

# Combined treatment of imeglimin (Twymeeg) for aged patient with type 2 diabetes (T2D)

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## Abstract

**Background:** For oral hypoglycemic agent (OHA), imeglimin (Twymeeg) has been in focus.

**Case presentation:** The patient is 83-year-old female with type 2 diabetes (T2D). She skipped visiting clinic and taking HOAs for several months due to COVID-19 prevalence in the society.

**Result:** She was hospitalized with HbA1c 10.3%. Combined treatment of Twymeeg 2000mg/day and linagliptin was initiated, and HbA1c decreased to 6.9% in 12 weeks. She felt no gastrointestinal adverse effects (GIAEs).

**Discussion and conclusion:** Trials of IMeglumin for Efficacy and Safety (TIMES) 2 and 3 showed clinical efficacy of combined treatments. This elderly case had satisfactory clinical effect.

**Keywords:** imeglimin (Twymeeg); COVID-19; gastrointestinal adverse effects (GIAEs); Trials of IMeglumin for Efficacy and Safety (TIMES) 2; Hospital Anxiety and Depression scale (HADS)

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## Introduction

From biological, medical and social points of view, non-communicable diseases (NCDs) have been crucial problems in the world [1]. Among NCDs, type 2 diabetes (T2D) has been most prevalent disease with several comorbidities of macroangiopathy, microangiopathy, frailty and others [2]. For treatment of T2D, three fundamental therapies include nutrition, exercise and pharmacological intervention [3]. Beneficial agents for T2D have been introduced for medical practice, such as glucagon-like-peptide 1 receptor agonist (GLP1-RA), sodium-glucose cotransporter 2 inhibitor (SGLT2i) and so on [4]. These agents have been known to show positive effects for various diseased states, including diabetes, hypertension, chronic kidney disease (CKD) and chronic heart failure (CHF).

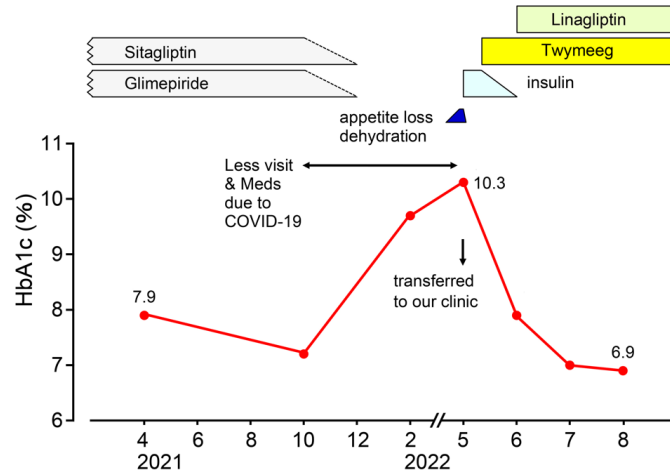
For long years, metformin has been a first-line medicine for T2D and it has been prescribed widely across the world [4]. Due to pharmacological research, a new type of derivative for metformin has been developed and introduced to medical practice [5]. It is imeglimin, in which its characteristic would be the existence of tetrahydrotriazine-containing drug [6]. Metformin and imeglimin have mutual similar molecules, and the latter has triazine ring [7]. Generic name of imeglimin has been known as Twymeeg [8]. For impressive function of imeglimin, it shows dual action mechanisms of stimulating insulin secretion and reducing insulin resistance [9]. There have been some clinical trials so far, in which clinical efficacy for decreasing blood glucose levels were found [10].

Authors and collaborators have continued clinical research and practice for NCD, T2D, hypertension, chronic kidney disease (CKD), cardiovascular disease (CVD), and so on [11,12]. We also showed some information of imeglimin for T2D [13]. Some cases were reported with clinical efficacy of Twymeeg [14,15]. In our recent practice, an impressive elderly case with T2D has been provided Twymeeg. Its general progress and some perspectives will be discussed in this article.

## Presentation of cases

### Medical history

The case is an 83-year-old female who has been treated for hypertension and T2D for about 9 years. In spring 2021, her HbA1c was 7.9% and almost stable for the age of more than 80 years. She visited clinic in Oct 2021, but after that she felt feared for possible infection of COVID-19 around her circumstances. Then, she has showed less visiting to clinic associated with less medications for hypertension and T2D. During Oct 2021 to May 2022, she seldom had her regular medicine (Figure 1). In early May, she developed appetite loss, dehydration and slight fever for 3 days and was transferred to our diabetes clinic because of hyperglycemia of 454 mg/dL. She complained of slight chest discomfort, and HbA1c was proved to be 10.3%. Consequently, she was admitted to our hospital for further evaluation, urgent blood glucose control and early hydration.

