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PUBTEXTO

Investigation for Daily Profile of Blood Glucose by the Administration of Canagliflozin and Xultophy (IdegLira)

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Abstract

Background: American Diabetes Association (ADA) presented 2022 guideline, and indicated the benefit of sodium-glucose transporter 2 inhibitor (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP-1RA). Xultophy is a combined agent of insulin degludec/liraglutide (IDegLira), which is recently clinically useful.

Patient and Method: The case is 72-year-old man with type 2 diabetes mellitus (T2DM). He has been treated by some oral hypoglycemic agents (OHAs) with unstable HbA1c levels.

Results: When HbA1c was 9.9% in 2018, his daily profile of blood glucose three times a day ranged 208-289 mg/dL. By starting canagliflozin, blood glucose decreased for 145-194 mg/dL. As HbA1c increased to 8.8% in 2021, blood glucose ranged 179-192 mg/dL. By starting Xultophy 12 doses per day, it decreased to normal level for 73-155 mg/dL. HbA1c was reduced to 6.7% half year later. Changes in eGFR showed the decrease from 80 to 51 mL/min/1.73 m^2 during unstable HbA1c period in 2018-2019, and stable 50-60 mL/min/1.73 m^2 during stable HbA1c period in 2020-2021 with Xultophy therapy.

Discussion: SGLT2i, GLP-1RA and Xultophy seem to be beneficial for cardiovascular and renal function. Furthermore, these agents seem to be adequate for diabetic patients with chronic kidney disease (CKD) and/or diabetic kidney disease (DKD).

Keywords: American Diabetes Association (ADA); Xultophy (IDegLira); Insulin Degludec/Liraglutide; Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA); diabetic kidney disease (DKD); Daily Profile Of Blood Glucose

Introduction

Diabetes mellitus (DM) has been one of the most crucial diseases in the clinical practice. American Diabetes Association (ADA) presented a new guideline of standards of medical care on Jan 1, 2022 [1]. Regarding various diabetic patients, adequate managements for atherosclerotic cardiovascular disease (ASCVD) and diabetic kidney disease (DKD) would be required [2].

Authors and collaborators have continued medical practice and research for diabetology [3]. Among them, we have proposed low carbohydrate diet (LCD), meal tolerance test (MTT), analysis for insulin secretion response to carbohydrate loading, and so on [4,5]. Furthermore, effective therapeutic methods were reported such as sodium-glucose transporter 2 inhibitor (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP-1RA) [6,7].

Recently, clinical efficacy of GLP-1RA and insulin has been known with several evidence. Consequently, combined injectable agent was developed, which is a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) [8]. It has been made and supplied as Xultophy from Novo Nordisk Pharmaceutical Company [9].

In recent years, Xultophy has been administered to type 2 diabetes mellitus (T2DM), and its clinical effects have been attracting attention [10]. Authors and collaborators have continued diabetic practice and research for long [11]. Among them, some reports have been presented concerning application of Xultophy with lower amount of dose than usual [12]. During our clinical activity, we have an experience to treat a patient with T2DM associated with efficacy of Xultophy. The clinical course of the case with some discussion will be described in this article.

Case Presentation

History & Physical

The patient is a 72-year-old male patient with Type 2 Diabetes Mellitus （T2DM）. He was diagnosed to have T2DM about 25 years ago. After that, he has treated with some oral hypoglycemic agents (OHAs). They include metformin 1500mg, mitiglinide 30mg, voglibose 0.6mg/ and teneligliptin 20mg/day. For 3 years, his diabetic variability was rather unstable (Figure 1). For his physical exam, consciousness, vitals, lung, heart, abdomen and neurological findings were unremarkable. In 2018, HbA1c increased to 8.8%, and then Canagliflozin was started. Further, HbA1c increased to 8.8% in Feb 2021, and then Xultophy was started for adequate treatment for T2DM.

