Omalizumab and the risk of malignancy: Results from a pooled analysis

William Busse, MD,[a] Roland Buhl, MA, PhD,[b] Carlos Fernandez Vidaurre, MD, MPH,[c] Martin Blogg, BSc (Hons), CStat,[d] Jin Zhu, PhD,[e] Mark D. Eisner, MD, MPH,[e] and Janice Canvin, MD, FRCPC[d] *Madison, Wis, Mainz, Germany, East Hanover, NJ, Horsham, United Kingdom, and South San Francisco, Calif*

Background: Since initial registration, the omalizumab clinical trial database has expanded considerably, with a doubling of patients exposed in the clinical trial environment. Previous pooled data (2003) from phase I to III studies of omalizumab showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%). The previous analysis was based on limited available data, warranting further investigation.

Objective: We sought to examine the incidence of malignancy using comprehensive pooled data from clinical trials of omalizumab-treated patients.

Methods: This pooled analysis included data from 67 phase I to IV clinical trials. The prespecified primary analysis assessed the incidence of primary malignancy in 32 randomized, double-blind, placebo-controlled (RDBPC) trials.

Results: There were 11,459 unique patients in all clinical trials (7,789 received omalizumab). The primary analysis identified malignancies in 25 patients (RDBPC trials): 14 in 4,254 omalizumab-treated patients and 11 in 3,178 placebo-treated patients. Incidence rates per 1,000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 (95% CI, 2.26-6.94) and 4.45 (95% CI, 2.22-7.94), respectively; the corresponding rate ratio was 0.93 (95% CI, 0.39-2.27). Primary malignancies were of varying histologic type and occurred in a number of different organ systems; no cluster of histologies was identified.

Conclusions: In this pooled analysis no association was observed between omalizumab treatment and risk of malignancy in RDBPC trials; the rate ratio was below unity. The data suggest that a causal relationship between omalizumab therapy and malignancy is unlikely. (J Allergy Clin Immunol 2012;129:983-9.)

Key words: *Asthma, allergy, IgE, anti-IgE, omalizumab, malignancy, pooled analysis*

Omalizumab (Xolair; Genentech, South San Francisco, Calif, or Novartis, East Hanover, NJ), a humanized anti-IgE mAb, is approved as an add-on therapy for the treatment of inadequately controlled severe persistent allergic (IgE-mediated) asthma in adults, adolescents, and children (≥6 years of age) in the European Union[1] and in adults and adolescents (≥12 years of age) with moderate-to-severe persistent allergic asthma in the United States.[2] Omalizumab prevents the binding of IgE to receptors on mast cells, thus inhibiting the generation of a resultant cascade of inflammatory mediators and consequent symptoms in susceptible subjects.[3-9]

Previous pooled data (2003) from phase I to III studies of omalizumab showed a numeric imbalance in malignancies arising in omalizumab recipients (0.5%) compared with control subjects (0.2%).[10] These findings are reflected in both the European Union and US labels for omalizumab.[1,2] The biological plausibility of free IgE reduction or indeed allergic disease itself as a cause of malignancy has not been established[11-16]; nevertheless, because of labeled information, the possible association between omalizumab therapy and malignancy remains a concern for clinicians and patients.[17,18]

Two further strategies have been undertaken since 2003 to assess the possible association between omalizumab and malignancy risk. First, a US-based 5-year registry of more than 7000 omalizumab-treated and non–omalizumab-treated patients with moderate-to-severe persistent allergic asthma (the EXCELS study) was initiated to evaluate omalizumab's long-term safety and clinical effectiveness[19]; this registry is ongoing. Second, since the original analysis, the omalizumab clinical trial database has expanded considerably, and this has allowed for a more robust analysis to be performed. This article presents the results of the recent pooled analysis of 67 clinical trials of omalizumab conducted over 2 decades.

