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Combined Treatment of Vildagliptin/Metformin (Equmet) and Imeglimin (Twymeeg) with Clinical Efficacy

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Abstract

Background: Vildagliptin/Metformin (EquMet) and imeglimin (Twymeeg) are effective oral hypoglycemic agents (OHAs) for patients with type 2 diabetes (T2D).

Case Presentation: The patient was a 68-year-old male with T2D and fatty liver for several years. In November 2022, his HbA1c had increased to 8.2%, and he was started on Twymeeg, followed by EquMet.

Results: Over the course of four months, the patient's HbA1c value successfully decreased from 8.2% to 6.7%, and he did not experience any gastrointestinal adverse effects (GIAEs).

Discussion and Conclusion: The combined treatment of EquMet and Twymeeg demonstrated clinical efficacy without any adverse effects. The Trials of IMeglimin for Efficacy and Safety (TIMES) provided various evidence of imeglimin's effectiveness.

Keywords

Vildagliptin / Metformin (Equmet), Imeglimin (Twymeeg), Gastro-Intestinal Adverse Effects, Trials of Imeglimin for Efficacy and Safety, Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes

Abbreviations

GIAEs: Gastro-Intestinal Adverse Effects; TIMES: Trials of Imeglimin for Efficacy and Safety; VERIFY: Vildagliptin Efficacy in combination with metfoRmIn For earlY Treatment of Type 2 Diabetes

Introduction

The American Diabetes Association (ADA) has proposed the latest protocol for the management of type 2 diabetes (T2D) in the "Standards of Care in Diabetes" [1]. For decades, T2D has been one of the most important lifestyle-related diseases that must be adequately controlled [2]. The crucial point of diabetic treatment is to achieve the same quality of life and overall health as a healthy individual [3]. Recently, several oral hypoglycemic agents (OHAs) have been introduced to diabetic medical practice [4,5]. They have presented significant effects in maintaining glucose variability, including dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like-peptide 1 receptor

agonist (GLP1-RA), sodium-glucose cotransporter 2 inhibitor (SGLT2i), and others [6]. The latest topic in OHA would be imeglimin (Twymeeg), which has a characteristic efficacy of a dual mechanism [5,7].

Imeglimin is a novel OHA that presents a similar molecule type to that of metformin [8]. Metformin has been the first-line OHA for T2D globally in actual practice [9]. It is useful as monotherapy and as an add-on treatment in combination with other OHAs or insulin therapy [10]. These two OHAs have similar molecule types and have been prescribed as a combined treatment with other OHAs. Among the similar prescriptions of these agents, the common method includes administration twice a day. Imeglimin (Twymeeg) has been reported to demonstrate clinical dual effects thus far [11].

On the other hand, the effective treatment of T2D has been discussed concerning the changes in diabetic perspectives. In the previous period, stepwise treatment was almost common for T2D. However, early combined treatment for T2D has become prevalent and seems to be a useful measure [12]. In the case of the combination of EquMet (vildagliptin/metformin), the large study of VERIFY has been well-known. VERIFY stands for Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes. It included a 254 multi-center study from 34 countries, where newly-diagnosed T2D cases were included for a double-blind, randomized, and parallel-group investigation method [13]. As a result, there was a significant decrease in initial treatment failure in the combination group compared with the monotherapy group, as a hazard ratio (HR) of 0.51. As for the reverse effect, both groups showed unremarkable results. Thus, the initiation of combined vildagliptin/metformin agents can provide larger and longer-lasting effects than previous measures of metformin monotherapy. Furthermore, EquMet is given twice a day, which can decrease glucose variability during midnight to early morning. This merit can contribute greatly to better glucose control.

The authors' diabetic research group has been reporting for a long time, covering areas such as Carbo-70g breakfast loading, meal tolerance test (MTT), low carbohydrate diet (LCD), and various cases with continuous glucose monitoring (CGM) and OHAs [14,15]. Among their recent reports, pharmacological efficacy of imeglimin (Twymeeg) has been introduced [16]. Furthermore, the annual seasonal changes of HbA1c were analyzed for many cases of T2D [17,18]. We present an impressive case that received the combined agents of Twymeeg and EquMet, which showed clinical efficacy of glucose variability. We will describe the general clinical progress and some discussions in this report.