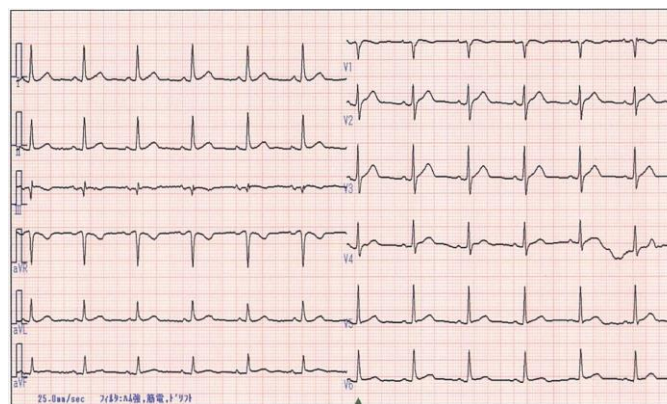


**Figure 1:** Clinical progress of the case concerning HbA1c and treatment.

**Physicals and examinations**

Her physical examination on admission revealed the following status: vitals are BT 38.2, P 84/m, BP 124/78 mmHg, SpO<sub>2</sub> 94%, speech normal, consciousness alert, no remarkable changes in the heart and lung. She did not complain of any abdominal pain, discomfort or urination abnormalities. Her neurological examination was intact. Urgent examination showed blood glucose 469 mg/dL, HbA1c 10.3%, WBC 15500/ $\mu$ L, CRP 14.0 mg/dL. Urinalysis revealed that glucose four plus positive, bilirubin (-), ketone bodies (+/-), specific gravity 1.010, occult blood (+), pH 5.0, protein (-), urobilinogen (+/-), WBC (+).

Biochemical examination on admission showed the data in the following: Na 133 mEq/L, K 3.6 mEq/L, Cl 93 mEq/L, RBC 3.42 x 10<sup>6</sup> / $\mu$ L, Hb 10.0 g/dL, Ht 30.1 %, MCV 87.9 fL (80-98), MCH 29.1 pg (27-33), MCHC 33.1 g/dL (31-36), WBC 15500/ $\mu$ L, Plt 9.1 x 10<sup>4</sup> / $\mu$ L, TP 6.9 g/dL, Alb 3.5 g/dL, T-Bil 0.5 mg/dL, AST 23 U/L, ALT 25 U/L, ALP 98 U/L (38-113), r-GT 15 U/L, Uric Acid 6.0 mg/dL, BUN 30 mg/dL, Cre 0.54 mg/dL, HDL 44 mg/dL, LDL 88 mg/dL, TG 123 mg/dL, T-Cho 157 mg/dL, Chest X-P revealed unremarkable changes. Electrocardiogram (ECG) showed pulse 72/m, P-R 0.158 sec, QT 0.378 sec, axis 22 degree, SV1 0.51 mV, RV5 1.20 mV, R+S 1.71 mV, ordinary sinus rhythm (OSR) and no apparent ST-T changes (Figure 2).



**Figure 2:** Electrocardiogram (ECG) on admission.

**Clinical course**

After urgent admission to the hospital, she was diagnosed as T2D, dehydration and possible urinary tract infection. She was treated for control of blood glucose using insulin by sliding scale method, hydration and administration of antibiotics. In middle May, her general condition was improved with almost normal range of glucose profile, CRP 1.7 mg/dL and Pubtexto Publishers | [www.pubtexto.com](http://www.pubtexto.com)

unremarkable problems. Concerning daily nutrition for T2D, the following content was calculated and conducted: height 153cm, weight 52.6kg, BMI 22.9 kg/m<sup>2</sup>, IBW 52kg, Alb 3.5 g/dL, nutrition status is good, energy 1400 kcal/day, protein 60g, NaCl 7g, water 1500mL per day. She could actually have all of regular meals, and her daily profile of blood glucose has been improved. For the treatment of T2D, she was provided insulin for 10-14 days as follows: 1) Glargine in the morning from 12, 10, 8, 6, 4, to 0

units, 2) Novo rapid insulin two times at noon and evening from 16, 12, 10, 8, 6, 4 to 0 units. When insulin doses were decreasing, Twymeeg 2000mg/day was initiated for diabetic control, followed by linagliptin 5mg per day. Her HbA1c was decreased to 7.9%, 7.0% and 6.9% in early June, July and August (Figure 1). She did not have any gastrointestinal adverse effects (GIAEs) due to imeglimin.

