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Effective Treatment for Type 2 Diabetes (T2D) by Imeglimin (Twymeeg) and Vildagliptin/Metformin (EquMet)

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Abstract

Background: Among several oral hypoglycemic agents (OHAs), Imeglimin (Twymeeg) and vildagliptin/metformin (EquMet) has been in focus.

Case presentation: The patient is 59-year-old female with obesity and type 2 diabetes (T2D).

Result: For unstable HbA1c during 2022, EquMet was started and afterwards Twymeeg was added. HbA1c decrease was 0.4% in 4 months and 0.6% in 3 months, respectively.

Discussion and Conclusion: Large studies of Twymeeg and EquMet were Trials of IMeglimin for Efficacy and Safety (TIMES), and Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes (VERIFY). Combined these treatments may bring more beneficial clinical efficacy.

Keywords: Oral hypoglycemic agents (OHAs); Imeglimin (Twymeeg); Vildagliptin/Metformin (EquMet); Trials of IMeglimin for Efficacy and Safety (TIMES); Vildagliptin Efficacy in combination with metfoRmIn For early treatment of type 2 diabetes (VERIFY)

Introduction

Type 2 diabetes (T2D) has been crucial disease from medical, social and economic points of view worldwide [1]. On Jan 2023, American Diabetes Association (ADA) presented latest "Standards of Care in Diabetes" [2]. The purpose of diabetic therapy would be maintaining the same QOL and ordinary health as healthy people for reducing various macro- and micro-angiopathy [3]. In recent years, various oral hypoglycemic agents (OHAs) have been developed and introduced to actual medical practice [4]. They have shown satisfactory clinical efficacy for improving glucose variability, such as sodium–glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist (GLP1-RA), dipeptidyl peptidase-4 inhibitor (DPP-4i), and other agents [5]. Among them, imeglimin (Twymeeg) is in focus for beneficial dual effects [6,7].

As regards to imeglimin, it shows the similar molecule with metformin [8]. Metformin has been known for the first-line medicine of T2D for long over the world [9]. Metformin can be used for monotherapy and also for combined therapy with other OHA or insulin [10]. It is indeed that imeglimin has similar molecule with metformin, but both OHAs are often used for combination therapy. The characteristic prescription method includes the twice medication per day. From pharmacological point of view, imeglimin has been provided for T2D associated with clinical efficacy until now [11].

Furthermore, recent topic for effective diabetic treatment includes the changes in the perspectives for diabetic treatment. Stepwise therapy was previously rather common. But early combination therapy is recently evaluated as longer-lasting positive efficacy. Among them, combination therapy of vildagliptin and metformin has shown beneficial treatment protocol [12]. Related to the combination of vildagliptin/metformin (EquMet), VERIFY study has been known, which stands for Vildagliptin Efficacy in combination with metfoRmIn for earlY treatment of type 2 diabetes. It was conducted for 254 multi centers in 34 countries, as a randomized, double-blind, parallel-group investigation

against newly-diagnosed T2D patients [13]. The compared results showed that significant decrease of initial therapy failure was found in combined group for 5 years, in comparison with monotherapy group (hazard ratio, HR =0.51). For adverse effects, approaches in both groups showed unremarkable problems. Consequently, earlier start of combined treatment of vildagliptin/metformin can give greater and also durable longer-acting beneficial efficacy in comparison with previous metformin monotherapy. In addition, EquMet is prescribed twice daily, where clinical efficacy of decreasing blood glucose can be observed from midnight to early morning.

Authors have diabetic team group and reported clinical research for years. The content includes meal tolerance test (MTT), Carbo-70g test for breakfast, low carbohydrate diet (LCD), continuous glucose monitoring (CGM) and pharmacological diabetic treatment [14,15]. Clinical effects of Twymeeg were reported for several T2D cases [16]. Furthermore, lots of T2D patients treated with EquMet for 6 years were analyzed for the seasonal changes [17]. We have recently experienced impressive patient who had the treatment of both of EquMet and Twymeeg. Its general clinical progress as well as some perspectives will be described in this article.

