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Case Report

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Effective Single Twymeeg Administration for Elderly Patient with Type 2 Diabetes (T2D), Arthralgia and Depression as Common Medical Problems

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Abstract

Background: Imeglimin (Twymeeg) has been effective for patients with type 2 diabetes (T2D).

Case Presentation: The patient is an 82-year-old female with T2D, arthralgia, and depression.

Results: She was given duloxetine hydrochloride (Cymbalta) and Twymeeg, leading to improved symptoms of low back pain (LBP), knee osteoarthritis, osteoporosis, depression, and possible mild cognitive impairment (MCI). HbA1c decreased from 8.8% to 7.1% for 4 months with a single administration of Twymeeg 2000mg/day.

Discussion: In recent clinical practice, elderly cases often tend to have simultaneously these problems, which are medical and social crucial problems. Twymeeg and Cymbalta may be indispensable agents for future practice.

Keywords

Imeglimin, Twymeeg, Duloxetine Hydrochloride, Cymbalta, Type 2 Diabetes, Depression, Mild Cognitive Impairment

Abbreviations

Twymeeg: Imeglimin; Cymbalta: Duloxetine Hydrochloride; T2D: Type 2 Diabetes; MCI: Mild Cognitive Impairment

Introduction

Across the world, diabetes mellitus has been a crucial medical and social problem for lots of patients and also primary care providers [1]. The number of patients with diabetes has gradually increased [2]. Current issue would be the elevated prevalence of undiagnosed diabetes mellitus (UDM), which indicates 44.7% in the world, 24.2% in America, 51.3% in South-East Asia, 52.8% in Western Pacific and 53.6% in Africa. In particular, adequate management for elderly people would be important [3]. The latest guidelines for diabetes were announced by the American Diabetes Association (ADA), and recent applicable therapy for Type 2 Diabetes (T2D) has been recommended [4]. For evidence-based medicine (EBM), the ADA summarizes the grading system as

four levels, where A: clear evidence, B: supportive evidence from well-conducted, C: supportive evidence from poorly controlled, and E: expert consensus or clinical experience [1].

Recent topic would be the novel oral hypoglycemic agent (OHA) which has beneficial effects on glucose variability [5]. In diabetic practice, the first-line agent for T2D has been for long metformin. It revealed a rather desirable metabolism for the drug delivery system (DDS) in the light of pharmacokinetics. For a molecule similar to metformin, a novel OHA imeglimin was developed as a tetrahydrotriazine-containing agent [6]. The characteristic point shows a triazine ring for cyclic small molecules [7]. Its mechanism has the dual action of decreasing insulin resistance for peripheral organs and increasing insulin secretion from the beta-cell [8]. Imeglimin has been introduced to clinical practice under the brand name Twymeeg [9]. Authors et al. have reported some cases with satisfactory efficacy in T2D patients [10,11].

Authors and collaborators in our team have continued diabetic practice and research for a long [12]. For the research area, continuous glucose monitoring (CGM), low carbohydrate diet (LCD), meal tolerance test (MTT), and others have been included [13]. Antidiabetic agents were also reported, such as glucagon-like peptide 1 receptor agonist (GLP-1RA) and sodium-glucose transporter 2 inhibitor (SGLT2i) [14,15]. Furthermore, recent reports for imeglumin have been found concerning clinical efficacy [10,11,16]. We have recently experienced an elderly female who showed a satisfactory response to imeglimin. Her clinical progress and related perspectives will be described in the current article.

Case Presentation

Medical History and Physicals:

The patient for this case report is an 82-year-old female. In her history, she had some pain in the lower back and bilateral knees for 10 years. She had no medically noteworthy illness for the internal medicine department.

For her current medical history, she slipped and fell at the front door of her home when she was waiting for the bus for day service care. She got stuck in her butt and could not move at all. She was found by the staff of the care facility picking her up at her home and was transferred to the emergency room in the hospital by ambulance. She was found to have a compression fracture of the 1st lumbar spine, mild paresis of both lower limbs, knee osteoarthritis, and osteoporosis, associated with mild lower limb weakness. At that time, the HbA1c value was 5.7%, and apparent diabetes was not observed. Since then, her QOL and ADL of daily life have gradually declined with lower activity.

