



Practical Effects of Oral Twymeeeg for Type 2 Diabetes (T2d) Patient with Special Habit Taking Much Carbs

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Abstract

Background: Oral semaglutide (imeglimin) has been prescribed for patients with type 2 diabetes (T2D) as Twymeeeg.

Case presentation: The patient is 77-year-old male with hypertension, previous cerebral vascular accident (CVA). He continued unbalanced meal with preference of much carbohydrate. In Sept 2021, he became diabetic with HbA1c 8.8%.

Results: Imeglimin 2000mg/day was started improving to 6.7% for 2 months.

Discussion: Complete blood count (CBC) showed decreased Hb and increased MCV, suggesting macrocytic anemia for lack of vegetables. Much carbohydrate intake may bring T2D. Remarkable diabetic improvement may be from dual mechanisms for increasing insulin secretion and decreasing insulin resistance.

Keywords: Oral semaglutide; Imeglimin; Twymeeeg; Macrocytic anemia; Trial for Imeglimin Efficacy and Safety (TIMES)

Introduction

Applicable therapy for type 2 diabetes (T2D) has been in discussion for years. Latest perspectives for T2D were presented from European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) [1]. Furthermore, useful guideline was introduced and prevalent from ADA in Jan 2022 [2]. This practical strategy can contribute the actual management for increasing number of T2D patients across the world [3]. Recent topics concerning diabetic treatment include several injectable and oral agents for T2D [4]. Among them, pharmacologically novel agent has been applied for T2D cases for actual clinical practice associated with some beneficial mechanism for improving diabetic situation [5]. From pathophysiological point of view, T2D has been known as the combination situation of decreased insulin secretion and increased insulin resistance. For this perspective, recently introduced agent has novel mechanisms acting for these dual aspects [6]. This novel agent was pharmaceutically developed from metformin that has been the first-line oral hypoglycemic agent (OHA) for long

years [7]. It is the product of imeglimin, which includes fundamentally small molecule similar to that of metformin, whereas it shows the different point of cyclic molecule with a triazine ring. From these characteristics, imeglimin shows pharmacologically benefit for diabetic patients. It provides stimulating insulin secretion, decreasing insulin resistance and increasing insulin sensitivity [8]. Imeglimin has been already applied to clinical practice for T2D, as the prevalent brand name Twymeeeg. Authors and collaborators have reported clinical efficacy of imeglimin [9]. For T2D patients, satisfactory reduction of HbA1c was observed with stable clinical progress [10]. We have experienced an impressive T2D patient. In this article, the elderly case will be described with some perspectives.

Case Presentation

History and physicals

The patient is a 77-year-old man. For his past history, he underwent a surgery of tumor of renal pelvis at the age of 72. In winter 2020, he was treated for cerebral haemorrhage and

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pneumonia. At that time, he was pointed out persistent high blood pressure and then started to have antihypertensive drugs. No diabetes has been observed for his previous history. Postprandial blood glucose was 162 mg/dL in Dec 2020, and 156 mg/dL in Jun 2021. The patient had a slight unbalanced diet and tended to prefer carbohydrate intake too much. In Sept 2021, hyperglycemia was firstly found at 388 mg/dL. HbA1c value was proved to be elevated as 8.8%, indicating T2D. His physical examination showed that vitals, consciousness, lung, heart, abdomen were unremarkable in Sept 2021. Regarding his physique, the height was 162 cm and body weight was 48 kg with BMI 18.3 kg/m². His weight 2 years ago was 50kg, and the weight has been not changed so acutely and seemed to be almost stable. Until Sept 2021, his medical problems and medication were summarized as follow: i) hypertension and previous CVA with amlodipine 5mg/day, ii) protection for possible seizures from CVA with zonisamide 200mg/day, iii) Gastro Esophageal Reflux Disease (GERD) and occasional general malaise with sulpiride 50mg/day.

Laboratory examinations

The biochemical and blood results of Sept 2021 were in the following. They are AST 11 U/L, ALT 16 U/L, γ -GT 18 U/L, ALP 163 U/L (38-113), LDH 106 U/L (124-222), T-Bil 0.4 mg/dL, TP 6.6 g/dL, Alb 3.4 g/dL, CPK 46 U/L (30-200), BUN 21 mg/dL, Cr 0.7 mg/dL, UA 3.9 mg/dL, Na 139 mEq/L, K 4.0 mEq/L, Cl 103 mEq/L, T-C 111 mg/dL, HDL-C 35 mg/dL, LDL-C 56 mg/dL, TG 100 mg/dL. RBC 3.42 x 10⁶ / μ L, Hb 11.9 g/dL, Ht 34.7%, MCV 101.3 fL (80-98), MCH 34.6 pg (27-33), MCHC 34.2 g/dL (31-36), WBC 5800 / μ L, Plt 19.8 x 10⁴ / μ L. Chest X-P showed unremarkable abnormal findings for lung and heart, and ECG showed the findings within normal limits.

