



## Clinical Response to Xultophy Possibly Varies from Each Different Metabolic Function

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### Abstract

Two patients with Type 2 Diabetes Mellitus (T2DM) were treated with Xultophy. Xultophy consists of degludec and liraglutide (IDegLira). It is the combination of long-acting insulin and Glucagon like Peptide-1 Receptor Agonist (GLP-1RA) and is characteristic for effective agent for improving glucose variability for patients with T2DM. However, clinical responses are not always satisfactory due to different complication and background of each patient. We have experienced two impressive T2DM cases. Case 1 was 59-year-old male with hypertension for 20 years and T2DM for 3 years. He was treated on Novolin 30R 30/21 units twice a day, and after that Xultophy 32 doses brought him successful glucose profile. Case 2 was 78-year-old male with hypertension, bronchial asthma, hyperuricemia, and others with heavy alcohol drinking for 50 years. He was formerly treated by Insulin detemir, Liraglutide, exenatide and Degludec/NovoRapid, but has been recently unstable in glucose control. Xultophy up to 40 doses could not successfully improve glucose variability. One of the less responsiveness to Xultophy would be due to impaired liver function. Clinical progress of both cases associated with several perspectives from various points of view are discussed in this article.

**Keywords:** Insulin Degludec and Liraglutide (IDegLira), glucagon-like peptide 1 (GLP-1), DUAL (Dual Action of Liraglutide and Insulin Degludec), European Xultophy Treatment Retrospective Audit (EXTRA), Japan LCD Promotion Association (JLCDPA).

**Abbreviations:** NCDs-Non-Communicable Diseases, CR- Calorie Restriction, LCD- Low Carbohydrate Diet, JLCDPA- Japan LCD Promotion Association, MTT- Meal Tolerance Test, CVA- Cerebral Vascular Accident, OHAs- Oral Hypoglycemic Agents, CLD- Chronic Liver Dysfunction.

### Introduction

Diabetes has been recently more prevalent across the world, associated with several diseased states. They include obesity, metabolic syndrome, Non-Communicable Diseases (NCDs), liver diseases, and so on [1]. As to the direction of diabetic treatment, optimal therapy of T2DM would include patient-oriented goals associated with normalized glucose variability, and minimized influences of hypoglycemia and weight gain, and reduced risk of macroangiopathy and microangiopathy as diabetic complications [2].

Regarding the treatment for diabetes, the basic principle is nutritional therapy. There has been Calorie Restriction (CR), which was formerly standard diet therapy. After that, Low Carbohydrate Diet (LCD) was introduced to medical practice and health care area [3]. The evidence of clinical efficacy of LCD was presented by several researchers [4,5]. Authors and collaborators have continued developing LCD for several opportunities medically and socially [6]. For useful method in the daily life, three kinds of LCD were proposed broadly, which are super-LCD, standard-LCD and petite-LCD [7]. We have published textbooks of LCD, prepared workshops and seminars for LCD through the activity of Japan LCD Promotion

Association (JLCDPA) [8]. Furthermore, various diabetic research has continued concerning CR, LCD, Meal Tolerance Test (MTT), Continuous Glucose Monitoring (CGM), and so on [9]. For pharmacological diabetic options, rather new foci include the clinical application of several kinds of Glucagon like Peptide-1 Receptor Agonists (GLP-1RAs) [10]. GLP-1RAs include liraglutide, exenatide, lixisenatide, dulaglutide and others. Recently, a Network Meta-Analysis (NMA) for GLP-1RAs were conducted for evaluating glycemic control and safety outcomes [11]. The research included 23209 cases with 18 GLP1-RA regimens from 54 studies, concluded the efficacy of glycemic control and cardiometabolic benefits, and recommended patient-oriented clinical decisions for the consideration of comparative profiles.

Among several GLP-1RAs, liraglutide has been rather widely used in medical practice. Related to liraglutide, Xultophy has been introduced to diabetic treatment, which is the combination of liraglutide and insulin degludec [12]. In comparison with GLP-1RA, the combined agent was evaluated to show clinical beneficial effect [13]. GLP-1RA can decrease Fasting Plasma Glucose (FPG) and reduce the post-prandial response of blood glucose [14]. Furthermore, basal insulin can



decrease FPG, and the combination of the fixed ratio can control the diabetic situation with simple and useful manner. Consequently, Xultophy will improve the function of beta cell and also maintain the cardioprotective activity [15]. As a matter of fact, Xultophy has been evaluated for its beneficial effect and been gradually more used. Authors have continued diabetic treatment for T2DM patients with various background and complications. We have experienced two diabetic cases with impressive clinical progress treated by Xultophy. Their general outlines with some discussion will be presented in this article.

