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Changed Diabetic Treatment from Multiple Daily Injection (MDI), Dulaglutide to Xultophy

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Abstract

The patient is a 56-year old (yo) female with type 2 diabetes mellitus (T2DM). Medical histories include persisting T2DM from 35yo, renal stone at 43yo, hypertension from 45yo, photocoagulation for retinopathy on 54yo. An incidentaloma was found in the left adrenal gland, where endocrinological exams were negative for functional tumor. Her diabetic control situation became worse with HbA1c > 10%, then the treatment has been changed from multiple daily injection (MDI), Dulaglutide to Xultophy which is combined agents of degludec and liraglutide (IDegLira). It was provided 10-18 doses daily, and then glucose variability profile was improved satisfactory, suggesting the dual synergistic effects.

Keywords

Xultophy, Degludec and Liraglutide, Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist, Dual Action of Liraglutide and Insulin Degludec, European Xultophy Treatment Retrospective Audit

Abbreviations

IDegLira: Degludec and Liraglutide; GLP-1RA: Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist; DUAL: Dual Action of Liraglutide and Insulin Degludec; EXTRA: European Xultophy Treatment Retrospective Audit

Introduction

Diabetes has been one of the crucial non-communicable diseases (NCDs) across the world [1]. Its prevalence has been increasing in developed and developing countries [2]. It may bring a variety of influences in the light of medical and economic aspects [3]. Regarding diabetic treatments, several options have been introduced, including oral hypoglycemic agents (OHAs) and injectable agents [4].

For the development of various treatment agents for diabetes, a recent important topic includes glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA) [5]. After GLP-1RA showed clinical efficacy for diabetes, the combination of basal insulin and GLP-1RA was proposed for more beneficial efficacy [6]. There have been fixed-ratio combined agents with basal degludec and liraglutide and are known as Xultophy (IDegLira) [7].

Its beneficial effects of these combined agents are observed [6]. In other words, they show complementary efficacy on glucose variability from degludec and liraglutide. The former degludec can

lower fasting plasma glucose (FPG), and the latter can lower FPG and decrease postprandial glucose response [8]. Moreover, the latter can improve beta-cell function and restore prandial insulin response/cardioprotective properties [9].

As to the fixed-ratio combination of IDegLira, there was a study of the DUAL (Dual Action of Liraglutide and Insulin Degludec) clinical trial program [10,11]. The safety and effect were investigated in a series of DUAL programs. They showed that the superior or noninferior glycemic control was found with several comparators, associated with the benefit for lower risk of hypoglycemia and weight gain in comparison with other insulin agents [12,13].

Regarding diabetic practice, authors and collaborators have continued a variety of research. They include low carbohydrate diet (LCD), calorie restriction (CR), meal tolerance test (MTT), continuous glucose monitoring (CGM), treatment of insulin, GLP-1RA and Xultophy, and so on [14,15]. Especially, we have applied Xultophy to patients with multiple problems and dialysis [16,17]. Xultophy has been known to be clinically effective for patients with various diseased states such as renal insufficiency or chronic renal failure, or limited treatment options [18]. This would be due to the beneficial efficacy of combined pharmacological agents. Authors have experienced an impressive diabetic case who has changed the treatment of multiple daily injection (MDI) insulin therapy to dulaglutide and also to Xultophy. In this article, general clinical progress associated with some discussion will be presented.

Case Presentation

Present History:

The patient is a 56-year old female. As a medical history, diabetes was detected at 35 years old (yo), urinary tract stones at 43 yo, hypertension from 45 yo, photocoagulation for diabetic retinopathy from 54 yo, and surgery for cataract at 55 yo. A space-occupying lesion (SOL) 2 cm in size was found in her left adrenal gland at a medical examination in June 2020. An endocrinological examination for adrenal tumors was performed at another hospital in July. As a result, the excessive concentration of cortisol and catecholamine was denied. The value of HbA1c has been elevated at a high value of 8-9%.

Physical Examination:

Her consciousness was alert, and her vitals are stable, such as body temperature 36.8, pulse 87/min, BP 112/67 mmHg. Her physique showed stature 151.2 cm, weight 58.6 kg, standard weight 50.2 kg, BMI 25.6 kg/m^2, abdominal circumference 87cm. Skin showed normal turgor, no thyromegaly, no swollen lymph nodes. Conjunctiva was not anemic or icteric. Her chest showed regular rate rhythm in the heart and no rale in the lung. The abdomen was slightly distended, and extremities showed no pretibial edema. There were no clear signs of the moon face, buffalo hump, or central obesity. Neurologically, there were no sensory abnormalities such as peripheral neuropathy.

