

# Effective and convenient treatment of Xultophy with lower doses for elderly diabetic patient

## Abstract

The case is an 82-year-old female patient with Type 2 Diabetes Mellitus (T2DM) for 22 years. She developed right empyema in early January, 2021 and was treated by antibiotics and CT-guided drainage. After improving the status, she was transferred to Hayashi hospital, Tokushima, Japan. Treatment for T2DM was initially multiple daily insulin injection (MDI), but it could not continue because of injection several times a day by the family. Then, Xultophy was started once a day, which brought satisfactory glucose variability with lower doses. Consequently, Xultophy would be effective and useful agent from bio-psycho-social points of view.

**Keywords:** multiple daily insulin injection (MDI), Xultophy, Type 2 Diabetes Mellitus (T2DM), bio-psycho-social, multiple daily injection (MDI)

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## Introduction

In the world, diabetes has been one of the representative non-communicable diseases (NCDs).<sup>1</sup> The prevalence and incidence are increasing in developing and developed countries and districts.<sup>2</sup> From medical and economic points of view, increasing diabetes has brought various crucial influences.<sup>3</sup> As to diabetic therapy, some options have been continued for years such as oral hypoglycemic agents (OHAs) and also some injectable agents.<sup>4</sup>

Among various topics concerning the treatment agents for diabetes, glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) have been in focus for actual practice.<sup>5</sup> After several years for recognizing the clinical effect of GLP-1RAs, the combined agent of GLP-1RA and basal insulin was introduced to medical treatment associated with more benefit involvement.<sup>6</sup> Xultophy includes two agents of liraglutide and basal insulin degludec with a fixed ratio. It is often described as IDegLira.<sup>7</sup>

IDegLira reveals the beneficial efficacy from each agent.<sup>6</sup> Consequently, complementary effects are observed from liraglutide and degludec. The former can lower fasting blood glucose and the post-prandial glucose response. Further, the former can improve  $\beta$ -cell function, maintain the post-prandial insulin response and restore the cardioprotective properties.<sup>8</sup> In contrast, the latter degludec can reduce the level of fasting blood glucose because of it can influence glucose level for long hours.<sup>9</sup>

As to the fixed-ratio combination of IDegLira, there was a study of DUAL<sup>TM</sup> (Dual Action of Liraglutide and Insulin Degludec) clinical trial program.<sup>10,11</sup> 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.<sup>12,13</sup>

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, Xultophy, and so on.<sup>14,15</sup> Especially, Xultophy has been applied to patients with multiple problems and dialysis.<sup>16,17</sup> 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.<sup>18</sup> This would be due to the beneficial efficacy of combined pharmacological agents. An impressive diabetic case was observed who has changed the treatment of multiple daily injection (MDI) insulin therapy to Xultophy only one injection per day. In this article, general clinical progress associated with some discussion will be presented.

## Case presentation

### Medical history

The case is a 82-year-old female patient with Type 2 Diabetes Mellitus (T2DM). She was pointed out to have diabetes at 60 years old. She has received DM treatment at another hospital in recent years. The treatment included Lantus XR 4 units, glimepiride 6mg, miglitol 150mg, vildagliptin 100mg, metformin 500mg per day, but her diabetic control was poor as HbA1c 10.2%.

She developed headache from Dec 23, 2020 cough and low back pain from Dec 25, 2020 and visited the hospital. As a treatment, she was treated with celecoxib but the symptoms did not relieved. Then, she visited another hospital on Jan 6 and was proved to be negative for PCR examination of COVID-19.

She was referred to the Tokushima Red Cross Hospital (TRCH) and was diagnosed with empyema in the right lung and was hospitalized. The treatments included Tazobactam and Piperacillin Hydrate (TAZ /

PIPC) 2.25g (Zocin<sup>®</sup>) q 6hrs, and also CT-guided drainage procedure. The culture result from the abscess revealed the *Streptococcus anginosus*. The discharge from the drain was disappeared, then the drainage was removed on Jan 13, 2021. For diabetic status, serum C-peptide 0.62ng/mL was in lower value, suggesting insulin deficiency. Consequently, multiple daily insulin injection (MDI) was started with insulin human for 3 times and Lantus XR once. The patient was transferred to Hayashi hospital which is situated nearby TRCH on Jan 14, 2021.

