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PUBTEXTO

Impressive clinical progress of atopic dermatitis and renal dysfunction in Type 2 Diabetes (T2D) patient treated with cyclosporin A (CyA) and imeglimin (Twymeeg)

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Abstract

Current case was 65-year-old Type 2 Diabetes (T2D) male with stable situation of HbA1c 7.6%, creatinine 0.71 mg/dL. He developed atopic dermatitis (AD), and was treated in the university hospital with cyclosporin A (CyA). He took CyA intermittently due to impaired renal function of adverse effect (AE). HbA1c and creatinine were followed for years, and they showed exacerbation in Jan 2023 with 10.2% and 1.48 mg/dL. By the administration of vildagliptin and metformin (EquMet) and imeglimin (Twymeeg), his general situation was improved to 7.1% and 1.34 mg/dL. It suggested clinical efficacy of imeglimin for T2D and impaired renal function.

Keywords: Atopic Dermatitis (AD); Cyclosporin A (CyA); Vildagliptin and Metformin (EquMet); Imeglimin (Twymeeg); Estimated Glomerular Filtration Rate (eGFR)

Introduction

Type 2 Diabetes (T2D) has been crucial disease to be properly managed for years, and its standard guideline was presented from American Diabetes Association (ADA) as "Standards of Care in Diabetes" [1]. T2D shows macroangiopathy, microangiopathy, and other multiple organ damages due to impaired blood vessels [2]. For patients with T2D, the ideal goal is to have the same Quality of Life (QOL) as healthy people [3]. For decades, some novel oral hypoglycemic agents (OHAs) were used for actual clinical practice [4,5]. Their representative OHAs include sodium–glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like-peptide 1 receptor agonist (GLP1-RA), dipeptidyl peptidase-4 inhibitor (DPP-4i), and others [6]. Further, most recently introduced OHA was imeglimin as Twymeeg. It has dual function for insulin secretion and resistance [5,7].

Concerning imeglimin, it shows the similar molecule with the construction of metformin [8]. Metformin has been for long the first-line OHA for treating T2D worldwide as standard treatment for T2D [9]. It shows clinical effectiveness for monotherapy and also add-on therapy method with other OHAs or insulin therapy [10]. These two OHAs shows the similar kinds of molecule, and they can be prescribed together as the combination of other OHAs. As common administration measure, they are provided twice per day. Metformin and imeglimin are known to have clinical actual efficacy by bis in die (bid) method until now [11].

Furthermore, effective OHA for T2D includes vildagliptin (Equa). It is provided by bid, and shows benefit for twice administration associated with efficacy for all day long [12]. For T2D, early combination of OHAs would contribute the better clinical course [13]. Concerning combined treatment of metformin and vildagliptin, large investigations were conducted as Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) studies [14]. Thus, the combination of OHAs as EquMet has been provided bid, which brings suppressing blood glucose for night and day [12].

Authors et al. have reported diabetic research until now. They cover low carbohydrate diet (LCD), meal tolerance test (MTT) and other case reports treated by OHAs [15]. For recent period, some pharmacological effects of imeglimin (Twymeeg) were presented [16]. Furthermore, seasonal changes in HbA1c value were analyzed for lots of T2D cases [17]. T2D has various clinical complications with immune and dermatological problems [18]. Among them, atopic dermatitis (AD) has been crucial medical problems with rather difficult to obtain the stable situation [19]. We recently experienced a case who was given EquMet and Twymeeg associated with the problems of AD and adverse effect (AE) of agent. In this article, general clinical course and related perspectives are described.

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Presentation of the case

Medical History

The patient is 65-year-old male with T2D for 11 years. He had been almost stable until 2019 with stable HbA1c about 7%. His laboratory data in July 2019 were as follows: HbA1c 7.6%, creatinine 0.71 mg/dL and estimated glomerular filtration rate (eGFR) 86 mL/min/1.73m^2. During 2019 to May 2021, his renal function was gradually decreased. He developed skin lesion from May 2021, and it was diagnosed as atopic dermatitis (AD). Then, further evaluation was conducted in the dermatology department of the university hospital.

Physicals Examination

His physical examination during Sept-Oct 2021 was in the following. Consciousness was alert, vitals were stable, lung, heart and abdomen were unremarkable. Neurological findings were intact.

Dermatological findings were summarized. On the surface of the head, there were many red bean-sized papules and infiltrative erythema. These lesions were strongly infiltrating on the forehead, neck, shoulder blades, buttocks, and forearms. These eruptions gathered on the back, and scratch marks could also be seen. The infiltrative erythema on the back was slightly brownish, but most of the nodules had blood crusts. No obvious blisters were observed. Diagnosed by dermatologists, these findings were recognized under the category of atopic dermatitis, which also includes factors such as prurigo nodularis or chronic prurigo multiforme. Furthermore, BP180 antibody was negative, which suggests autoimmune bullous disease-related antibody.

