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Clinical Efficacy of Imeglimin (Twymeeg) for Elderly Patient with Type 2 Diabetes Mellitus (T2DM)

Masaki OKADA[1], Hiroshi BANDO[1,2,3*], Noboru IWATSUKI[1], Tomoya OGAWA[1], Kazuki SAKAMOTO[1]
[1]*Sakamoto Hospital, Higashi Kagawa city, Kagawa, Japan*
[2]*Tokushima University/Medical Research, Tokushima, Japan*
[3]*Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan*

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** ORCID iD
Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;
Email: pianomed@bronze.ocn.ne.jp
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Abstract

Background: As an oral hypoglycaemic agent (OHA), imeglimin (Twymeeg) has been recently introduced to clinical practice for patients with type 2 diabetes mellitus (T2DM) as Twymeeg. It has beneficial pharmacological mechanisms, which are improving insulin secretion, increasing insulin sensitivity and decreasing insulin resistance.

Case Presentation: The case is 84-year-old men with mild cognitive impairment (MCI) for 3 years. He visited late August, 2021 our clinic for general malaise and was pointed out to have post-prandial blood glucose 336 mg/dL and HbA1c 8.6%. He was diagnosed as T2DM.

Results: He was started to be given imeglimin 1000mg twice a day, and then HbA1c value was decreased to 7.3% in 4 weeks and 5.7% in 8 weeks. During 9-12 weeks, he felt loss of appetite and reduced food intake. Biochemical examination on 12 weeks showed decreased values of TP, Alb, HbA1c, glucose, free T_3 and normal values of TSH, free T_4. Doses of imeglimin were 500 mg twice a day for 9-12 weeks and discontinued after 12 weeks.

Discussion: Regarding appetite loss, possible causes may include MCI, previous history of gallbladder dyskinesia, adverse effect of imeglimin, and so on. Further development of research will be expected for imeglimin in the future.

Keywords

Oral Hypoglycemic Agent, Imeglimin, Twymeeg, Type 2 Diabetes Mellitus, American Diabetes Association

Abbreviations

OHA: Oral Hypoglycemic Agent (OHA); T2DM: Type 2 Diabetes Mellitus; ADA: American Diabetes Association

Introduction

Adequate treatment for type 2 diabetes mellitus (T2DM) has been discussed for long. Professional practice committee of American Diabetes Association (ADA) has announced the guideline in Jan 2022 [1]. International Diabetes Federation (IDF) has managed diabetic situation in the world. When observing the diabetic situation across the world, the prevalence has

been progressively increasing [2]. IDF has stated that about half adults (20-79 years) with diabetes do not know their diabetic situation [3]. DM has been a chronic and multifaced disease leading to significant physical detriment to many patients. During 2019, there were 463 million diabetic patients present across the world, and among them 90% are suffering from T2DM [4]. The adequate medical treatment would be fit for each patient from ideal medical point of view.

Regarding pharmacological treatment for T2DM, metformin has been a widely used medication for T2DM despite the introduction of some newer anti-diabetic agents. Metformin is one of the most used oral hypoglycemic agents (OHAs), and it has desirable pharmacokinetics. Recently, imeglimin was produced for OHA. It has basically a small molecule similar to metformin, but it has a cyclic molecule containing a triazine ring [5]. For its characteristics, it has beneficial pharmacological mechanisms. They are improving insulin secretion, increasing insulin sensitivity and decreasing insulin resistance [6]. It has been introduced to actual medical practice for patients with T2DM as the brand name Twymeeg. In this report, an older patient with T2DM will be presented and discussed who has taken Twymeeg with clinical efficacy.

Case Presentation

History & Physical:

The patient is an 84-year-old male patient with Type 2 Diabetes Mellitus (T2DM). He was diagnosed to have mild cognitive impairment (MCI) about 3 years ago. In March 2021, he felt fatigue and was found to have some exacerbation of MCI. He had been treated in another clinic. When he visited our clinic in August, 2021, he received general blood laboratory examination. The results showed moderate degree of diabetes with post-prandial blood glucose 336 mg/dL and HbA1c 8.6%.

