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Original article

Safety and efficacy of liraglutide treatment in Japanese type 2 diabetes patients after acute myocardial infarction: A non-randomized interventional pilot trial☆

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ABSTRACT

Background: Glucagon-like peptide 1 analogs are expected to exert a cardio-protective action due to their effective glucose-lowering action and favorable potency on multifactorial metabolic pathways. However, the safety and tolerability of liraglutide treatment after a recent acute coronary syndrome (ACS) in Japanese patients with type 2 diabetes mellitus (T2DM) have yet to be fully established.
Methods: A total of eight T2DM patients were recruited within 2 weeks after the onset of a ST-elevation myocardial infarction (STEMI) followed by successful percutaneous coronary intervention (PCI). The patients continued to receive liraglutide (up to 0.9 mg once daily) for 24 weeks after the ACS combined with standard treatment such as a statin or beta-blocker. Changes in various metabolic parameters from pre-liraglutide treatment values were evaluated 24 weeks after liraglutide treatment, and included glycemic and lipid profiles, and cardiac systolic and diastolic function assessed by cardiac ultrasonography.
Results: Twenty-four weeks of treatment with liraglutide reduced body weight (67.0 ± 5.8 kg to 62.0 ± 7.8 kg, $p = 0.003$) and HbA1c level (6.6 ± 0.5% to 5.9 ± 0.5%, $p = 0.006$) and increased the level of 1,5-anhydroglucitol (12.8 ± 6.9 μg/mL to 18.7 ± 8.2 μg/mL, $p = 0.008$) without development of hypoglycemia. There were no significant changes over 24 weeks in left ventricular systolic or diastolic function assessed by cardiac ultrasonography. No participant developed a major adverse cardiac event during the 24 weeks of liraglutide treatment, defined as cardiac death, new onset or recurrence of myocardial infarction, or needing target lesion revascularization.
Conclusions: The present trial demonstrated that liraglutide treatment after onset of STEMI was well-tolerated in Japanese patients with T2DM over 24 weeks, and provided the first evidence to support clinical application of liraglutide treatment even just after ACS in Japanese high-risk T2DM patients.

Introduction

Type 2 diabetes mellitus (T2DM) is a major contributor to the development of systemic vascular failure and subsequent micro- and macro-vascular complications [1–3]. Compared to patients without diabetes, patients with T2DM have greater risk for cardiovascular events, such as myocardial infarction and stroke, leading to life shortening [4,5]. Despite recent

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progression of procedures and devices for coronary revascularization, T2DM has also been shown to be related closely to poorer prognosis and mortality 30 days and 1 year after onset of acute coronary syndrome (ACS) [6]. Therefore, appropriate management of T2DM should be emphasized to reduce the risk of cardiovascular events. Although hyperglycemia is a central part of the pathophysiology of T2DM, previous studies showed that intensive glucose-lowering treatment had little beneficial effects on cardiovascular outcome. However, there may be a legacy effect over longer periods [7–12]. It is therefore essential to ameliorate comprehensive metabolic abnormalities to improve mortality in patients with T2DM.

Endogenous glucagon-like peptide 1 (GLP-1) is an incretin hormone that promotes insulin secretion in response to food intake and elevated levels of plasma glucose [13]. The GLP-1 analog is a novel type of anti-diabetes agent that mimics the action of native GLP-1 and is resistant to inactivation by dipeptidyl 4 (DPP-4). Besides its effective and safe glucose-lowering effect [14], it has been reported that GLP-1 analogs ameliorate glucose homeostasis by inhibiting endogenous glucagon production, suppress appetite, and improve insulin resistance [15,16]. Because GLP-1 receptors are expressed in various organs and tissues including heart and vessels, it has been speculated that enhanced GLP-1 signaling may exert cardiovascular protective effects via anti-inflammatory and anti-atherosclerotic pathways [17]. Several cardiovascular outcome trials on GLP-1 analogs are now ongoing and some have been published recently [18,19]. Of these, the LEADER trial using liraglutide, an intermediate-acting GLP-1 analog, showed that compared to placebo, liraglutide added-on to the standard therapy significantly reduced the rate of composite cardiovascular events in T2DM patients with high risk for cardiovascular events [19]. However, patients who developed ACS within 14 days prior to registration were excluded in the LEADER trial and the dose of liraglutide used was greater than that approved in Japan. Therefore, the clinical efficacy and safety of liraglutide in Japanese patients with T2DM with a recent ACS are yet to be determined.