METHODS

Study designs and analysis populations

All clinical trials of omalizumab conducted by either sponsor company (Novartis or Genentech) with available data were considered eligible and included in this analysis. In total, data from 67 completed phase I to IV trials investigating the efficacy, tolerability, and safety of omalizumab were included in the pooled analysis (see Table E1 in this article's Online Repository at www.jacionline.org). Data collected in follow-up studies (eg, during extension periods) were captured as part of the original trial. Studies were included if patients received intravenous or subcutaneous omalizumab,

From [a]the Department of Medicine, University of Wisconsin Medical School, Madison; [b]the Pulmonary Department, University Hospital, Johannes Gutenberg-University, Mainz; [c]Novartis Pharmaceutical Corp, East Hanover; [d]Novartis Horsham Research Centre, Horsham, West Sussex; and [e]Genentech, Inc, South San Francisco.

Supported by Novartis Pharma AG, Switzerland, and Genentech, Inc.

Disclosure of potential conflict of interest: W. Busse is on advisory boards for Centocor and Merck; has consultant arrangements with AstraZeneca, Boehringer Ingelheim, Novartis, TEVA, GlaxoSmithKline, Amgen, Pfizer, MedImmune, and Genentech; and receives research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases, the National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, AstraZeneca, GlaxoSmithKline, MedImmune, and Ception. R. Buhl is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Nycomed, and Pfizer and is on advisory boards for Boehringer Ingelheim, Novartis, and Nycomed. C. Fernandez Vidaurre, M. Blogg, and J. Canvin are employed by Novartis. J. Zhu and M. D. Eisner are employed by Genentech.

Received for publication September 2, 2011; revised December 23, 2011; accepted for publication January 5, 2012.

Available online February 23, 2012.

Corresponding author: William Busse, MD, Department of Medicine, University of Wisconsin Medical School, K4/910 CSC, MC 9988, 600 Highland Ave, Madison, WI 53792. E-mail: wwb@medicine.wisc.edu.

0091-6749/$36.00

doi:10.1016/j.jaci.2012.01.033

Abbreviations used
AE: Adverse event
NMSC: Nonmelanoma skin cancer
RDBPC: Randomized, double-blind, placebo-controlled

regardless of the dose, formulation, (lyophilized or liquid), or dosing frequency (single-dose studies were included). Patients were either randomized within a controlled trial (with a placebo or active control arm) or received omalizumab in a single-arm study. Registry, postmarketing surveillance, or compassionate-use studies were excluded, but continuous-access extensions to controlled trials were included. In addition, each clinical trial had to be conducted by the sponsor companies, so that individual patient-level data were available. Patients with a prior history of malignancy were included in 11 clinical trials, which corresponded to those completed before registration; later studies excluded patients with a history of prior malignancy.

All analyses considered the number of patients with events and not the number of events. Assessments are presented for 3 study cohorts. The prespecified primary analysis group comprised patients from randomized, double-blind, placebo-controlled (RDBPC) trials (32/67 studies). RDBPC trials were considered least prone to bias because randomization ensures balance of baseline characteristics and adverse events (AEs) are reported in a blinded fashion. The "controlled clinical trials" group comprised patients from RDBPC trials and any other controlled trial whether blinded, unblinded, randomized, or allocated (40/67 studies). The "all clinical trials" group comprised patients from all 67 eligible studies. This final cohort also included all patients in the controlled clinical trials population and any uncontrolled trials, such as those with a single-omalizumab arm only or any study with more than 1 omalizumab-treated arm but without any non–omalizumab-treated control arm. Patients who received placebo in a controlled clinical trial and subsequently received omalizumab in an extension study were counted in each respective treatment group for the appropriate time period.

In addition to the clinical trials database, the ARGUS safety database, which is a global Novartis safety and pharmacovigilance database, was used to capture additional events that occurred in patients exposed to omalizumab during the clinical trials after study termination. Occasionally, entries can be made into the ARGUS database after study completion but before unblinding; this can generate information for patients who were in the placebo or control arms. Typically, only patients receiving active treatment (omalizumab) were captured in the ARGUS database. All data collection occurred between 1994 and 2010 in clinical trials that had completed by February 28, 2010.

Patients

Patients were included in the analysis if they received at least 1 dose of study medication and provided any posttreatment data on or after their first treatment date. Studies included patients with asthma (atopic and nonatopic), allergic rhinitis, atopic dermatitis, and urticaria, and patients undergoing immunotherapy.