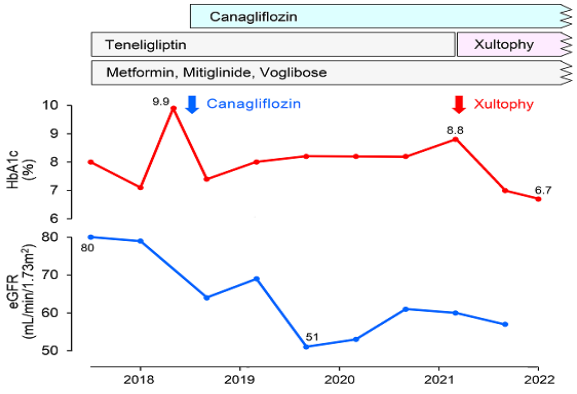

Figure 1: *metformin, mitiglinide, voglibose and teneligliptin.*

Several Exams

The biochemical results of Nov 2021 were summarized in the following: AST 29 U/L, ALT 21 U/L, γ-GT 26 U/L, ALP 71 U/L (38-113), TP 7.2 g/dL, Alb 4.2 g/dL, BUN 27 mg/dL, Cr 1.0 mg/dL, eGFR 57 mL/min/1.73m^2, UA 6.1 mg/dL, Na 142 mEq/L, K 4.7 mEq/L, Cl 103 mEq/L, T-C 196 mg/dL、HDL-C 58 mg/dL, LDL-C 126 mg/dL, TG 60 mg/dL. RBC 5.31 x 10^6 /μL, Hb 15.3 g/dL, Ht 47.6%, MCV 90.0 fL (80-98), MCH 28.8 pg (27-34), MCHC 32.1 g/dL (31-36), WBC 8900 /μL, Plt 23.3 x 10^4 /μL. For examinations for DM, HbA1c 7.0 %, fasting blood glucose 72 mg/dL, Urinalysis data were presented as protein (-), glucose (++), urobilinogen (+/-). Chest X-P was negative for lung and heart, and ECG showed unremarkable.

Results

His clinical course for 3 years was summarized (Figure 1). HbA1c value has kept rather higher level, and it decreased to 6.7% after providing Xultophy in 2021. Value of eGFR was 80 mL/min/1.73m^2 in 2017, but it gradually decreased to 51 mL/min/1.73m^2 in 2019 and kept similar level as 50-60 mL/min/1.73m^2 until now.

When his HbA1c increased to 9.9% in 2018, he was hospitalized for treatment. At that time, the standard amount of nutritional intake was instructed. It included the data as follows: height 162.8 cm, body weight 56.4 kg, BMI 21.3, ideal body mass (IBM) 58.0 kg, Alb 4.5 g/dL, daily energy intake 1700 kcal, protein 65 g, water 1700 ml, salt 8 g per day. His daily profile of blood glucose for starting of Canagliflozin is shown in (Table 1) (upper). On admission, glucose variability was rather higher range, but Canagliflozin brought better glucose control. The daily profile of blood glucose showed decreased glucose levels during all day long. After this situation, HbA1c was decreased to 7.4%.

In spring 2021, his HbA1c increased to 8.8%, then he was started the injection of Xultophy on out clinic. Daily profile of blood glucose for this period is shown in (Table 1) (lower). The daily profile of blood glucose showed lower glucose levels. Especially, pre-prandial glucose level after overnight fasting has decreased apparently.

Table 1: *Changes in Daily Profile of Blood Glucose.*

Day	Breakfast	Lunch	Supper	Supper	Canagliflozin	Xultophy
	Pre-Prandial 0700h	Pre-Prandial 11300h	Pre-Prandial 1730h	Post-Prandial 2100h	(mg) 0730h	(Doses) 0730h
-2			289			
-1	208	285	283	280		
1	208	217	178		100	
2	250	199	184		"	
3	149	242	176		"	
4	154	180	175		"	
5	170	192	193		"	

6	163	186	155		"	
7		189			"	
8	145				"	
9		194			"	
10			183		"	
11		188			"	
-3	192				100	
-2		179			"	
-1			181		"	
3	86				"	12
5		164			"	"
7			167		"	"
10	95				"	"
12		186			"	"
15			99		"	"
17	76				"	"
19		181			"	"
21			100		"	"
24	73				"	"
26		106			"	"
28			155		"	"

- Canagliflozin was provided with detail study of blood glucose in 2018.
- Xultophy was provided with detail study of blood glucose in 2021.
- Pre-prandial and postprandial glucose levels show 0 and 120 minutes.

