https://doi.org/10.33805/2690-2613.126
Volume 4 Issue 1 | PDF 126 | Pages 2

EDELWEISS PUBLICATIONS
OPEN ACCESS

Edelweiss Journal of Biomedical Research and Review

Editorial ISSN 2690-2613

Beneficial Novel Anti-Diabetic Agent Associated with Positive Mechanism for Anti-Aging

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Citation: Bando H. Beneficial novel anti-diabetic agent associated with positive mechanism for anti-aging (2022) Edel J Biomed Res Rev 4: 1-2.

Received: Apr 11, 2022
Accepted: May 16, 2022
Published: June 23, 2022

Abstract

Latest Standards of Medical Care in Diabetes-2022 was presented from American Diabetes Association (ADA) on Jan 2022. A topic of Oral Hypoglycemic Agent (OHA) has been imeglimin. It may work through multiple action mechanism such as increasing insulin secretion, decreasing β-cell dysfunction, and preventing death of epithelial cells. Clinically, it decreases HbA1c by 0.5-1.0% for 1000mg twice a day. Diabetes and anti-aging medicine have common background pathophysiologically. Astaxanthin (AX) is the nephroprotective as mitochondrial regulator. AX-functioning mechanism includes to ameliorate insulin resistance and glucose intolerance. Imeglimin normalizes insulin sensitivity and glucose tolerance with maintaining mitochondrial function, suggesting common mechanism.

Keywords: Astaxanthin, Anti-aging medicine, oral hypoglycemic agent, Imeglimin.

Abbreviations: ADA-American Diabetes Association, WHO-World Health Organization, OHAs-Oral Hypoglycemic Agents, TRPM2-Transient Receptor Potential Melastatin 2, NSCCs-Non-Selective Cation Channel, TEAE-Treatment Emergent Adverse Event, GI-Gastrointestinal.

Introduction

Regarding the latest guideline, the Standards of Medical Care in Diabetes-2022 was announced from American Diabetes Association (ADA) on Jan 2022 [1]. Furthermore, World Health Organization (WHO) has presented diabetic situation regularly concerning various fact across the world [2]. Diabetic patients have been recently increased, especially in developing countries than developed countries [3]. The main strategy for diabetic therapy includes nutrition, physical activity and medication [4]. Among medical agents, recent topic has been imeglimin, that is one of Oral Hypoglycemic Agents (OHAs). Some perspectives of imeglimin would be described in this article.

In the light of fundamental mechanism, Imeglimin has been novel OHA for Type 2 Diabetes (T2D). It is the first agent for tetrahydrotriazine-containing class as glimins [5]. Imeglimin can work through multiple action mechanism and it can increase insulin secretion, decrease pancreatic β-cell dysfunction, and prevent death of epithelial cells [6]. The detail of these mechanism is not completely clarified, but it includes the enhancement of Glucose-Stimulated Insulin Secretion (GSIS). In the GSIS process, Transient Receptor Potential Melastatin 2 (TRPM2) channel is activated, and it promotes the plasma membrane depolarization for one type of Non-Selective Cation Channel (NSCCs) in pancreas β-cells [7]. From the experiment of TRPM2-knockout (KO) and wild-type mice, imeglimin increases through NSCC, which may be involved in the releasing effect of insulin. Imeglimin may cause activation of TRPM2 channels in pancreas β-cells through NAD+ /cADPR production, leading to GSIS potentiation. Moreover, imeglimin contributes to calcium mobilization for the amplification pathway of insulin secretion [8].

For clinical practice, imeglimin shows new pharmacological mechanism. As it is a novel category of OHA, it can give multiple mechanisms for one medication. The function includes to improve insulin secretion, to increase insulin sensitivity and to decrease insulin resistance for peripheral tissue. It has clinical efficacy of reducing HbA1c value for adult patients with T2D. For recent phase 2 and 3 clinical trials, imeglimin was proved to decrease HbA1c level by 0.5-1.0%, as given 1000mg twice a day [9]. When 1,500 mg of imeglimin twice daily was provided in addition to DPP4i or to metformin, HbA1c was further reduced for 0.6% and 0.65%, respectively [10]. As to adverse effects, there are no remarkable major adverse reports, cardiovascular events, or elevated ratio of hypoglycemia for T2DM treated by imeglimin [11].

