

Correspondence

EXCELS study results do not rule out potential cancer risk with omalizumab

To the Editor:

We would like to highlight study design issues that limit the interpretation of the study results presented by the authors of the recent publication “Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab.”¹ The article presents data from the Epidemiologic Study of Xolair Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), a 5-year observational cohort study conducted in patients 12 years or older with moderate-to-severe asthma to evaluate the long-term safety of omalizumab, primarily the risk of malignancy. The authors conclude that the results “suggest that omalizumab is not associated with an increased risk of malignancy.” However, the potential for unmeasured/uncontrolled confounding, the selection biases introduced by the enrollment of “prevalent users” (previously exposed to omalizumab) and the initial exclusion of patients with a history of cancer or a premalignant condition, and the high study discontinuation rate significantly limit the ability of the study to rule out a malignancy risk with omalizumab treatment.

The study was not designed to capture the experience of patients with a history of cancer or a pre-malignant condition, as the authors suggest. The original protocol, which excluded patients who had an increased risk of malignancy or cancer history, was amended only after 56% of the patients had been enrolled. As a result, the inclusion of patients with a cancer history was too low (9.3% in the omalizumab-treated cohort) to sufficiently capture the risk among these patients.

The study’s prevalent user design likely underestimates the cancer risk among patients who had pre-enrollment omalizumab exposure, because the study did not capture pre-enrollment cancer events for most of the subjects. Furthermore, any prevalent users who discontinued omalizumab because of cancer-related adverse events had a lower probability of entering the study compared with continuous users who were cancer free at enrollment (selection bias). This could potentially result in

enrichment of the omalizumab-treated cohort with cancer-resilient patients compared with a new-user cohort. Although Long et al¹ suggest that the consistency of malignancy rates between omalizumab new users and the non-omalizumab-treated cohort provides evidence against the selection bias, the small number of new users (11.5%) is insufficient to make such a conclusion. Therefore, the study was not designed to address the research question that is of primary interest to physicians: What is the malignancy risk for patients who are new users of omalizumab versus those who have never used it? Instead, the study addressed the question: What is the malignancy risk for patients continuing on omalizumab treatment versus those who never start omalizumab?

Finally, the high and differential study discontinuation rates (43.5% of the omalizumab-treated cohort vs 35.2% of the non-omalizumab-treated cohort) make it difficult to estimate accurately the malignancy risk in omalizumab patients because of the missing data.

In summary, because of the limitations in the study design, we believe that a definitive conclusion regarding the risk of malignancy with omalizumab treatment cannot be made on the basis of EXCELS study results.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2014.09.017>