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Original article

Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma

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AEs, adverse events; ER, emergency room; EOT, end of the treatment period; ELISA, enzyme-linked immunosorbent

ABSTRACT

Background: Omalizumab is effective and well-tolerated in children with moderate to severe allergic asthma. However, the effects of long-term treatment with omalizumab in this population haven't been well investigated. The objective of this study is to evaluate the long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with uncontrolled severe asthma.
Methods: Thirty-eight Japanese children (aged 7–16 years) who completed the 24-week treatment core study were included in an uncontrolled extension study, in which treatment with omalizumab continued until the pediatric indication was approved in Japan (ClinicalTrials.gov number: NCT01328886).
Results: Thirty-five patients (92.1%) completed the extension study. The median exposure throughout the core and extension studies was 116.6 weeks (range, 46.9–151.1 weeks). The most common adverse events were nasopharyngitis, influenza, upper respiratory tract infection, and asthma. Serious adverse events developed in 10 patients (26.3%), but resolved completely with additional treatments. Incidence of adverse events didn't increase with extended exposure with omalizumab. Twenty-nine patients (76.3%) achieved completely- or well-controlled asthma compared with 9 patients (23.7%) at the start of the extension study. QOL scores, the rates (per year) of hospitalizations and ER visits were significantly improved compared with the baseline of the core study [39.0 vs 48.0 (median), $p < 0.001$ for QOL, 1.33 vs 0.16, $p < 0.001$ for hospitalization, 0.68 vs 0.15, $p = 0.002$ for ER visits]. Remarkably, the mean total IgE level showed a decreasing trend while exposure to omalizumab remained at steady-state.

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assay; FP, fluticasone propionate; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; JPAC, Japanese pediatric asthma control program; JPGL, Japanese pediatric guideline for the treatment and management of asthma; LOCF, last observation carried forward; LTRA, leukotriene receptor antagonist; LABA, long-acting β_2-agonist; QOL, quality of life; SAEs, serious adverse events

Conclusions: Long-term treatment with omalizumab is well-tolerated and effective in children with uncontrolled severe allergic asthma. No new safety findings were identified.

Introduction

Asthma in children is often poorly controlled, usually as a result of under-treatment with controller medications and poor inhaler technique; however, some children have poor asthma control despite current optimal therapies with high-dose inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA) or leukotriene receptor antagonist (LTRA) or theophylline.[1,2] Uncontrolled severe asthma results in a high risk of asthma exacerbations and impaired quality of life.[3] Asthma exacerbations are associated with hospital admissions and emergency room (ER) visits,[4] time lost from work and school[5] and decline in lung function.[6] In addition, a history of asthma exacerbation increases the risk of further asthma exacerbations requiring hospitalizations, ER visits or corticosteroids bursts.[7] Asthma exacerbations are frequently treated with systemic [oral or intravenous] corticosteroids, which, if used in multiple bursts over a period of years, could be associated with a reduction in bone mineral accretion and increased risk for osteopenia.[8] Chronic use of high dose ICS was also found to result in a suppression of growth velocity and adrenal function.[8,9]

Omalizumab, a humanized monoclonal anti-IgE antibody, is indicated for the treatment of moderate to severe allergic asthma that is inadequately controlled despite current recommended therapies.[10–12] Several randomized placebo-controlled studies, which have shown a significant decrease in asthma exacerbations, have established omalizumab as an effective and well-tolerated agent for use as add-on therapy in pediatric patients with moderate to severe asthma.[13–15] We also have previously demonstrated the noticeable clinical effects of omalizumab in Japanese children (6–15 years) with severe asthma in a 24-week treatment, single-arm, open-label phase III study.[16] However, especially in childhood asthma population, effects of long-term treatment with omalizumab have remained to be investigated. Therefore, to evaluate comprehensively the long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma in a condition close to a real-life, we conducted a single-arm, open-label phase III extension study following the 24-week core study.[16]

Methods

Study design and patients

This multicenter, single-arm, open-label phase III study, conducted at 15 centers in Japan, was an extension to the 24-week treatment core study in Japanese children (6–15 years) with uncontrolled severe allergic asthma despite ICS (>200 μg/day fluticasone propionate [FP] or equivalent) and two or more controller therapies out of LTRA, LABA, theophylline, sodium cromoglycate, and oral corticosteroid.[16] The extension study consisted of a treatment period and an optional follow-up investigation for anti-omalizumab antibodies at 16 weeks after the last dosing (Fig. 1). The start of the extension study (restarting of treatment with omalizumab) was on the same day of the follow-up investigation for anti-omalizumab antibodies of the core study, and administration of omalizumab continued until the pediatric indication was approved in Japan (20-Aug-2013).

Patients who completed the core study and who in the investigator's clinical judgment benefited from continued treatment with omalizumab were eligible for the extension study. Patients

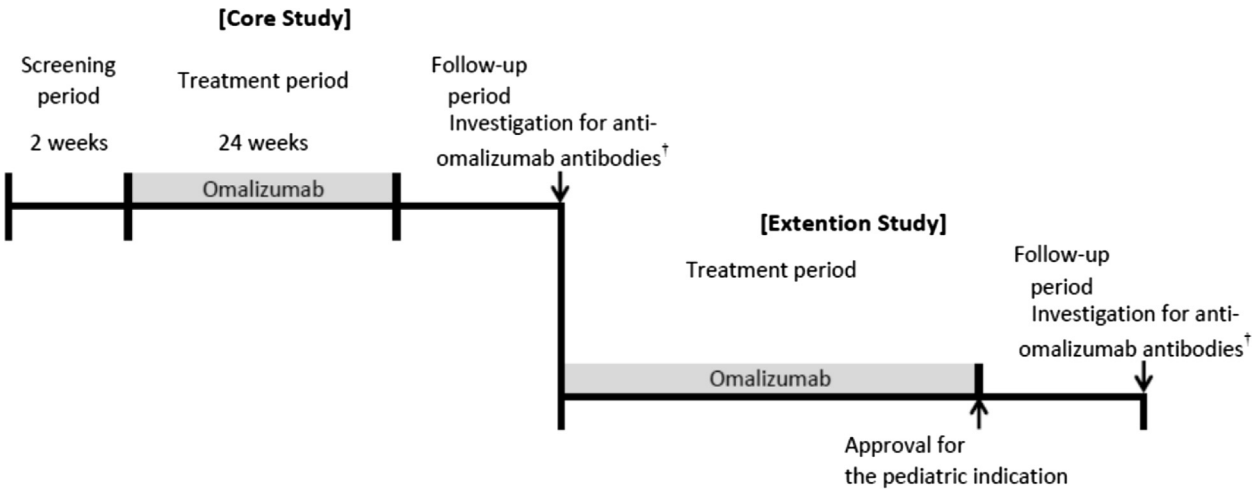

Fig. 1. Study design. This study was extension to the core study which included a 2-week screening period, a 24-week treatment period, and a follow-up investigation for anti-omalizumab at 16 weeks after the last dosing. The extension study consisted of a treatment period and an optional follow-up investigation for anti-omalizumab antibody at 16 weeks after the last dosing. Start of the extension study (restarting of treatment with omalizumab) was at the same day of follow-up investigation for anti-omalizumab antibody of the core study, and the treatment with omalizumab lasted until omalizumab was approved for the pediatric indication in Japan (20-Aug-2013). †16 weeks after the last dosing.