In June 2020, she visited the neurosurgery (NS) department. She was diagnosed with a probable slight depressive state and possible mild cognitive impairment (MCI). Due to her psychological instability, administration of prochlorperazine 5 mg/day was started. In April 2021, she complained of low back pain, hip pain and knee pain, and then duloxetine hydrochloride 20 mg/day seemed to be adequate for controlling the pains. This treatment could reduce her joint pain with clinically actual effect. In Nov 2021, blood glucose levels increased to 301 mg/dL with HbA1c 8.7%. She was diagnosed with apparent T2D, and received detailed evaluations of biochemistry tests.

Laboratory Examinations:

The biochemical results in Nov 2021 were as follows. They are AST 30 U/L, ALT 39 U/L, γ-GT 23 U/L, ALP 141 U/L (38-113), T-Bil 0.4 mg/dL, D-Bil 0.1 mg/dL, TP 6.5 g/dL, Alb 3.8 g/dL, CPK 75 U/L (45-176), BUN 15 mg/dL, Cr 0.7 mg/dL, UA 3.5 mg/dL, Na 138 mEq/L, K 4.5 mEq/L, Cl 103 mEq/L, RBC 4.82 x 10^6 /μL, Hb 14.7 g/dL, Ht 45.5%, MCV 94 fL (80-98), MCH 30.5 pg (27-33), MCHC 32.3 g/dL (31-36), WBC 7700 /μL, Plt 24.2 x 10^4 /μL. Chest X-P showed negative findings for heart and lung, and ECG showed ordinary sinus rhythm with no ST-T changes.

Clinical Course:

The HbA1c value in Nov 2020 was elevated to 8.7%. Then, she decided to take imeglimin (Twymeeg) 1000 mg twice a day, which is one of the recently introduced oral hypoglycemic agents (OHAs) (**Fig-1**). HbA1c values decreased to 7.1% for 4 months. The dose of Twymeeg was stable and continued for 2000mg per day. The

case did not show any adverse effects for several months.

Ethical Standards:

The current study has complied with the ethical standard of the Helsinki Declaration. It has also complied with Japan's personal information protection act. It was performed along with the ethical principles for medical research including human subjects. These guidelines are from the public announcement of the Ministry of Health, Labour and Welfare [MHLW] and also the Ministry of Education, Culture, Sports, Science Technology [MEXT]. The author and colleagues established the ethical committee for the current study. It was present in the hospital, which includes the hospital director, physicians, head nurse, nutritionist, pharmacist, and legal professional. All members have discussed the matter enough and agreed to the protocol. The informed consent was taken from the patient as per the written style of the agreement document.

