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Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: A long-term post-marketing study in Japan

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ABSTRACT

Background: Omalizumab (anti-IgE monoclonal antibody) is an approved add-on therapy for Japanese patients with severe allergic asthma. As directed by the Ministry of Health, Labor and Welfare Japan, a post-marketing surveillance (PMS) study on omalizumab was conducted between 2009 and 2017.

Methods: The PMS observed safety and efficacy of omalizumab in patients treated with open-label omalizumab for 52 weeks (with optional 2-year extension period). Primary safety outcomes included incidence and severity of adverse events (AEs) and adverse drug reactions (ADRs). Primary efficacy outcomes included physician-assessed global evaluation of treatment effectiveness (GETE). Asthma-exacerbation-related events including requirement for additional systemic steroid therapy, hospitalization, emergency room visits, unscheduled doctor visits, and absenteeism were also evaluated.

Results: Of 3893 patients registered, 3620 (age [mean ± SD] 59.3 ± 16.11 years) were evaluated for 52 weeks; 44.12% were aged ≥65 years and 64.45% were women. Overall, 32.24% reported AEs and 15.30% reported serious AEs. ADRs were seen in 292 (8.07%) patients. GETE results showed that the majority of patients experienced clinical improvements (58.29% at 16 weeks and 62.40% at 52 weeks). Nearly half of all patients (47.96%) were free from asthma exacerbations after therapy. Omalizumab also reduced all events related to asthma exacerbations. No specific ADRs were observed in the elderly population.

Conclusions: This post-marketing study confirmed the clinically meaningful benefits of omalizumab in a majority of patients from Japan, and showed safety and efficacy in a real-life clinical setting to be consistent with previous reports.

1. Introduction

Asthma is a chronic disease presenting a personal and societal burden for more than 350 million individuals worldwide, and the number of affected patients is expected to increase to 400 million by 2025 [1–3]. More than half of asthma patients (51–64%) are inadequately controlled on currently available treatments, signifying an urgent and unmet need that is further exemplified in those with severe asthma [4–6]. Nearly 3 million people in Japan have asthma (30% with moderate asthma and 7% with severe asthma) [7], and the national asthma prevalence among adults (> 20 years) is 9.1% [8].

Omalizumab is a validated and well established add-on therapy for inadequately controlled persistent allergic asthma despite GINA (Global Initiative for Asthma) Step 5 treatment [9,10]. It was introduced in Japan in 2009 for use in adult asthma (Japanese guidelines for adult asthma [JGL]) [11], and expanded in 2013 for use in pediatrics (≥6 years). Immunoglobulin E (IgE), the target molecule of omalizumab, is a potent and early stage mediator of airway inflammation that coordinates allergic pathogenesis through mast cells, basophils, and dendritic cells. IgE also plays an indirect role in the recruitment of eosinophils at the site of inflammation [12–14]. Allergy is the underlying cause of asthma in approximately 75–80% of cases in cohort

Abbreviations: ADRs, adverse drug reaction; AEs, adverse events; GETE, global evaluation of treatment effectiveness; GINA, Global Initiative for Asthma; HCRU, health care resource utilization; ICS, inhaled corticosteroid; IgE, Immunoglobulin E; IU, international units; JGL, Japanese guidelines for adult asthma; LABA, long-acting β_2-agonist; LTRA, leukotriene antagonist; OCS, oral corticosteroid; PMDA, Pharmaceutical and Medical Devices Agency; PMS, post marketing surveillance; Q, quartile; SABA, short-acting β_2-agonist; SAEs, serious adverse events; SD, standard deviation

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studies of severe asthma conducted in the EU and the US [15,16], and a recent study from Japan showed that 60% of Japanese patients with severe asthma had allergy [17,18]. The observed efficacy of omalizumab on asthma exacerbations, lung function, symptoms, quality of life, health care resource utilization (HCRU) and oral corticosteroid (OCS) sparing in clinical trials and real-world practice can be attributed to direct inhibition of IgE and disruption of the allergic cascade, attenuation of early and late-phase allergic responses, and restoration of antiviral mucosal immunity [12,19–30].

Despite the available treatment standards and improved therapies, 40% of Japanese patients with severe asthma remain poorly controlled [31–33]. Further, evaluations of long-term safety and effectiveness of omalizumab in Japanese clinical settings are limited. This prospective, non-interventional, post-marketing surveillance (PMS) study aims to describe the safety and efficacy of omalizumab in a real-world clinical practice environment for the first time following approval in Japan.

