Allergology International 64 (2015) 364–370

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy

Hiroshi Odajima [a, *], Motohiro Ebisawa [b], Toshikazu Nagakura [c], Takao Fujisawa [d], Akira Akasawa [e], Komei Ito [f], Satoru Doi [g], Koichi Yamaguchi [h], Toshio Katsunuma [i], Kazuyuki Kurihara [j], Naomi Kondo [k], Kazuko Sugai [l], Mitsuhiko Nambu [m], Akira Hoshioka [n], Shigemi Yoshihara [o], Norio Sato [p], Noriko Seko [p], Sankei Nishima [a]

[a] Department of Pediatrics, Fukuoka National Hospital, Fukuoka, Japan
[b] Department of Allergy, Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan
[c] Yoga Allergy Clinic, Tokyo, Japan
[d] Institute for Clinical Research, Mie National Hospital, Mie, Japan
[e] Division of Allergy, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan
[f] Department of Allergy, Aichi Children's Health and Medical Center, Aichi, Japan
[g] Department of Pediatrics, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, Japan
[h] Department of Pediatrics, The Fraternity Memorial Hospital, Tokyo, Japan
[i] Department of Pediatrics, Jikei Daisan Hospital, Tokyo, Japan
[j] Department of Allergy, Kanagawa Children's Medical Center, Kanagawa, Japan
[k] Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Japan
[l] Department of Pediatrics, Fukuyama Medical Center, Hiroshima, Japan
[m] Department of Pediatrics, Tenri Hospital, Nara, Japan
[n] Department of Allergy and Rheumatology, Chiba Children's Hospital, Chiba, Japan
[o] Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan
[p] Clinical Development, Novartis Pharma K.K., Tokyo, Japan

ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form
7 April 2015
Accepted 1 May 2015
Available online 10 June 2015

Keywords:
Bronchial asthma
Children
Japanese
Omalizumab
Quality of life

Abbreviations:
AE, Adverse event; ELISA, Enzyme-linked immunosorbent assay; ER, Emergency room; $FEF_{25-75\%}$, Forced expiratory flow rate at 25%–75% of forced vital capacity; FEV_1, Forced expiratory volume in one second; FP, Fluticasone propionate; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; IV, Intravenous;

ABSTRACT

Background: Omalizumab has demonstrated clinical benefits in children with moderate to severe allergic asthma. However, no studies have been performed in Japanese asthmatic children. The aim of this study was to evaluate the efficacy including free IgE suppression and safety of omalizumab in Japanese children with severe allergic asthma. The primary objective was to examine whether omalizumab decreases serum free IgE levels to less than 25 ng/ml (target level of suppression).
Methods: Thirty-eight Japanese children (6–15 years) with uncontrolled severe allergic asthma despite inhaled corticosteroids (>200 μg/day fluticasone propionate or equivalent) and two or more controller therapies received add-on treatment with omalizumab in a 24-week, multicenter, uncontrolled, open-label study.
Results: The geometric mean serum free IgE level at 24 weeks was 15.6 ng/mL. Compared with baseline, total asthma symptom scores, daily activity scores and nocturnal sleep scores at 24 weeks were significantly improved. The rates of asthma exacerbation and hospitalization due to asthma were reduced by 69.2% and 78.2%, respectively ($p < 0.001$), versus baseline. Quality-of-life scores were also significantly improved ($p < 0.001$). In addition, 11 (28.9%) patients reduced the dose of any asthma controller medications. Thirty-six (94.7%) patients experienced at least one adverse event during the treatment period. All adverse events were mild or moderate in severity and no new safety concerns were detected. No patients discontinued the study.
Conclusions: In Japanese children with severe allergic asthma, omalizumab decreased free IgE levels to less than 25 ng/mL. Omalizumab improved asthma control and was well-tolerated, as well.

* Corresponding author. Department of Pediatrics, Fukuoka National Hospital, 4-39-1 Yakatabaru, Minami-Ku, Fukuoka 811-1394, Japan.
E-mail address: odaji@mfukuoka2.hosp.go.jp (H. Odajima).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.05.006

JPGL, Japanese pediatric guideline for the treatment and management of asthma;
LABA, Long-acting β_2-agonist;
LTRA, Leukotriene receptor antagonist;
PEF, Peak expiratory flow; QOL, Quality of life; SAE, Serious adverse event

Introduction

Asthma is one of the most common chronic diseases in childhood. In Japan, as well as in Western countries, the prevalence of pediatric asthma is increasing: between 1982 and 2002, it increased from 3.2% to 6.5%, representing a two-fold increase in just 20 years.[1] Asthma in children is often poorly controlled, usually as a result of undertreatment with controller medications; however, some children have poor asthma control even with the highest level of controller medications.[2,3]

Uncontrolled severe asthma results in a high risk of asthma exacerbations and impaired quality of life.[4] In particular, asthma exacerbations are associated with decline in lung function,[5] hospital admissions and emergency room (ER) visits,[6] and time lost from work and school.[7] They are frequently treated with systemic (oral or intravenous [IV]) corticosteroids, which, if used in multiple bursts over a period of years, can result in serious side effects such as a reduction in bone mineral accretion and an increased risk of osteopenia.[8]

The majority of children with asthma are atopic, and pediatric patients with severe asthma have higher mean immunoglobulin E (IgE) levels than those with moderate or mild asthma,[9] providing a particularly strong rationale for investigating anti-IgE therapy in this population.