Case Presentation

Medical History:

The current case involves a 66-year-old male patient with T2D, hypertension, hyperuricemia, hypercholesterolemia, and fatty liver. He has experienced several episodes of cerebral vascular accidents (CVA) over the past 8 years and has been a heavy drinker. His HbA1c values were stable until 2021, but increased in 2022. In May 2022, he experienced dizziness and mild hemiparesis in hot weather and was diagnosed with a possible CVA in the emergency department. His CVA symptoms were quickly resolved, and he was advised to discontinue empagliflozin, an SGLT2 inhibitor. He did not experience any significant CVA symptoms thereafter. His HbA1c value increased to 8.3% in November 2022, and further evaluation was conducted (**Fig-1**).

Physical Examination:

Consciousness was alert, and speech was normal. Vitals were stable as BP 136/78 mmHg, pulse 76/min, SpO_2 98%. His head, neck, heart and lung were unremarkable. Abdomen revealed flat and soft with no abnormal bowel sound. For neurological examination, he did not show remarkable findings such as motor disturbance, incomplete hemiparesis, sensory disturbance or other impairments. His physique was stature 175cm, weight 95.2kg and BMI 31.1 kg/m^2.

The patient was alert and conscious, and his speech was normal. His vital signs were stable, with a blood pressure of 136/78 mmHg, a pulse rate of 76 beats per minute, and oxygen saturation (SpO_2) of 98%. There were no abnormal findings in his head, neck, heart, or lungs. Upon abdominal examination, his abdomen was

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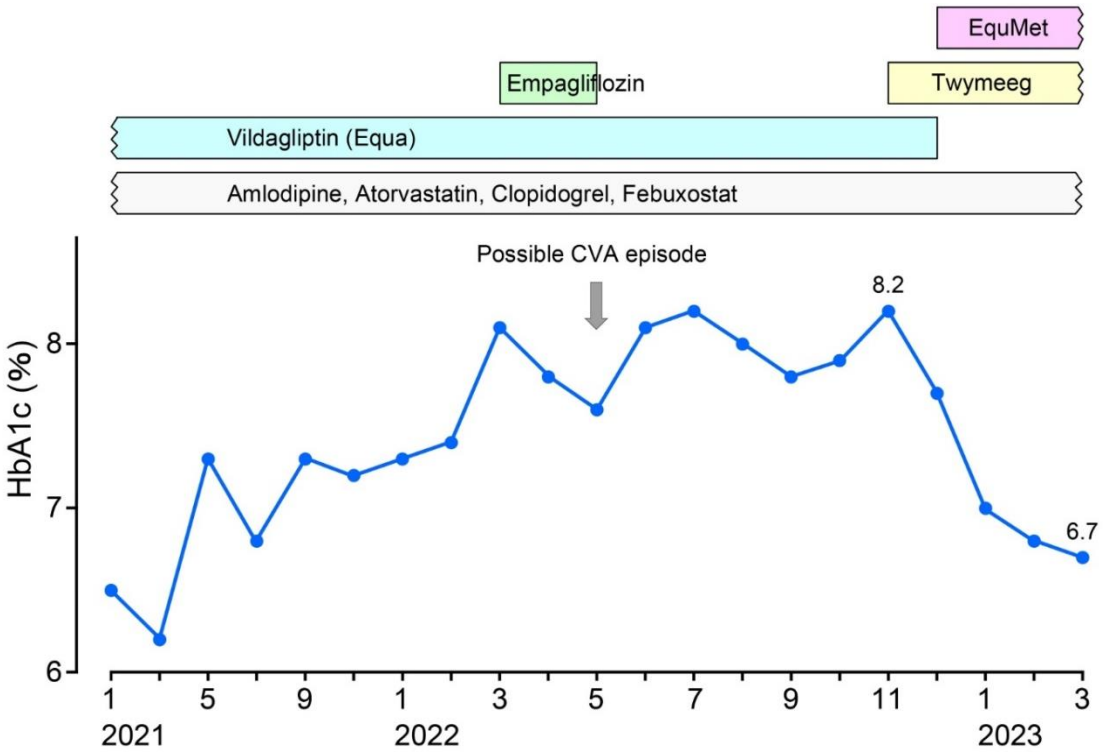

