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Retrospective analysis of safety and efficacy of liraglutide monotherapy and sulfonylurea-combination therapy in Japanese type 2 diabetes: Association of remaining β-cell function and achievement of HbA1c target one year after initiation

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ABSTRACT

Aims: The GLP-1 receptor agonist liraglutide improves impaired pancreatic β-cell function, thereby exerting glucose-lowering effects. However, the association of remaining β-cell function with long-term therapeutic efficacy of liraglutide remains largely unknown.
Methods: Patients with type 2 diabetes who started liraglutide as monotherapy or sulfonylurea-combination therapy were retrospectively analyzed to identify possible associations of indices related to β-cell function including increments of C-peptide immunoreactivity in glucagon stimulation test (GST-ΔCPR) with achievement of HbA1c <7.0% at 54 weeks after liraglutide initiation.
Results: Among 165 subjects continuing liraglutide for 54 weeks, 66 received additional oral anti-diabetic drugs (OADs) during the period. Of those continuing liraglutide without receiving additional OADs, 41 subjects achieved HbA1c <7.0% at 54 weeks, while 49 subjects did not. Subjects achieving HbA1c <7.0% showed higher values of GST-ΔCPR. Receiver-operating analysis revealed 2.34 ng/mL as the cut-off value for HbA1c <7.0% achievement in these subjects. Subjects with GST-ΔCPR >2.34 ng/mL showed continuous and substantial HbA1c reduction throughout the 54 weeks. In Kaplan–Meier analysis, subjects with GST-ΔCPR >2.34 ng/mL showed longer therapeutic durability of initial liraglutide therapy with no additional OADs or insulin.
Conclusions: Despite numerous limitations, these results indicate that long-term efficacy of liraglutide is associated with remaining β-cell function at initiation.

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1. Introduction

Type 2 diabetes is a heterogeneous disease characterized by β-cell dysfunction and insulin resistance (DeFronzo, 1988; Stumvoll, Goldstein, & van Haeften, 2005; Yabe, Seino, Fukushima, & Seino, 2015). Due to progressive decline in β-cell function, anti-diabetic treatment regimens must be adjusted over time based on estimates of the remaining insulin secretory capacity. Conventional anti-diabetic drugs that compensate for reduced insulin secretion include insulin and sulfonylurea (SU), both of which have been shown to maintain optimal glycemic control and to prevent progression of diabetes-related complications (Anonymous, 1999; Holman, Paul, Bethel, Matthews, & Neil, 2008). However, insulin and SU are associated with varying degrees of hypoglycemia and weight gain (Anonymous, 1998; Best et al., 2012). Glucagon-like peptide-1 (GLP-1) receptor agonists are emerging anti-diabetic drugs that enhance insulin secretion glucose-dependently as well as suppress glucagon secretion and slow gastric emptying, thereby improving glycemic control and reducing bodyweight in patients with type 2 diabetes (Meier, 2012; Yabe, Kuwata, Usui, Kurose, & Seino, 2015; Yabe & Seino, 2014). Clinical trials of GLP-1 receptor agonists comparing their efficacy and safety with those of insulin or SU show that GLP-1 receptor agonists are capable of achieving appropriate glycemic control with reduced risk of hypoglycemia and bodyweight gain (Meier, 2012; Yabe, Kuwata, Usui, Kurose, & Seino, 2015; Yabe & Seino, 2014). However, the long-term therapeutic effects of GLP-1 receptor agonists in clinical practice need to be evaluated.

