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Original article

Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma

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Abbreviations:
ACQ, Asthma Control Questionnaire; AE, adverse event; CI, confidence interval; ED, emergency department; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IV, intravenous; LS, least squares; MCID, minimal clinically important difference; mITT, modified intent-to-treat; PEF, peak expiratory flow; OCS, oral corticosteroids; QoL, quality of life; RR, rate ratio; SGRQ, St George's Respiratory Questionnaire; SAE, serious adverse event; SC, subcutaneous; SE, standard error; SoC, standard of care; URTI, upper respiratory tract infection

ABSTRACT

Background: The MENSA trial assessed the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma. This report describes the efficacy and safety of mepolizumab in Japanese patients from MENSA.

Methods: A post hoc analysis of the Japanese subgroup from the randomized, double-blind, placebo-controlled, double-dummy, Phase III MENSA trial (NCT01691521). Patients ≥12 years with severe eosinophilic asthma received mepolizumab 75 mg intravenously (IV), 100 mg subcutaneously (SC), or placebo, every 4 weeks for 32 weeks. The primary endpoint was the annualized rate of exacerbations. Secondary and other endpoints included annualized rate of exacerbations requiring emergency department (ED) visit/hospitalization, morning peak expiratory flow (PEF), St George's Respiratory Questionnaire (SGRQ) score and eosinophil counts. Adverse events (AEs) were monitored.

Results: In the Japanese subgroup ($N = 50$), the rate of clinically significant exacerbations was reduced by 90% (rate ratio [RR]: 0.10; 95% confidence interval [CI]: 0.02–0.57; $P = 0.010$) with mepolizumab IV and 62% (RR: 0.38; 95% CI: 0.12–1.18; $P = 0.094$) with mepolizumab SC, versus placebo. No exacerbations requiring ED visit/hospitalization were reported with mepolizumab IV; exacerbations were reduced by 73% (RR: 0.27; 95% CI: 0.06–1.29; $P = 0.102$) with mepolizumab SC versus placebo. Compared with placebo, mepolizumab IV and SC numerically increased morning PEF from baseline by 40 L/min and 13 L/min, improved quality of life by greater than the minimal clinically important difference (SGRQ: 9.5 [$P = 0.083$] and 7.9 [$P = 0.171$] points) and reduced eosinophil counts. AE incidence was similar between treatments. Results were broadly consistent with the overall population.

Conclusions: Mepolizumab was efficacious and well tolerated in Japanese patients with severe eosinophilic asthma, producing similar responses to the overall MENSA population.

Introduction

Severe asthma is defined by the Japanese Asthma Guidelines and Global Initiative for Asthma (GINA) guidelines as asthma requiring high-dose inhaled corticosteroids (ICS) and a second controller medication and/or oral corticosteroids (OCS) for symptom control, or disease that remains uncontrolled despite these therapies.[1,2] The proportion of Japanese patients with asthma

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characterized as severe is reported to range from 5.7% to 7%,[3,4] which is similar to the incidence in western countries (5–10%).[5,6] Severe asthma is a heterogeneous condition, and a subset of patients include those with increased eosinophils, termed severe eosinophilic asthma.[7,8] These patients experience frequent exacerbations, poor symptom control, decreased quality of life (QoL), and increased risk of lung function decline despite high doses of standard maintenance therapies such as ICS.[1,8–12]

Mepolizumab is a humanized monoclonal antibody targeting interleukin-5. In clinical trials, mepolizumab has been shown to reduce eosinophil counts,[7,13,14] the number of asthma exacerbations,[7,15,16] and OCS maintenance dose[17,18] in patients with severe eosinophilic asthma compared with placebo, when used as add-on therapy to standard of care (SoC). The global Phase III MENSA trial was conducted in Australia, East Asia, Europe, North America, and South America. It demonstrated that both mepolizumab 75 mg intravenous (IV) and 100 mg subcutaneous (SC) treatment resulted in similar reductions in the rate of clinically significant asthma exacerbations, increased lung function, and improved QoL compared with placebo, when used as add-on therapy to SoC.[15]

For the majority of licensed pharmacological therapies, interethnic differences likely to affect treatment responses have been rarely identified.[19–21] Moreover, the profiles of the majority of monoclonal antibody therapies have demonstrated limited therapeutically relevant ethnic differences, with most licensed doses being the same in Japan and the USA.[22] However, differences in patient characteristics between ethnic groups could alter therapeutic responses.[22,23] Currently, there are data on the pharmacodynamics but no reports on the clinical efficacy and safety of mepolizumab in Japanese patients.[24] Therefore, the objective of this subanalysis was to describe the efficacy and safety of mepolizumab in the Japanese subgroup of patients with severe eosinophilic asthma from the MENSA trial.[15]