Laboratory Examinations:

The biochemical results of September 2021 were summarized as follows: AST 17 U/L, ALT 23 U/L, γ-GT 20 U/L, ALP 154 U/L (38-113), LDH 159 U/L (124-222), T-Bil 1.6 mg/dL, TP 8.0 g/dL, Alb 3.8 g/dL, CPK 109 U/L (30-200), BUN 25 mg/dL, Cr 0.8 mg/dL, UA 4.2 mg/dL, Na 144 mEq/L, K 3.2 mEq/L, Cl 107 mEq/L, T-C 149 mg/dL、HDL-C 38 mg/dL, LDL-C 89 mg/dL, TG 109 mg/dL. RBC 4.26 x 10^6 /μL, Hb 13.9 g/dL, Ht 41.9%, MCV 98.4 fL (80-98), MCH 32.7 pg (27-34), MCHC 33.3 g/dL (31-36), WBC 8100 /μL, Plt 16.6 x 10^4 /μL. Chest X-P showed normal for lung and heart, and ECG was within normal limits.

Clinical Progress

He was diagnosed as T2DM. For diabetic treatment, he and his family received nutrition therapy for adequate regular meal. His age has been rather higher, then he was advised to have slight limited intake of carbohydrate amount per day. It was about 40% of calorie ratio of total meal a day. For diabetic medication, he was started to be provided Imeglimin (Twymeeg R) 1000 mg twice in the morning and evening (**Fig-1**). After 4 weeks, blood glucose improved to 225 mg/dL and HbA1c 7.3%, and the blood glucose improved to 131 mg/dL and HbA1c 5.7% after 8 weeks. From 9 weeks, imeglimin was decreased from 1000mg x 2 to 500mg x 2. The case had normal renal function for Cr 0.8 mg/dL and eGFR 69.4 mL/min/1.73 m^2.

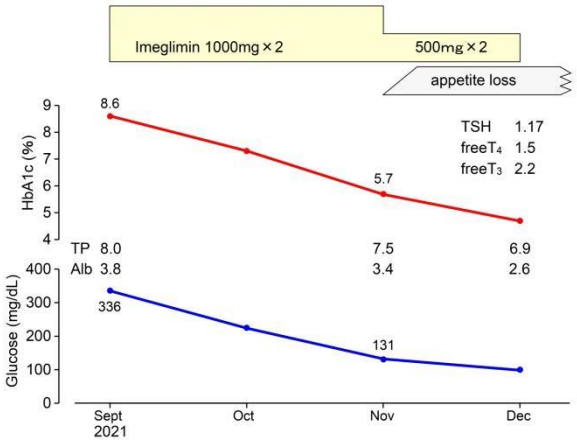

Fig-1: Clinical progress of the case for exams and medication

During 9-12 weeks, the patient had loss of appetite and reduced food intake. Regarding this status, unremarkable causes related to this situation were detected or suggested. Biochemical examination was conducted at the point of 12 weeks. TP and Alb on 0 week vs 12 weeks were 8.0g/dL vs 6.9 g/dL, 3.8 g/dL vs 2.6 g/dL, respectively. Diabetic and endocrinological exams on 12 weeks included HbA1c 4.7%, blood glucose 100 mg/dL, TSH 1.17 μIU/ml (0.5-5.0), free T_4

1.5 ng/mL (0.9-1.7), free T_3 2.2 pg/mL (2.3-4.3). Due to the biochemical exams on 12 weeks, Twymeeg was discontinued, and glucose variability has been followed up after that.

Ethical Considerations

This study has been basically conducted along with the ethical principles on the Declaration of Helsinki. Moreover, several comments were obtained from Ethical Guidelines for Research for Humans, which are associated with Good Clinical Practice (GCP). The author and collaborators related to this study have established an ethical committee. It is in our hospital, including the president and director of the hospital, associated with physician, pharmacist, nurse, nutritionist and the legal professional. We have discussed enough and performed for adequate manners, and decided to present the agreements for this study protocol. The informed consent associated with written style of the agreement document were taken from the patient.