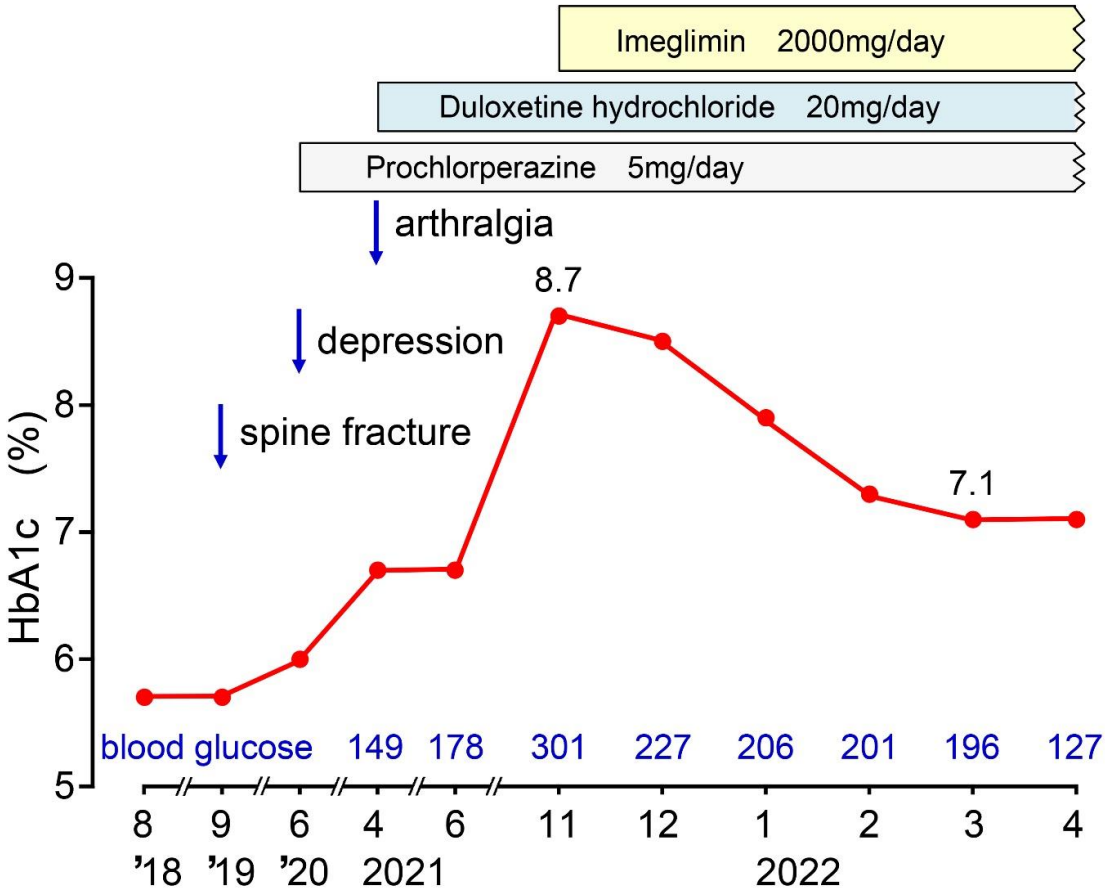

Fig-1: Clinical progress of the case with HbA1c, glucose and medication

Discussion

The case reported here is an 82-year-old female with T2D. From a medical point of view, some characteristics are found as follows. 1) She was pointed out to have T2D at the age of 82, and then imeglimin was started. Single administration was effective for a 1.6% reduction in HbA1c for 4 months, associated with no adverse effects. 2) At the age of 80, she had a vertebral compression fracture, knee osteoarthritis, and osteoporosis with arthralgia. One year later, she developed mild depression. For these situations, duloxetine was initiated with satisfactory efficacy. 3) A series of problems such as diabetes, chronic low back pain (CLBP), knee pain, depression, and MCI like this case are crucial challenges in current medical care. Many older people have similar problems, which are medically and also socially important. We will discuss the above three issues in this order.

Firstly, this case was fully effective with single imeglimin administration. She has had no particular diseases in the past, but HbA1c has been slowly increasing over the last few years. Possible causes include decreased physical activity due to vertebral compression fractures, the presence of depression, possible MCI, and unstable meal patterns in her daily life. Diabetes shows a relationship with an increased risk of MCI and/or dementia [17]. Diabetic cases show a higher prevalence of some types of dementia, which is +73% for all types, +56% for Alzheimer's, and +127% for vascular dementia compared with healthy cases without diabetes [18]. According to the latest guidelines, such cases with diabetes and MCI should receive simplified treatment regimens to minimize hypoglycemic risk to level B [19].

Regarding single administration of imeglimin, a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial was conducted [20]. The subjects were T2D Japanese patients with HbA1c 7.0-10.0%, who were divided into imeglimin and placebo groups. They were provided 2000mg/day of imeglimin and followed for 24 weeks. As a result, the HbA1c decrease from baseline was 0.87% [0.69-1.04] in comparison with that of the placebo group. In the light of the clinical effect of imeglimin, a report meta-analysis was performed [21]. The protocol included 1555 cases from 8 studies and a comparison of imeglimin group and the control group. As a result, the imeglimin group showed a better decrease in HbA1c and glucose variability. Further, no significant differences were observed for triglyceride, LDL, HDL, and HOMA-R.

From a basic medicine point of view, imeglimin is characteristic for tetrahydrotriazine-containing agent [6]. It possibly has multiple pathway mechanisms including preventing epithelial cell death, improving β-cell function, and elevating insulin secretion [22]. The mechanism may be involved in the enhancement of glucose-stimulated insulin secretion (GSIS). This process is via activated transient receptor potential melastatin 2 (TRPM2) channels. Consequently, plasma membrane depolarization would be progressed, that exists in non-selective cation channels (NSCCs) of β-cell [23]. Furthermore, insulin secretion would be influenced by calcium mobilization for the amplification pathway [24].

