

Beneficial Xultophy Treatment from Medical and Social Points of View

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Abstract

The case is a 65-year-old male who has been treated for Type 2 diabetes mellitus (T2DM) for 26 years. He has no previous history of cerebral vascular accident (CVA) or coronary heart disease (CHD). He has been treated on insulin therapy, and recently his glucose variability became worse due to the irregular lifestyle. Then, diabetic treatment was changed to Xultophy, which consists of insulin degludec and liraglutide. Providing 16 units of Xultophy brought him a satisfactory daily profile of blood glucose, which seemed to be lower doses compared with the ordinary standard amount. Treatment of Xultophy seems to be effective and some discussion would be described from several points of view.

Keywords: Xultophy; Degludec and liraglutide (IDegLira); Glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA); DUAL (Dual Action of Liraglutide and Insulin Degludec); European Xultophy Treatment Retrospective Audit (EXTRA)

Introduction

The prevalence of diabetes across the world is increasing with higher speed in developed countries and also developing countries (1). It may cause large influences on any district and country from medical and economic points of view (2). As the number of diabetes increases, medical problems from diabetic microangiopathy and macroangiopathy increase in a variety of situations (3). Consequently, optimal therapy and applicable treatment for diabetes would be required. According to the current guideline of diabetes society, several kinds of new oral hypoglycemic agents (OHAs) and injectable agents have been introduced, which have been expected to reveal evident beneficial results (4).

As to the standard therapy of Type 2 Diabetes Mellitus (T2DM), OHAs are usually used for the first-line treatment. When these treatments are not so effective, insulin therapy would be applied (4). The ideal pattern of insulin administration was believed to provide multiple daily injections (MDI) (5). Then, the MDI has been standard and more prevalent in recent years. However, the new injectable agents were introduced to medical practice, and the clinical situation has been changing now. It may be from two agents. One is the clinical application of Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) (6). There are several kinds of GLP-1RAs and show beneficial effects for blood glucose variability. Another would be the combined factors of basal insulin and GLP-1RA, such as Xultophy (7).

There were a series of the study for Xultophy in multiple centers, that was the European Xultophy Treatment Retrospective Audit (EXTRA) study. Among them, a real-world evidence (RWE) study (EXTRA) was summarized from European countries (8). It showed beneficial efficacy for T2DM, indicating a satisfactory reduction of HbA1c level for half a year as minus 0.7%. Furthermore, weight reduction was also a significant result for half a year as minus 2.4kg. In addition to these data, another EXTRA study was performed with 611 patients in five countries (9). The results revealed that a substantial decrease of HbA1c for 6 months was minus 0.9%. Thus, it has a satisfactory effect for patients with T2DM by simple and convenient injection and easy continuation of treatment for a long period.

The authors and co-researchers have been involved in clinical matters of diabetes and Xultophy for years. The intake of carbohydrates causes post-prandial elevation of blood glucose. In contrast, fatty food with high calories does not increase blood glucose. Both of these are equivalent to calorie restriction (CR) which was the previous standard diet, and low carbohydrate diet (LCD) which has been recently in focus (10). There is various evidence of the beneficial result for LCD so far (11,12).

We have proposed three patterns of LCD, such as super-LCD, standard-LCD, and petite-LCD (13). They are simple and easy to understand and continue LCD habits. Authors have developed LCD medically and socially through continuous activities of the Japan LCD Promotion Association (JLCDPA) (14). In these healthcare and medical areas, glycemic control is needed and better control is expected.

In addition to the research of LCD and Meal Tolerance Test (MTT) (15), we have reported on several research on GLP-1RA (6,16). Furthermore, we have continued to present the reports on Xultophy (17,18). Both are clinically useful and their effectiveness is evaluated (19). Among various experiences, authors have treated an impressive T2DM male case. He has continued poor compliance with daily insulin treatment due to his social profession. Xultophy could contribute to improving clinical progress for its beneficial function. In this article, general information will be described associated with the discussion.

Presentation of the Case

Medical & Social History

The patient is a 65-year-old male, who has been treated with T2DM for 26 years. As to history, he did not have a remarkable disease or health problems including cerebral vascular accident (CVA) and coronary heart disease (CHD). Family history was negative for diabetes, hypertension, CVA, CHD, and so on.