## Ethical standards

This case study is complied with standard ethical guideline of the Declaration of Helsinki. Further, some commentary has been along with the rules of personal information protection. The principle is from the ethical rules for clinical research and practice for the related human subjects. Some guidelines are based on the public announcement for the Japanese Ministries. They include two ministries of Ministry of Education, Culture, Sports, Science Technology, Japan and Ministry of Health, Labour and Welfare, Japan. The authors and co-researchers have established the ethical committee for this study, which is present in the Sakamoto hospital of Kagawa, Japan. The committee has several medical and legal professionals, which are the director of the hospital, surgeon, physicians, registered nurse, pharmacist, registered dietitian and legal professional. All of the members discussed enough the current case matter and agreed for the research protocol. The informed consent was obtained from the aged patient for the written style document.

## Discussion

Concerning the novel oral hypoglycemic agent (OHA), imeglimin shows the characteristic mode of action for mitochondria in the  $\beta$ -cell of the pancreas. It has both mechanism for increasing insulin secretion and decreasing insulin resistance [16]. For clinical efficacy, imeglimin administration of 2000-3000 mg/day for half year can bring 0.5-1.0% reduction of HbA1c for monotherapy. In the case of add-on treatment of metformin and sitagliptin, 0.6% reduction was observed [17]. However, some cases have GIAEs, in which the ratio and degree of GIAEs would be not so remarkable. Consequently, imeglimin has been in focus for its novel function for T2D [16].

In this case, HbA1c was decreased to enough degree by the administration of imeglimin for 3 months. Imeglamin is characterized for its add-on therapy with several kinds of OHAs. There were several kinds of larger studies for imeglimin so far. A series of the investigation were called as Trials of IMeglamin for Efficacy and Safety (TIMES) with versions of 1,2 and 3. Among them, clinical efficacy for combined therapy compared to monotherapy was reported in TIMES 2 [18]. Several results have summarized for the degree of HbA1c reduction as follows: i) monotherapy of imeglimin 0.46%, ii) combined therapy of

glinides 0.70%, SU 0.56%, biguanides 0.67%,  $\alpha$ -GI 0.85%, SGLT2i 0.57%, DPP4-I 0.92%. Among these, the combined treatment with DPP-4i would be most effective as 0.92%. Furthermore, additional results were reported from TIMES 3 [19]. In the case of GLP-1RA for injection administration, reduced level of combined treatment was proved to be 0.12%. It showed large difference with the result of DPP-4i (0.92%) and insulin (0.63%). From these results of TIMES 2 and 3, the action mechanism may be different through another route, where imeglimin function and mitochondria pathway are involved with complex situation.

The current case was provided Twymeeg and linagliptin after insulin treatment by sliding scale method. Its combination was imeglimin and DPP-4i, which seemed to be most effective add-on therapy from TIMES 2 and 3. She showed HbA1c 6.9% after 12 weeks of admission, which seems to be satisfactory clinical efficacy. This case is aged female with 83 years old, then some examinations for dementia and medium cognitive impairment (MCI) were conducted. The results were normal ranges by Hasegawa's Dementia Scale-Revised (HDS-R) and Mini-Mental State Examination (MMSE) [20,21]. When presuming the reason for her less visit and less medication for several months, the prevalence of COVID-19 around her circumstances would be the main factor. She stated that no particular symptoms or signs were observed during the period. Her cognitive function would be within normal range, but various influences of COVID-19 have to be considered in our current social life from bio-psycho-social points of view.

As regards to COVID-19, various crucial influences and problems have been observed across the world [22]. Among them, we have reported impressive situation of COVID-19 in Japan concerning negative excess mortality [23,24]. Japanese people are always able to control daily lives for protecting virus infection including washing hands, masking, keeping calm and also avoiding gathering [25]. Consequently, successful decline was observed by enough understanding, cooperation and actual practice [26]). However, we have to know the background of behavior characteristic of Japanese people. The important traits of Japanese seem to possess anxiety, depression and peer pressure. This situation may bring less visit to clinic. For a recent study, 450 Japanese received some questionnaires such as Hospital Anxiety and Depression scale (HADS) and Japanese version of the Fear of COVID-19 Scale (FCV-19S) [27]. Consequently, psychological perspectives related to COVID-19 problems and continuous treatment would be considered in the clinical practice [28].

Certain limitations may exist in the report. This elderly female case discontinued to visit the clinic for several months due to COVID-19 prevalence in the society. Then, she showed hyperglycemia, elevated HbA1c associated with appetite loss and dehydration. Possible other reasons could be involved in this episode. Administration of Twymeeg seemed to be effective associated with linagliptin, which showed most effective combination of imeglimin

and DPP-4i. Other factors could probably influence the clinical progress.

In summary, the case was 83-year-old female with T2D who was provided Twymeeg with satisfactory clinical effect. She did not have any GIAEs during clinical course, which seems to be safe treatment for aged T2D patient. It is expected that this report will contribute the development of diabetic research and practice.

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