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PUBTEXTO

Improved HbA1c value by combined treatment of Dulaglutide and Imeglimin for patient with type 2 diabetes mellitus (T2DM)

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Abstract

Background: As a novel oral hypoglycemic agent (OHA), imeglimin has been recently applied for patients with type 2 diabetes mellitus (T2DM) as Twymeeg. It has beneficial twin mechanisms associated with increasing insulin secretion, and decreasing insulin resistance. It has a triazine ring and become the first OHA for tetrahydrotriazine-containing agent in the category of the glimins.
Case presentation: The case is 84-year-old female with T2DM and mild cognitive impairment (MCI). Her HbA1c was 9.3% a year ago.
Results: She was begun to receive Dulaglutide 0.75mg/week and showed 1.3% HbA1c reduction for 6 months. However, HbA1c was elevated again to 8.5%, and then she was provided Twymeeg 2000mg/day. HbA1c decreased from 8.5% to 7.5% in 3 months. [Discussion and conclusion] From combined treatments of imeglimin and other agents in the previous study, mean HbA1c reduction showed single imiglimin -0.46%, DPP-4i -0.92% and GLP-1RA -0.12%. Possible reason for the difference between the latter two suggests that multiple action mechanisms of imeglimin may be present including the enhancement of glucose-stimulated insulin secretion (GSIS). In contrast, she showed satisfactory HbA1c reduction by the combination of imeglimin and GLP-1RA. The pathophysiology is not clear, and future follow up the clinical progress will be required.

Keywords: Oral Hypoglycemic Agent (OHA); Imeglimin; Twymeeg; Glucose-Stimulated Insulin Secretion (GSIS); Type 2 Diabetes Mellitus (T2DM)

Introduction

Patients with diabetes mellitus (DM) have been increasing across the world. International Diabetes Federation (IDF) pronounced the latest diabetic situation in 2022 [1]. For 215 countries and territories, undiagnosed diabetes mellitus (UDM) prevalence was investigated. The results of UDM showed worldwide 44.7%, Africa 53.6%, Western Pacific 52.8%, South-East Asia 51.3% and North America 24.2%. For appropriate diagnosis and treatment of DM, American Diabetes Association (ADA) has presented the standard guideline in Jan 2022 [2]. Several types of antidiabetic agents have been found including oral hypoglycemic agents (OHAs) and some kinds of injection [3]. Among them, recent topic has been an introduction of novel OHA that shows rather satisfactory medical efficacy [4].

For long, the first-class agent for type 2 diabetes mellitus (T2DM) has been metformin. Metformin has been evaluated to show desirable pharmacokinetics for the investigation of drug delivery system (DDS). As similar molecule of metformin, recent developed agent is imeglimin, which has cyclic small molecule including a triazine ring [5]. It is the firstly-introduced OHA for tetrahydrotriazine-containing agent in the category of the glimins [6]. For its benefit, dual mechanisms have been observed for increasing secretion of insulin from the pancreas and decreasing insulin resistance in peripheral organ [7]. Actual application of imeglimin was conducted, where the brand name is Twymeeg. Clinical efficacy was found by the administration of imeglimin [8].

Authors and diabetic team have continued diabetic research and practice for years [9]. Among them, various studies have been included such as meal tolerance test (MTT), low carbohydrate diet (LCD), continuous glucose monitoring and others [10]. Various antidiabetic agents were also reported including sodium-glucose transporter 2 inhibitor (SGLT2i), glucagon-like peptide 1 receptor agonist (GLP-1RA) [11,12]. In addition, reports concerning imeglumin have been presented with clinical effects [8,13]. We have recently experienced a diabetic patient who was provided dulaglutide and imeglimin associated with several impressive matters. General outline of the case and some discussion will be described in this article.

Case Presentation

Medical History

The case is an 84-year-old female patient with Type 2 Diabetes Mellitus （T2DM） and other problems. She has been treated as T2DM, hypertension, dyslipidemia, gastroesophageal reflux disease (GERD), mild cognitive impairment (MCI) and possible slight cerebral vascular accident (CVA) for several years. Formerly, she had been treated in other hospitals, in which her HbA1c was 11.3% 2 years ago. In Jan 2021, she was introduced to our hospital for further evaluation and treatment. Her HbA1c was 8.8%, and had been provided voglibose 0.6mg/day and glimepiride 1mg/day for oral hypoglycemic agents (OHAs).

