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PUBTEXTO

Improvement of Glucose Variability in Diabetic Patient with Mild Cognitive Impairment (MCI) Using Novel Imeglimin (Twymeeg)

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Abstract

Background: Recent diabetic topic includes imeglimin (Twymeeg) as a novel oral hypoglycemic agent (OHA).

Case Presentation: The patient is 69-year-old female who has been diabetic for years and developed cognitive problem.

Result: Her HbA1c increased to 11.1%, and then Twymeeg 2000mg/day was started. She showed clinical improvement as 7.9% in 4 months. She received Montreal Cognitive Assessment (MoCA), Voxel-based Specific Regional analysis system for Alzheimer's disease (VSRAD) score and clock drawing test (CDT) associated with diagnosis of mild cognitive impairment (MCI).

Discussion: MCI may be one of the diabetic complications and the case will be carefully followed-up.

Keywords: Imeglimin (Twymeeg); Montreal Cognitive Assessment (MoCA); Voxel-based Specific Regional analysis system for Alzheimer's disease (VSRAD); Clock drawing test（CDT); Mild cognitive impairment (MCI); Trials of IMeglimin for Efficacy and Safety (TIMES)

Introduction

In recent decades, non-communicable diseases (NCDs) have been prevalent across the world [1]. Among them, type 2 diabetes (T2D) becomes the main problem from medical, social and economic points of view. Diabetes has various complications such as microangiopathy, macroangiopathy, frailty, sarcopenia and cognitive impairment [2]. American Diabetes Association (ADA) has presented latest diabetic standard guideline in Jan 2022 [3]. Among various information for diagnosis and therapy, adequate treatment for T2D has been summarized. Current recommended anti-diabetic agents include metformin, sodium–glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist (GLP1-RA) and others. Generally, metformin is characteristic for its first-line med for long years, SGLT2i has beneficial efficacy for T2D, blood pressure, chronic heart failure (CHF), chronic kidney disease (CKD) and GLP-1RA is highly evaluated for various effects for T2D [4].

Furthermore, novel type of oral hypoglycemic agent (OHA) has been developed. It is imeglimin that was recently introduced to medical practice. It has been a chemical moiety of metformin and can modulate the activity of mitochondrial complex [5]. The characteristic point would be the presence of tetrahydrotriazine-containing drug [6]. It includes the triazine ring of small cyclic molecule [7]. The generic name imeglimin is known for brand name Twymeeg [8]. The specific action reveals double mechanism of increasing insulin secretion and decreasing insulin resistance [9]. Several clinical trials were reported, which showed the clinical effects for improving blood glucose control situation [10].

Authors et al. have so far continued medical practice and research for T2D, NCD, cardiovascular disease (CVD), chronic kidney disease (CKD) and others [11-12]. We have also presented some case reports and general information about Twymeeg [13-14]. In our actual diabetic practice, a meaningful patient with T2D and mild cognitive impairment (MCI) has been present associated with the treatment of Twymeeg. In this article, general clinical course and discussion will be described.

Presentation of Cases

Medical History

The case is a 69-year-old female who has been diabetic more than 10 years. She has treated as T2D, dyslipidemia, and hypertension for several years. The changes of HbA1c had been rather stable around 7%, and unremarkable problems of daily life or treatment were observed until 2019. Glycemic control deteriorated from 2020, and HbA1c increased to 10.3% in June 2020.

