Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma

Carlos Iribarren, MD, MPH, PhD,[a] Abdelkader Rahmaoui, MD,[b] Aidan A. Long, MD,[c] Stanley J. Szefler, MD,[d] Mary S. Bradley, MS,[b] Gillis Carrigan, PhD, MSc,[b] Mark D. Eisner, MD, MPH,[b] Hubert Chen, MD, MPH,[b] Theodore A. Omachi, MD, MBA,[b] Michael E. Farkouh, MD, MSc,[e] and Kenneth J. Rothman, DrPH[f] *Oakland and South San Francisco, Calif; Boston and Cambridge, Mass; Aurora, Colo; Toronto, Ontario, Canada; and Research Triangle Park, NC*

Background: EXCELS, a postmarketing observational cohort study, was a commitment to the US Food and Drug Administration to assess the long-term safety of omalizumab in an observational setting, focusing predominantly on malignancies.
Objective: The aim of this study was to examine a potential association between omalizumab and cardiovascular (CV)/cerebrovascular (CBV) events in EXCELS.
Methods: Patients (≥12 years of age) with moderate to severe allergic asthma and who were being treated with omalizumab (n = 5007) or not (n = 2829) at baseline were followed up for ≤5 years. Analyses included overall CV/CBV events, but focused on the subset of arterial thromboembolic events (ATEs), comprising CV death, myocardial infarction, ischemic stroke, transient ischemic attack, and unstable angina. A prespecified analysis of the end point of ATE was conducted to control for available potential confounders. A blinded independent expert panel adjudicated all events.
Results: At baseline, the 2 cohorts had similar demographic characteristics, but severe asthma was more common in the omalizumab versus the non-omalizumab group (50% vs 23%). Omalizumab-treated patients had a higher rate of CV/CBV serious adverse events (13.4 per 1,000 person years [PYs]) than did non–omalizumab-treated patients (8.1 per 1,000 PYs). The ATE rates per 1,000 PYs were 6.66 (101 patients/15,160 PYs) in the omalizumab cohort and 4.64 (46 patients/9,904 PYs) in the non-omalizumab cohort. After control for available confounding factors, the hazard ratio was 1.32 (95% CI, 0.91-1.91).
Conclusion: This observational study demonstrated a higher incidence rate of CV/CBV events in the omalizumab versus the non-omalizumab cohort. Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in risk cannot be excluded. (J Allergy Clin Immunol 2017;139:1489-95.)

Key words: *Adverse event, arterial thromboembolic event, clinical trials, moderate to severe asthma, omalizumab, safety, serious adverse event*

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Omalizumab (Xolair; Genentech, Inc, South San Francisco, Calif) is a recombinant humanized monoclonal antibody directed against IgE. In randomized, placebo-controlled trials and in open-label studies in patients on maintenance therapy with inhaled corticosteroids (ICSs) and/or long-acting β-agonists, the addition of omalizumab has been shown to reduce asthma exacerbations,[1-9] decrease the use of ICSs and rescue medications,[1,3,5,8,10] and improve symptom control and quality of life.[1,5,8,10]

In EXCELS (Epidemiologic Study of Xolair [Omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate to Severe Asthma), a postmarketing observational cohort study, the primary objective was to assess the long-term (≤5 years) clinical safety profile of omalizumab, with a focus on malignancy. This observational study was designed to compare adverse events in patients with asthma whom health care providers had treated with omalizumab to those in patients with asthma who had not been treated with omalizumab. A numeric imbalance in malignancy rates in patients with allergic asthma in pivotal trials was the motivation for EXCELS.[3,5] Accordingly, the primary outcome measures were primary malignancies, all

From the [a]Division of Research, Kaiser Permanente Medical Care Program, Oakland; [b]Genentech, Inc, South San Francisco; the [c]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston; Harvard Medical School, Cambridge; the [d]Pediatric Asthma Research Program, Breathing Institute, Children's Hospital Colorado and the University of Colorado School of Medicine, Aurora; the [e]Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre of Excellence, University of Toronto, Toronto; and [f]RTI Health Solutions, Research Triangle Park.

