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Efficacy and safety of dulaglutide in patients with absolute insulin deficiency

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Objective. While dulaglutide has been approved inpatients with type 2 diabetes (T2DM) in combination with insulin, it has not been studied in insulin-deficient patients, not whether they have type 1 diabetes (T1DM) or T2DM. The aim of this study is to assess the efficacy and safety of dulaglutide 0.75 mg/once weekly (QW) in patients with absolute insulin deficiency (n=10).

Subjects and Results. Significant reductions of HbA1c (9.30±1.03% to 8.61±1.21%; p<0.02) and body mass index (BMI; 23.61±3.95 to 23.41±4.24; p<0.02) levels were observed at 3 months with the addition of dulaglutide to the existing pharmacotherapy. However, in all the patients, post-meal C-peptide levels remained undetectable. One patient had gastrointestinal adverse events and discontinue dulaglutide within the first month. One patient was a non-responder, who had little if any changes in HbA1c levels at 3 months.

Conclusions. The results indicate that dulaglutide is effective in patients with T1DM or T2DM with absolute insulin deficiency, though gastrointestinal adverse events might be of concern. The improvements in glycemic control could not be due to enhanced insulin secretion, but may be as a result of a combination of the other effects of glucagon like peptide 1 (GLP-1), such as postprandial glucagon suppression, delayed gastric emptying, and weight loss.

Key words: GLP-1 agonist, dulaglutide, type 1 diabetes, insulin deficiency

A number of abnormalities or defects in the glucose metabolism/homeostasis contribute to the difficulty in achieving glycemic targets in patients who completely lack of endogenous insulin secretory capacity, not whether they have T1DM or T2DM. Increasing the dose of insulin could be a solution. However, in practice, this strategy may cause an increased risk of hypoglycemia and weight gain. In addition to insulin deficiency, several other underlying metabolic disturbances have been linked to patients with T1DM. These include, for example, paradoxical excess production of glucagon in the presence of hyperglycemia leading to inappropriate gluconeogenesis, increased lipotoxicity (free fatty acids), rapid gastric emptying, and decreased sensation of satiety (Caprio et al. 1990; Carlsson et al. 2000; Sherr et al. 2014; Emami et al., 2017).

Glucagon like peptide 1 (GLP-1) is secreted from the intestine after meal. GLP-1 stimulates insulin secretion and inhibits glucagon secretion, thereby contributing to limit postprandial glucose excursions. GLP-1 also inhibits gastric acid secretion and gastric emptying, thus it delays entry of diets to the intestine and thus lowers post-prandial glucose elevation. GLP-1 also appears to be a physiological regulator of appetite and food intake, thus it reduces body

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weight (Sandoval and D'Alessio 2015). GLP-1 and GLP-1 receptor agonists are associated with enhanced beta-cell function, making them a good therapeutic option in the early stage of the disease, when the patients still have sufficient levels of beta-cell function (Kutoh and Hori 2013). However, it remains to be found out, whether they are still effective in patients completely lacking residual beta-cell function (no endogenous insulin secretory capacity; e.g. T1DM or T2DM). Recently, GLP-1 and one of the GLP-1 receptor agonists, liraglutide, have been shown to be effective with C-peptide positive or negative patients with T1DM, though this is an off-label use of this drug (Kielgast et al. 2010; Kielgast et al. 2011).

Dulaglutide is a long-acting, human GLP-1 receptor agonist approved as a once-weekly subcutaneous injection for the treatment of T2DM (Kugler and Thiman 2018). So far, no study has demonstrated whether dulaglutide is effective in those without residual beta-cell function. The present study investigates the efficacy and safety of dulaglutide 0.75 mg once weekly (QW) to the ongoing insulin regimen with islet-antibody positive T1DM and T2DM patients lacking functional beta-cell function. Although these patients have very different diabetic backgrounds, the common denominator is that they are absolutely insulin-deficient.

Subjects and methods

Patients. Inclusion criteria were those with islet-antibody (against glutamic acid decarboxylase; GAD) positive T1DM (n=8) or T2DM (n=2) patients whose post-meal C-peptide levels were below detectable range; <0.1 ng/ml) and were in poor glycemic control.

