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Original article

Evaluation of unmet medical need among Japanese patients with type 2 diabetes mellitus and efficacy of Lixisenatide treatment among Asian type 2 diabetes mellitus patients

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ABSTRACT

Aims: This study determined the unmet medical need of basal insulin therapy among type 2 diabetes patients who participated in the ALOHA study. Also a meta-analysis of the GetGoal-Duo1, -L, and -L-Asia trials was conducted to examine the impact of lixisenatide add-on treatment to basal insulin therapy ± OADs specifically among Asian type 2 diabetes patients.

Methods: The proportions of Japanese patients with an unmet need of diabetes management, defined as not achieving an HbA1c < 7% despite having a fasting plasma glucose (FPG) < 130 mg/dL, and without an unmet need, defined as having an endpoint HbA1c < 7%, regardless of FPG level, were determined for the ALOHA study population, which was conducted as a post-marketing survey for insulin glargine in Japan. For the meta-analysis, all Asian modified intent-to-treat patients with baseline and endpoint HbA1c measurements reported from the 3 GetGoal trials were included.

Results: Among 1013 Japanese type 2 diabetes patients in the ALOHA study, 36% had an unmet need. In the GetGoal-Duo1, -L, and L-Asia trials, 237 Asian patients were treated with lixisenatide add-on treatment to basal insulin and 226 received placebo. Lixisenatide add-on treatment vs. placebo was associated with the following significant mean changes in efficacy outcomes at week 24: HbA1c: −0.6%, $p = 0.005$; FPG: −13.3 mg/dL, $p = 0.004$; PPG: −101.4 mg/dL, $p < 0.001$; weight: −0.5 kg, $p = 0.018$; basal insulin dose: −1.6 U, $p < 0.001$.

Conclusions: Lixisenatide add-on treatment may provide a viable option to address the unmet need of basal insulin therapy among Asian type 2 diabetes patients.

1. Introduction

Type 2 diabetes is a progressive metabolic disease resulting from insulin resistance and insulin deficiency. As the disease progresses maintaining optimal glycemic control becomes more challenging and treatment intensification is needed to avoid complications of chronic hyperglycemia [1]. Initiation of basal insulin therapy is one method used to manage type 2 diabetes when diet, exercise, and oral anti-diabetic drugs (OAD) are no longer efficacious in maintaining glycemic control [1]. Clinical trials have demonstrated that initiation of basal insulin therapy can improve glycemic control in many type 2 diabetes patients; however between 40% and 50% still do not achieve an HbA1c ≤7–7.5% [2–4]. Basal insulin therapy is useful for reducing fasting hyperglycemia, but it does not significantly influence postprandial hyperglycemia, which may be the rate-limiting factor for achieving optimal glycemic control for many type 2 diabetes patients [5,6]. Basal insulin therapy in combination with an incretin mimetic has been proposed as a glucose-lowering strategy as the treatments are complementary in that basal insulin therapy effectively lowers fasting plasma glucose (FPG) levels, while incretin therapy substantially lowers postprandial glucose (PPG) levels [5,6]. Additionally, incretin therapies may reduce the risk for weight gain that frequently occurs with basal insulin therapy and possibly promote weight loss [5,6].

Lixisenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. The efficacy and safety of lixisenatide add-on treatment to basal insulin therapy for the treatment of type 2 diabetes were evaluated in the GetGoal-Duo1, GetGoal-L, and GetGoal-L-Asia trials [7–9]. The results of these multi-center, multi-country,

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randomized, placebo-controlled trials demonstrated that lixisenatide add-on treatment to basal insulin therapy ± OADs enhances glycemic control relative to placebo add-on treatment primarily by reducing PPG levels [7–9]. In particular, among the overall trial populations lixisenatide add-on treatment was associated with mean HbA1c reductions that ranged between −0.3% and −0.9% and mean reductions in PPG levels 2 h during a standardized meal test that ranged between −57 and −140 mg/dL [7–9].

The Asian-Pacific Type 2 Diabetes Policy Group reported that type 2 diabetes is a major public health concern among countries in the Asian-Pacific region and has become epidemic in a number of Asian countries [10]. For this study, we had two related objectives to better examine the impact of lixisenatide add-on treatment to basal insulin therapy specifically among Asian type 2 diabetes patients. The first objective was to determine the unmet medical need of basal insulin therapy, defined as not achieving an HbA1c < 7% despite having a FPG < 130 mg/dL among type 2 diabetes patients who participated in the ALOHA study, which was a 24-week, prospective, open-label, multicenter, observational assessment of the safety and effectiveness of BOT (basal supported oral therapy) with insulin glargine for treating Japanese patients with type 2 diabetes [11]. The second objective was to conduct a meta-analysis on patient data from the GetGoal-Duo1, -L, and -L-Asia trials to examine the efficacy and safety of lixisenatide add-on treatment to basal insulin therapy ± OADs among all Asian type 2 diabetes patients who participated in these trials.