Regarding social history, he was formerly a tennis player and has been a coach/manager of a tennis club for long years. He likes sports and takes part in various sports activities with many people. Such fantastic activity and reliable personal character have been highly evaluated, and then he was recommended to become a city council member in 2018. After that, he has been extremely busy and could not continue his regular life. He needed to give insulin shots twice a day, but it was not possible because of frequent unexpected official work.

Physicals and exams

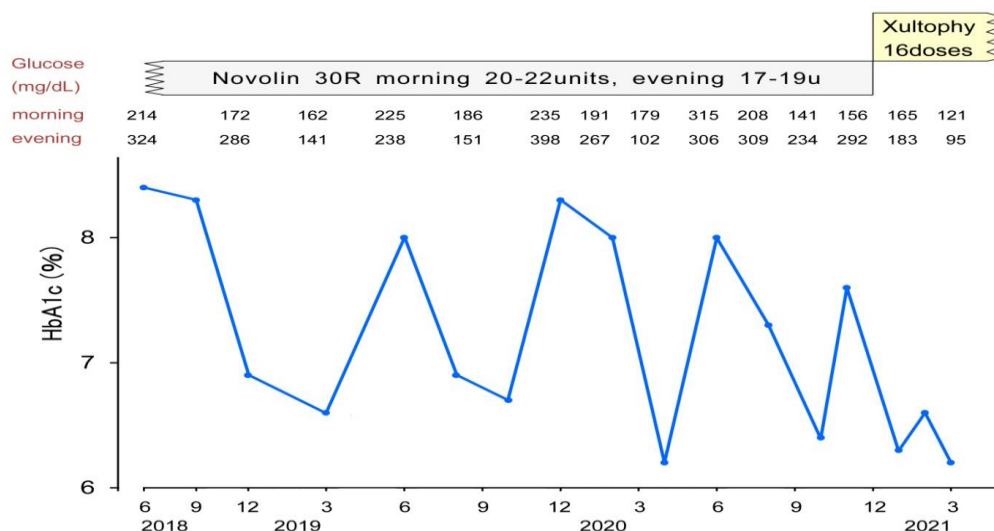
His physical examination showed as follows: Consciousness and vitals were unremarkable. Height 160 cm, weight 60 kg, BMI 23.4 kg/m². Chest showed normal with no rale in the lung, regular rate rhythm in the heart, the abdomen is soft and flat and bowel sound is audible. He has no abnormality of a neurological condition such as diabetic neuropathy, or no signs and symptoms concerning retinopathy and nephropathy.

Various laboratory and physiological data in June 2018 were in the following. HbA1c 8.4%, pre-prandial glucose 133 mg/dL, TP 7.0 g/dL, Alb 4.5 g/dL, AST 17 U/L, ALT 13 U/L, r-GT 21 U/L, ALP 148 U/L (100-340), uric acid 7.3 mg/dL, BUN 16 mg/dL, Cr 0.6 mg/dL, eGFR 96 mL/min/1.73m², Na 141 mEq/L, Cl 102 mEq/L, K 3.9 mEq/L, LDL-C 130 mg/dL, HDL 62 mg/dL, TG 89 mg/dL, Hb 14.2 g/dL, RBC 448 x 10⁶ /μL, WBC 7200 /μL, Plt 26.5 x 10⁴ /μL, CRP 0.06 mg/dL. Chest X-P was negative, and electrocardiogram (ECG) was within normal limits.

Clinical course

His diabetic control has been rather unstable (Figure 1). HbA1c values varied from 6.2 to 8.4% because of irregular lifestyle as a city council member. Previous data of blood glucose in the morning and evening were shown in Figure 1. Those data were compared to the changes in HbA1c values for several years.

Figure 1: Clinical progress with the changes in HbA1c and treatment.



The HbA1c value was rather higher in the autumn of 2020, then diabetic treatment was changed from Novolin 30R twice daily to Xultophy injection once daily, which consists of insulin degludec and liraglutide. The actual blood glucose values are summarized in Table 1. Before starting Xultophy, Novolin 30R was provided twice as 21 units and 19 units, associated with unstable blood glucose for 75-195 mg/dL. Xultophy was begun at 8 units and was gradually increased. Just after the given doses became 16 units, the profile of blood glucose was normalized for 93-165 mg/dL. Glucose variability from day 8 to day 16 seemed to be stable (Table 1).

Table 1: Changes in blood glucose for the case.

