximab.

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1. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med* 2008;358:1109-17.

the low affinity of binding of antibodies to uncharged carbohydrates.² We believe that a blood test for IgE specific for the oligosaccharide on cetuximab would be the easiest and most reliable screening test. Any plan for screening will also have to factor in the geographic area that needs to be covered.³

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1. Commins SP, Lucas S, Hosen J, et al. Anaphylaxis and IgE antibodies to galactose-alpha-1,3-galactose (alphaGal): insight from the identification of novel IgE antibodies to carbohydrates on mammalian proteins. Presented at the American Academy of Allergy, Asthma, and Immunology Annual Meeting, Philadelphia, March 14-18, 2008. abstract.

2. Macher BA, Galili U. The Gal α 1,3Gal β 1,4GlcNAc-R (α -Gal) epitope: a carbohydrate of unique evolution and clinical relevance. *Biochim Biophys Acta* 2008;1780:75-88.

THE AUTHORS AND A COLLEAGUE REPLY: The patients with cancer had been treated with cetuximab before we were aware of the relevance of IgE antibodies to galactose- α -1,3-galactose and were not available for skin testing. Some of the patients who presented with delayed anaphylaxis after eating beef, pork, or lamb have undergone skin testing with mammalian proteins and cetuximab itself.¹ Despite skin-prick testing with 100 μ g of cetuximab, the wheal size was not predictive of the serum titer IgE antibodies to galactose- α -1,3-galactose. The absence of significant skin responses to similar testing in patients receiving cetuximab (Kulczycki A: personal communication) may reflect

THIS WEEK'S LETTERS

- 2735 **Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose- α -1,3-Galactose**
- 2736 **Vasopressin in Septic Shock**
- 2738 **Five Genetic Variants Associated with Prostate Cancer**
- 2741 **Genetics of Warfarin Response**
- 2744 **Acute Pulmonary Embolism**
- 2746 **Imatinib as a Possible Cause of Severe Rhabdomyolysis**

3. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North

Carolina and the association with atopic history. *J Clin Oncol* 2007;25:3644-8.

Vasopressin in Septic Shock

TO THE EDITOR: The results of the Vasopressin and Septic Shock Trial (VASST), reported by Russell et al. (Feb. 28 issue),¹ do not fully support the conclusion that “low-dose vasopressin did not reduce mortality.” The secondary hypothesis that “the beneficial effects of vasopressin would be more pronounced . . . in the subgroup of patients with more severe (as opposed to less severe) septic shock” was clearly refuted. However, in the vasopressin-treated patients with less severe shock, the 25.8% relative reduction in 28-day mortality is both striking and significant. Since the subgroup stratification was done prospectively, this result appears to be more than merely “hypothesis generating.” Moreover, rather than being surprising or paradoxical,² these results are consistent with our recent findings in isolated arteries, in which the “beneficial” synergistic effect of low-dose vasopressin (on norepinephrine responsiveness) was preserved in conditions mimicking less severe septic shock but was eliminated in a model of more severe shock.³ Accordingly, survival effects in the subgroups of patients in VASST parallel our results in vessels and appear to support our hypothesis that “larger amounts of vasopressin may be needed in patients with more severe septic shock.” That hypothesis should be considered in future clinical trials.

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1. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;358:877-87.
2. Parrillo JE. Septic shock — vasopressin, norepinephrine, and urgency. *N Engl J Med* 2008;358:954-6.
3. Leone M, Boyle WA. Decreased vasopressin responsiveness in vasodilatory septic shock-like conditions. *Crit Care Med* 2006;34:1126-30.

TO THE EDITOR: We believe that the study population in VASST was unlikely to benefit from vasopressin. The rationale for vasopressin therapy in

vasodilatory shock is to reduce high, potentially toxic, catecholamine dosages to ranges with a reasonable benefit-risk ratio. A cohort study indicated that 0.6 μ g of norepinephrine per kilogram of body weight per minute might constitute such a critical limit.¹ Since the mean norepinephrine dose at randomization in VASST was 0.27 μ g per kilogram per minute, the risk of catecholamine toxicity may have been low, and thus, few advantages could be expected from lowering catecholamine dosages. In contrast, patients more likely to benefit from vasopressin-mediated decreases in catecholamine dosages — such as severely sick patients who were expected to die within 12 hours, patients in unstable condition who were receiving vasopressin before study enrollment, and patients with high-risk cardiac disease who were sensitive to catecholamines — were excluded from the trial. According to one report, 0.067 IU of vasopressin per minute resulted in better hemodynamic stabilization than 0.033 IU per minute.² This could explain why no survival benefit was achieved with 0.01 to 0.03 IU of vasopressin per minute in patients requiring more than 15 μ g of norepinephrine per minute.

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1. Luckner G, Dünser MW, Jochberger S, et al. Arginine vasopressin in 316 patients with advanced vasodilatory shock. *Crit Care Med* 2005;33:2659-66.
2. Luckner G, Mayr VD, Jochberger S, et al. Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock. *Crit Care Med* 2007;35:2280-5.

TO THE EDITOR: A mortality-end-point study of vasopressin in patients with septic shock has been of interest to us since our finding that such patients are vasopressin-deficient.¹⁻³ However, the study by Russell et al. showed no benefit of vasopressin. Negative studies discourage further research, but since it is likely that vasopressin was in fact beneficial in some patients, we believe that there is a need for additional trials. As the authors