Allergology International xxx (2017) 1–7

Contents lists available at ScienceDirect

Allergology International

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

Original article

Efficacy and safety of benralizumab in Japanese patients with severe, uncontrolled eosinophilic asthma

Ken Ohta [a, *], Mitsuru Adachi [b], Yuji Tohda [c], Tadashi Kamei [d], Motokazu Kato [e], J. Mark Fitzgerald [f], Masayuki Takanuma [g], Tadahiro Kakuno [g], Nobuyuki Imai [g], Yanping Wu [h], Magnus Aurivillius [i], Mitchell Goldman [h]

[a] National Hospital Organization, Tokyo National Hospital, Tokyo, Japan
[b] International University of Health and Welfare Sanno Hospital, Tokyo, Japan
[c] Kindai University Faculty of Medicine, Osaka, Japan
[d] Kamei Respiratory Clinic, Takamatsu, Japan
[e] Kishiwada City Hospital, Osaka, Japan
[f] The Lung Centre, Vancouver General Hospital, UBC Institute for Heart and Lung Health, Vancouver, BC, Canada
[g] Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan
[h] AstraZeneca, Gaithersburg, MD, USA
[i] AstraZeneca, Mölndal, Sweden

ARTICLE INFO

Article history:
Received 14 August 2017
Received in revised form
26 September 2017
Accepted 29 September 2017
Available online xxx

Keywords:
Asthma
Biologic
Eosinophil
Exacerbation
Interleukin-5 receptor

Abbreviations:
CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IL-5, interleukin-5; LABA, long-acting β_2-agonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks

ABSTRACT

Background: In the Phase III CALIMA trial, benralizumab significantly reduced asthma exacerbations, increased lung function, and alleviated symptoms for patients with severe, uncontrolled eosinophilic asthma. The aim of this subgroup analysis was to evaluate the efficacy and safety of benralizumab for Japanese patients in the CALIMA trial.
Methods: CALIMA was a randomised, controlled trial of 1306 patients (aged 12–75 years; registered at ClinicalTrials.gov: NCT01914757) with severe asthma uncontrolled by medium- to high-dosage inhaled corticosteroids and long-acting β_2-agonists (ICS/LABA). Patients received 56 weeks' benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses Q4W), or placebo Q4W. The primary analysis population was patients receiving high-dosage ICS/LABA with blood eosinophils $\geq$300 cells/μL. This subgroup analysis covered Japanese patients from this group.
Results: Of 83 patients randomised in Japan, 46 were receiving high-dosage ICS/LABA and had blood eosinophils $\geq$300 cells/μL. Compared with placebo, benralizumab reduced the annual rate of asthma exacerbations by 66% (Q4W; rate ratio 0.34, 95% CI, 0.11–0.99) and 83% (Q8W; rate ratio 0.17, 95% CI, 0.05–0.60); increased prebronchodilator FEV_1 by 0.334 L (Q4W; 95% CI, 0.020–0.647) and 0.198 L (Q8W; 95% CI, −0.118 to 0.514); and decreased total asthma symptom score by 0.17 (Q4W; 95% CI, −0.82 to 0.48) and 0.24 (Q8W; 95% CI, −0.87 to 0.40). Percentages of adverse events were consistent with the overall CALIMA group.
Conclusions: Benralizumab reduced annual asthma exacerbations and symptoms, increased lung function, and was well-tolerated by Japanese patients with severe, uncontrolled eosinophilic asthma.
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Introduction

Asthma is a common chronic inflammatory disease of the airways that affects upwards of 315 million persons worldwide.[1] It is estimated that 8–13% of persons in Japan have asthma, and the prevalence is rapidly increasing.[2,3] A significant number of patients with asthma have moderate to severe asthma and require maintenance treatment with medium- to high-dosage inhaled corticosteroids and long-acting β_2-agonists (ICS/LABA) to control their symptoms.[2,4] However, despite the availability of ICS/LABA therapy, many patients' symptoms remain uncontrolled, resulting in increased morbidity and reduced health-related quality of life.[5] Therefore, additional well-tolerated and effective treatment options are needed.

Benralizumab is an afucosylated, humanised, anti-eosinophil, monoclonal antibody against the interleukin-5 (IL-5) receptor α.[6]

* Corresponding author. Center for Pulmonary Diseases, National Hospital Organization, Tokyo National Hospital, 3-1-1 Takeoka, Kiyose-shi, Tokyo 204-8585, Japan.
E-mail address: kenohta@tokyo-hosp.jp (K. Ohta).
Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2017.10.004
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Please cite this article in press as: Ohta K, et al., Efficacy and safety of benralizumab in Japanese patients with severe, uncontrolled eosinophilic asthma, Allergology International (2017), https://doi.org/10.1016/j.alit.2017.10.004

In Phase III clinical trials, benralizumab significantly reduced annual asthma exacerbation rates, increased lung function, and alleviated asthma symptoms, alongside near-complete depletion of blood eosinophils, for patients with severe, controlled, eosinophilic asthma.[7,8] For patients with oral corticosteroid (OCS)-dependent asthma, add-on therapy with benralizumab substantially reduced OCS dosages, and many patients receiving benralizumab were able to stop maintenance OCS treatment completely.[9]

In a Phase IIa dose-ranging trial conducted in a South Korea and Japan, benralizumab 2, 20, and 100 mg reduced asthma exacerbations, increased lung function, and improved asthma control for East Asian patients with severe, uncontrolled eosinophilic asthma.[10] CALIMA was a Phase III trial of benralizumab 30 mg for patients with severe, uncontrolled asthma, conducted across 11 countries in Asia, Europe, and North America, including Japan.[8] The aim of this subgroup analysis was to further characterise the efficacy and safety of the target clinical dosage of benralizumab for Japanese patients using data obtained from the CALIMA trial.