Presentation of Case

Medical history

The presented case is 59-year-old female with obesity and Type 2 diabetes (T2D). She has been obese for long years, and was previously diagnosed as T2D in 5 years ago. She has been on several oral hypoglycemic agents (OHAs) until now. Her HbA1c has been almost stable around 6.0-6.7% for years (Figure 1). Her blood pressure has been increased about 2 years ago. After that, she has been provided anti-hypertensive agent (AHA), and her BP has been stable until now.

Physicals and various exams

Her physical examination showed the following condition in Jan 2022. Her consciousness is alert, conversation and speech are normal, her vital signs are within normal limits, BP 132/80 mmHg. Her lung, chest and abdomen were negative, and neurological findings were intact. Her physique showed 151cm in height, 84.1kg in weight and BMI 36.8 kg/m^2.

Laboratory exam revealed the follow results: HbA1c 7.0%, post-prandial blood glucose 208 mg/dL, RBC 5.84 x 10^6 /μL, Hb 15.6 g/dL, Ht 52.0 %, MCV 89.0 fL (80-98), MCH 26.7 pg (27-33), MCHC 30.0 g/dL (31-36), WBC 8200/μL, Plt 25.4 x 10^4 /μL, AST 18 U/L, ALT 23 U/L, γ-GT 23 U/L, Uric Acid 7.2 mg/dL, BUN 24 mg/dL, Cre 0.88 mg/dL, HDL 46 mg/dL, LDL 154 mg/dL, TG 252 mg/dL.

Chest X-P revealed negative findings. Electrocardiogram (ECG) showed pulse 72/min, ordinary sinus rhythm, and no specific ST-T changes. She received detail test of mechanocardiogram and also sphygmogram. The results showed as follows: Bilateral ankle brachial index（ABI）in right/left were 1.12/1.18, respectively. The values of brachial-ankle pulse wave velocity (baPWV) in right/left showed 1352/1458, respectively (Figure 2). When analyzed the detail values of upstroke time (UT) and % mean arterial pressure (%MAP), they were in normal range.

Clinical course

HbA1c level was increased to 7.0% in Jan 2022, and then the medication was changed for more effective treatment. She started to have the combined medicine of vildagliptin/metformin (EquMet) from Jan 2022 (Figure 1).

After that, HbA1c value was decreased for several months. However, HbA1c increased to 6.9% in Nov 2022 again. For effective administration of OHA, she was provided to begin imeglimin (Twymeeg) from Nov 2022. Her glucose variability was improved, and HbA1c was decreased to 6.3% in Jan 2023. As to the changes in body weight, it was 84kg in Mar 2022, and it decreased to 78kg in Feb 2023. She did not complain of any gastro-intestinal adverse effects (GIAEs) for EquMet or Twymeeg.

Ethical standards

This case report was complied with the standard ethic guideline that was previously presented in Helsinki Declaration. Moreover, some commentary was associated with the protection regulation concerning personal information. This principle was along with the ethical rules against usual clinical practice and research for human beings. Certain guideline is presented from Japanese Ministry. This information is related with the Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science Technology. Current authors have established our ethical committee about this research that was present at Kanaiso Hospital in Tokushima, Japan. It contains medical and also legal personnels that has the president, physicians, surgeon, pharmacist, head nurse, dietitian and legal professional. These members discussed in thorough manner concerning the case, and agreed for current protocol.

Discussion

Concerning this case, the characteristic point was the combined treatment of Twymeeg and EquMet. From the introduction of Twymeeg to clinical practice, the usefulness of EquMet was re-evaluated again. The reason includes i) both meds are given twice a day at morning and night, ii) hypoglycemic effects can be expected during midnight to early morning, iii) this combination

actually includes actually three kinds of OHA, which are biguanide, DPP4-I and imeglimin. For the current case, HbA1c value was improved by Twymeeg as 0.6% for 3 months. Imeglimin was chosen for dual efficacy of decreasing insulin resistance and elevating insulin secretion [18]. She did not feel any symptoms of gastro-intestinal adverse events (GIAE) [19]. As to imeglimin, multi-center studies were found, which are Trials of IMeglimin for Efficacy and Safety (TIMES) 1,2,3 [20]. Among them clinical effect was analyzed for monotherapy and combination therapy. Reduction of HbA1c was 0.46% for monotherapy, 0.56% for sulfonyl urea, 0.67% for biguanides, 0.85% for alpha-glucosidase and 0.92% for DPP4-i [21]. In contrast, combined therapy with GLP-1RA showed only 0.12% decrease of HbA1c. From these data, different mechanism may be present concerning mitochondria function that is related to DPP4-i and GLP-1RA [22].