### Physical status

Vitals and consciousness showed unremarkable acute abnormalities. She revealed SpO<sub>2</sub> level as 96% in room air. Chest showed that regular rate rhythm in the heart and rather weaker breath sound in right lung. Abdomen revealed flat and soft with ordinary bowel sound. No abnormalities were observed in neurological examination.

### Several examinations

Several examinations on admission were as follows: Chest X-P and chest CT scan revealed the presence of the Empyema in the right lung. The lesion was found at first in the size of 8.2cm x 4.6cm in the lower lobe of the right lung, which was reduced 7.1cm x 3.2cm in 7 days. ECG showed unremarkable changes.

The laboratory examination were in the following: RBC 3.11 x 10<sup>6</sup>/μL, Hb 10.0g/dL, Ht 29.7%, MCV 95.5 fL (80-98), MCH 32.2pg (27-34), MCHC 33.7g/dL (31-36), WBC 5740/μL, Plt 30.5 x 10<sup>4</sup>/μL, AST 32U/L, ALT 23U/L, γ-GT 37U/L, ALP 94U/L, LDH 233U/L (100-340), T-Bil 0.5mg/dL, TP 6.3g/dL, Alb 2.3g/dL, A/G ratio 0.79, Alb 44.25 %, α<sub>1</sub>-glb 4.4%, α<sub>2</sub>-glb 12.2%, β-glb 10.4%, γ-glb 28.8%, CRP 2.16mg/dL, BUN 13mg/dL, Cr 0.81mg/dL, eGFR 51mL/min/1.73m<sup>2</sup>, Na 136mEq/L, K 4.7mEq/L, Cl 101mEq/L, T-C 149mg/dL, HDL-C 50mg/dL, LDL-C 84mg/dL, TG 67mg/dL.

Other specific tests revealed as follows: Urinalysis data; protein (-), glucose (-), urobilinogen (+/-), bilirubin (-) ketone bodies (2+), pH 7.5, occult blood (-), specific gravity 1.015, bacteria (+/-), urine C-peptide excretion 19.1μg/day (23-155), urinary albumin 5.4mg/day (2-20), tumor markers: CEA 3.9ng/ml, (-5.0), SLX 22.8U/mL, (-38), SCC Ag 0.8ng/mL (-1.5), CYFRA 1.5ng/mL (-3.5), NSE 9.4ng/mL (-16.3).

### ADL status

Before the hospitalization, her ADL was self-reliant. She could move freely associated with grasping the handrail in slow pace. Current episode with treatment in the hospital has brought her power reduction of the legs. After the operation on January 7, she started rehabilitation from an early stage using a rehabilitation walker. The value of SpO<sub>2</sub> during rehabilitation did not decrease keeping around 94-96% in the room air, and her rehabilitation could be continued. With the treatment walker, she was able to walk 120 meters with light assistance. Basic movements were required mild to moderate assistance in usual ADL until January 13, and some improvements are expected in the future.

### Medical problems

From mentioned above, the medical problems of this patient are summarized as follows: #1 empyema (right lung), #2 Type 2 diabetes mellitus (T2DM), #3 hypertension, #4 hyperlipidemia.

Related to these problems, current medication concerning #2,3,4 includes amlodipine besilate (Amlodine<sup>®</sup>) 5mg 1T, azilsartan (Azilva<sup>®</sup>) 20mg 1T, atorvastatin (Lipitor<sup>®</sup>)10mg 1T and vonoprazan fumarate (Takecab<sup>®</sup>)10mg 1T.