Day	Blood glucose		Xultophy dose	30R x 2 units
	morning	evening		
-3	115	195		21 + 19
-2	168	201		21 + 19
-1	75	149		21 + 19
1	158	131	8	
2	243	169	10	
3	244	302	10	
4	216	219	12	
5	209	259	12	
6	214	202	14	
7	213	214	14	
8	126	120	16	
9	93	165	16	
10	126	129	16	
11	151	138	16	
12	135	151	16	
13	149	126	16	
14	131	85	16	
15	162	-	16	
16	158	172	16	

Discussion

In this article, we report the impressive clinical progress of a 65-year-old man with T2DM. This case has characteristic points from medical and social points of view. As a social predisposition, he was elected to be a city council member of the community. Then, he could not continue regular stable life. As a result, diabetes control became unstable and HbA1c levels fluctuated from 6.2-8.4% (Figure 1). Novolin 30R twice daily could not give enough glucose control (20). Regarding this treatment way, he was formerly provided in a university hospital. This method was not recommended method, but he hoped to continue the protocol. Recently, his glucose variability became unstable, and then Xultophy was started once daily (7). Consequently, satisfactory control was obtained in a short period of time. These processes seemed to be very impressive. Various factors seem to be involved in these situations mentioned above. Here, some perspectives are discussed from three aspects in the following.

The first is the effectiveness of GLP-1RA. In this case, the total amount of insulin was necessary for 40 units formerly. As Xultophy was started, satisfactory control was found at only 16 units for 8-9th days. The 16 dose contains 16 units of long-acting insulin degludec and 0.576 mg of liraglutide of GLP-1RA. One of the reasons why only 16 units of Xultophy could give a satisfactory control would be the beneficial effect of GLP-1RAs and/or the high sensitivity of patients.

GLP-1RAs have been evaluated to show enough response for improving glucose variability, including several kinds of agents (6). They include liraglutide, exenatide, lixisenatide, dulaglutide, and others. Recently, a Network Meta-Analysis (NMA) for GLP-1RAs was conducted for evaluating glycemic control and safety outcomes (21). 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.

The second is the general benefit of Xultophy. The standard method has been known to get started with Xultophy. When the diabetic patient was already on insulin therapy and changed to Xultophy, the initial doses would be 16 units according to the guideline in the usual way (7). When the case was not on insulin treatment and naïve situation, the initial doses would be 10 units. The author and collaborators have several experiences to give Xultophy in various cases. Among them, unlike European and North American countries, an adequate method would be to start with a small amount in Japan. Some possible reasons include that Japanese people are usually rather small in stature and may have a better response to insulin and GLP-1RA combinations (22). In our previous report, to start with 5 units and to maintain 5 units of Xultophy showed sufficient control of blood glucose (17). In the case of this report as well, the total amount of insulin was 40 units formerly, but better glucose control was obtained at only 16 units of Xultophy starting from 8-10 units. Furthermore, Xultophy shows the beneficial points of fewer frequencies of hypoglycemia, weight gain, or gastrointestinal reverse effects in comparison with those of GLP-1RA alone. In this case, lower doses of Xultophy were enough to control blood glucose, and then it seemed to be preferable due to less possibility of adverse effects (23). In the future, further accumulation of various cases and their detailed study will be expected.

The third is the involvement of social history of the case, which may be important factor for the patient and also the adequate therapy (24). Major differences for people's lifestyles exist between Western countries and Japan. In Europe and the United States, they usually have rather clear regular lives with on and off, which mean work hours and home hours. On the other hand, Japan has different situation from cultural aspect. Several professionals such as doctors, lawyers, council members and other officials often continue working very long hours at the expense of their private lives. The same is true for the case of this report (25). In other words, he has always on various jobs from morning to night. He has to treat himself by injecting twice a day. Due to unexpected meetings or opportunities, he could not inject insulin or keep regular lifestyle. Consequently, it was formerly rather difficult for him to maintain proper compliance and resilience in his daily life (26).

In summary, this case had been formerly provided insulin injections twice a day. However, due to his duties as a council member in the community, his daily life became extremely irregular. He could not even inject insulin himself in certain regular time, resulting in poor glycemic control. When the treatment was changed to Xultophy, glucose variability became more stable than expected with low doses by only one injection. Some possible reasons include the beneficial effect of GLP-1RAs and/or the high sensitivity of

patients. The case obtained satisfactory results from medical, psychological and social points of view. It is expected that medical application of Xultophy will increase and contribute the overall happiness in patients with T2DM.

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