Physicals and Examinations

Her physical examination on Jan 2021 showed the following: consciousness alert, speech normal, vitals are stable, unremarkable changes in the lungs, heart or abdomen, intact neurological examination. Biochemical examination showed the data in the following: HbA1c 10.9 %, TP 8.5 g/dL, Alb 4.9 g/dL, AST 14 U/L, ALT 11 U/L, LDH 203 (106-211), r-GT 12 U/L, CPK 242 U/L (30-200), Uric Acid 2.2 mg/dL, BUN 12 mg/dL, Cre 0.32 mg/dL, Na 140 mEq/L, 3.9 mEq/L, Cl 102 mEq/L, HDL 66 mg/dL, LDL 157 mg/dL, TG 60 mg/dL, T-Cho 235 mg/dL, WBC 9200 /μL, RBC 4.93 x 10^6 /μL, Hb 14.9 g/dL, Ht 46.2 %, MCV 93.7 fL (80-98), MCH 30.2 pg (27-33), MCHC 32.2 g/dL (31-36), Plt 28.3 x 10^4 /μL. Further detail examination for thyroid and vitamin concentration was conducted. They were TSH 1.58 μIU/ml (0.5～5.0), free T_3 3.2 pg/ml (2.3～4.0), free T_4 1.3 ng/dl (0.9～1.7), Vitamin B_1 51 ng/mL (24～66), Vitamin B_{12} 250 pg/mL (180～914), which were within normal range.

Other exams were conducted Sept 2021-Feb 2022. Chest X-ray showed no abnormal findings and electrocardiogram (ECG) revealed ordinary sinus rhythm (OSR) with unremarkable ST-T changes. She received the volume pulse wave (plethysmogram, PTG) for the check of peripheral artery disease (PAD). As a result, the ankle brachial index（ABI）was 1.08/1.04 (right/left), and cardio-ankle vascular index (CAVI) showed 8.9/8.8 (right/left). These data were within normal limits.

Exams for MCI

Some related exams for depression, mild cognitive impairment (MCI) and cerebral vascular accident (CVA) were conducted; Geriatric depression scale short version (GDS-15) was applied to the patient. The result was 3 points (pts), where normal range is 0-4, slight depression is 5-10, heavy depression is 11-15. For standard exams for screening of detecting MCI, Montreal Cognitive Assessment (MoCA) was performed. The result was 19 points, where full score 30pts, normal range > 26 pts, screening of MCI for < 25pts. It indicates the presence of MCI for her case.

Radiological examination of MRI and MRA was conducted. The results showed the slight stenosis of right middle brain artery (rMCA), the presence of multiple infarctions/micro bleeding and unremarkable atrophy. For the possibility of Alzheimer Dementia (AD), the score of VSRAD (Voxel-based Specific Regional analysis system for Alzheimer's disease) was calculated [15]. The patient showed 1.3 pts, where almost no atrophy for 0-1 pt, 1-2 pts for some atrophy for 1-2, moderate atrophy for 2-3 pts and strong atrophy suggesting AZ for >3 pts [16].

In the MoCA, the overall score was 19/30, and the patient was diagnosed with mild cognitive impairment (MCI). As for the details, the date and time and orientation were perfect, the location was 5/6, and the memory and re-recognition disorders were 0/5, and the work of the cube and clock drawing test（CDT）was incomplete. Overall, frontal lobe dysfunction was noted.

Clinical Course

In January 2022, the HbA1c value increased sharply to 11.1%. In response to diabetic exacerbation, administration of imeglimin (Twymeeg) 2000 mg/day was started, which has been attracting attention as a diabetes drug in recent years. As a result, HbA1c decreased to 7.9% in 4 months, indicating satisfactory clinical effect (Figure 1).