Physical Exam and Various Exams

As physical status, she showed unremarkable consciousness, speech, behaviors, vitals, lung, heart, abdomen and neurological findings. Her stature showed 144.8 cm, 43.3 kg and BMI 20.7 kg/m^2. Her usual daily life has been stable visiting day services a few times a week. The biochemical results of June 2021 were in the following: TP 7.7 g/dL, Alb 4.1 g/dL, T-Bil 0.4 mg/dL, AST 45 U/L, ALT 64 U/L, γ-GT 22 U/L, CPK 42 U/L (30-200), UA 3.0 mg/dL, BUN 11 mg/dL, Cr 0.5 mg/dL, Na 141 mEq/L, K4.0 mEq/L, Cl 101 mEq/L, T-C 199 mg/dL, HDL-C 51 mg/dL, LDL-C 125 mg/dL, TG 117 mg/dL, RBC 4.18 x 10^6 /μL, Hb 12.8 g/dL, Ht 38.7%, MCV 92.5 fL (80-98), MCH 30.6 pg (27-34), MCHC 33.1 g/dL (31-36), WBC 8100 /μL, Plt 32.0 x 10^4 /μL. Her chest X-ray revealed unremarkable, and ECG was within normal limit.

Clinical Progress

She had been continued to receive OHA, and her HbA1c increased to 9.3% in March 2021. Then, she was initiated to have dulaglutide 0.75mg/week for further treatment. After that, her HbA1c was gradually decreased and it revealed 7.9% in Oct 2020. However, her diabetic control became exacerbation with HbA1c 8.5%. Consequently, we started to give her imeglimin (Twymeeg) 2000 mg/day, which are actually provided 1000mg in the morning and 1000mg in the evening. After that, her HbA1c was gradually decreased as 8.3%, 8.1% and 7.5% in Feb 2022 (Figure 1).

During the clinical course, she complained of a skin lesion at the inner malleolus of the right foot. It was an infiltrative erythema with 41mm x 41mm in size, associated with yellow scabs attached to the margins. The lesion was diagnosed as Bowen's disease by dermatologist. For the treatment strategy, she and her family decided not to undergo surgery but to treat with 5-FU ointment, that is an anticancer agent for conservative therapy.

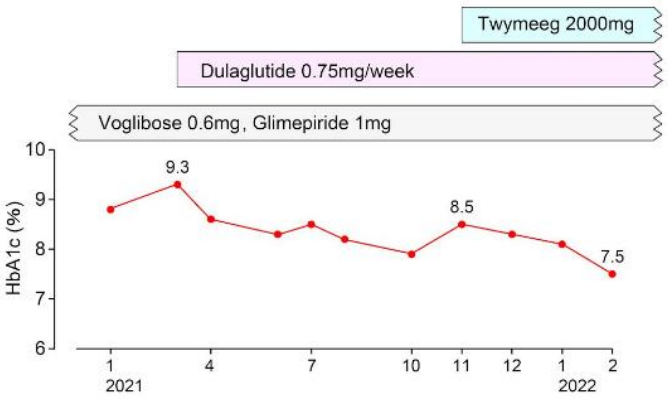

Figure 1: *Clinical progress of the case indicating the efficacy of dulaglutide and imeglimin.*

Ethical Considerations

Current case study is fundamentally according to the ethics that is the principles for the Declaration of Helsinki. Further, some commentary was added from the Ethical Guidelines for Research for Humans. Its guidelines are accompanied by the Good Clinical Practice (GCP). The authors have fully discussed and established a hospital ethical committee. It consists of several professional staffs such as the president of the hospital, administration director, physician, surgeon, registered nurse, pharmacist, nutritionist and legal professional person. Our committee has enough discussion by adequate manners and concluded the total agreements for this investigation. The informed consent and also written document were obtained from the patient.

Discussion

This case is T2DM and was treated with imeglimin that is a novel oral hypoglycemic agent (OHA). In this discussion, various perspectives of imeglimin and some characteristics of this case are described in this order. Imeglimin has been reported to have multiple mechanisms pharmacologically. It shows clinical effects in the light of improving insulin secretion and also decreasing insulin resistance against peripheral tissue. Some reports revealed the reduction of HbA1c approximately 0.5-1.0% by single medication of 1000mg x 2 per day [14,15]. Moreover, additional effects were observed by add-on therapy (AOT), in which combined treatment of dipeptidyl peptidase-4 inhibitor (DPP4i) showed more HbA1c reduction of 0.6-0.65% [15]. As to adverse effects, remarkable major reports were not observed, including hypoglycemia attack or cardiovascular events and so on [16].