The subjects were undertaking intensive insulin treatment (mean insulin doses per day 47.8±19.1 units) together with oral hypoglycemic drugs including metformin, sodium glucose co-transporter (SGLT-2) inhibitor (canagliflozin), alpha-glucosidase inhibitors (acarbose) and dipeptidyl peptidase (DPP)-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, teneligliptin), but the glycemic control remained poor (mean HbA1c 9.16±1.07%). DPP-4 inhibitors were withdrawn when dulaglutide was introduced, since combination of dulaglutide and DPP-4 inhibitors are not permitted in Japan. The doses of insulin and/or other oral hypoglycemic/non-hypoglycemic drugs were unchanged during the study period. The doses of these non-diabetes drugs were also unchanged during the study period. The informed consent was obtained from the patients and the protocol was approved by the institutional review board (IRB) of Gyoda General Hospital. This study was conducted in accordance with principles of Good Clinical Practice.

Laboratory measurements. The primary end point was the changes in HbA1c levels from baseline to 3 months. The secondary end point included the changes in BMI (body mass index) levels. Blood was collected at the post-meal state and the standard techniques were used to measure these parameters. Measurements of HbA1c were performed once a month. C-peptide was measured at the start (baseline) and at the end (3 months) of the study (measured at LSI Medience or BML, Tokyo, Japan). Hepatic (glutamic oxalacetic transaminases, AST; glutamic pyruvic transaminases, ALT; alkaline phosphatase, ALP; and gamma-glutamyl transpeptidase, γ-GTP) and renal (blood urine nitrogen, BUN, and creatinine, CRE) functions were also monitored one month after administration of dulaglutide. In the case of any significant increases of these parameters, administration of dulaglutide was planned to discontinue.

Statistical analysis. Descriptive statistics for all the parameters studied included the mean changes from baseline to 3 months. Paired Student's t-test was used to analyze the changes. The results were expressed as the mean ± SD. Throughout the statistical analysis, values of $p<0.05$ were considered significant. Statistical analysis was performed with PAST program from Oslo University (http://folk.uio.no/ohammer/past/). One patient was dropped out due to adverse events and was excluded from data analysis.

Results

The baseline characteristics of the patients are summarized in Table 1. These patients completely lacked endogenous insulin secretory capacity as defined by the undetectable levels of post meal C-peptide (<0.1 ng/ml). After the addition of dulaglutide to the existing therapy, significant reductions of HbA1c (9.30±1.03% to 8.61±1.21%; $p<0.02$; Figure 1A) and BMI (23.61±3.95 to 23.41±4.24; $p<0.02$; Figure 1B) levels were observed at 12 weeks. One patient was a non-responder whose HbA1c levels had slightly increased (from 9.9 to 10.1%). No changes in the doses of insulin and/or oral hypoglycemic drugs were made. No clinically significant elevations of hepatic or renal parameters were noted (results no shown). One patient had gastrointestinal problems and discontinued dulaglutide within the first month. This patient was excluded from the data analysis. Post meal C-peptide levels remained undetectable in all the patients after the addition of dulaglutide.

Discussion

This report presents cases where the addition of dulaglutide 0.75mg/QW to the ongoing insulin and other pharmacotherapy was considerably effective in lowering HbA1c levels in patients whose insulin secretory capacities were completely absent (Figure 1A). However, post-meal C-peptide levels remained undetectable after the addition of dulaglutide, implicating that no improvements of beta-cell functions were noted with this drug in such insulin deficient patients. Though the lowest limit of detection of C-peptide levels was 0.1 ng/ml in this study, one is not able to completely exclude the possibility that minimal changes of C-peptide levels may have escaped the analysis. Alternatively, a small peripheral increase, or an intra-islet increase of endogenous insulin levels cannot be ruled out as well.