Identification of malignant events

A comprehensive clinical and statistical analysis of malignancies observed across all clinical trials was undertaken. Any AE with a start date on or after the patient's date of first study medication in any clinical trial or phase was considered. No cutoff was applied, and thus all events on or after the first dose of medication were considered when reported (ie, patients entering a follow-up study or events that occurred in the transition between clinical trials were included). All AEs identified from the clinical trial database had been reported by an investigator through the sponsor's data collection systems as part of routine data collection in the clinical trial. In addition, a search of the ARGUS database was conducted to increase the capture of potential malignancies. The ARGUS search identified additional AEs in predominantly omalizumab-treated patients that occurred after the clinical trials had ended and includes events even if they occur substantively after the last exposure to treatment within a clinical trial, in which case the clinical trial database will have closed (there is no time limit for recording events within ARGUS). The combined search of the clinical trial database and the ARGUS database ensures the most complete case ascertainment.

AEs were categorized by using the Medical Dictionary for Regulatory Activities (version 13.0) either at the time the study was reported or coded during the data pooling work (see Fig E1 in this article's Online Repository at www.jacionline.org). Potential malignancies in the pooled dataset were identified by means of a Standardized Medical Dictionary for Regulatory Activities Query search for "malignancy" or by a System Organ Class search for "neoplasms benign, malignant and unspecified (including cysts and polyps)."

For all potential cases identified, blinded patient narratives were initially screened by a physician from each sponsor company to eliminate cases clearly not related to malignancy, such as benign nevi. Only cases in which both reviewers agreed that the event was clearly a benign condition were excluded from analysis. The remaining cases were reviewed by an external independent oncology panel ("adjudication panel"), also in a blinded fashion, to confirm the event as a primary malignancy. Both "definite" and "possible" cases of malignancy were included as events to ensure all potential events were captured in the analysis. Recurrent malignancies or metastasis of pre-existing malignancies were not included as events; a new-onset malignancy that presented with metastasis was included.

The first study-emergent primary malignancy occurring in a patient was recorded, which included the specific malignancy type. Events that were assessed as malignancies in the previous pooled analysis were recorded as malignancies in the present analysis; no further adjudication was carried out on these events (ie, the status of events considered malignant remained unchanged).

An additional analysis of primary malignancies was performed, which excluded nonmelanoma skin cancer (NMSC). Because NMSC is one of the most common forms of cancer worldwide, patients who attend frequent clinic visits within clinical trials might have a greater likelihood of reporting skin changes as part of a routine visit. Because NMSC has a specific set of known risk factors (eg, fair skin complexion, age >40 years, sun exposure, and sunburn), an analysis excluding this more common cancer was performed.

Statistical analysis

The primary analysis assessed the incidence of primary malignancy in the RDBPC trials, recorded as the number of patients with a malignancy and not the number of events and accounted for observation time. Observation time is the time from the date of first study drug administration to the latest date available for a patient, censored at the first malignancy event date if such an event is observed, and was not restricted to the time the patient was receiving study medication (this is the exposure to study medication). The overall incidence rate for malignancy events was calculated per 1000 patient-years from the number of patients with malignancies/observation time in patient-years, with exact 95% CIs. Exact 95% CIs for the rate ratio of the omalizumab versus placebo or control groups were also calculated, along with the 95% CIs for the rate difference. Kaplan-Meier curves for the time to first diagnosed malignancy are presented, and a log-rank test was used to compare the treatment groups. A Cox proportional hazards model was used to estimate the hazard ratio. The incidence of primary malignancies was also summarized by age at baseline (<18, 18-64, and ≥65 years), sex, and total IgE level at baseline for both treatment groups. After excluding patients in single-dose studies, duration of exposure to study medication for omalizumab-treated patients and categorical cumulative dose of omalizumab (900 to ≤1950, >1950 to ≤3900, and >3900 mg) was assessed; the categorical cumulative dose analysis used a cumulative dose of 900 mg or less of omalizumab as the reference category. Additional statistical methodology can be found in the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

Patients

There were 11,459 unique patients in the entire clinical trials cohort (67 studies; 7,789 patients received omalizumab), 9,424