Secondly, duloxetine hydrochloride (Cymbalta) has been effective for this case, which is one of the Serotonin Noradrenaline Reuptake Inhibitors (SNRIs). SNRI can exhibit anti-depressant mechanism by improving and increasing the action of neurotransmitters. Furthermore, noradrenalin (NA) and serotonin (5-HT) will activate descending pain suppression system, that is significantly involved in pain suppression mechanism in the brain. Cymbalta has been used widely in clinical practice, which is N06AX21 by ATC code [25]. It is often prescribed to elderly patients who are suffering from low back pain (LBP), knee pain, arthralgia of other joints, light degree of depression, diabetic neuropathy, and other pathology. According to the package insert of Duloxetine hydrochloride, a report of duloxetine administration for chronic low back pain (CLBP) is observed [26]. It is Study CLBP-1 and CLBP-3 for achieving various levels of pain relief for 24-hour average pain severity. As a result, the point of 50% degree for improvement of in pain from baseline shows that 34% of patients were improved.

Common problems of LBP for the efficacy, safety, and acceptability of antidepressant agents were investigated [27]. Internet surveys such as Medline, Central, ClinicalTrials.gov, and Embase were conducted for RCT studies. From 23 RCT reviews, antidepressants reduced pain levels by 4.33 points [2.5-6.2] compared to placebo, for a 0-100 scale evaluation. This treatment stopped other therapies compared to control with OR 1.27 [1.03-1.56]. As regards to clinical effect and safety of duloxetine, 9 RCTs were analyzed for two groups (duloxetine vs placebo) for patients with osteoarthritis or CLBP [28]. As a result, the weighted mean difference (WMD) was -0.67 for 24-h average pain, -0.65 for weekly average pain, and -0.41 for global impression for improvement, respectively. In contrast, duloxetine showed higher treatment-emergent adverse events (TEAEs) (RR:1.25) and discontinuations for adverse events (AEs) (RR: 2.31).

Thirdly, related to QOL and ADL for daily life, Visual Analogue Scale (VAS) is one of the useful pain rating

scales for long [29]. For LBP from osteoporosis, clinical efficacy for duloxetine was investigated. Subjects were 300 elderly patients with LBP and osteoporosis, and they were divided into two groups (each n=150) [30]. VAS score for LBP was 3.5 vs 1.7 in duloxetine and control group, respectively. Duloxetine seems to present proper relief effect on LBP for elder patients, and it can contribute improving pain sensitization. Concerning diabetic peripheral neuropathic pain (DPNP), comparative study was performed for trials on duloxetine versus gabapentin by internet search for related data [31]. From the results of 7 related studies, no significant differences were found for VAS score and overall response rate in both groups. However, duloxetine showed significant superiority to gabapentin in the light of adverse reaction incidence (RR=0.59). Thus, duloxetine showed clinical usefulness for common pain control.

In the light of health survey, Japanese patients with chronic knee pain due to OA were analyzed for long-term efficacy, tolerability and safety of duloxetine [32]. Protocol included 323 cases and evaluation methods of 36-item Short-Form Health Survey (SF36), Patient Global Impression-Improvement (PGI-I), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and others. In conclusion, it is well tolerated with continuous improvements of pain control and health related QOL. Out of 111 OA patients of knee and hip OA patients, duloxetine was provided and followed 8 weeks [25]. As a result, 44% showed enough reduced pain in comparison with 0% for care-as-usual group ($p<0.001$). By using two evaluation methods of Knee injury and Osteoarthritis Outcome Score (KOOS) or Hip disability and Osteoarthritis Outcome Score (HOOS), duloxetine group showed 11.3 points better compared with control group. Knee group showed significantly better result than hip group, which are 18.7 versus 6.0 points improved, respectively.

Some limitations are present in this report. The case has spinal compression fracture, depression, T2D and possible MCI. She was provided by Cymbalta and Twymeeg with satisfactory efficacy. However, this is only case, and this situation cannot generalize for other patients. Several factors would be investigated and future follow up will be required.

In summary, aged female case was presented with clinical progress and some discussion. Elderly cases often tend to have simultaneously these problems, which are medical and social crucial problems. Twymeeg and Cymbalta may be indispensable agents for future practice. The authors hope the probable contribution of this report for diabetic future development of practice and research.

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Competing Interests

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

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