### Presentation of Case 1

**History and Physicals:** The patient is a 59-year-old male, who has been treated hypertension for 20 years. He was pointed out hyperglycemia with HbA1c 10% in 2018, and has been treated by insulin with Novolin 30R twice a day. He felt sensory disturbance and slight motor abnormality in the left extremities in January 2020, and was admitted for further evaluation and treatment. He was diagnosed as Cerebral Vascular Accident (CVA) in subtle degree. However, head Computed Tomography (CT) scan did not show the clear evidence of CVA. Several laboratory data in January 2020 were as follows. HbA1c 9.0%, pre-prandial glucose 182 mg/dL, TP 6.9 g/dL, Alb 4.3 g/dL, AST 17 U/L, ALT 15 U/L, g-GT 79 U/L, uric acid 4.3 mg/dL, BUN 13 mg/dL, Cr 1.0 mg/dL, eGFR 61 mL/min/1.73m<sup>2</sup>, LDL-C 118 mg/dL, HDL 50 mg/dL, TG 241 mg/dL, Hb 15.1 g/dL, RBC 483 x 10<sup>6</sup> /μL, WBC 7200 /μL, Plt 26.6 x 10<sup>4</sup> /μL, CRP 0.06 mg/dL.

### Clinical Progress

Successively, he has been treated hypertension, CVA and T2DM and received rehabilitation of sensory disturbance in subtle degree. He has only felt some numbness in left hand and leg, and not show any clear symptoms or signs of left hemiparesis, speech disturbance, or other motor disturbance. As to the treatment, he was given Nifedipine CR 20mg 1Tab, Clopidogrel 75mg 1Tab, Linagliptin 5mg 1Tab, and Novolin 30R twice in the morning and evening. The changes in HbA1c and treatment of T2DM are shown in (Figure 1). Regarding insulin treatment, Novolin 30R has been provided at 14-30 units in the morning and 8-21 units in the evening. HbA1c value has been unstable ranging from 7.3% to 11.3%. For the improvement of glucose variability, the treatment was changed from insulin to Xultophy in December, 2020.

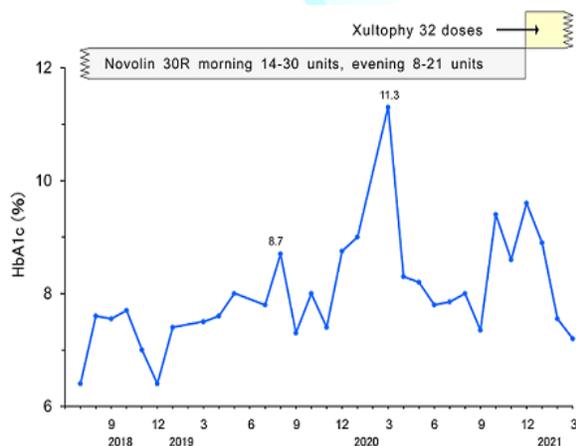


Figure 1: Clinical progress of Case 1.

The detail progress of provided doses was summarized in (Table 1). It shows gradual increase doses of Xultophy and responsive glucose decrease for about 2 weeks. When Xultophy was provided up to 32 doses, the profile of blood glucose was improved at satisfactory level. Consequently, case 1 seems to show successful efficacy of Xultophy for better control of blood glucose variability.

Day	Blood glucose		30R x 2 units	Xultophy dose
	morning	evening		
-3	192	333	30 + 21	-
-2	169	281	30 + 21	-
-1	184	263	30 + 21	-
1	198	269	-	16
2	192	377	-	16
3	199	275	-	18
4	237	314	-	20
5	215	192	-	23
6	170	225	-	23
7	160	265	-	25
8	213	196	-	25
9	150	220	-	27
10	175	251	-	27
11	171	124	-	29
12	159	282	-	30
13	170	327	-	31
14	165	168	-	32
15	119	123	-	32
16	125	152	-	32

Table 1: Changes in blood glucose in Case 1.