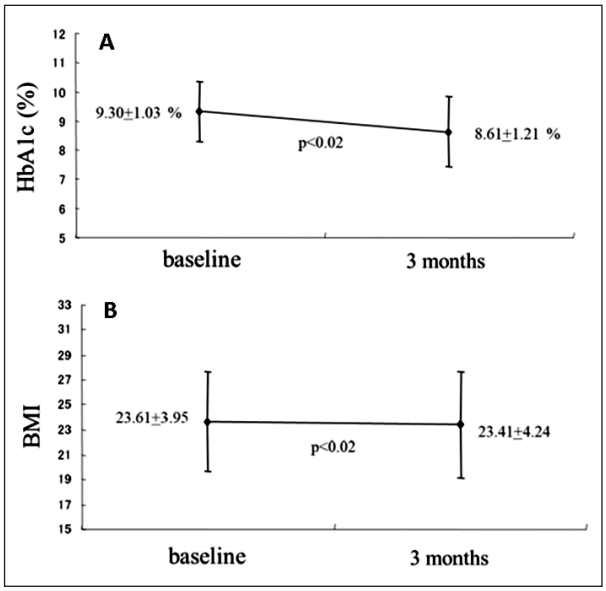
So, what are the potential mechanisms of the improved glycemic control with dulaglutide in those patients? Several explanations could be postulated. Firstly, it may be due to suppression of glucagon, which is one of the most important biological properties of GLP-1 receptor agonist (Sandoval and D'Alessio 2015). The precise mechanism by which GLP-1 suppresses glucagon is far from being elucidated and furthermore it is unclear whether endogenous insulin is a required factor for this effect. Patients with T1DM are unable to suppress glucagon during meals, which contributes to postprandial hyperglycemia (Sherr et al. 2014; Emami et al. 2017). Thus, this suppression of glucagon with dulaglutide may be one of the reasons for the good glycemic efficacy in patients who are absolutely insulin deficient. Similarly, it has been reported that infusion of GLP-1 could reduce elevated postprandial blood glucose and glucagon levels, and could increase glucose utilization in C-peptide negative patients with T1DM (Gutniak et al. 1987).

Secondly, the improvements of the glycemic control with dulaglutide in these patients could be due to the other pharmacological effects of GLP-1; for example, delayed gastric emptying, reduced food intake (increased satiety), and decreased insulin resistance secondary to body weight loss (Sandoval and D`Alessio 2015). Indeed, significant reductions of BMI levels were observed (Figure 1B). The use of dulaglutide or other GLP-1 receptor agonists could be considered in T1DM patients who are overweight and not under optimal glycemic control despite intensive insulin therapy together with high doses of oral hypoglycemic drugs. The most common side effect following intensive insulin treatment is weight gain and hypoglycemia. Dulaglutide may be able to challenge this problem. One of the major drawbacks of dulaglutide was gastrointestinal adverse events.

Table 1
Baseline characteristics of the patients

Parameter	Mean ± SD
Age (years)	61.2±11.9
Sex (female/male)	4/6
T1DM/T2DM	8/2
Duration of diabetes (years)	16.4±7.3
Mean insulin dose (units per day)	47.8±19.1
HbA1c (%)	9.16±1.07
Body weight (kg)	62.36±13.24
BMI	23.44±3.86
Oral Drugs	(n)
Metformin	7
Canagliflozin	1
anti-hypertension (ACE-I/ARB/CCB/alpha-blocker)	5
Anti-hyperlipidemia (statins)	2
others	4

Abbreviations: ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker.



Figures 1. (A) Changes of HbA1c levels. **(B)** Changes of BMI levels. Paired student's t-test was used to analyze the changes of HbA1c and BMI levels with the addition of 0.75 mg dulaglutide/QW at 3 months. Abbreviations: BMI – body mass index; QW – once weekly.

One out of 10 patients discontinued dulaglutide due to this side effect. However, these gastrointestinal events could be linked to decreased appetite followed by weight reduction. Otherwise, dulaglutide was quite tolerable and no adverse events on liver/kidney functions were noted. No hypoglycemic events were reported as well. In conclusion, once weekly dulaglutide can be an easy and effective option for poorly controlled patients with absolute insulin deficiency, whether or not they are T1DM or T2DM.

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