Laboratory Examination

Biochemical exam was conducted, and the results in July 2022 were revealed in the following. They are HbA1c 8.1%, post-prandial blood glucose 235 mg/dL, RBC 5.29 x 10^6 /μL, Hb 15.7 g/dL, Ht 48.4 %, MCV 92.0 fL (80-98), MCH 29.7 pg (27-33), MCHC 32.4 g/dL (31-36), WBC 7800/μL, Plt 27.2 x 10^4 /μL, GOT 22 U/L, GPT 40 U/L, γ-GTP 23 U/L, ALP (IFCC) 134 U/L (38-113), Uric acid 5.8 mg/dL, BUN 22 mg/dL, Cre 1.26 mg/dL, HDL 40 mg/dL, LDL 159 mg/dL, TG 332 mg/dL (post-prandial). Urinalysis: urobilinogen (+/-), glucose (4+), protein (2+), pH 6.6, ketone bodies (-), occult blood (+/-), specific gravity 1.017. Chest X-ray test showed within normal limit. Electrocardiogram (ECG) showed ordinary sinus rhythm, normal axis deviation, pulse 72/min, and unremarkable ST-T changes.

Clinical Course

His medical problems in July 2021 could be summarized in the following: #1 T2D, #2 CKD or DKD, #3 hypertension, #4 dyslipidemia, #5 atopic dermatitis, #6 treatment of cyclosporin A (CyA) due to #5. According to his atopic dermatitis, he started to intake CyA from July 2021 [Figure 1]. The administration of CyA was intermittently provided. When CyA was given, skin lesion of atopic dermatitis can be improved. However, renal dysfunction would become worse during the intake of CyA.

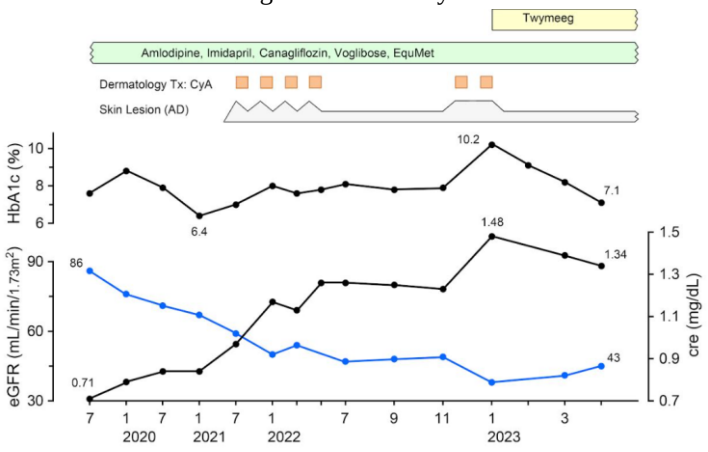

Figure 1: Clinical course of HbA1c, serum creatinine and eGFR.

His general status had been stable from Jul 2022 to Nov 2022. During this period, HbA1c, serum creatinine and eGFR were stable. During Nov 2022-Jan 2023, his skin lesions were exacerbated, and then CyA was provided. On Jan 2023, HbA1c was increased to 10.2% associated with elevation of creatinine 1.48 mg/dL. Consequently, one of the novel oral hypoglycemic agents (OHAs), imeglimin (Twymeeg) was initiated for better glucose variability. After that, HbA1c was decreased to 9.1%, 8.2%, 7.1% in Feb, Mar, Apr 2023 associated with remarkable clinical efficacy.

Ethical Standards

The case has been along with the ethic guideline for Declaration of Helsinki. Moreover, some commentaries were recognized for the standard protection regulation regarding the personal information. The fundamental principle was based on the ethical rules concerning clinical practice and research for human being. Some guidelines were used for the proposal of Japan Ministry. These are on the Ministry of Health, Labor and Welfare and also the Ministry of Education, Culture, Sports, Science Technology. The authors and co-researchers have established the related ethical committee for this research, which exists in Sakamoto Hospital of Kagawa, Japan. It has several medical and also legal persons, including hospital director, physicians, registered nurse, pharmacist, dietitian and legal professionals. These hospital staffs have discussed enough about current case, and we agreed the research protocol.