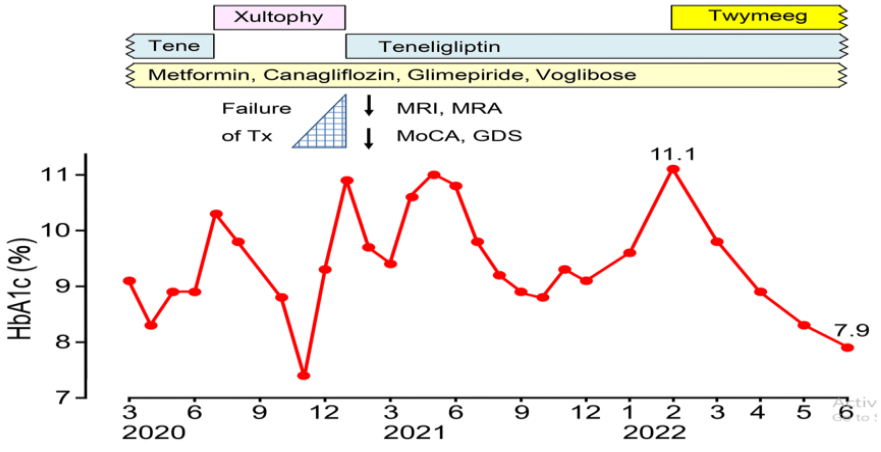

Figure 1: *Clinical progress of the case concerning HbA1c and treatment.*

In particular, gastrointestinal adverse effects (GIAEs) were not observed, or remarkable changes in neuropsychiatric symptom/signs were not found. The changes in the main items of biochemical examinations are summarized for 3 years (Table 1).

Table 1: *Changes in biochemical data for a few years.*

Category	Test	2019	2019	2020	2020	2021	2021	2022	Unit
		3	9	3	10	2	7	1	
Diabetes	HbA1c	6.5	7.2	9.1	7.4	8.8	9.8	9.6	(%)
	BS	145	88	127	73	106	146	137	(mg/dL)
Liver	TP	7.9	7.7	8	7.7	8.5	7.9	7.6	(g/dL)
	GOT	19	20	21	22	27	20	20	(U/L)
	GPT	13	14	15	16	17	15	16	(U/L)
	AlP	194	209	-	228	-	-	-	(U/L)
	GGT	12	14	13	10	12	13	11	(U/L)
Renal	Cre	0.48	0.46	0.37	0.4	0.32	0.39	0.4	(mg/dL)
	eGFR	96.2	111	-	117	-	-	117.0	(mL/min/1.73m2)
Lipids	LDL	144	141	142	145	157	84	89	(mg/dL)
	HDL	56	58	61	67	66	62	59	(mg/dL)
	TG	79	33	52	48	60	36	31	(mg/dL)
Others	Hb	13.8	14.3	14.2	14.5	14.9	13.6	14.4	(g/dL)
	CRP	0.02	0.03	0.6	0.01	0.6	-	0.05	(mg/dL)

It shows some fluctuations in HbA1c levels, but otherwise unremarkable changes were found for liver, renal, lipids and complete blood test.

Ethical Standards

This study has been complied with the standard ethics of the Declaration of Helsinki. The commentary is also along with the personal information protection rules. This principle is conducted with ethical principles for clinical practice and research for human subjects. Certain guidelines are from public announcement of the Japanese Ministries. They include Ministry of Health, Labour and Welfare [MHLW] and also Ministry of Education, Culture, Sports, Science Technology [MEXT]. The authors and collaborators established the ethical committee for current study. It is present in Sakamoto hospital, Kagawa, Japan. It includes several professionals such as the president of the hospital, physicians, surgeon, pharmacist, registered nurse, nutritionist and legal professional. All members have fully discussed the matter and agreed for this protocol. The informed consent was taken from the case for the written style document.

Discussion

Regarding imeglimin, the mode of action includes improved mitochondrial function of beta cell in the pancreas. By administration of imeglimin 2000-3000mg per day for 6 months, HbA1c reduction was 6-11 mmol/mol (0.5-1.0%) in the case of monotherapy. Further, 7 mmol/mol (0.6%) reduction was found in the case of add-on therapy of sitagliptin and metformin [17]. There are some GIAEs in imeglimin, but the incidence is rare and this case did not have any GIAEs. Thus, Imeglimin has attracted attention for novel mechanism for T2D [18].

For the current case, intake of imeglimin revealed remarkable reduction of HbA1c for 4 months. She has simultaneous OHAs as teneligliptin, metformin, canagliflozin, glimepriride and voglibose because of insufficient glucose control for long. Some clinical studies for OHAs in addition to Imeglimin were performed until now. These trials are named as **T**rials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) version 1, 2 and 3. Out of them, TIMES 2 has showed the medical effect for monotherapy and/or combined treatment [19]. From these investigations, impressive results have been revealed in the following: i) imeglimin for monotherapy was 0.46%, ii) combined treatment with OHA or injection was glinide agents 0.70%, sulfonyl urea 0.56%, biguanide agents 0.67%, alfa-glucosidase inhibitors 0.85%, SGLT2i 0.57%. When comparing of clinical efficacy of imeglimin for this case, several combination OHAs in this case would be involved. Further, TIMES 3 showed the impressive results [20]. Reduction degree was 0.12% for GLP-1RA, 0.92% for DPP-4i and 0.63% for insulin treatment. From combined data for TIMES 2 and 3, actual action route may be different in these agents including mitochondria pathway metabolism and imeglimin function mechanism.

