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Editorial

Dual Action Mechanism of Insulin Resistance and Insulin Secretion by Imeglimin for Diabetic Treatment

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ABSTRACT

Imeglimin (Twymeeg) is novel oral hypoglycemic agent (OHA) developed in the glimin category. It has dual action mechanisms of reducing insulin resistance and increasing insulin secretion. Trials of imeglimin for efficacy and safety 1 (TIMES 1), TIMES 2 and TIMES 3 were performed with significant clinical efficacy. Among them, HbA1c decrease for 52 weeks showed single imeglimin -0.46%, combined therapy of dipeptidyl peptidase-4i (DPP-4i)-0.92%, Glucagon-like peptide-1 receptor agonists (GLP-1RA)-0.12% and insulin -0.63%. From physiological and pharmacological points of view, the mechanism may include the enhancement action of glucose-stimulated insulin secretion (GSIS). For GSIS progress, transient receptor potential melastatin 2 (TRPM2) channel is activated.

Keywords
Imeglimin; Twymeeg; Trials of imeglimin for efficacy and safety 2 (TIMES 2); Glucose-stimulated insulin secretion (GSIS); Transient receptor potential melastatin 2 (TRPM2) channel.

For non-communicable disease (NCD), diabetes has been crucial medical and social problem worldwide. Medical and health care for diabetes has been managed by International Diabetes Federation (IDF). IDF reported the increased prevalence of diabetes and undiagnosed diabetes mellitus (UDM).[1] Furthermore, latest standard guideline for diabetes was pronounced by American Diabetes Association (ADA) in Jan 2022.[2] It presents recommendation of medical care in diabetes.[3] Recent topics include some types of pharmacological treatment for diabetes. Among them, clinical effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) has been known.[4] GLP-1RA has been recently prescribed more. Cases of 932 type 2 diabetes mellitus (T2DM) were 63.8-years in average and used dulaglutide (65.7%) or liraglutide (29.1%).[5] Hemoglobin A1C (HbA1c) decreased for 6-months from 8.3% to 7.8%, and ratio of HbA1c<7.0% increased from 14.4% to 22.9%. Clinical efficacy of liraglutide and dulaglutide in real world was compared for 179 T2DM patients.[6] HbA1c decreased 8.9% to 7.4% in liraglutide, and 8.7% to 7.5% in dulaglutide for 12-months. Both effects were actually comparable. Thus, GLP-1RA would be in focus for injectable agent for diabetes in the medical practice.

On the other hand, oral hypoglycemic agents (OHAs) have played main role of treating diabetes for long. Metformin has been widely prescribed for first-line medicine with desirable pharmacokinetics. Similar to metformin, a novel OHA has been recently developed, that is imeglimin associated with a triazine ring.[7] It is in the glimin category, which has tetrahydrotriazine-containing agent.[8] The characteristic function shows the dual action mechanism of reducing insulin resistance for peripheral organs and also increasing insulin secretion from beta cell in the pancreas.[9] Imeglimin has been introduced to clinical application, and authors have prescribed the adequate T2DM patients who had successful effects.[10] In our report, T2DM case showed HbA1c decrease from 8.6% to 5.7% in 8-weeks.[11]

From clinical practice points of view, three series of investigations were carried out. They are trials of imeglimin for efficacy and safety 1 (TIMES 1), TIMES 2 and TIMES 3. For TIMES 1, double-blind, randomized, parallel-group, placebo-controlled phase 3 trial was conducted in 30 sites in Japan.[12] Protocol included imeglimin group (2000 mg/day, n=106) and placebo (n=107) for 24-weeks. As a result, HbA1c change from baseline was -0.87% at

24-weeks.