Clinical progress

He was diagnosed as T2D in Sept 2021. For adequate diabetic therapy, he and related families were advised to take decreased carbohydrate meal. However, it was rather difficult to change into balanced meal. The reason was he likes to have carbohydrate very much such as rice, bread, noodles and so on. For pharmacological diabetic treatment, he was begun to given Imeglimin (Twymeeg) 2000 mg per day that was divided into morning and evening (Figure 1).

HbA1c values were 8.8%, 7.3% and 6.7% in Sept, Oct and Nov, respectively. He showed remarkable clinical efficacy of decreasing HbA1c for 8 weeks. Successively, the doses of Twymeeg were reduced from 2000mg to 1000mg per day. Clinical changes in several biomarkers were summarized in Table 1. It showed data concerning diabetes, anaemia, nutrition and renal function. Related to his daily meal style, he has revealed

slight anaemia, associated with decreased Haemoglobin (Hb) and increased mean cell volume (MCV), mean cell haemoglobin (MCH). These results indicated the presence of macrocytic anaemia. Concerning his meal contents in detail, he rarely takes vegetables and states that such situation has persisted for long.

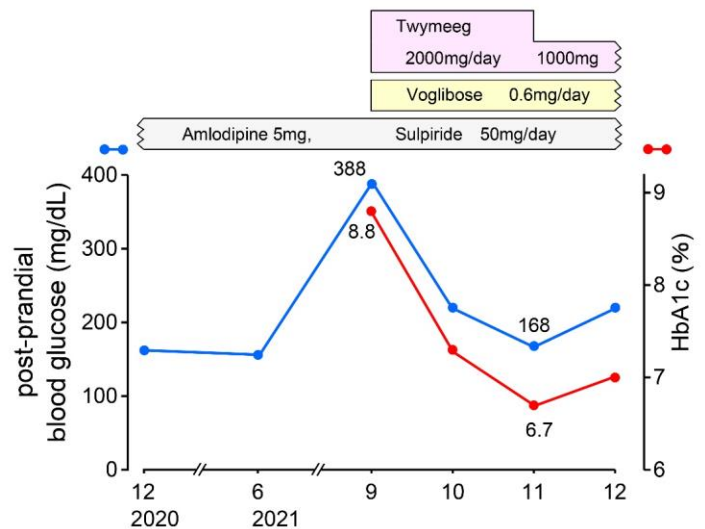


Figure 1: Clinical progress of the case with HbA1c and medicine.

Ethical standards

This investigation has been fundamentally complied with the ethical principles set forth from the Helsinki Declaration. Furthermore, it has been complied with Japan's personal information protection act, which was conducted along the ethical guidelines for medical research involving human subjects. These guidelines are from public notice of Ministry of Education, Culture, Sports, Science [MEXT] and Technology/Ministry of Health, Labour and Welfare [MHLW]. The author and co-researchers have established an ethical committee for this study. It exists in Sakamoto hospital, which includes the director of the hospital, physician, nurse, pharmacist, nurse, dietician and legal professional. We have fully discussed for proper manners, and decided to agree for this protocol. The informed consent with written style of the agreement document were taken from the patient.

Discussion

In current case report, 77-year-old male patient with T2D were given imeglimin, associated with clinical efficacy of decreasing HbA1c and blood glucose variability. Some discussion will be presented from some points of view, including i) the characteristic of this patient, ii) possible involvement of medicine for T2D onset, iii) relationship between this case and imeglimin and iv) characteristic aspect of imeglimin as OHA. Firstly, this patient had some clinical problems including T2D, hypertension, previous CVA, Gastroesophageal reflux disease (GERD), specific

habit of carbohydrate preference in his daily life. The case has taken several oral agents for these diseases. They are Twymeeeg and voglibose for T2D, amlodipine for hypertension and CVA, sulpiride for GERD and occasional slight general malaise. Related to his tendency of much carbohydrate intake, the results

of complete blood count (CBC) were analysed. It showed anaemia of decreased Hb, increased MCV and MCH. These results were not apparent level, but it indicated possible macrocytic anemia [11].

Table 1: Changes in markers from several points of view.

