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Effects of linagliptin monotherapy compared with voglibose on postprandial blood glucose responses in Japanese patients with type 2 diabetes: Linagliptin Study of Effects on Postprandial blood glucose (L-STEP)

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ABSTRACT

Aims: To compare the efficacy on glycemic parameters between a 12-week administration of once-daily linagliptin and thrice-daily voglibose in Japanese patients with type 2 diabetes.

Methods: In a multi-center, randomized, parallel-group study, 382 patients with diabetes were randomized to the linagliptin group ($n = 192$) or the voglibose group ($n = 190$). A meal tolerance test was performed at weeks 0 and 12. Primary outcomes were the change from baseline to week 12 in serum glucose levels at 2 h during the meal tolerance test, HbA1c levels, and serum fasting glucose levels, which were compared between the 2 groups.

Results: Whereas changes in serum glucose levels at 2 h during the meal tolerance test did not differ between the groups, the mean change in HbA1c levels from baseline to week 12 in the linagliptin group (−0.5 ± 0.5% [−5.1 ± 5.4 mmol/mol]) was significantly larger than in the voglibose group (−0.2 ± 0.5% [−2.7 ± 5.4 mmol/mol]). In addition, there was significant difference in changes in serum fasting glucose levels (−0.51 ± 0.95 mmol/L in the linagliptin

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group vs. −0.18 ± 0.92 mmol/L in the voglibose group, $P < 0.001$). The incidences of hypoglycemia, serious adverse events (AEs), and discontinuations due to AEs were low and similar in both groups. However, gastrointestinal AEs were significantly lower in the linagliptin group (1.05% vs. 5.85%; $P = 0.01$).

Conclusions: These data suggested that linagliptin monotherapy had a stronger glucose-lowering effect than voglibose monotherapy with respect to HbA1c and serum fasting glucose levels, but not serum glucose levels 2 h after the start of the meal tolerance test.

1. Introduction

Early type 2 diabetes is characterized by postprandial hyperglycemia [1]. Postprandial hyperglycemia plays an important role in the development of cardiovascular complications in patients with type 2 diabetes mellitus (T2DM) [2] and people with impaired glucose tolerance (IGT) [3]. Postprandial hyperglycemia also plays an important role in accelerating pancreatic β-cell failure by imposing increased insulin secretory demands on pancreatic β cells, leading to the development of T2DM in patients with IGT. Thus, postprandial glycemic excursion is a favorable treatment target for patients with early stage T2DM, with respect to the inhibition of both disease progression and cardiovascular complications.

Alpha-glucosidase inhibitors (α-GIs) prevent the digestion of carbohydrates, and reduce postprandial blood glucose excursion [4,5]. The α-GI acarbose was shown to improve postprandial hyperglycemia and impaired endothelial function in patients with T2DM [6,7] and to attenuate the risk of cardiovascular events in patients with T2DM [8] and in individuals with IGT [4]. Voglibose, another α-GI, when used together with lifestyle modifications, can prevent the development of T2DM in high-risk Japanese individuals with IGT [5]. Supported by evidence from these clinical trials, α-GIs have been widely prescribed as a primary treatment in Japan for patients with T2DM that cannot be controlled by lifestyle modifications.

On the other hand, dipeptidyl peptidase (DPP)-4 inhibitors prevent the degradation of endogenous glucagon-like peptide-1 (GLP-1), which in turn enhances glucose-dependent insulin secretion from pancreatic β cells, and reduces glucagon secretion from α cells, which potentially suppresses postprandial glycemic excursions [9–11]. DPP-4 inhibitors are generally well tolerated and do not affect body weight.

Linagliptin is a highly selective, once-daily oral DPP-4 inhibitor used worldwide in more than 80 countries, including the United States, Europe, and Japan for the treatment of patients with T2DM. Whereas many other DPP-4 inhibitors that are available today are excreted mostly via the renal route [12], linagliptin is selectively excreted via the bile and gut, making it suitable for use without dose adjustment in patients with renal dysfunction [13]. In clinical studies, linagliptin was reported to be as effective on glycemic parameters as metformin and sulfonylureas [14]. The safety profile of linagliptin was more favorable than that of a sulfonylurea regarding hypoglycemia and body weight gain. A composite endpoint (consisting of a combination of HbA1c < 7% without hypoglycemia and without weight gain) was achieved more frequently in patients treated with linagliptin in comparison with patients treated with the sulfonylurea glimepiride [14]. Linagliptin had a better safety profile than glimepiride with respect to a combined cardiovascular endpoint, including stroke [14].

To date, the effect of two types of diabetes agents, namely, the DPP-4 inhibitor linagliptin, and the α-GI voglibose on postprandial glucose response in patients with T2DM has not been directly compared. We hence conducted a randomized prospective multicenter study that we named the Linagliptin Study of Effects on Postprandial blood glucose (L-STEP) to compare the effects of linagliptin and voglibose on postprandial hyperglycemia, as assessed by the meal tolerance test and other glycemic parameters in patients with T2DM and those with insufficient glycemic control despite diet and exercise.

2. Methods

2.1. Study design and patients

Japanese patients with T2DM who periodically visited the outpatient clinic of the 44 institutions in Japan listed in the supplementary material (Appendix S1) were asked to participate in this study. The first patient was enrolled on October 12, 2012, and the last patient visit occurred on April 16, 2014.

The study enrolled patients with T2DM who were 20 years of age or older and who had inadequate glycemic control (haemoglobin A1c [HbA1c] 6.2–9.4% [44.2–79.2 mmol/mol] in those previously untreated with oral anti-diabetes drugs (OADs) irrespective of sex; and 6.2–9.4% [44.2–79.2 mmol/mol] after washout in those already receiving one or two OADs for ⩾12 weeks). Key exclusion criteria were (1) type 1 or secondary diabetes, (2) presence of severe infectious disease either before or after surgery, or severe trauma, (3) history of myocardial infarction, angina pectoris, cerebral stroke, or cerebral infarction, (4) severe liver dysfunction (aspartate aminotransferase [AST] ⩾ 100 IU/L), (5) moderate or severe heart failure (New York Heart Association stage III or greater), (6) receiving treatment with an incretin preparation, such as other DPP-4 inhibitors, at the start of the study, (7) received treatment with any type of antidiabetes drug within the previous 3 months and/or a history of known intolerance, allergy, or hypersensitivity to voglibose or any other concomitant