Supported by Genentech, Inc, South San Francisco, Calif, and Novartis Pharma AG, Basel, Switzerland. Medical writing support for this manuscript was funded by Genentech, Inc, and Novartis Pharmaceuticals Corporation. ClinicalTrials.gov identifier: NCT00252135.

Disclosures and potential conflicts of interest: C. Iribarren and A. A. Long are members of the EXCELS Advisory Panel. A. Rahmaoui, M. S. Bradley, G. Carrigan, M. D. Eisner, H. Chen, and T. A. Omachi and are employees of Genentech, Inc. S. J. Szefler was a member of the EXCELS Advisory Panel; has consulted for and served on respiratory advisory panels for Aerocrine, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Merck, Novartis, and Roche; and has received research grants from GlaxoSmithKline. M. E. Farkouh chaired the adjudication committee for cardiovascular and cerebrovascular events in EXCELS. K. J. Rothman is an employee of RTI Health Solutions, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.

Received for publication December 21, 2015; revised May 23, 2016; accepted for publication July 1, 2016.

Available online September 14, 2016.

Corresponding author: Abdelkader Rahmaoui, MD, 1 DNA Way, South San Francisco, CA 94080. E-mail: abdelkar@gene.com.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2016.07.038

Abbreviations used

ATE: Arterial thromboembolic event
CBV: Cerebrovascular
CV: Cardiovascular
EXCELS: Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate to Severe Asthma
FDA: US Food and Drug Administration
ICS: Inhaled corticosteroid
MI: Myocardial infarction
OCS: Oral corticosteroid
PY: Person year
SAE: Serious adverse event

malignancies excluding nonmelanoma skin cancer, and overall serious adverse events (SAEs). Details regarding the study design and methodology, including patients' baseline characteristics, have been published elsewhere.[11] In EXCELS, the incidence rates of primary malignancies (per 1000 person years [PYs]) were similar among patients treated with omalizumab and non–omalizumab-treated patients (12.3 vs 13.0); however, study limitations precluded definitively ruling out a malignancy risk with omalizumab.[12] In an interim effectiveness analysis, patients who started on treatment with omalizumab at enrollment showed clinically relevant improvements in asthma control that were maintained during 2 years of follow-up.[13]

This analysis focused on cardiovascular (CV) and cerebrovascular (CBV) SAEs that occurred during EXCELS. EXCELS was not originally designed specifically to assess CV/CBV events. A numeric imbalance in various CV/CBV events was first observed in an interim analysis presented to the US Food and Drug Administration (FDA), prompting a disclosure of such findings by the FDA in 2009.[14] The interim analysis also resulted in the development of a prespecified statistical analysis plan supporting methodology for the ascertainment of CV-related events, including external adjudication, as detailed subsequently. An analysis of data pooled from multiple randomized, double-blind, placebo-controlled clinical trials of omalizumab was also planned after the results from the EXCELS interim analysis were evaluated.[15]

METHODS

Overview of EXCELS

EXCELS (ClinicalTrials.gov identifier: NCT00252135) was conducted as part of a postmarketing commitment to the FDA to assess the long-term safety and effectiveness of omalizumab in the clinical practice setting. Patients (≥12 years of age; N = 7857) with moderate to severe asthma, willing to participate in a 5-year study, and with a history of either a positive response to allergy skin testing or *in vitro* serum–specific IgE reactivity to an aeroallergen were recruited from 445 US-based practice centers according to the use of omalizumab at or within 30 days of enrollment (2:1 ratio; omalizumab, n = 5007; non-omalizumab, n = 2829). Patients were excluded from EXCELS if they had: (1) a contraindication to omalizumab; (2) an asthma exacerbation that required initiation or increased doses of systemic corticosteroids, doubling of inhaled corticosteroid dosing, or an emergency department visit or hospitalization in the 2 weeks before screening; (3) acute flare of significant systemic disease or hospitalization for that disease in the 2 months prior to screening; and/or (4) use of an experimental drug within 30 days of screening, cystic fibrosis diagnosis, or participation in a blinded omalizumab study at screening or any time during the study. Patients in the non-omalizumab group could not have received any prior treatment with omalizumab. A small number of patients (n = 21) who had previously been treated with omalizumab but were not taking the drug at study enrollment were not included in the analyses. Assessments included the collection of detailed information regarding demographic and clinical characteristics, physician-assessed asthma severity, spirometry, and patient-reported outcome measures. Study assessments were conducted every 6 months for the 5-year study duration.