Liraglutide is a once daily injectable GLP-1 receptor agonist, with a Lys34Arg substitution and the addition of a C16-fatty acid at Lys26 in human GLP-1 (Best et al., 2012; Faber & Binder, 1977; Fujita et al., 2015; Funakoshi et al., 2011; Gjessing, Matzen, Froland, & Faber, 1987; Greenbaum et al., 2008; Hendriksen, Faber, Drejer, & Binder, 1977; Iwao, Sakai, & Sata, 2013; Iwata et al., 2014; Kajinuma et al., 1979; Kaku, Rasmussen, Clauson, & Seino, 2010; Kaku, Rasmussen, Nishida, & Seino, 2011; Kondo et al., 2013; Kozawa et al., 2012; Lapolla et al., 2015; Matsuda, Kamata, Iwamoto, Sakamoto, & Kuzuya, 1985; Meier, 2012; Ponzani, 2013; Retnakaran, Kramer, Choi, Swaminathan, & Zinman, 2014; Saisho et al., 2011; Seino, Rasmussen, Clauson, & Kaku, 2012; Seino, Rasmussen, Nishida, & Kaku, 2010; Seino et al., 2010; Shao, Yuan, Feng, Zhang, & Guo, 2014; Toyoda, Yokoyama, Abe, Nakamura, & Suzuki, 2014; Usui et al., 2013; Vilsboll et al., 2008; Yabe, Kuwata, Usui, Kurose, & Seino, 2015; Yabe & Seino, 2011, 2014; Yamada et al., 2006). This endows resistance to degradation of GLP-1 mediated by dipeptidyl peptidase-4 and its stabilization in human circulation as an albumin bound form. Liraglutide has been shown to exert its glucose-lowering effects partly by ameliorating impaired glucose-dependent insulin secretion from β-cells, one of the major defects in type 2 diabetes (Seino et al., 2012; Vilsboll et al., 2008). It has been reported that early liraglutide initiation in type 2 diabetes as well as in experimental animals exerts superior improvement on β-cell function and better glycemic control (Retnakaran et al., 2014; Shao et al., 2014), suggesting that remaining β-cell function might predict the glucose-lowering effects of liraglutide. While several clinical studies have demonstrated that liraglutide results in greater HbA1c reduction in early stage diabetes (Iwao et al., 2013; Lapolla et al., 2015; Ponzani, 2013; Toyoda et al., 2014), clinical investigations of direct association of β-cell function with glucose-lowering effects of liraglutide, especially at longer time points, are few. To assess β-cell function in patients with type 2 diabetes in clinical settings, several indices using serum C-peptide immunoreactivity (CPR) are used: glucagon-stimulated increments of CPR (Faber & Binder, 1977; Fujita et al., 2015; Gjessing et al., 1987; Hendriksen et al., 1977), fasting and postprandial C-peptide index (CPI) (Funakoshi et al., 2011; Saisho et al., 2011), and secretory units of islets in transplantation (SUIT) (Funakoshi et al., 2011; Iwata et al., 2014; Yamada et al., 2006). While glucagon-stimulated increments of CPR are ideal for assessment of β-cell function, CPI and SUIT were used because they are more readily evaluated in actual clinical settings. These CPR-related indices for β-cell function have been used to predict requirements for insulin injections in patients with type 2 diabetes (Funakoshi et al., 2011; Iwata et al., 2014; Saisho et al., 2011). We and others have reported that these CPR-related indices can predict successful switch from insulin to liraglutide (Kondo et al., 2013; Kozawa et al., 2012; Usui et al., 2013), but the associations of these CPR-related indices with long-term therapeutic efficacy of liraglutide have not been investigated.

In the current study, we evaluated the role of remaining β-cell function in relation to long-term therapeutic efficacy of liraglutide in Japanese patients with type 2 diabetes.

2. Materials and methods

2.1. Participants

Two hundred seventy-two patients with type 2 diabetes who started liraglutide therapy at Kansai Electric Power Hospital between June 2010 and March 2012 were retrospectively analyzed in the current study. None of the patients had type 1 diabetes, pancreatic disease, liver disease, renal disease, malignancy or were taking diabetogenic medication or were pregnant. Type 1 diabetes was diagnosed by auto-antibodies such as anti-GAD antibody and anti-IA-2 antibody according to the diagnostic criteria of type 1 diabetes by the Japan Diabetes Society (Seino, Nanjo, et al., 2010). Patients with renal failure and/or those taking dialysis were excluded, since serum CPR levels are modified in these conditions. Insulin-dependent patients were also excluded for lack of β-cell function. Insulin-dependency was defined by combinations of fasting CPR ≤0.5 ng/mL, stimulated CPR ≤1.0 ng/mL, and urinary CPR ≤20 μg/day (Matsuda et al., 1985). The duration of type 2 diabetes was defined as years after diagnosis of the disease according to the criteria of the Japan Diabetes Society. Physical and laboratory data including HbA1c were acquired in all patients before and every 6 weeks after starting liraglutide therapy. Inclusion and exclusion of the study subjects are summarized in Fig. 1. Of the 272 patients, 22 were excluded from analysis because they were referred to other clinics or stopped hospital visits for unknown reasons during the 54 week period. The baseline clinical profiles and parameters of the remaining 250 patients are shown in Table 1. Of them, 26 patients discontinued liraglutide during the 54 weeks due to adverse events (nausea n = 6, skin rash n = 1, others n = 19), and 59 patients discontinued liraglutide due to hyperglycemia. Sixty-six patients received additional OADs during the 54 weeks (8 patients, HbA1c at 54 weeks was not available), and the remaining 99 patients continued liraglutide during the 54 weeks without adding any OAD (9 patients, HbA1c at 54 weeks was not available). Severe hypoglycemia was defined as requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Non-severe hypoglycemia was not evaluated in the current study, since its definition varied among the physicians in charge.

2.2. Measurements

HbA1c was measured using high performance liquid chromatography with cation-exchange resins that separate the stable form of β-N1-mono-deoxyfructosyl Hb; the values are shown in National Glycohemoglobin Standardization Program units as recommended by the Japan Diabetes Society (Seino, Nanjo, et al., 2010). Glucagon stimulation test (GST) was carried out after an overnight fast by measuring serum CPR at fasting or 6 min after intravenous injection of 1 mg glucagon (CPR-0 min and CPR-6 min, respectively) (Kajinuma et al., 1979). In patients who received insulin therapy before starting liraglutide therapy, insulin injections were continued to avoid hyperglycemia until the night before measuring fasting and/or