However, some Gastrointestinal (GI) adverse effects were observed for imeglimin concerning abdominal pain, nausea and vomiting. The incidence for GI disorders showed parallel situation to given doses. It was enough tolerated for 1000mg twice daily than 1500mg twice daily [9]. In the case of patients with CKD or hepatic dysfunction, some reports are found. Regarding the metabolism of imeglimin, it is excreted unchanged through kidneys and has been substrate of organic cation transporters, that are expressed in the liver and kidney. From the pharmacokinetic study for patients with hepatic impairment, Cmax and AUC values showed 1.3-fold and 1.5-fold, respectively, and it was not clinically meaningful [12]. From actual medical practice for diabetes, comparative studies were conducted. Monotherapy or combination therapy of imeglimin and other agents were continued for 52 weeks [13]. The subjects were 714 Japanese patients with T2D. The results showed that monotherapy (n=134) and combination therapy of α-GI (n=64), biguanide (n=64), DPP4-i (n=63), glinide (n=64), GLP1-RA (n=70), SGLT2i (n=63), sulphonylurea (n=127), and thiazolidinedione (n=65). There was unremarkable serious Treatment Emergent Adverse

Event (TEAE), laboratory tests or physical examination. One year later, HbA1c reduced by 0.46% by imeglimin monotherapy, 0.56-0.92% by OHA combination therapy, 0.12% by GLP1-RA injection combination therapy. Most large HbA1c decrease was 0.92% for combined treatment of imeglimin and DPP4i. Consequently, monotherapy and combined therapy showed well-tolerated and safe effect [13].

For evaluating the effect of imeglimin on the changes in glucose variability, insulin resistance and lipid parameters, meta-analysis investigation was conducted [14]. As a whole, 1555 patients from 8 studies were analyzed. As a result, imeglimin group showed the superiority to the control group for HbA1c and fasting blood glucose. On the other hand, no significant changes were found in HOMA-IR, triglyceride, HDL-C and HDL-C. Concerning agent safety, it showed safe and tolerate situation without serious adverse events. These analyses showed safety and improved glucose variability with reduced HbA1c and blood glucose. However, beneficial efficacy was not found concerning insulin resistance or lipid parameters. Further evaluation would be expected for high-quality RCTs with higher doses of imeglimin [14]. Concerning actual diabetic patient, the outline of a case with T2D can be described. Authors and collaborators have continued diabetic practice and research for long. We recently had an experience to treat a diabetic patient for imeglimin. The case was 84-year-old man with post-prandial blood glucose 336 mg/dL and HbA1c 8.6% in August 2021. He was provided Imeglimin 1000 mg twice in the morning and evening as medication for diabetes. After 5 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 9 weeks. The case had normal renal function for Cr 0.8 mg/dL and eGFR 69.4 mL/min/1.73 m2.

Both of diabetes and anti-aging medicine have common background from pathophysiological point of view. Astaxanthin (AX) has been the nephroprotective as a mitochondrial regulator in a mouse model of diabetes mellitus [15]. The functioning mechanism of AX includes to ameliorate significantly insulin resistance and glucose intolerance through AMPK activation and to strengthen exercise tolerance and also metabolism of exercise-induced fatty acid [16]. Imeglimin can normalize insulin sensitivity and glucose tolerance, which is maintaining mitochondrial function and progressing lipid oxidation. Regarding the pathophysiological mechanism, both of AX and imeglimin seem to include common pathway [17]. In summary, a novel OHA for T2D, imeglimin was introduced to clinical practice. It is meaningful for its characteristic aspect from pharmacological point of view. It has several positive mechanisms for diabetes, which may contribute to beneficial health maintenance in anti-aging medicine. Additional research will be expected for further development in the future.

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