This case has received the examination of MoCA, VSRAD evaluation and Clock Drawing Test（CDT） during her clinical progress. MoCA has been presented for evaluating multi-regional ability such as attention, memory, language, calculation, orientation and conceptional thinking [21]. MoCA has been translated to many languages so far, and used widely for evaluating MCI [22]. The

items include trail making, cubic drawing, CDT, target detection, and others, with 30 points of full score. The main purpose is to make screening for MCI, where normal is >26 pts and possible MCI is < 25pts. The sensitivity and specificity are reported to be 93% and 87%, respectively [22].

In clinical practice for Alzheimer's disease (AD), VSRAD software has been widely applied. Comparative studies were conducted for i) 19 AD patients and 28 healthy subjects, ii) 30 early AD patients and 13 healthy subjects, and iii) 65 healthy subjects between VSRAD-1.5-tesla and 3-tesla [15]. As a result, no significant differences were observed among them, except for the score of whole white matter atrophy. Patients with clinical cognitive dysfunction (n=67) showed a significantly higher z-score in VSRAD analysis than control subjects [16]. The differences were 2.57 vs 1.15, $p<0.01$ in both groups. Concerning the diagnosis of cognitive impairment, the sensitivity vs specificity showed 80% vs 48% for Mini-Mental State Examination (MMSE), 100% vs 89% for z-score and 100% and 90% for combined of MMSE and z-score, respectively. From radiological point of view, Alzheimer disease (AD) has typical pathology for the atrophy of the medial temporal region (parahippocampal gyrus, tonsils and hippocampus) near the center of the brain. Therefore, it is the key to diagnostic imaging in early-stage AD for evaluating the degree of medial collateral atrophy. VSRAD expresses the degree of medial collateral atrophy in four stages.

By CDT, this case showed incomplete drawing of clock scheme, indicating dysfunction of frontal lobe [23]. CDT has been evaluated for excellent tool for screening of cognitive function test [24]. In the exam of CDT, basic requirement for the drawing the schema of the time 11:10. The intention of CDT would be to elicit the stimulus bound response (SBR) [25]. SBR is regarded as a marker of higher executive dysfunction. The usefulness of CDT for post-stroke cognitive impairment (PSCI) was investigated [26]. The protocol included 168 CVA cases followed up 12.8 months in average. During the period, MCI 18.9 % and dementia 18.0% were recorded. By detail analysis, lower CDT baseline score (< 6.55) showed higher associated risk of PSCI during follow-up as HR 2.022, $p<0.05$. For screening of cognitive function, drawing tests have been prevalent. In order to compare the diagnostic ability between image drawing method for screening MCI/dementia and drawing by verbal instructions [27]. The research included 92 studies with 22085 cases. CDT was applied for the majority of trials. As a result, sensitivity vs specificity was 71%vs 83% in image drawing test, and 71% vs 83% in drawing by verbal instructions. From these findings, both methods would show similar diagnostic abilities, supposing the future application in the hospital and/or at home [27].

Some limitations may be found in this report. This case showed satisfactory efficacy of imeglimin as OHA. Furthermore, she developed MCI in recent years, where MCI may be involved in diabetic complication. From diabetic and neuro-psychological points of view, careful follow-up would be required. In summary, the case is 69-year-old female with T2D and MCI who received detail exams including MoCA, VSRAD evaluation and CDT. She was treated with imeglimin with satisfactory reduction of HbA1c. These medical progress and perspectives will be hopefully useful for clinical diabetic practice and research in the future.

Conflict of Interest

The authors declare no conflict of interest.

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