### Clinical progress

The patient with empyema was relieved by the administration of antibiotics and the procedure of drainage treatment. Regarding antibiotics, Tazobactam and Piperacillin Hydrate (TAZ/PIPC) were initially administered, and then amoxicillin hydrate, potassium clavulanate were administered for 2 weeks. In addition, carbocisteine 500mg 3 Tablets was provided for facilitating the sputum discharge. From these combined treatments, empyema was completely cured.

The changes in various biomarkers with the clinical course were shown in Table 1. Among them, during Jan 6-14, leukocytosis was improved from 10520/μL to 5740/μL and elevated CRP was decreased from 18.1mg/dL to 2.2mg/dL. During Jan 14-Feb 17, total protein was increased from 6.3g/dL to 7.6g/dL and albumin was also increased from 2.3g/dL to 3.5g/dL.

**Table 1** Changes in several biomarkers

		01/06	01/09	01/14	02/04	02/17
WBC	(/μL)	10520	5720	5740	6340	5800
Hb	(g/dL)	11	9.7	10	12.1	12.2
CRP	(mg/dL)	18.1	6.8	2.2	0.27	0.3
TP	(g/dL)	-	6.1	6.3	-	7.6
Alb	(g/dL)	-	2.0	2.3	-	3.5
T-Bil	(mg/dL)	0.7	0.5	0.5	0.7	0.5
AST	(U/L)	35	29	32	23	36
Na	(mEq/L)	130	138	136	136	138
K	(mEq/L)	4.5	4.5	4.7	4.8	4.7
Cr	(mg/dL)	0.7	0.8	0.8	0.6	0.7

Furthermore, the relationship between diurnal fluctuations in blood glucose and treatment for diabetes was summarized in Table 2. Initially, blood glucose was measured four times a day and insulin treatment was performed by the sliding scale method. Multiple daily insulin injection (MDI) is ideal, but when this planning method was explained to the patient and families, it was proved to be difficult to carry out. Then, the treatment was changed to the injection of Xultophy once a day. The starting amount was 6 doses, and the profile of blood glucose became stable at 5 doses. The HbA<sub>1c</sub> level was initially 10.5%, but improved to 7.5% at the time of discharge in late February.

**Table 2** Progress of blood glucose and treatment

Date	Daily profile of blood glucose				Treatment		
	Morning	Noon	Evening	Night	Rapid	Lantas	Xultophy
	(mg/dL)	(mg/dL)	(mg/dL)	(mg/dL)	(unit)	(unit)	(doses)
Jan	16	172	179	277	244	3-3-5	4
	23	118	213	234	220	2-4-4	6
	29	111	203	176	215	2-4-3	7
	30	66	138	178	248	0-2-3	8
	31	101	168	140	214	2-3-2	8
Feb	1	69	204	197	235		6
	4	62	157	201	228		6
	8	124		178			5
	11	108		169			5
	15	103		169			5
	18	78		230			5
	22	101		256			5
	25	113		224			5

## Discussion

In this report, clinical effect and related matters of Xultophy were described and discussed, which has the combinations of GLP-1RA and basal-bolus insulin. There were some papers concerning the comparative study of basal insulin and Xultophy. In the investigations on Xultophy, DUAL studies have been known,<sup>10,11</sup> which stands for Dual Action of Liraglutide and Insulin Degludec clinical trial program. Other previous outcomes of studies on Xultophy were generally aligned with those of DUAL studies. They include significant reduction of HbA1c value, decreasing trend of body weight, low risk episodes for hypoglycemia compared with standard baseline regimens.<sup>19</sup> The basal-bolus treatment has been evaluated to be effective for glucose-lowering method, but it shows higher ratio of hypoglycemia episodes in comparison with other anti-diabetes treatments.<sup>20</sup>

