

Reply to Y. Pointreau et al

We thank Pointreau et al¹ for their comments on our recently published article reporting the case of a fatal infusion reaction to cetuximab, which occurred in a 63-year-old patient with metastatic colorectal cancer.² In this report, after documenting the dramatic sequence of events leading to the death of the patient, we pointed out that the mechanisms underlying the development of hypersensitivity reactions to cetuximab still need to be elucidated and that no definitive data exist as to the exact role of factors such as atopic history or previous hypersensitivity. Also, we stated that the early occurrence of symptoms would argue against the causative role of an immunoglobulin E (IgE)–mediated process.

In their letter, Pointreau et al¹ acknowledge that infusion reactions to cetuximab represent a serious clinical problem (they mention two fatal reactions that occurred in their center over the past 2 years) and admire our desire to communicate the potential life-threatening consequences after the use of this anti–epidermal growth factor receptor monoclonal antibody. However, they express astonishment regarding our statement that the pathogenesis of hypersensitivity is a critical, still unsolved issue. Rather, they affirm that anaphylaxis to cetuximab is the result of antidrug IgE antibodies present patient serum before therapy.

To support their view, Pointreau et al¹ quote an article by Chung et al³ published in the *New England Journal of Medicine* in 2008. In this article, the authors investigated the hypothesis that IgE antibodies directed against the oligosaccharide galactose- α -1,3-galactose (α 3Gal), present in the Fab portion of the cetuximab heavy chain, could mediate hypersensitivity reactions to the drug. They analyzed the pretreatment serum samples from 76 patients with head and neck and colorectal cancers treated with cetuximab and found that 17 of 25 patients who had developed a hypersensitivity reaction tested positive for IgE antibodies against cetuximab. On the other hand, only one of 51 patients who had not experienced an infusion reaction was demonstrated to have a serum positive test for such antibodies. The difference was statistically significant ($P = .03$).

However, this study has some objective limits that we think are worth discussing. First, the study does not demonstrate that hypersensitivity to cetuximab is consistently associated with the presence of IgE antibodies against α 3Gal in pretreatment serum. Indeed, only 68% of the patients in the study who had experienced an infusion reaction had a positive serum test.³ Then, a different pathogenic mechanism other than the proposed IgE-mediated process would likely explain the reactions occurring in the remaining quite sizeable 32% of patients.

Second, the study by Chung et al³ was an analysis restricted to a US population, and it included only patients who were treated at US centers located in areas with a remarkably high reported frequency of cetuximab-related reactions and history of hypersensitivity to mammalian meat.³ Given the geographic variability in both pattern of immune background and degree of cetuximab tolerability as regis-

tered in different states across the United States,⁴ the results of the study might not be confirmed in a differently selected population. To our knowledge, a similar study investigating the potential correlation between the presence of IgE antibodies against α 3Gal and the development of infusion reactions to cetuximab has never been conducted in a European population.

Furthermore, the limited sample size and retrospective design of the study could have introduced some important biases affecting the final results. It is worth noting that the case definition and grading of hypersensitivity as retrospectively interpreted by the authors (and used for the statistical analysis) significantly differed from those of the original reports by the treating physicians.³

The characteristics of the reaction we reported² do not even seem to fit the clinical frame of the IgE-mediated mechanism postulated by Pointreau et al.¹ Indeed, the absence of a history of hypersensitivity to mammalian meat, timing of reaction, and cascade of clinical events, as dramatically documented in the text and figures of our article, indeed support the idea of an acute respiratory distress syndrome triggered by a multiple cytokine–release process, similar to that previously described after the infusion of rituximab in patients with B-cell chronic lymphocytic leukemia⁵ or the anti-CD28 monoclonal antibody TGN1412 in a phase I trial enrolling healthy young male volunteers.⁶

In conclusion, we think that the issue of identifying the pathogenic mechanism underlying hypersensitivity to cetuximab is far from reaching its conclusion. Additional evidence is needed before it can be claimed that a resolution has been found.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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