This study was conducted in accordance with FDA regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable country laws. Institutional review board approval was obtained at each study site, and informed consent was obtained from all research subjects.

Identification and adjudication of CV and CBV SAEs

In EXCELS, the definition of an SAE was any untoward medical occurrence that, after enrollment, resulted in a patient's death, was life-threatening, required prolonged inpatient hospitalization, was disabling, was a congenital anomaly/birth defect, or was medically significant or required medical or surgical intervention to prevent one of these outcomes, and was based on the definition of an SAE as outlined by the FDA.[16]

During EXCELS, verbatim terms for all study-emergent SAEs were coded and analyzed using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes, High-Level Terms, and Preferred Terms. An independent panel of experts performed a blinded review of patient narratives and supporting documents for all SAEs that resulted in death and all potential CV/CBV SAEs identified using Standardized MedDRA Queries (Medical Dictionary for Regulatory Activities; http://www.meddra.org/standardised-meddra-queries) (Fig 1). This approach allowed for the identification of cases that were highly likely to have represented the condition of interest as well as the identification of all possible cases. The panel also classified the CV/CBV SAEs into standardized categories: myocardial infarction (MI), unstable angina, congestive heart failure, ischemic stroke, transient ischemic attack, hemorrhagic stroke, pulmonary embolism, venous thrombosis, pulmonary hypertension, arterial ischemic vascular disease, atrial fibrillation/flutter, and ventricular tachycardia/fibrillation.

An additional composite end point, arterial thromboembolic event (ATE), was defined using an approach adapted from the 2002 Antiplatelet Trialists' Collaboration.[17] The ATE category comprised CV/CBV events sharing a common pathophysiologic mechanism of arterial injury and/or inflammation and included CV death, MI, ischemic stroke, transient ischemic attack, and unstable angina.

Descriptive analyses

Data were analyzed in terms of *PYs of observation*, defined as the time from study day 0 to the date of death, date of event of interest, study completion, or the last completed clinic visit in those who discontinued from the study, whichever came first. Overall incidence rates per 1000 PYs of observation of adjudicated CV/CBV-related deaths and SAEs were calculated in each cohort and are reported with 95% CIs. Crude rate differences were calculated with 95% CIs. The same analyses were performed for each of the adjudicated event categories and for all event categories combined (CV or CBV SAEs).

The prespecified analysis of ATEs was applied to the cumulative adjudicated data for the evaluation of events with a common pathophysiology. As described for CV/CBV SAEs, overall incidence rates per 1000 PYs were calculated with 95% CIs for both cohorts. Crude rate differences and rate ratios were calculated with 95% CIs. Similarly, the rates of patients experiencing ≥1 ATE event, expressed per 1000 PYs of observation time, were calculated by treatment cohort and reported with 95% CIs. A sensitivity analysis was conducted in which event rates per 1000 PYs were computed by treatment cohort for the set of ATEs that excluded deaths not associated with any of the following SAEs: MI, ischemic stroke, ventricular tachycardia, or ventricular fibrillation.

To adjust for potential confounders, we used a Cox proportional hazards regression model. The *time to a patient's first ATE* was defined as the number of months from study day 0 to the date of onset of symptoms of the first SAE experienced by the patient that met the ATE definition. Data from patients not experiencing an ATE were censored at the earliest of the following