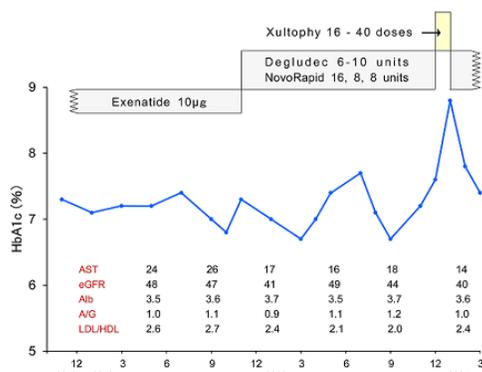
### Presentation of Case 2

**History and Physicals:** The patient is a 78-year-old male, who has multiple medical problems and complications. T2DM was pointed out at the age of 54, and Oral Hypoglycemic Agents (OHAs) were provided for long years. After that, he was suffered from hypertension, occasional bronchial asthma, and diabetic nephropathy at 3rd stage, hyperuricemia, reflux esophagitis associated with various treatments. He had been also a heavy drinker taking about 80g of pure alcohol on average per day for 50 years. In recent 2 years, additional problem included pneumonia, adhesive ileus, and Alzheimer dementia and so on. As to the treatment of T2DM, he received gliclazide and pioglitazone in 1996, glimepiride and pioglitazone in 2008, Revemil (insulin detemir 5 units/day) in 2009, Victoza (liraglutide 18mg/day) in 2011 and Byetta (exenatide 10μg/ day) in 2013. He developed unstable condition associated with general malaise, heartburn, diarrhea and other symptoms in the autumn of 2019. Then, he was admitted for further evaluation and treatment.

Physicals showed no remarkable abnormalities of vitals, consciousness, chest, abdomen and neurological findings. Laboratory data were in the following. Hb 13.0 g/dL, RBC 413 x 10<sup>6</sup> /μL, WBC 3500 /μL, Plt 16.2 x 10<sup>4</sup> /μL, TP 6.8 g/dL, Alb 3.6 g/dL, BUN 26 mg/dL, Cr 1.2 mg/dL, uric acid 5.9 mg/dL, eGFR 47 mL/min/1.73m<sup>2</sup>, TG 111 mg/dL, HDL-C 41 mg/dL, LDL-C 110 mg/dL, AST 26 U/L, ALT 28 U/L, g-GT 29 U/L, urine protein 0.31 g/gCr (-0.15). Several exams included that no retinopathy in fundus, nerve conduction velocity within normal limits, the coefficients of variation of RR intervals (CVRR) 1.95%, abdominal echo showed chronic liver disease and hemangioma in the segment 5 (10 x 7 x 10mm), carotid artery showed plaque bilaterally, cardiac echography is unremarkable, ankle brachial index (ABI) 1.13/1.19. cardio-ankle vascular index (CAVI) 10.0/10.0.

### Clinical Progress

After the evaluation of diabetic exam and general condition, the treatment for T2DM was changed into Tresiba (Degludec) 6 units and NovoRapid 16-8-8 units (Figure 2). Within a few months, the therapeutic amount was changed to 8-10 units and 8-8-8 units. In November and December, 2020, HbA1c was elevated. Although the treatment doses of Degludec and NovoRapid were increased, control of glucose variability was not enough. Consequently, the administration of Xultophy (IDegLira) was started, which include degludec and liraglutide.



**Figure 2:** Clinical progress of Case 2 with the changes of treatment and laboratory data.

The detail progress of provided doses starting 16 doses was summarized in (Table 2). The amount of Xultophy was rapidly increased up to 40 doses. His blood glucose was rather decreased in the morning, but it persisted rather higher in the evening. This treatment was continued about 2 weeks, and then patient came to complain of general malaise, nausea, thirsty, polydipsia and polyuria in the afternoon and evening. Those symptoms became rather exacerbated, where this treatment was evaluated to be not tolerated. Consequently, the treatment was changed back to the previous method with Degludec and Novorapid. Just after the same units of them started again, the blood glucose showed rather controlled level. From mentioned above, Xultophy seemed to be not effective in this case.

**Table 2 Changes of glucose in Case 2**

Day	Blood glucose morning	glucose evening	Degludec + Rapid 3 times	Xultophy dose
-3	166	225	10 + 12, 7, 8	-
-2	142	212	10 + 12, 7, 8	-
-1	169	300	10 + 12, 7, 8	-
1	208	363	-	16
2	248	489	-	16
3	240	442	-	18
4	315	478	-	20
5	171	454	-	20
6	168	471	-	22
7	194	393	-	24
8	221	362	-	26
9	182	361	-	28
10	161	447	-	30
11	221	364	-	32
12	153	331	-	34
13	100	429	-	36
14	114	109	10 + 12, 7, 8	-
15	79	120	10 + 12, 7, 8	-
16	80	226	10 + 12, 7, 8	-