As a reliable investigation, the European Xultophy Treatment Retrospective Audit (EXTRA) study was conducted in European region. In some of the real-world evidence (RWE) studies of EXTRA, there were significant decreases of HbA1c of 0.7% and weight reduction of 2.4kg for 6 months in the diabetic cases that changed from MDI to Xultophy.<sup>21</sup> According to the recent study in 2021, patients with T2DM changed the treatment from basal-bolus insulin to Xultophy, in which they started at 16 doses.<sup>22</sup> The participants were indicated to titrate the doses to maintain fasting glucose value at 90-130mg/dL two times a week. They can adjust the doses for plus 2 or minus 2 doses when titrating. As a result, HbA1c level for half year was 7.4% vs 8.4% in Xultophy group and control group, respectively.<sup>22</sup>

The authors' group has practiced and researched primary care (PC) medicine and integrative medicine (IM) for long.<sup>23</sup> Common perspectives for PC and IM would be patient-oriented medicine. Three important points have been found, which are bio-psycho-social aspects. As regard to these, the example of diabetic patient will be presented.<sup>24</sup>

The first is bio-aspect. Due to the current status of glycemic variability, oral hypoglycemic agents (OHAs) are not sufficient, and newer injectable agents are required such as GLP-1RA or Xultophy. The second is psycho-aspect. Some diabetic patients cannot tolerate limited diet for long period. From this feeling, it is not possible to actually continue appropriate behavior suitable for diabetes.<sup>25</sup> The third is social-aspect. There are several diabetic patients who can not maintain proper lifestyle due to various temptation from friends and others. Further, it may be difficult to obtain the understanding and cooperation of family members. As mentioned above, these bio-psycho-social aspects will be used as the fundamental perspectives in actual medical practice and care in the future.

Regarding the social aspect of the patient, she is elderly and does not work in particular. Her home has two households in the same location. One is for the patient and her husband, and another is for his son and wife. During the daytime, both her son and wife are absent for working. So far, there has been no smooth communication between the two households.<sup>26</sup> The patient's personality keeps a certain distance from his son and wife from a social and psychological point of view.<sup>27</sup>

From psychological point of view, the nature of the patient has been rather stubborn. She has continued to spend her life for long as she likes. Some feud may be present between the patient and her son and wife. She does not want to be involved in various matters with the son. In fact, social and psychological factors may affect the relationship of personal communication and also insulin treatment.<sup>28</sup>

When she was transferred from TRCH, MDI were recommended for obtaining the ideal blood glucose control. Simultaneously, the insulin doses were decided by sliding scale method. However, the patient or the family cannot perform such complex way. The patient did not want to ask the procedure to her son, then MDI and/or sliding scale method were not possible for the patient and family.<sup>29</sup>

Xultophy can contribute to the treatment for diabetic patients with difficult therapeutic process. The reason includes useful procedure that it can be injected once a day at any time of the day.<sup>7</sup> It is beneficial points from medical, psychological and social points of view. There were also characteristics regarding the amount of dose that could be controlled. In European and North American countries, patients who are already given insulin will start Xultophy at 16 doses, and those who are naive for insulin will start Xultophy at 10 doses.<sup>8</sup> However, rather lower doses of Xultophy can be started in Japan. In our previous study, the cases with starting Xultophy from small doses were reported, which were sufficiently effective.<sup>16</sup> Probable reasons for these phenomena include smaller body physique, relatively regular lifestyle and synergistic effect of high sensitivity for combined insulin and GLP-1RA.<sup>30</sup>

There is a limit to the investigation of this case report. The case had several complications besides diabetes for years, and currently developed lung infection, in which mutual influences were not completely clarified yet. Xultophy was applied for bio-psycho-social reasons and the glycemic response was stable. However, problems include relatively high blood sugar in the afternoon, with pending status in the future. Xultophy will applied to recommended treatment according to the general situations.<sup>31</sup>

In summary, a case of 82-year-old female with T2DM developed emphysema. Her treatment was changed from MDI to Xultophy, and effective and simple injection brought her stable situation. From bio-psycho-social points of view, some perspectives were described in this article. Current report will hopefully serve as a reference in the future diabetic practice and research.

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## Conflicts of interest

The authors declare no conflict of interest.

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