Ethical Considerations

This research study was fundamentally conducted according to the ethical principles on the Declaration of Helsinki. In addition, some comment was from the Ethical Guidelines for Research for Humans, associated with the concept of Good Clinical Practice (GCP). The authors which are related to this manuscript have established an ethical committee. It is in the hospital, which included the president and director of the hospital, physician, nurse, pharmacist, nutritionist and the professional of legal specialty. Discussion was performed for adequate manners, and it decided to show the agreements for current research Protocol. The informed consent and also written style of the agreement document were obtained from the subject.

Discussion

From historical point of view, several types of pharmacological treatment for diabetes have been found. Among them, recent beneficial medicines include sodium-glucose transporter 2 inhibitor (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP-1RA). In the case of SGLT2i, it was introduced to clinical practice for its efficacy for diabetes [13]. After that, it was proved to have positive effect on heart failure for its beneficial influence on water and electrolyte metabolism [14]. Successively, SGLT2i was reported to have clinical benefit for chronic kidney disease (CKD). Thus, application of SGLT2i for several diseases has been expanding [3].

Regarding GLP-1RA, several kinds of new GLP-1RAs have been found [15]. They include liraglutide, dulaglutide, exenatide, lixisenatide, semaglutide, and others [16]. From the data of Network Meta-Analysis (NMA), clinical practice and research evaluation showed the positive outcomes for glucose variability and also outcomes of cardiovascular disease [17]. Consequently, GLP-1RA regimens have shown cardiovascular and renal benefits.

Among several GLP-1RAs, liraglutide has been effective and widely used for T2DM. In addition to this prevalence of liraglutide, Xultophy has been produced for the combined agents of liraglutide and also basal insulin degludec [9,18]. When compared with the effect of each agent, the combined clinical efficacy was increased [19]. Consequently, Xultophy can maintain general efficacy of cardio and renal protectivity by holding the beta cell function of the pancreas [20].

Regarding the treatment of diabetes, adequate glycemic control is crucial, and maintenance of renal function is also important [21]. In

daily practice, it is indispensable to carefully observe the course of HbA1c, which is an index of glycemic control, and also eGFR, which is an index of renal function [22]. For T2DM case in this article, HbA1c showed unstable and high values from 2018 to 2019, and eGFR decreased from 80 to 51 mL/min/1.73 m^2 during unstable period. After that, eGFR was maintained at the level of 50-60 mL/min/1.73 m^2 in 2020-2021. Thus, exacerbation of renal function may be involved during periods of unstable glycemic variability and higher HbA1c values. As a treatment for this case, SGLT2i was administered, which has minimal effect on renal function [23]. Successively, Xultophy was also administered, which is a combination of insulin and GLP-1. Consequently, these agents seemed to have little effect on renal function, and this selection of medicine was considered to be appropriate treatment for DM patients with CKD or DKD.

As for efficacy of Xultophy, clinical investigation of DUAL study has been known [9]. It means Dual Action of Liraglutide and Insulin Degludec clinical trial program, associated with several studies [24]. They showed significant beneficial effects of reducing HbA1c level, weight reduction, and less risk of hypoglycemia compared with previous standard treatments. Basal bolus therapy can present effective lowering glucose value, but it showed higher hypoglycemia episodes [25].

There has been the European Xultophy Treatment Retrospective Audit (EXTRA) study for Xultophy investigation [26]. Among these studies, significant improvement of weight and HbA1c was found in real-world evidence (RWE) [27]. When starting the administration of Xultophy, the standard doses would be 10 units for naïve patients for insulin, and 16 units for already insulin-treated patients [28]. In this patient, HbA1c value was rather high, then 12 doses of Xultophy was started. The response of lowering blood glucose was satisfactory, and then the same doses were continued. Authors have some previous reports for successful Xultophy therapy with less doses of Xultophy [11,29]. Such situation suggests that Japanese people may have higher sensitivity of insulin and/or GLP-1RA, diet habit or smaller body physique [30].

There are several limitations present for this article. Several different factors may be involved in the clinical progress, where their influences are not clearly apparent. It would be necessary to follow up the diabetic complications and laboratory tests in the future. In summary, patient with T2DM showed efficacy for SGLT2i and Xultophy. Renal function has been monitored as the changes in eGFR which gradually decreased for years. The description of this article would be expected to be some reference in future diabetic practice and research.

Conflict of interest

The authors declare no conflict of interest.

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