Fig-1: Clinical Progress of HbA1c, CVA Episode and Medication

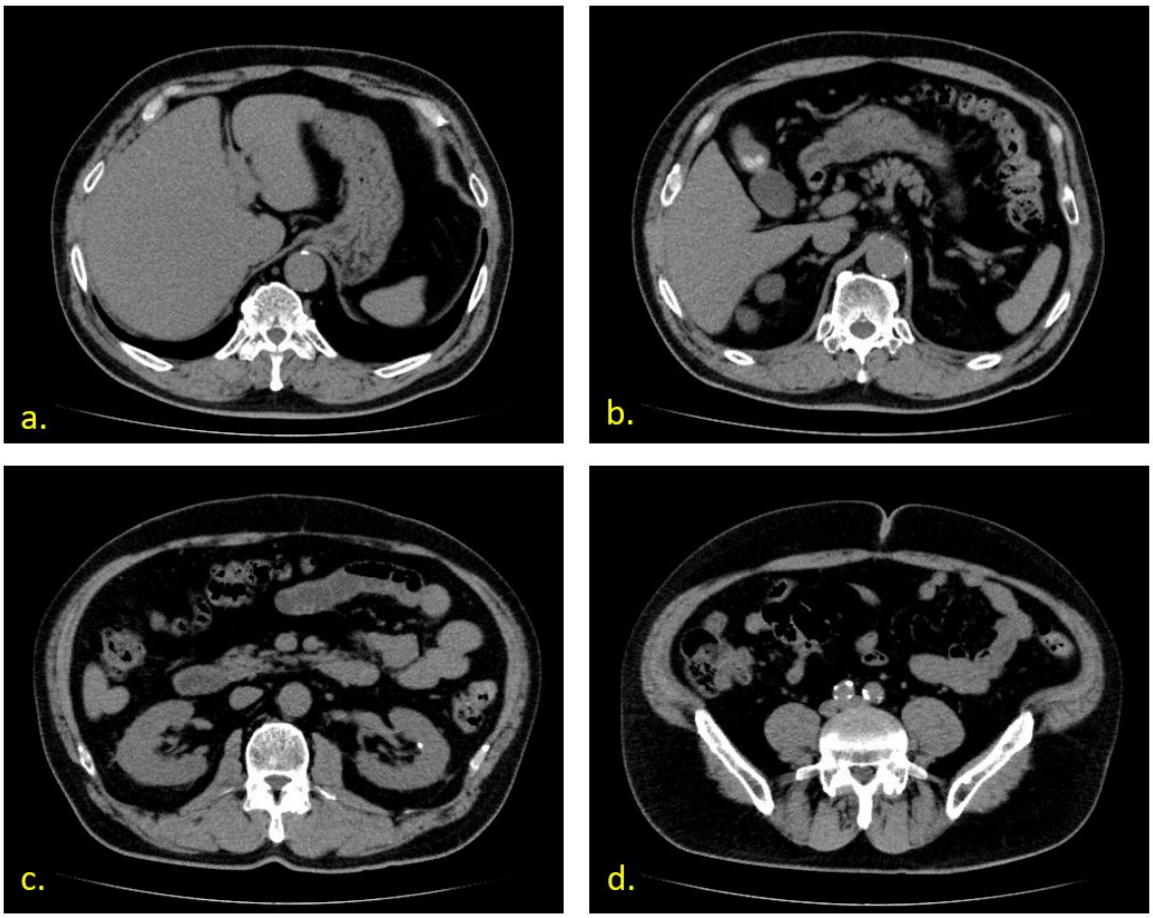

Fig-2: Abdominal CT Scan

2a: Fatty Liver, 2b: Gall Stone, 2c: Renal Stone, 2d: Arteriosclerosis

flat and soft, with no abnormal bowel sounds. During the neurological examination, there were no remarkable findings such as motor disturbance, incomplete hemiparesis, sensory disturbance, or other impairments. The patient's physical characteristics included a height of 175cm, weight of 95.2kg, and a BMI of 31.1 kg/m^2.

Laboratory Examination:

The data of the laboratory examination were in the following: HbA1c 8.2%, post-prandial blood glucose 221 mg/dL, RBC 4.69 x 10^6 /μL, Hb 14.6 g/dL, Ht 43.3 %, MCV 93.8 fL (80-98), MCH 31.5 pg (27-33), MCHC 33.7 g/dL (31-36), WBC 5600/μL, Plt 17.9 x 10^4 /μL, GOT 39 U/L, GPT 33 U/L, γ-GTP 57 U/L, Uric acid 6.5 mg/dL, BUN 21 mg/dL, Cre 0.91 mg/dL, HDL 45 mg/dL, LDL 129 mg/dL, TG 136 mg/dL. Urinalysis: protein (-), glucose (+), urobilinogen (+/-), pH 6.0, ketone bodies (-), urinary Alb/Cre ratio 24.3 mg/g·Cre (0-30). Chest X-ray exam showed negative. Electrocardiogram (ECG) showed normal axis, pulse 72/min, ordinary sinus rhythm, and unremarkable ST-T changes. Abdominal CT showed the presence of fatty liver, gall stone, left renal stone and arteriosclerosis (**Fig-2**).