Discussion

In this report, a new OHA, imeglimin was administered to T2DM patient, which showed beneficial clinical effect. It seems to be a novel category of OHA, because it has multiple mechanisms for one medication. Clinical efficacy includes improved insulin secretion and decreased insulin resistance for peripheral tissue. It showed HbA1c reduction of about 0.5-1.0% by simple administration of 2000mg/day [7]. Furthermore, add-on therapy (AOT) reveals additional efficacy, where HbA1c was 0.6-0.65% more decreased in the case of dipeptidyl peptidase-4 inhibitor (DPP4i) agents [8]. Regarding adverse effects of imeglimin, no remarkable major reports were observed, such as various cardiovascular events, or increased hypoglycemia and others [6].

What is the fundamental characteristic mechanism for imeglimin? It has been the first medicine for tetrahydrotriazine-containing class agent as glimins [9]. It may work by multiple pathway mechanism such as increasing insulin secretion, improving beta-cell function and preventing epithelial cell death [10]). The detail mechanism is not fully understood, however it may work through the enhancement of glucose-stimulated insulin secretion (GSIS). This GSIS process includes activated transient receptor potential melastatin 2 (TRPM2) channels. As a result, it can promote the plasma membrane depolarization, which is one of non-selective cation channels (NSCCs) of beta-cells [11]. Moreover, imeglimin can be involved in the calcium mobilization for the amplification pathway during insulin secretion process [12].

In this case, administration of imeglimin reduced HbA1c enough to satisfactory level until 8 weeks. This degree of improvement is comparable to previous reports [6]. During 9-12 weeks, appetite loss had developed associated with the decrease in total protein, albumin, HbA1c and blood glucose values. For thyroid function, serum TSH and free T_4 were within normal range, and free T_3 showed slightly decreased, which suggested the situation of low T_3 syndrome. This physiology has been often found in the elderly people, and no significant changes were observed in his endocrine and metabolic functions.

What could be the cause of loss of appetite in his clinical course? The case has suffered from some problems of mild cognitive impairment (MCI) or dementia. Then, it is possible that MCI caused a change in appetite. In addition, a previous history of dyskinesia in the gallbladder was found from detail history-taking. However, no abdominal pain or other abdominal symptoms were found in recent period. Another possibility would be from the adverse effect of imeglimin for GI symptoms [13]. However, there was no significant change in his symptoms during 0-8 weeks, and the problem started after 9^{th} weeks. Consequently, it is not likely to be involved.

For Imeglimin, there is a report concerning treatment-emergent adverse events (TEAE). When imeglimin 500, 1000 or 1500 mg and placebo is provided twice a day, the ratio observing any symptom and/or sign would be 68.0%, 62.2%, 73.3% and 68.0%, respectively [6]. Slight increase of gastrointestinal (GI) adverse effects would be observed with the 1500 mg dose level. Hypoglycemia was found in similar percentage for these groups. Consequently, imeglimin was well tolerated and beneficial for improving glucose variability without significant increase of hypoglycemic events compared with

placebo. From some reports concerning 1000mg vs 1500mg, the former shows fewer events for GI problems.

Imeglimin possibly becomes a first-in-class agent for T2DM, which mainly shows excretion unchanged through the kidneys. The pharmacokinetic (PK) characteristics were investigated for the optimal amounts of doses in T2DM with chronic kidney disease (CKD) [14]. The recommended amount calculated from area under the curve (AUC) was 500mg provided twice morning and evening for patient with eGFR 15-45 mL/min/1.73 m^2. Similary, 1000mg of imeglimin taken twice daily seems to be optimal for patient with eGFR > 45 mL/min/1.73 m^2. Additional study will be expected for larger doses of 1500mg twice daily in AUC method or eGFR value.

For clinical efficacy of imeglimin, meta-analysis study was conducted [7]. Data are from 8 studies including 1555 cases. Compared with control group, imeglimin group had the superior results for HbA1c and blood glucose. In contrast, there were not significant differences on HDL, LDL, triglyceride and HOMA-IR. Various researches will be required concerning monotherapy and combined therapy for imeglimin [13].

In summary, T2DM case with successful efficacy of imeglimin (Twymeeg) was described in this article. The mechanism of this agent has dual aspects, and it may become a new category of diabetic OHAs. Further development of diabetic practice and research will be expected for imeglimin and related matters in the future.

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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