According to the TIMES 2 study of Imiglimin, changes in HbA1c was investigated for single imiglimin and combined treatments of other antidiabetic agents for 52 weeks [16]. The mean reduction of HbA1c showed that single imiglimin -0.46%, sulfonyl urea -0.56%, alfa-GI -0/85%, glinide -0.70%, biguanides -0.67%, thiazolidine -0.88%, DPP-4i -0.92%, SGLT2i -0.57%, GLP-1RA -0.12%. Furthermore, TIMES 3 study showed similar investigation, in which

combined treatment of imiglimin and insulin resulted in -0.63% [16]. Among these, three agents can be compared including DPP-4i (per os), GLP-1RA (injection) and insulin (injection). Although DPP-4i and GLP-1RA have common pharmacological pathway, but clinical effects showed large difference as -0.92% and -0.12%, respectively. The effect of insulin revealed -0.63%, that is in the midst of DPP-4i and GLP-1RA.

What kind of mechanism makes this difference? Related to this issue, three possible pathways exist leading to insulin secretion from the beta-cell [17].

i. The stimulation of glucose causes the activation of cyclic AMP (cAMP), exchange protein directly activated by cAMP 2A (Epac2A）, and transient receptor potential melastatin 2 (TRPM2), which leads to the 1st phase secretion of insulin.

ii. The stimulation of GLP-1, Glucose-dependent insulinotropic polypeptide (GIP) and exendin-4 may activate cAMP as same pathway of glucose stimulation.

iii. The third pathway seems to be present through several mechanism via mitochondria, which is physiological characteristic aspect of imeglimin. The promotion of insulin secretion would be observed depending on the glucose level. In other words, multiple action mechanisms including the enhancement of glucose-stimulated insulin secretion (GSIS) may be present. For GSIS function, TRPM2 channel would be activated. TRPM2 channel is one of the non-selective cation channel (NSCCs) in β-cells, and it will promote the depolarization of plasma membrane [17].

In the clinical course of this case, HbA1c value was elevated in Mar 2021. Then, Dulaglutide injection weekly was started. Successively, HbA1c value increased again in autumn 2021, and imeglimin was initiated to be given. From the previous reports, the combined use of GLP-1RA and imeglimin is said to be less effective [16]. However, this case showed that administration of imeglimin brought reduced HbA1c by 1.0%, which was evaluated to be effective. During this period, there were no particular changes in other factors such as daily life, appetite, and intake of medicine. Consequently, this effect was due to medical efficacy of imeglimin. No other specific sign or symptom was not observed. This case has T2DM and MCI, in which MCI was slight degree without remarkable influence for her usual daily life. Diabetes has been known to show association with elevated risk of dementia and/or mild cognitive impairment (MCI) [18]. Diabetic patients reveal the elevated ratio of some types of dementia, which are all types (+73%), Alzheimer (+56%), vascular dementia (+127%), in comparison with usual people without diabetes [19]. In the presence of MCI, diabetes treatment regimens should be simplified as possible and tailored to minimize hypoglycemia risk (level B) [20].

Furthermore, current case developed Bowen's disease in the foot. In the elderly, various diseases in the dermatology are apt to be found more including skin, nail and hair [21]. Some skin lesions may be related to diabetes, acanthosis, pigmented Bowen's disease and others [22]. Regarding diabetes, cancer has been recognized for the leading cause of death [23]. It is approximately 1.2 folds of elevated risk of all-site of cancer except for prostate. Wider amplitude of glycemic excursion may induce inflammation, oxidative stress and endothelial dysfunction. Inadequate quality of management or care may bring wide amplitude glycemic variability (GV), leading to poor outcomes [24]. Short term glucose measurement cannot analyze glycemic excursions. In contrast, long term GV associated with multiple data of glycemic values can evaluate detail glycemic variability and HbA1c [25,26]. Further, micro-/macrovascular complications and mortality perspectives in T1DM and T2DM [27,28]. Within the previous studies, there seems to be no remarkable specific association between the onset of Bowen's disease and diabetes.

There are some limitations concerning this report. The patient has several medical problems who was treated dulaglutide and imeglimin (Twymeeg). It has been known to reveal less clinical effect in the case of combined treatment of GLP-1RA. In contrast, this case showed enough effect by this combination, where the reason has been not clarified yet. Several factors may be involved in the result, including characteristic constitution of the case, mutual influence of antidiabetic agents, possible changed lifestyle and others. Future following up the clinical progress would become helpful for clarifying total pathophysiological situation. In summary, elderly patient with T2DM received the treatment of dulaglutide and imeglimin (Twymeeg). Her clinical effect was satisfactory with enough decrease of HbA1c. Various perspectives are described in this report. It will hopefully become a reference for diabetic practice and research in the future.

Conflict Of Interest

The authors declare no conflict of interest.

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