Regarding TIMES 2, clinical efficacy of the combination of imeglimin and other antidiabetic agents for 52-weeks was investigated.[13] It was a phase 3, pivotal, open-label trial including 714 T2DM patients. They were provided 1000 mg of imeglimin twice a day for single therapy or combined therapy of other agents. The primary endpoint was set for maintaining the safety such as adverse events, laboratory results or electrocardiography (ECG). The results showed the following: single imiglimin -0.46%, sulfonyl urea -0.56%, glinide -0.70%, biguanides -0.67%, α-GI -0.85%, thiazolidine -0.88%, sodium/glucose cotransporter-2 inhibitors (SGLT2i) -0.57%, dipeptidyl peptidase-4i (DPP-4i) -0.92% as OHAs, and GLP-1RA -0.12% as injection.

As TIMES 3, combined therapy of imeglimin and insulin was performed for 35 multi-center study. The protocol was double-blind, randomized, parallel-group phase 3 trial with 215 cases.[14] As a result, mean difference in HbA1c between study and control group was -0.60 to -0.64% during 16-52-weeks. Thus, Imeglimin revealed a novel option for add-on therapy (AOT) to insulin therapy.

Among these, impressive comparison would be the combined therapy of DPP-4i (-0.92%), GLP-1RA (-0.12%) and insulin (-0.63%).[13] Common pathway of pharmacological mechanism action has been recognized in the DPP-4i and GLP-1RA. As a matter of fact, however, the clinical effect showed much difference. The efficacy of additional insulin revealed the middle value of those of DPP-4i and GLP-1RA.[14] Possible reason for this phenomenon includes the different pathway of action mechanism of these agents and dual function of imeglimin through mitochondria metabolism.

From basic physiological and pharmacological points of view, imeglimin has been characteristic dual mechanisms.[8] It has an ability for increasing insulin secretion, decreasing β-cell dysfunction, and preventing epithelial cells death.[15] The complete physiological mechanism of imeglimin has not been clarified yet. However, it is suggested for the enhancement action of the glucose-stimulated insulin secretion (GSIS). Concerning GSIS progress, the channel of the transient receptor potential melastatin 2 (TRPM2) is activated, and then it will promote the depolarization of plasma membrane as non-selective cation channel (NSCC) of the β-cell.[16] By the experiment using wild-type and TRPM-knockout type mice, imeglimin shows the action through NSCC. This process will bring the insulin secretion. Consequently, imeglimin may proceed the TRPM changes activation in the beta cells. Its mechanism is through nicotinamide adenine dinucleotide (NAD(+))/Cyclic adenosine diphosphate ribose (cADPR) production, which leads to potentiation of GSIS. Moreover, imeglimin would be involved in the calcium mobilization, that proceeds to the amplification function for insulin secretion.[17]

The mechanism mentioned above would be probable insulin secretion by imeglimin. Other pathways were known to be involved in the insulin secretion.[18] One is the stimulation by glucose, which leads to cyclic adenosine monophosphate (cAMP) activation, exchange protein by cAMP2A (exchange protein directly activated by cAMP 2 (Epac2A)) and TRPM2. These pathways bring the first phase of insulin secretion. Another is the stimulation by GLP-1, exendin-4 and glucose-dependent insulinotropic polypeptide (GIP), that may activate cAMP production as the same route of glucose pathway.

From these basic pharmacological mechanisms, imeglimin can contribute much for actual diabetic practice. As to chronic kidney disease (CKD), pharmacokinetic (PK) characteristics were studied.[19] Consequently, usual doses of 1000 mg of imeglimin twice daily can be given for case with estimated glomerular filtration rate (eGFR)>45 mL/min/1.73 m^2, and 500 mg twice is recommended for case with eGFR 15-45 mL/min/1.73 m^2. Study of imeglimin for patient with hepatic impairment was conducted by area under the curve (AUC) and maximum observed plasma concentration (C_{max}). The result showed 50% higher AUC and 30% higher C_{max}, indicating safe and well-tolerated administration of imeglimin for hepatic impairment.[20] Meta-analysis investigation was performed for 1555 cases from 8 studies. As a result, Imeglimin group showed decreased HbA1c and no significant changes in homeostasis model assessment-estimated insulin resistance (HOMA-IR), triglyceride, and HDL-C.[21] In summary, this article will be hopefully useful reference in the future diabetic research.

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