Methods

Study design

This was a post hoc subgroup analysis of the Japanese population from the MENSA trial. Full details of the MENSA trial have previously been reported.[15] In brief, MENSA was a multicenter, randomized, double-blind, placebo-controlled, double-dummy, parallel-group, Phase III trial conducted between October 2012 and January 2014 (NCT01691521; GSK ID: MEA115588). Patients ≥12 years of age with a clinical diagnosis of asthma who had experienced two or more asthma exacerbations requiring treatment with OCS in the previous year while on maintenance therapy with high-dose ICS were eligible for inclusion in the study. Following the 1–6-week run-in period, patients were randomized (1:1:1) to receive treatment with mepolizumab 75 mg IV, mepolizumab 100 mg SC, or placebo every 4 weeks for 32 weeks, as add-on therapy to intensive SoC asthma treatment (Fig. 1).[15]

Study endpoints

The primary study endpoint was the annualized rate of clinically significant exacerbations, defined as a worsening of asthma requiring systemic corticosteroids administered IV or orally for ≥3 days or a single intramuscular dose, or an emergency department (ED) visit or hospitalization. Patients using maintenance systemic corticosteroids were required to have used at least double their existing maintenance dose for ≥3 days. Secondary and other endpoints included the annualized rate of severe exacerbations requiring an ED visit and/or hospitalization and the annualized rate of exacerbations requiring hospitalization. Change from baseline in daily morning peak expiratory flow (PEF) at Weeks 29–32, and the change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1) at Week 32 were assessed in a non-centralized manner using individual sites' own spirometry equipment. St George's Respiratory Questionnaire (SGRQ) total score and Asthma Control Questionnaire (ACQ-5) score at Week 32 were also assessed. Additionally, the global response to therapy questionnaire was completed at Week 32 by physicians and patients using a 7-point scale (1 = significantly improved, 7 = significantly worsened). Pharmacodynamic assessment of the change from baseline in blood eosinophil counts was also determined. Safety was assessed by monitoring of adverse events (AE), clinical laboratory testing and vital signs. The levels of anti-mepolizumab and mepolizumab neutralizing antibodies were measured at baseline (Week 0) and Weeks 16, 32, and 40 (12 weeks post-final mepolizumab administration). The anti-mepolizumab antibody assay is a bridging electrochemiluminescent immunoassay. The neutralizing antibody assay is an indirect ligand binding immunoassay using electrochemiluminescent detection.

Statistical analysis

The modified intent-to-treat (mITT) population included all patients randomized to and receiving ≥1 dose of study treatment. Two patients who were randomized in error and two patients who were withdrawn due to issues obtaining an IV line were not included in this population; none of these patients were in the Japanese subgroup. The mITT population was the primary analysis population for safety and efficacy endpoints in the overall population and the Japanese subgroup. Statistical analysis methods used for comparisons between treatment groups in the Japanese subgroup were as previously described.[15] The rate of exacerbations used a negative binomial model with covariates of treatment, baseline use of maintenance OCS, exacerbations in the previous year and baseline percent predicted FEV_1. Change from baseline in PEF, FEV_1, and ACQ-5 used a mixed model repeated measures analysis including the above covariates as well as additional ones for baseline, visit, and interaction for visit with baseline and visit with treatment; change from baseline SGRQ used analysis of covariance with the addition of a baseline covariate.

Results

Patients

Of the 576 patients randomized and included in the overall mITT population, 50 (9%) patients from 18 centers in Japan were included in the Japanese subgroup (mean age: 55, range: 14–82 years). Of these patients, 17 received mepolizumab IV, 17 mepolizumab SC, and 16 placebo. In total, 44 (88%) patients (mepolizumab IV, $N = 14$; mepolizumab SC, $N = 15$ and placebo, $N = 15$) in the Japanese subgroup completed the full study. Six patients were withdrawn from the study, with the reason 'withdrawal by subject' in all cases. Of the 6 patients that withdrew, 5 chose not to continue when the original investigator ceased employment at the hospital. Patient demographics and baseline characteristics were broadly similar between the Japanese subgroup and the overall study population (Table 1). However, some differences in the Japanese subgroup included a trend for lower daily OCS dose, higher blood eosinophil counts and decreased reversibility to bronchodilators compared with the overall population. Additionally, in the Japanese subgroup, the mean number (standard deviation [SD]) of exacerbations in the previous year (4.6 [3.6]) was higher than in the overall population (3.6 [2.6]).