On the basis of this background, the aim of the READ trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results Trial in Japan) was to evaluate the efficacy and safety of liraglutide treatment in Japanese patients with T2DM and a recent ACS.

Methods

Study design

The READ trial was a non-randomized, prospective, open-label, single-arm, single-center, pilot trial registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry system (UMIN ID: 000006817). We conducted the trial from July 2011 to June 2014 at Shin-Koga Hospital, Kurume, Japan. Prior to initiation, the study protocol was approved by the local ethics committee and institutional review board at Saga University and Shin-Koga Hospital. The trial was conducted in full compliance with the Declaration of Helsinki and was carried out according to the Ethical Guidelines for Clinical Research established by the Ministry of Health, Labour, and Welfare.

Study participants

Eligible patients in the trial were T2DM patients (aged ≥20 years) who developed ACS within 14 days and undertook percutaneous coronary intervention (PCI) prior to initiation of liraglutide treatment. Exclusion criteria were patients with cardiogenic shock, serious liver dysfunction (aspartate aminotransferase >100 IU/L or alanine aminotransferase >100 IU/L), end-stage renal failure (serum creatinine >5.0 mg/dL or hemodialysis), a diabetic condition dependent on insulin such as type 1 diabetes mellitus, patients with allergy or hypersensitivity to the test drug, a history of malignant neoplasm, or pregnant or breastfeeding. Prior to registration, every participant was required to receive an adequate explanation of the trial plan, and written informed consent was obtained from each participant.

Treatment outline

All patients enrolled in the trial started liraglutide treatment within 14 days after successful PCI due to ACS. Liraglutide was initially administered subcutaneously 0.3 mg once daily and was increased by 0.3 mg up to 0.9 mg per day as a maintenance dose over a minimum period of at least 7 days (Fig. 1). If adverse events occurred during drug titration such as hypoglycemia or gastrointestinal symptoms, the increase in dose of liraglutide was

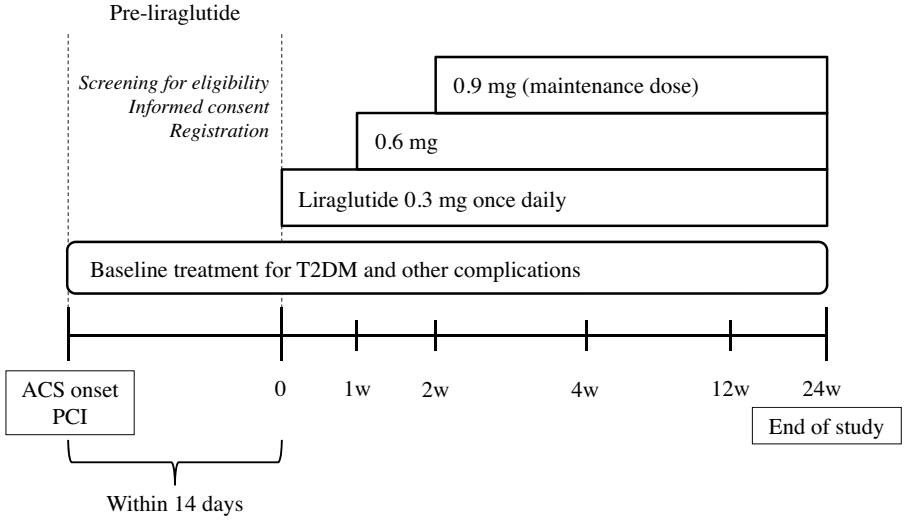

Fig. 1. Outline of the trial. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

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