Omalizumab is a humanized monoclonal anti-IgE antibody that binds IgE, rapidly suppressing free IgE concentrations; it prevents IgE from interacting with high-affinity IgE receptors on mast cells and basophils, thereby interrupting the allergic cascade.[10,11] Omalizumab is approved for the treatment of adults and adolescents (≥12 years) with moderate-to-severe (USA) or severe (EU) allergic (IgE-mediated) asthma,[12,13] and also for the treatment of adults with severe allergic asthma in Japan.[14] In the EU, the indication has recently been extended to include children (6–<12 years) with severe allergic asthma. In a randomized, double-blind, placebo-controlled study in children (6–<12 years) with moderate-to-severe allergic asthma, omalizumab significantly reduced asthma exacerbations compared with placebo.[15,16]

In the current study, the efficacy including free IgE suppression and safety of omalizumab in Japanese children aged 6–15 years with uncontrolled severe persistent allergic asthma were investigated for the first time, to confirm whether the outcome of treatment in a Japanese/Asian population is consistent with findings in previously studied populations.

Methods

Participants

Eligible patients were aged 6–15 years with a diagnosis of severe persistent allergic asthma according to the Japanese pediatric guideline for the treatment and management of asthma (JPGL) 2008.[17] All patients had uncontrolled asthma despite receiving inhaled corticosteroids (ICS) (>200 μg/day fluticasone propionate [FP] dry powder inhaler [or equivalent]) and two or more controller medications (leukotriene receptor antagonist [LTRA], long-acting β_2-agonist [LABA], theophylline, sodium cromoglycate, and oral corticosteroid), consistent with step 4 treatment (i.e. the most intensive treatment step) of the JPGL 2008. 'Uncontrolled' was defined as meeting one of the following criteria during the screening period: (1) asthma symptoms every day; (2) night-time symptoms in ≥2 out of the last 14 days; (3) limitation of daily activities in ≥2 out of the last 14 days.

In addition, patients had to have a history of two or more documented asthma exacerbations requiring treatment with a doubling of the maintenance ICS dose for at least 3 days and/or systemic (oral or IV) corticosteroids; one of these had to have occurred in the previous 12 months.

Patients were also required to have IgE sensitization to one of the perennial aeroallergens, demonstrate at least an increase of 12% in forced expiratory volume in one second (FEV_1) within 30 min of taking a short-acting β_2-agonist (SABA), and have serum total IgE levels of 30–1300 IU/mL and body weights of 20–150 kg to allow optimal dosing of omalizumab.

Patients were excluded if they had: (1) active lung disease, other than allergic asthma, that could potentially interfere with the outcome; (2) a history of food or drug-related severe anaphylactoid or anaphylactic reactions; (3) a positive skin test to omalizumab at screening; (4) platelet level ≤ 100,000/μL (100×10^9/L) at screening; or (5) a serious medical condition (e.g. cancer, hepatic failure, renal failure).

Study design

This was a multicenter, uncontrolled, open-label study, conducted at 17 centers in Japan, with a 2-week screening period, a 24-week treatment period (consisting of a 16-week fixed phase and an 8-week adjustable phase), and a follow-up investigation at 16 weeks after final dosing.

Omalizumab 75–375 mg was administered every 2 or 4 weeks by subcutaneous injection, with the dose being selected from a standard dosing table (Fig. 1)[15,18,19] according to baseline serum total IgE level and bodyweight.

The doses of ICS and other controller medications for asthma were kept constant for 4 weeks before the screening period, and were maintained during the screening period and the fixed phase of the treatment period (unless adjustment was required for an asthma exacerbation). During the first 4 weeks of the adjustable phase of the treatment period, doses could be adjusted downward according to the JPGL 2008 based on the investigator's judgment. During the remaining 4 weeks of the adjustable phase, the doses established during the first 4 weeks of the adjustable period were kept stable. Rescue medication use was permitted as required throughout the study.

Patients self-monitored and recorded their asthma symptoms, limitation of daily activities, sleep disturbances and rescue medication use in their diaries during the screening and treatment periods; they also measured and recorded their peak flow daily.

The study was conducted in accordance with good clinical practice, and the protocol was approved by each institution's ethics committee. Parents or legal guardians were informed of study procedures and medications, and provided written informed consent before their child's enrollment. The study was registered at http://clinicaltrials.gov with the identifier: NCT01155700.