Methods

Study design and patients

This was an analysis of the subset of Japanese patients who participated in the CALIMA trial (registered at ClinicalTrials.gov: NCT01914757). Full details of the CALIMA trial have been published.[8] CALIMA was a randomised, double-blind, parallel-group, placebo-controlled Phase III trial that included 1306 patients (aged 12–75 years) with a history of physician-diagnosed asthma that required treatment with medium- to high-dosage ICS/LABA (>250 μg [medium] or ≥500 μg [high] fluticasone dry powder formulation or equivalent total daily dosage) for 12 months before enrolment. Enrolled patients must have had two or more asthma exacerbations in the 12 months prior to enrolment that required use of a systemic corticosteroid or temporary increase in the patient's usual maintenance OCS dosage. Patients also must have had treatment with ICS (≥500 μg/day fluticasone propionate dry powder formulation or equivalent total daily dosage) plus LABA for ≥3 months prior to enrolment. Patients were recruited to the trial with blood eosinophil counts ≥300 and <300 cells/μL in a 2:1 ratio. An independent ethics committee or institutional review board for each study centre approved the final study protocol. Patients gave written informed consent and patient anonymity was preserved using methods approved by the Ethics Committee.

The CALIMA trial consisted of an enrolment visit (Week −4), a screening phase (Weeks −4 to 0), randomisation (Week 0), the treatment period (Weeks 0–56), and a follow-up visit (Week 60). Qualified patients were randomised 1:1:1 to receive 56 weeks' double-blind treatment with benralizumab 30 mg by subcutaneous injection either every 4 weeks (Q4W) or Q4W for the first three doses, then every 8 weeks thereafter (Q8W; placebo was administered in the 4-weekly interim visits to maintain blinding), or placebo Q4W (see Supplementary Fig. 1 in the Appendix; benralizumab and placebo were provided by AstraZeneca, Gaithersburg, MD, USA). Patients in the Q4W arm received their last dose of benralizumab at Week 52, and patients in the Q8W arm received their last dose of benralizumab at Week 48. Patients continued to receive their background asthma controller medications without dosage modification throughout the trial.

Study endpoints

The primary efficacy endpoint was the annual rate of asthma exacerbations. An exacerbation was defined as a worsening of asthma that led to use of systemic corticosteroids (or a temporary increase in background OCS dosage) for at least 3 days, an emergency department or urgent care visit for <24 h because of asthma that required use of systemic corticosteroids, or an inpatient hospitalisation for ≥24 h because of asthma. Worsening of asthma was defined as new or increased asthma signs or symptoms that were concerning to the patient or related to an Asthma Daily Diary alert.

The key (multiplicity-protected) secondary endpoints were prebronchodilator forced expiratory volume in 1 s (FEV_1) and total asthma symptom score. Spirometry was conducted at the study centres. In addition, patients recorded their asthma symptoms and results of peak expiratory flow measurements (taken using a handheld spirometric device) twice daily in the Asthma Daily Diary using an electronic patient-reported outcomes device. The Asthma Daily Diary was completed by patients in the morning, upon waking, and in the evening, prior to going to bed. The morning and evening assessments included questions on asthma symptoms, night-time awakenings, and rescue medication use. The total daily asthma symptom score was a composite of the morning and evening responses, scored on a 0–6 scale. Greater scores indicated a greater burden of symptoms. The electronic patient-reported outcomes devices were programmed to alert patients and the study centres when specific criteria were met for asthma worsening on ≥2 consecutive days/nights, including a decrease in morning peak expiratory flow of ≥30% compared with baseline, a ≥50% increase in rescue medication use or one new β_2-agonist nebuliser compared with the previous 7 days, nocturnal awakening because of asthma that required rescue medication use, and an increase in total asthma symptom score of two or more units above the screening average (or the maximum possible daily score of 6). Blood eosinophil counts were assessed as an exploratory endpoint. To evaluate safety, adverse events (AEs) were monitored throughout the study.

Statistical analyses

The primary analysis population was patients receiving high-dosage ICS/LABA with baseline blood eosinophils ≥300 cells/μL in the overall CALIMA trial population and the Japanese subgroup analysis. Annual exacerbation rates were estimated using a negative binomial model that included treatment, number of exacerbations in the previous year, and use of maintenance OCS as covariates. Least squares mean changes from baseline in FEV_1 compared with placebo were estimated using a mixed-effect model for repeated measures analysis, with adjustment for treatment, baseline prebronchodilator FEV_1, use of maintenance OCS, visit, and visit by treatment interaction. Least squares mean changes from baseline in bi-weekly average total asthma symptom score compared with placebo also were estimated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline total asthma symptom score, use of maintenance OCS, visit, and visit by treatment interaction. Adverse events were summarized using descriptive statistics. All data analyses were conducted using SAS system version 9.2 or later (SAS Institute, Cary, NC, USA).

Results

Patients

Overall, 1306 patients took part in the CALIMA trial, of whom 728 were receiving high-dosage ICS/LABA with baseline blood eosinophils ≥300 cells/μL and were included in the primary analysis set. A total of 180 Japanese patients were enrolled in CALIMA and 83 were randomly assigned to receive benralizumab or placebo (Supplementary Table 1; 94 patients did not meet the eligibility criteria, two were not randomised because of AEs, and one chose not to enter randomisation). Seventy-four Japanese patients

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