Category	Year		2021				
	Month		June	Sept	Oct	Nov	Dec
Diabetes	HbA1c	(%)		8.8	7.3	6.7	7.0
	post-prandial glucose	(mg/dL)	156	388	220	168	220
Anemia	Hb	(g/dL)	12.7	11.9	11.0	10.6	11.1
	MCV	(fL)	97	102	101	100	100
	MCH	(pg)	33.8	34.6	33.9	33	33.8
Nutrition	TP	(g/dL)	6.5	6.6	6.1	5.9	5.7
	Alb	(g/dL)	3.6	3.4	3.4	3.3	3.3
Renal	Cre	(mg/dL)	0.73	0.74	0.75	0.63	0.72
	K	(mEq/L)	4.6	4.0	4.1	3.9	4.4

It may be related to unbalance meal habit, much carbohydrate and shortage intake of vegetables. A reference report is found concerning macrocytic anaemia [12]. It revealed detail evaluation of HbA1c, Hb, MCV, reticulocyte count, smear of blood, vitamin B12, thiamine, folate, intrinsic factor antibody, TP, Alb, BUN, Creatinine, TSH and so on. These results were typical macrocytic anaemia. In contrast, these detail exams were not checked yet for our current case. Clinical progress would be followed up from several points of view. Secondly, the possible influence of provided medicine would be considered for the onset of diabetes. The patient has taken zonisamide for the protection of possible seizure. For diabetic cardiomyopathy (DCM) and cardiac hypertrophy, endoplasmic reticulum (ER) stress has been involved. Zonisamide can suppress ER stress-induced neuronal cell damages [13]. Furthermore, zonisamide can prevent cognitive impairment and reduce Alzheimer's disease (AD) pathology by attenuating ERS in experimental T2D mice [14]. Consequently, zonisamide does not seem to cause diabetic situation. As regards to sulpiride, no remarkable reports were found for leading to diabetic situation. On the other hand, sulpiride-induced hyperprolactinaemia may contribute protecting diabetic retinopathy [15]. Further, prolactin would show neuroprotective activities in the brain for diabetes-induced cognitive impairment [16]. Thus, sulpiride also shows lower possibility for involvement for diabetic onset. Thirdly, this case showed a remarkable reduction of HbA1c after starting Twymeeeg. HbA1c values 8.8% in Sept, 7.3% in Oct and 6.7% in Nov 2020. It seemed to show remarkable HbA1c reduction for short period. Clinical effect of imeglimin was investigated for a series of the Trial for Imeglimin Efficacy and Safety (TIMES). There are TIMES 1, 2 and 3 until

now [8]. TIMES 2 was the comparative research for 52-week, multicentre phase 3 trials [17]. HbA1c reduction in average was 0.46 +/- 0.07 % [0.330-0.591] by imeglimin monotherapy. Regarding combined therapy for oral hypoglycemic agents (OHAs), average HbA1c reduction was thiazolidine 0.88%, SGLT2i 0.57%, DPP-4i 0.92% and alfa-GI 0.85%, respectively. In this case, he was provided imeglimin and alfa-GI, and then actual effects was more than expected [17]. Thus, monotherapy and combined therapy for imeglimin revealed well-tolerated and safe efficacy [18]. What kind of factors have brought clinical efficacy? One possible cause may be that it was the first onset of T2D, in which he did not take any medicine for diabetes before. For other factors, he had slight GERD, hypertension and previous CVA, but had no other apparent non-communicable diseases (NCDs) such as dyslipidemia, hyperuricemia, coronary heart disease (CHD), peripheral artery disease (PAD) and so on. Fourthly, clinical research of imeglimin was conducted for the compared investigation of metformin monotherapy and Sitagliptin monotherapy [19,20]. These protocols were 12-week period, and the superior effects of decreased HbA1c reduction were 0.44% for metformin and 0.72% for sitagliptin [19,20]. After that, adequate dose was recognized as 1000mg twice per day for optimal effect, tolerability and safety [8]. This study was conducted for phase 3 program in Japan as TIMES. There were three pivotal studies completed for phase 3 trials, which was TIMES 1 [21]. As a result, clinical effect of monotherapy was confirmed, where 1000mg twice a day significantly decreased HbA1c as 0.87% compared with placebo group [18]. A systematic review has been reported [22]. When 2000mg per day of imeglimin is provided, approximately 0.5 to 1.0% decrease of HbA1c would be found by

simple administration. In summary, elderly male with T2D was given Twymeeg and clinical effect was observed with satisfactory HbA1c reduction. This improvement may be from dual mechanisms of imeglimin for increasing insulin secretion and decreasing insulin resistance. It will be expected to become first-line treatment for T2D and to develop further detail research in the future.

Conflict of Interest

The authors declare no conflict of interest.

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