In order to assess the effect of vildagliptin and metformin (Vil/Met), study was conducted for the comparative method. Using databases of RCTs for combined treatment of Vil/Met, 8533 cases from 11 RCTs were analyzed [23].

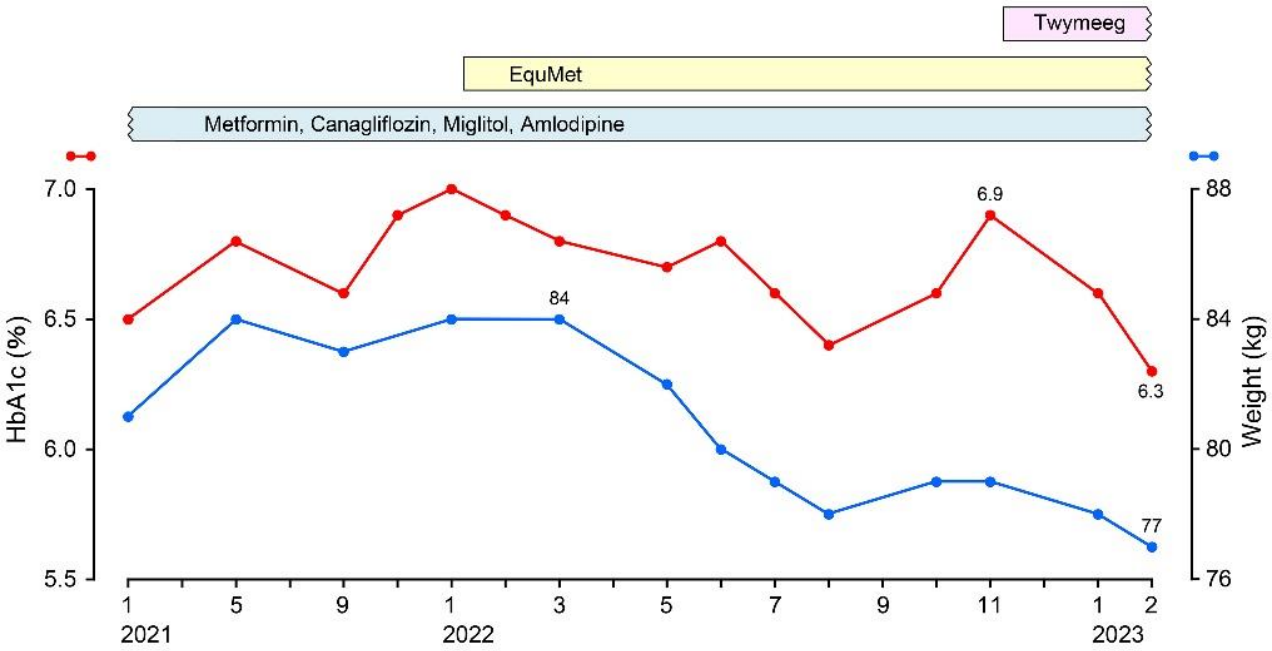

Figure 1: *Clinical progress of changes in HbA1c and weight.*

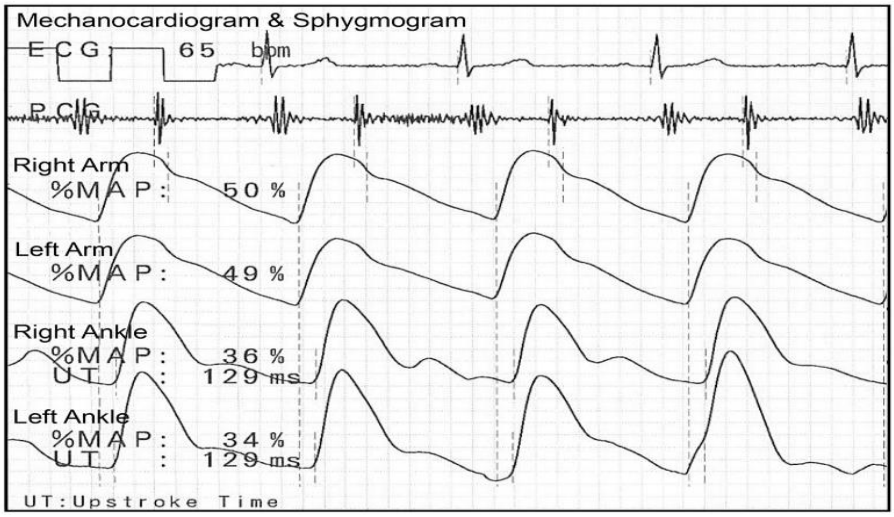

Figure 2: *The results of sphygmogram and mechanocardiogram.*

The method was the comparison for combination of Vil/Met and monotherapy of metformin (≥1500mg/day). For the degree of evidence, the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was applied. As a result, combination therapy showed significantly higher effect of HbA1c decrease as mean differences (MD) = -0.59. Total adverse events (AEs) were similar (Relative Ratio, RR = 0.98).

For comparison of clinical effect on diabetic initial therapy, administration of combination and/or monotherapy of Vil/Met was conducted [24]. The method included 4 groups, which are i) Vil + Met 50 mg + 1000 mg twice daily), ii) Vil + Met 50 mg + 500 mg twice), iii) Vil (50 mg twice) or iv) Met (1000 mg twice). As a result, HbA1c decrease for 24 weeks was 1.8%, 1.6%, 1.1% and 1.4%, respectively. When baseline HbA1c was higher (>10%), HbA1c reduction was 3.2%, 2.7%, 1.5% and 2.6%, respectively. Consequently, treatment-naïve diabetic patients showed superior effect of combined higher dose of Vil/Met compared with lower dose and monotherapies.

In addition, the report on vildagliptin was found in vivo study. Against diabetic rats, administration of vildagliptin has shown improved learning and memory ability, which was continued for 2 months [25]. For newly-diagnosed T2D patients (n=100), compared study was performed. The fundamental treatment was administrating Metformin, and add-on therapy was conducted [26]. The two groups were Met + glimepiride vs Met + vildagliptin. As a result, change in HbA1c value was 8.14 to 6.98 % vs 8.33 to 6.99%, respectively. Clinical efficacy was the same, but the latter did not show any reverse effect or hypoglycemic episode, indicating superior evaluation for 24 weeks.