2. Methods

2.1. Evaluation of unmet medical need among ALOHA study population

The proportions of type 2 diabetes patients with an unmet need of type 2 diabetes management, defined as not achieving an HbA1c < 7% despite having an FPG < 130 mg/dL (i.e. population for PPG management—"PPG target" population), and without an unmet need, defined as having an endpoint HbA1c <7%, regardless of FPG level (i.e. "good control") were determined for the ALOHA study population. Determination of "unmet medical need status" required that type 2 diabetes patients have both baseline and endpoint HbA1c and FPG levels reported and therefore, only a portion of the ALOHA study participants were included in this analysis. Those type 2 diabetes patients who neither achieved an HbA1c <7% nor a FPG <130 mg/dL at study endpoint were defined as the "uncontrolled" population and were not further analyzed in this study. The definition of an unmet medical need of type 2 diabetes management used in this study was based on the Japan Diabetes Society guideline of maintaining an HbA1c <7% and an FPG level <130 mg/dL for adequate glycemic control [12]. Statistical analyses were carried out among the patients grouped into the two cohorts of different unmet need status (yes vs. no). Patient demographics, clinical characteristics, and baseline, endpoint, and change from baseline in HbA1c, FPG, weight and basal insulin dose were summarized and compared. Statistical significance of differences in continuous variables was determined by ANOVA, and that for categorical variables was determined by Chi-square test. A p-value of 0.05 was used to determine the level of significance and the statistical analyses were carried out using SAS® 9.3 (Cary, NC).

2.2. Meta-analysis of effects of lixisenatide add-on treatment to basal insulin therapy vs. placebo add-on treatment

All modified intent-to-treat Asian patients from the GetGoal-Duo1, -L, and -L-Asia trials with baseline and endpoint HbA1c measurements reported were included in the meta-analysis. All three trials evaluated the efficacy and safety of lixisenatide add-on treatment to basal insulin therapy ± OADs and the primary efficacy outcome was the absolute change in HbA1c from baseline to week 24 [7–9]. In the trials lixisenatide treatment consisted of an once-daily injection in a two-step dose-increase regimen (10 μg for 1 week, 15 μg for 1 week, and then 20 μg up to the end of the study) [7–9]. All trials were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Further details of the trials can be found in each individual study publication [7–9].

2.3. Meta-analysis data collection

Patient demographics and clinical characteristics as well as measurements of efficacy and safety outcomes for each treatment arm (i.e. lixisenatide add-on treatment to basal insulin therapy, placebo add-on treatment to basal insulin therapy) in the GetGoal-Duo1, -L, and -L-Asia trials were collected. Efficacy outcomes included changes from baseline in HbA1c, FPG, PPG (standardized 2-h meal test), weight, and basal insulin dose. Other outcomes evaluated included the ratios of symptomatic hypoglycemia and of achieving an endpoint HbA1c <7%.

2.4. Meta-analysis approach

The efficacy and safety of lixisenatide add-on treatment vs. placebo for Asian type 2 diabetes patients were evaluated by performing a meta-analysis on the data from the clinical trials. Meta-analysis outcomes were assessed using a random effects model. Weighted mean differences with 95% confidence intervals (CI) were determined for continuous data using the inverse variance method. Mantel-Haenszel odds ratios for 95% CI were determined for all dichotomous outcome data. The meta-analysis was conducted using Review Manager (RevMan, version 5.1, Copenhagen: Cochrane Collaboration). Using RevMan, Tau^2, I^2 and Chi^2 statistics were calculated to assess the data heterogeneity. Chi^2-test with p-values was used to indicate the significance level of such heterogeneity. Z-test with p-value was used to assess whether the overall effect difference between the two comparison arms was statistically significant. A p-value of 0.05 was used to determine the level of statistical significance.

3. Results

3.1. Unmet medical need status of ALOHA study population

Among 1013 type 2 diabetes patients who participated in the ALOHA study, with both baseline and endpoint HbA1c and FPG values, 35.6% had an unmet medical need (HbA1c ≥7%, FPG <130 mg/dL) at study endpoint (Fig. 1), and 21.9% had HbA1c <7%.

3.2. Differences among type 2 diabetes patients with and without an unmet medical need

Baseline characteristics of the unmet need = yes (n = 361) and unmet need = no (n = 222) cohorts of the ALOHA study population are summarized in Table 1. Mean age of both cohorts was 62 years and gender distribution, mean basal insulin dose, mean body weight, and mean BMI did not significantly differ between cohorts. An unmet medical need was associated with a longer duration of diabetes (>5 years: unmet need = yes: 87.8% vs. unmet need = no: 79.5%, p = 0.01). Mean baseline HbA1c (9.3% vs. 9.0%, $p < 0.001$) was greater for the cohort with an unmet medical need, while mean FPG level (179.5 mg/dL vs. 196.6 mg/dL, p = 0.003) was lower in comparison to the cohort without an unmet need. The mean reduction in HbA1c during the study period was lower for the