**Table 2:** Changes in blood glucose in Case 2.

## Discussion

For standard method of diabetic treatment, T2DM patients are firstly started with oral hypoglycemic agents (OHAs) and then insulin will be provided if necessary. In order to control blood glucose as finely as possible, treatment was formerly basal-bolus injection regimen [16]. In other words, Multiple Daily Insulin Injection (MDI) was rather standard and prevalent. However, recent situation shows that once-daily injection has been increasing. One of the reasons would be increasing clinical application of Xultophy, which is evaluated as useful, convenient and effective treatment regimen [17]. A series of the investigation of clinical response of Xultophy have been found, which is the European Xultophy Treatment Retrospective Audit (EXTRA) study. From European diabetes centers, a Real-Word Evidence (RWE)

study (EXTRA) was reported [18]. The result showed a significant decrease of HbA1c value (-0.7%) and also of weight (-2.4 kg) for 6 months in the subjects who changed from MDI to Xultophy. Related to EXTRA study, large investigation included 611 cases from 5 countries. As a result, the initiation therapy showed substantial -0.9% reduction of HbA1c ( $p < 0.001$ ) after six months [19]. Consequently, Xultophy seems to be beneficial and convenient agent for T2DM associated with adequate continuation of regular lifestyle. In this article, two cases treated with Xultophy were presented. Regarding case 1, HbA1c value was formerly unstable from 6.2% to 11.3%. For insulin treatment, Novolin 30R was administered twice in the morning and evening [20].

The treatment was switched to Xultophy in order to improve the daily profile of blood glucose. After starting 16 doses, blood glucose levels were gradually decreased, and became stable at 32 doses of Xultophy. He felt formerly large daily glucose fluctuations from day to day, but after the change to Xultophy, blood glucose fluctuations became smaller and stabilized. It seems to be beneficial because it has the simple advantage of injection once a day, stabilizes daily blood glucose level, improves HbA1c, and has unremarkable adverse effects [21]. The case 2 showed characteristic point concerning glycemic variability. Fasting Plasma Glucose (FPG) in early morning has been almost in satisfactory range. On the other hand, FPG in the evening has been significantly elevated. In response to this situation, the dose of Xultophy was increased, but hyperglycemia in the evening did not improve. One of the reasons would be from the medical history that he had been a heavy drinker for 50 years [22].

Furthermore, the results of several examination may suggest the existence of Chronic Liver Dysfunction (CLD), including AST, Alb, A/G ratio and image data. For CLD situation, the function of converting glucose into glycogen is reduced in the liver, as well as reduced restoring function [23]. Then, the excess glucose may flow into the blood directly, resulting in abrupt glucose increase after meal. It brings post-prandial hyperglycemia. Furthermore, blood glucose in early morning is kept relatively low in this case. For CLD, gluconeogenesis in the liver is reduced, and then blood glucose tends to be lower on early morning fasting [24].

This may be the reason why this case shows rather lower blood glucose in early morning. Case 2 was formerly given exenatide for some period. He felt general malaise and discomfort in the abdomen after starting liraglutide in Xultophy. It may be involved in the adverse effect of GLP-1RA [25]. Gastrointestinal (GI) adverse events (AEs) have been found in GLP-1RAs. There were studies of GI-AEs for semaglutide vs other GLP-1RAs [26]. They include SUSTAIN (vs exenatide), SUSTAIN 7 (vs dulaglutide) and SUSTAIN 10 (liraglutide). GI-AEs symptoms show diarrhea, constipation and dyspepsia during dose escalation. Another study was comparative study of once-weekly semaglutide and once-daily liraglutide [27]. Consequently, unstable condition of the case might be related with the given liraglutide as GLP-1RA.

On the other hand, GLP-1RAs have beneficial efficacy for liver function or diseased state of fatty liver with diabetes. Among GLP-1RAs, liraglutide was investigated for the interaction of liver function in CLD patients [28]. Liver enzymes were not influenced for 2 years by this agent alone or combined with others. Liraglutide showed clinical efficacy associated with pioglitazone or sitagliptin for patients with diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD). Liraglutide has reduced diabetic parameters, body weight, inflammatory situation and liver fibrosis [29]. Recently, there was an impressive study that circulating levels of GLP-1 were compared between cirrhotic patients and healthy controls [30]. As a result, GLP-1 value was 95.3 vs 111.8 pg/mL ( $p = 0.017$ ), respectively. Further prospective investigation will be necessary with exploring the efficacy of incretin.



In conclusion, two cases treated with Xultophy were described with some perspectives. In actual practice for diabetes, Xultophy has been gradually used more because of its satisfactory clinical efficacy of decreased glucose and HbA1c values and unremarkable adverse effect. However, clinical responses are not always satisfactory due to different complication and background of each patient. In this report, there are some limitations. Two cases have different background, complications and T2DM conditions. Xultophy was effective in case 1, but not effective in case 2. One of the less responsiveness to Xultophy would be due to impaired liver function. Clinical progress of both cases associated with several perspectives from various points of view are discussed in this article. This report may become one of the reference data for various interrelationship among diabetes, liver function, endocrine and gastroenterological axes.

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