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Original Research

ASTHMA

Does Omalizumab Make a Difference to the Real-life Treatment of Asthma Exacerbations?

Results From a Large Cohort of Patients With Severe Uncontrolled Asthma

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Background: **Omalizumab has been shown to decrease the risk of hospitalization or ED visits in patients with uncontrolled severe allergic asthma compared with placebo. This longitudinal study observed the conditions under which omalizumab is prescribed in real-life settings and assessed whether its use as an add-on therapy alongside standard treatments decreases the risk of severe asthmatic exacerbations.**

Methods: **A cohort of adult patients with uncontrolled severe asthma despite optimal treatment with inhaled and oral corticosteroids and a long-acting β_2-agonist but no treatment with omalizumab upon entry was assembled. Risk of hospitalization or ED visits for asthma exacerbation was assessed using the Andersen-Gill extension of the Cox model for repeated events, controlling for age, sex, smoking history, BMI, gastroesophageal reflux, allergic status, allergic rhinitis, treatment, and hospitalization or ED visits for asthma in the 2 months prior to omalizumab treatment.**

Results: **Overall, 163 physicians recruited 767 patients, of whom 374 took omalizumab at least once (mean observation period, 20.4 months). Omalizumab use was associated with an adjusted relative risk of 0.57 (95% CI, 0.43-0.78) for hospitalization or ED visits for asthma. In users of omalizumab, the adjusted relative risk of hospitalization or ED visits for asthma during omalizumab treatment vs nontreatment periods was 0.40 (95% CI, 0.28-0.58).**

Conclusions: **Add-on omalizumab is associated with a significantly decreased risk of hospitalization or ED visits in patients with uncontrolled severe asthma in real-life practice.**

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Abbreviations: AHR = adjusted hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist

Asthma affects 300 million people worldwide, accounting for one in 250 deaths and 15 million disability-adjusted life years lost annually.[1,2] Up to 5% of adult patients have persistent symptoms and frequent exacerbations despite treatment with medium- to high-dose inhaled corticosteroids (ICSs) plus a long-acting β_2-agonist (LABA).[3,4] Potential consequences of uncontrolled disease in this patient subgroup, including fatal or near-fatal asthma exacerbations, represent an unmet clinical need with a disproportionate use of health-care resources. An increase from medium to high doses of ICSs provides relatively little additional benefit.[5] Moreover, adding oral glucocorticosteroids is associated with severe side effects. Alternative treatments, therefore, are necessary.

Evidence indicates that 50% to 80% of difficult-to-treat patients have an allergic component, with IgE playing a key role in triggering and maintaining allergic airway inflammation.[6-9] Omalizumab, a recombinant monoclonal anti-IgE antibody, has demonstrated

efficacy in clinical trials conducted in patients with moderate to severe and severe persistent allergic (IgE-mediated) asthma, reducing the risk of exacerbations, hospitalization, and ED visits.[6,10] The European Medicines Agency approved omalizumab for the treatment of inadequately controlled severe persistent allergic asthma despite the use of high-dose ICS plus LABA.[4] Omalizumab was granted prescription coverage by the national health insurance in France in 2006 for this indication provided that the manufacturer conducted an independent postmarketing usage and real-life effects study. Herein, we report the observations of the conditions under which omalizumab was prescribed and assess whether the real-life use of omalizumab would result in a decreased risk of severe asthma exacerbations as estimated by the number of asthmatic episodes requiring hospitalization or ED visits.

A cohort of patients with severe uncontrolled asthma free of omalizumab treatment at entry was historically assembled and described before and after marketing omalizumab. Physicians were free to prescribe drugs that they considered appropriate for their patients. Therefore, the effect of omalizumab treatment was observed under natural conditions by comparing the experience of patients before and after initiation of omalizumab in addition to that of patients whose asthma was uncontrolled despite the use of ICS plus LABA and no treatment with omalizumab.

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Materials and Methods

Centers and Participants

All French physicians recorded as pulmonologists were first invited by letter to participate in the study during June 2007; subsequent approaches were made by telephone. Participating pulmonologists identified all consenting patients aged ≥ 18 years with uncontrolled severe asthma and followed by the investigator for at least 1 year prior to identification. Asthma was considered uncontrolled if exacerbations had occurred in the previous year despite treatment with 1,000 μg beclomethasone equivalent, one LABA, and at least one of the following: (1) 5 mg prednisone equivalent per day for at least 6 months; (2) at least three courses of oral corticosteroids over 1 year; or (3) two courses of oral corticosteroids over 1 year, with at least one recent FEV_1 measurement < 80% predicted or personal best.

Entry into the cohort was set at 10 months before patient identification. Any patient who received omalizumab on or 2 months prior to that date were excluded. Patients were also excluded if unable to communicate or had a history of aspergillosis or Churg-Strauss syndrome. Participants were followed until the end of the study or loss to follow-up.

The study protocol was submitted to the Ethical Review Committee of Paris-Ile de France III (Comité de Protection des Personnes Ile de France III) and approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). All participants signed an informed consent form.

Collected Information

Patients were described according to the following risk factors: sex, age, BMI, history of asthma, smoking (current, past, or never), allergic rhinitis, urticaria, angioedema, allergy to drugs, gastroesophageal reflux, presence of chronic comorbid conditions, and allergies. Allergies were ascertained further by results from skin and serologic tests reported in the medical charts and were recorded as certain when a perennial aeroallergen or a specific IgE was recorded as positive, absent (nonallergic) when both were recorded as negative, and uncertain in all other instances. Circulating serum IgE levels were also reported.

To minimize observation bias, all data on drug exposure and outcomes (hospitalization and ED visits) were obtained by clinical research associates within the research team and independent of the investigator. The clinical research associates extracted this information through a medical chart review conducted on site. Several visits were necessary for centers with large patient recruitment.

The prescribed medicines were listed with the corresponding dates of prescription or renewal, dosage, and eventual dates of discontinuation. For omalizumab, motives for discontinuation were classified into adverse event occurrence, clinical improvement, patient preference, and none. Adverse drug reactions were recorded, and serious or severe adverse drug reactions were expeditiously reported.[11] All visits to EDs or hospitalization episodes (with corresponding dates and duration) were recorded for the year before and during the prospective follow-up period.

Statistical Analysis

Population Exposure Times: Population exposure times were calculated by adding the individual contributions to the cohort and were expressed in person-years (overall observation period from entry to end of follow-up). Population exposure times were categorized according to patients' exposure status into active omalizumab time, definite nonomalizumab time, and indeterminate exposure time. Active omalizumab time was defined from 60 days after the start of the first prescription (with time lag allowed to