Clinical Progress:

This case showed unremarkable laboratory results, and then he was initiated on Twymeeg 2000mg/day in November 2022. After four weeks, HbA1c had decreased to 7.7%, showing a 0.5% improvement. He did not experience any gastrointestinal adverse effects (GIAEs) from Twymeeg. Consequently, another OHA, EquMet, was given as an add-on treatment. EquMet includes both Equa and Metformin. He tolerated the combination of these OHAs well without GIAEs. His HbA1c decreased from 8.2% to 6.7% in four months. During this period, he showed no reverse effects of symptoms, signs, or laboratory findings.

Ethical Standards:

The current report complies with the standard ethical guidelines of the Declaration of Helsinki. Additionally, several measures were taken to protect personal information, including ethical rules about clinical practice and research involving human subjects. Specific guidelines have been proposed by the Japanese government, including the Ministry of Education, Culture, Sports, Science and Technology, as well as the Ministry of Health, Labour and Welfare. The authors established an ethical committee for this case at Kanaiso Hospital in Komatsushima, Tokushima, Japan, which included several hospital staff members and legal professionals, such as the hospital president, physician, registered nurse, pharmacist, and dietician. The committee fully discussed the current protocol and agreed that it was appropriate.

Discussion

This case involves several medical problems, including i) T2D, ii) fatty liver, iii) arteriosclerosis, iv) a previous history of CVA, v) a possible CVA in May 2022 leading to the discontinuation of empagliflozin as SGLT2i, and vi) a satisfactory clinical effect from the combined treatment of EquMet and Twymeeg (**Fig-1**). Among these issues, some perspectives will be discussed below.

Firstly, this case involves T2D, obesity with a BMI of 31.1, fatty liver, and arteriosclerosis. These diseases are interrelated in the context of metabolic syndrome. The patient has a long history of obesity, increased appetite, less exercise, and alcohol consumption, which have likely contributed to his current arteriosclerosis and CVA. He consumes some carbohydrates in his three daily meals as a dietary habit. A regular rice bowl weighs 160g and contains 55g of carbohydrates [19]. In the case of T2D, blood sugar rises by 3 mg at 1 gram of carbohydrates, and a rice bowl would raise blood glucose by 165 mg/dL [20]. One way to manage this is by ingesting vegetables first, which can suppress the postprandial rise in blood glucose to some extent [21]. Patients with mild T2D usually experience a post-prandial peak about 45-60 minutes after a meal [22].

Second, he started taking empagliflozin as an SGLT2 inhibitor when his HbA1c level was elevated in March 2022. After that, his body weight and HbA1c value decreased to some degree. It seemed to be effective for the control of T2D. However, two months later, he had an episode of a possible CVA and discontinued the SGLT2 inhibitor agent. Concerning this episode, hot weather and dehydration may have been involved in developing the symptoms and signs [23]. Indeed,

SGLT2 inhibitors have shown clinical effectiveness for T2D, chronic kidney disease (CKD), and chronic heart failure (CHF), but several factors should be considered, such as dehydration, water intake, water balance, urine volume, and related elements.

Third, this patient showed a 1.5% decrease in HbA1c in a short period. This suggests an effect of add-on therapy with Twymeeg and other OHAs. From the large studies of TIMES 1, 2, and 3, the results of the combination of imeglimin treatment were reported. They were 0.46% in monotherapy, 0.67% in biguanides, 0.92% in DPP4 inhibitors, 0.57% in SGLT2 inhibitors, 0.85% in alfa-GI, 0.70% in glinides, and 0.56% in SU agents [24]. Thus, DPP-4 inhibitors showed the largest efficacy. In contrast, the least efficacy was found for GLP-1RA, which was only 0.12% from the result of TIMES 3 [25]. Both agents were believed to have a pharmacological common mechanism, but this difference may suggest another bypass route [26]. The mechanism may be involved in various endothelial functions [27]. A recent report showed the detailed glucose variability by imeglimin using CGM [28]. Future research development would be expected for mitochondrial function [29].

Certain limitations may exist in this article. The remarkable clinical efficacy of the HbA1c decrease could be from the combination of some OHAs, but we cannot determine which OHA showed the predominant efficacy. Furthermore, in this case, SGLT2i was discontinued after a possible CVA episode, and the degree of influence on the relationship between dehydration and SGLT2i administration was not anticipated. Several problems need to be investigated in the future.

Conclusion

In summary, a 68-year-old male with T2D has shown clinical efficacy of combined EquMet and Twymeeg for a 1.5% HbA1c decrease for 4 months. Detailed analysis and follow-up will be required to determine the interrelationships among various factors. This report is expected to be a significant reference for diabetic research.

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Conflict of Interest

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

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