Examination Data:

The results of laboratory exams were shown in the following. The standard biochemical data were GOT 23 U/mL, GPT 27 U/mL, r-GTP 24 U/mL, Cre 0.7 mg/dL, BUN 19 mg/dL, Uric Acid 5.6 mg/dL, HDL-C 40 mg/dL, LDL-C 105 mg/dL, Triglyceride 298 mg/dL, RBC 4.37 x 10^6/μL, Hb 13.3 g/dL, WBC 5400 /μL, Plt 23.9 x 10^4/μL. Data concerning diabetes showed HbA1c 9.0%, post-prandial glucose 283 mg/dL.

Other examinations were as follows: i) ECG: pulse 76/min, ordinary sinus rhythm, no ST-T changes, ii) chest X-ray: WNL, iii) Ankle brachial index (ABI) / Pulse wave velocity (PWV): ABI showed 1.22/1.26 (r/l), and PWV 1715/1864 (>+2SD), iv) Coefficient of variation of R -R interval (CV R-R): it was 3.0% (normal is =< 2.0), v) renal examination: Ccr 80.2 ml/min, Urinary-Albumin 10.8 mg/day, serum CPR 1.71 ng/ml, vi) urinary C-peptide 92 μg/day (35-140).

Clinical Progress

This case has T2DM and other problems. She was pointed out (P/O) the presence of left adrenal incidentaloma, and after that, the possibility of Cushing syndrome was ruled out (R/O) (**Fig-1**). She has been provided Ipragliflozin L-proline (Sugra®, 50mg) 1 Tablet and Voglibose (Basen®, 0.3mg) 2 Tablets in the morning and evening as oral hypoglycemic agents (OHAs) for long period. For

injectable agents, she has given i) insulin glargine 10 units and Apidra 17-25-18 units, which was MDI insulin therapy, ii) Deglutide 0.75mg/week, iii) Xultophy 10-18 doses/day as shown in **Fig-1**. HbA1c value was 9.0% to 7.8% in MDI, 7.8% to 10.6% in Deglutide, and 10.6% to 8.2% in Xultophy.

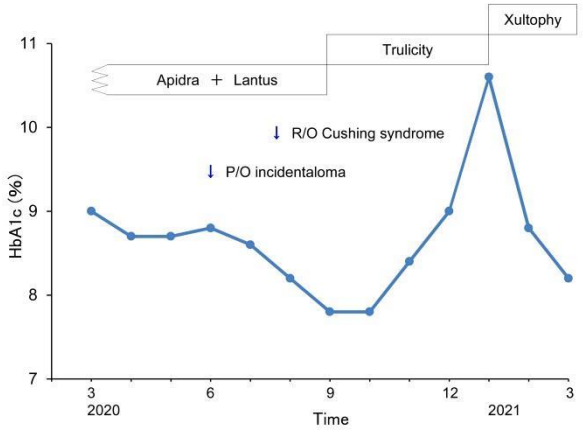

Fig-1: Clinical progress with the changes of HbA1c and treatment

When changing the treatment from Deglutide to Xultophy, the daily profile of blood glucose was studied for 2 weeks. The results are shown in **Table-1**. Dulaglutide has its clinical effect for 7 days, and glucose levels ranged from 159 mg/dL to 208 mg/dL during days 6-8 after the injection of Dulaglutide. Xultophy was started at 10 doses and gradually increased its dose. Glucose variability was improved for 108 mg/dL to 144 mg/dL for 11-12 days of administration.

Problems Lists:

Her current medical problems and treatment are summarized in the following.

1. T2DM: She has been provided OHAs and three injectable agents during the course (**Fig-1**).
2. Hypertension: Her blood pressure has been controlled by the administration of two anti-hypertensive agents (AHA), including Irbesartan 100mg and trichlormethiazide 1mg.
3. Hyperlipidemia: She was given Rosuvastatin (Crestor®, 2.5mg) with rather stable control of LDL-C, TG and HDL-C [19].
4. Osteoarthritis (OA) of the knees: She has felt pain in the knees. Current treatment includes Celecoxib (Celecox®, 100mg) 2 Tablets per day and pregabalin (Lyrica® 75mg) 2 Tablets per day [20].