The impressive research was recently found concerning administration of Met and/or Vil for streptozotocin-induced diabetic rats [27]. The protocol included 5 groups of Wistar rats (each n=10), and they were separated as i) control group (C), ii) diabetic control group (D), treated with iii) Met (DM), iv) vildagliptin (DV) and v) combined Met/Vil (DMV). They were treated 15 days and received some exams such as urination behavior and an open field test. For this test, staying in the center space means less anxiety, and staying in the periphery beside the wall means much anxiety. As a result, urination number was elevated in the D, DM, and DV in comparison with that of C, and was decreased in DMV in comparison with diabetic groups. From the open field evaluation, staying time in the center was i) lower in D and DM compared with C ($p<0.05$), and ii) remarkable higher in DMV compared with other groups ($p<0.01$). It suggests that combined therapy (Met+Vil) may contribute decreased anxiety, and that single Met or Vil may not be so effective.

For these results, gamma aminobutyric acid (GABA) may be involved in the mechanism. GABA has been an inhibitory neurotransmitter. When the expression or its receptor (named GABAA receptor) is decreased, it can cause anxiety situation [28]. Metformin has anxiolytic-like efficacy by changing the expression of GABAA receptors [29]. Furthermore, Metformin reduced anxiety by decreasing BCAA which regulates tryptophan, which is possible reason leading to anxiety [30].

Limitation may exist in the current report. Clinical efficacy of EquMet and Twymeeg was analyzed. Some factors can influence each other, such as taken carbohydrate amount, exercise situation and mutual medication relationship. Further evaluation would be required by following up the clinical progress in the future. In summary, a patient with obesity and T2D was reported accompanied by the combined OHA therapy. Accumulation of case analyses will contribute the development of diabetic research and adequate practice. This article becomes hopefully a useful reference data in the future.

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