2. Methods

2.1. Study design

This 52-week, open-label, multicenter observational study was conducted between March 2009 to January 2017 in accordance with good post-marketing study practice (GPSP) [34] as directed by the Pharmaceutical and Medical Devices Agency (PMDA) regulatory body of Japan, and as such, informed consent was not mandated nor obtained. The intent to cooperate in an all-patient survey was confirmed by a written document with medical institutions requesting a supply of omalizumab, and a contract for the survey was concluded with the head of the medical institution who agreed to participate in the survey. Japanese patients with severe allergic asthma were treated with omalizumab and followed up by physicians specializing in asthma care from multiple clinical centers (supplementary table 1). Patients with bronchial asthma who initiated the treatment with omalizumab due to poorly controlled refractory asthma symptoms despite standard therapy were included. The aim of the study was to conduct a comprehensive surveillance of asthmatic patients who were prescribed omalizumab, and excluded patients receiving omalizumab for on-label chronic spontaneous urticaria, for off-label uses other than asthma and any patients concomitantly receiving investigational (unapproved) therapies during the study period. Cases with incomplete documentation or poor data reliability were also excluded from the study. In patients remaining on omalizumab for ≥1 year, observation was extended for up to 2 years to follow incidence of malignancy events (supplementary figure 1).

Omalizumab dosing ranged from 75 mg to 600 mg subcutaneously every 2 or 4 weeks according to the dosing table, as appropriate to the patient's total serum IgE levels and body weight at baseline.

2.2. Study endpoints

The standard observation period per patient was 1 year. The primary safety outcomes included incidence of adverse events (AEs), serious AEs (SAEs) and adverse drug reactions (ADRs). AEs and ADRs were monitored throughout the study. Items of special interest (reported as ADRs of special interest) were categorized as anaphylaxis, eosinophilic syndromes, malignant tumor, autoimmune disease and bleeding tendency.

The primary efficacy outcomes included physician-reported global evaluation of treatment effectiveness (GETE) [35], events related to asthma exacerbations, and patient-reported asthma symptoms. Effective GETE was defined by “excellent” or “good” ratings, while ineffective GETE was defined by “moderate”, “poor”, or “worsening” ratings (supplementary table 2). If physicians did not observe any improvement in their patients by 16 weeks after the initiation of treatment, omalizumab was discontinued. All patients with baseline data completed the one-year observational period. Additionally, effective response to omalizumab took into consideration “moderate” GETE rating (slight improvement).

Annual asthma exacerbation frequencies before and after omalizumab treatment were calculated and analyzed for worsening of asthma symptoms requiring [1] hospitalization [2], emergency room visit [3], systemic steroid therapy [4], unscheduled doctor visit, and/or [5] absence from school/work (including housework).

Patient-reported asthma outcomes were collected every 4 weeks. Symptom severity was assessed 4 times a day (morning, daytime, evening, and at night), and activity of daily living (ADL) and quality of nighttime sleep was assessed once a day.

2.3. Statistical analyses

Target sample size assumed inclusion of all on-label omalizumab users following consultation with Japanese health authorities (PMDA). A study with 3000 patients would provide 95% power to detect at least one patient with onset of ADR with 0.1% of frequency. As an open label study, safety and efficacy outcomes were otherwise descriptive. For comparative tests among groups, Fisher's exact test was used between 2 groups with unpaired nominal data and the Mann–Whitney *U* test was used for 3 or more groups with unpaired ordinal data (exception: when the tabulation resulted in a 2 × 2 contingency table, Fisher's exact test was used). The Mantel–Haenszel test was used to examine confounding factors. The level of significance was 5% in 2-tailed hypothesis tests. Study results with a response of “Unknown or Not reported” were excluded from analysis.

3. Results

3.1. Study population

A total of 3893 patients registered for this study and 3673 (94.34%) patients from 1001 sites were with fixed case report forms (Fig. 1).

A total of 3620 patients were included in the safety set, of which 1497 (41.35%) patients discontinued or withdrew from the study. The most common reasons for discontinuation were insufficient efficacy of the drug (n = 471, 13.01%), improvement in symptoms (n = 247, 6.82%), onset of an AE (n = 288, 7.96%) and other reasons (n = 416, 11.49%) which included financial reasons (n = 152, 4.20%) and death (n = 16, 0.44%). Of the 3620 patients in the safety set, 27 patients (Fig. 1) were excluded and the remaining 3593 patients were included in the efficacy set.

Patient demographics and baseline characteristics are presented in Table 1. The age (mean ± SD) of patients was 59.3 ± 16.11 years. Special populations were categorized as pediatric (n = 7, 0.19%, if

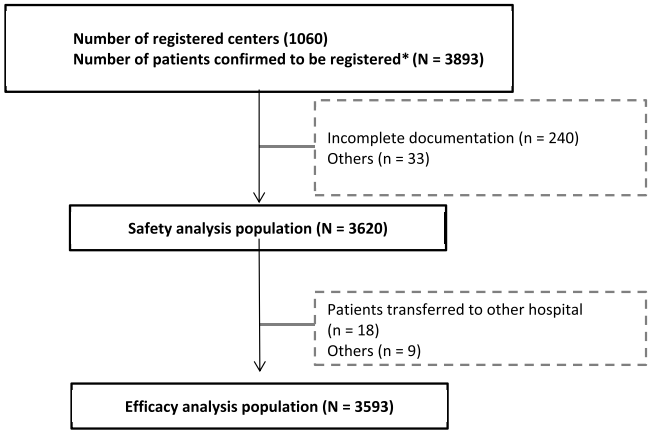

Fig. 1. Patient disposition.
*Patients transferred to another hospital are counted as 1 patient.