Table-1: Changes in blood glucose for Xultophy treatment

Day	Blood Glucose (mg/dL)			Xultophy	Dulaglutide
	Morning	Noon	Evening	dose	0.75mg/w
1			159		day 6
2	194	196	166		day 7
3	208	188	172		day 8
4	189	164	175	10	
5	190	181	193	12	
6	149	149	252	14	
7	174	140	149	14	
8	149	115	174	16	
9	126	107	118	16	
10	131	122	162	16	
11	135	91	102	17	
12	119	111	101	17	
13	140	147	165	17	
14	124	111	144	17	
15	108	110		18	

Discussion

This report is concerning to clinical efficacy of Xultophy, which contains basal-bolus insulin and GLP-1RA. Several papers were found about the comparative study of basal insulin and Xultophy. Previous outcomes of Xultophy were broadly aligned with the results of DUAL studies. They showed a significant decrease in HbA1c, reducing the tendency of body weight, lower risk of hypoglycemia episodes for half years in comparison with baseline regimens [21]. Despite being an efficacious glucose-lowering therapy, basal-bolus treatment is associated with a higher rate of hypoglycemia versus other anti-diabetes therapies [22].

In the European region, there has been the European Xultophy Treatment Retrospective Audit (EXTRA) study. Some real-world evidence (RWE) studies (EXTRA) showed that a significant HbA1c reduction (-0.7%) and weight reduction (-2.4kg) were found for half a year, in patients with changing treatment from MDI to Xultophy [23]. There is a recent study by Persano et al. (2021) [24]. T2DM patients had changed from basal-bolus insulin treatment to Xultophy starting with 16 doses. Subjects were trained to titrate the dose twice weekly to maintain 90-130 mg/dL fasting target glucose level. Their adjustments were made 2 doses at a time. The results showed that HbA1c values were 8.4 vs 7.4% in the control and Xultophy group in 6 months [24].

Regarding the background of the case, it is important to evaluate the situation of diabetic complications for microangiopathy and macroangiopathy. She has proliferative retinopathy with the treatment of photocoagulation and the operation of cataract but did not have clear evidence of neuropathy, nephropathy, or macroangiopathy of the brain, heart, and peripheral artery. When she received a health check-up in the spring of 2020, left adrenal incidentaloma was found. Several endocrinological tests showed negative results in plasma aldosterone concentration (PAC), plasma renin activity (PRA), PAC/PRA ratio [25], ACTH and cortisol values, overnight dexamethasone suppression test (1mg), and serum and urine catecholamine concentration. It was unlikely to exist the presence of Cushing's syndrome, pheochromocytoma, or primary aldosteronism (PA) [26]. Therefore, it was considered to be a non-functioning adenoma.

She has been treated for hypertension for a long. Her usual situation of blood pressure was stable with medication, not a fluctuating type, not clinical symptoms like pheochromocytoma, and catecholamine levels were within the normal range [27]. Since Cushing's disease is also negative, it is considered to be essential hypertension rather than secondary hypertension. Regarding dyslipidemia, triglyceride has been high for some time. In other words, it is thought to be associated with obesity and metabolic syndrome, and LDL-C is currently in the normal range by taking Crestor. A recent study showed the significant predominance of Rosuvastatin over atorvastatin in reducing LDL in T2DM as a mean reduction of 30.5 vs 29.6 mg/dL for 6 weeks ($p < 0.01$) [28].

Her current clinical course showed the exacerbation of HbA1c after changed to the treatment of Dulaglutide, and then the treatment of Xultophy was started. As the initial amount of Xultophy, 10 or 16 doses has been the standard value in a patient with insulin naïve or experienced case, respectively [29]. Furthermore, there may be another perspective that the standard starting dose would be 16 doses in Europe or 10 doses in Japan. This case is a Japanese woman with rather a small physique, then the starting dose was set to 10 doses. Furthermore, authors have various experiences to provide Xultophy T2DM patients with various situations and complications [16,17]. The method to titrate would be to control the doses every 3-4 days based on FPG. In the study of DUAL V, attended cases had adjusted the doses on Monday and Thursday of each week [10]. The maximum doses of Xultophy would be 50 doses, which means 50 units of Degludec and 1.8 mg of liraglutide [13,29]. As to the continuation of Xultophy, 2432 T2DM cases were investigated for 18 months. The results showed that 84% of cases continued Xultophy, associated with a mean reduction of HbA1c 1%, and weight reduction 1.1 kg, by 33 mean doses [30].

In summary, this article showed the impressive clinical progress of the changes in HbA1c and diabetic

agents from MDI, Dulaglutide to Xultophy. Xultophy may have dual synergistic effects of degludec and liraglutide (IDegLira). Consequently, combined treatment of insulin and GLP-1RA seemed to be effective for improving the glucose variability. This report will be hopefully one of the reference data for a future diabetic research study.

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Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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