Discussion

This patient was 65-year-old male, who developed T2D, CKD, hypertension, dyslipidemia. This report has three aspects for discussion. They are i) he was provided EquMet and Twymeeg associated with certain clinical effects, which are OHAs for T2D, ii) another clinical problem was atopic dermatitis (AD) that is not so easy to control, and cyclosporin A (CyA) has been intermittently

given to the case for the control of AD, and iii) renal dysfunction has been gradually developed, which supposed to be from diabetic nephropathy, diabetic kidney disease (DKD) and also from adverse effects (AEs) of CyA. These three perspectives are described in this order as follows:

Firstly, this case has taken OHAs as EquMet and Twymeeg. This combination seemed to be effective for improving glucose variability. EquMet is the combined agents of vildagliptin and metformin. It is characterized for the administration twice a day, in which it shows clinical efficacy for 24-hours duration. From detail evaluation of blood glucose profile and mean amplitude of glycemic excursions (MAGE) by continuous subcutaneous glucose monitoring (CSGM), vildagliptin showed stable MAGE with clinical benefit [12]. As a matter of fact, the case has meal habit of taking certain carbohydrate meal at supper. Consequently, EquMet was likely to bring lower glucose variability during night and day. Furthermore, Twymeeg has been known as dual effects for increasing the insulin secretion and reducing the insulin resistance. It has clinical efficacy of add-on treatment with other OHAs. According to the results of TIMES 1 to 3, the lowering HbA1c levels are as follows: monotherapy -0.46%, DPP4-i -0.92%, biguanides -0.67%, SGLT2i -0.57%, glinides -0.70%, α-GI -0.70% [20]. In this case, he took EquMet and Twymeeg, and then enough additive efficacy would be shown. Impressive result was observed for the comparison with DPP4-i and GLP-1RA. The former revealed -0.92%, but the latter revealed only -0.12% according to TIMES 3 [21]. These agents have common route of pharmacological mechanism, whereas the large difference may suggest another possible pathway [22]. By continuous glucose monitoring (CGM), detail glucose variability was observed during the administration of imeglimin [23]. Various function seemed to be involved in endothelial cell-related mechanism [24]. Further evaluation will be required for clinical efficacy of mitochondrial function [25].

Secondly, T2D has various complication, in which macroangiopathy, microangiopathy and impaired function of immune system. Among them, atopic dermatitis (AD) has been one of the crucial diseases to be treated adequately [26]. For the treatment of atopic dermatitis, calcineurin inhibitor (CNI) has been applied such as cyclosporin (CsA). CsA has been rather prevalent that has multiple effects for wider systems. For actual application in the clinical practice, however, immunosuppressants-induced kidney injury has been present [27]. It occurs in dose-dependent manner, and it can be improved by decreased dose or discontinuation of the agent [28].

Compared research was found for the therapy of AD. Drug survival (DS) rates were compared among cyclosporine A (CyA), azathioprine (AZA), dupilumab (DUP), methotrexate (MTX) and mycophenolate mofetil (MMF) [29]. As CyA is estimated 1.0, hazard ratio (HR) was calculated as AZA 1.18, MMF 0.98, MTX 0.87 and DUP 0.10. Among them, CyA, AZA and MTX showed frequent interruption from AEs.

Thirdly, this case showed renal dysfunction during his clinical progress. Such situation would be due to diabetic nephropathy and/or AEs of CyA. For CsA for AD (n=95), drug survival (DS) rate for 72 weeks was 21.05% [30]. About 71% (67/95) cases discontinued CsA, in which their causes are from AEs. CsA has been useful agent for AD, but AEs such as renal dysfunction may occur due to dose-dependent manner. From systematic review and meta-analysis, compared study for CsA was conducted between low-dose (<4 mg/kg) and high-dose (≥4 mg/kg) [31]. As a result, clinical efficacy of low-dose group was not inferior to high-dose group. Furthermore, high-dose CsA combined with other immunosuppressive agents have revealed a significantly lower incidence of AEs (0.72 of incidence rate ratio).

For recent topic, various agent options have been increasing in the case of rather severe AD. Consequently, latest movement has been in focus, where the expert panel from 12 professional specialists was established [32]. They conducted literature search and presented some clinical scenario for three major categories.

There are some limitations in the case report. He has been treated as T2D associated with AD and showed the exacerbation of renal function. It may be due to the administration of CyA, which was intermittently provided with careful attention. However, other factors are suggested to be involved in his clinical progress, such as aggravating blood glucose, hypertension, arteriosclerosis and so on. Further follow up the course would be needed in the current case.

In summary, 65-year-old male with T2D, CKD and renal function was described associated with various perspectives. Such impressive case with clinical problems will give clinically suggestive matters. We hope that this article will contribute medical development of research and actual practice.

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