



# Latest Topics on Novel Imeglimin with Various Mechanism and Safety for Oral Hypoglycemic Agent (OHA)

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## Abstract

A novel imeglimin (Twymeeeg) was developed as an oral hypoglycemic agent (OHA) in Japan. It has clinically dual action for increasing insulin secretion and reducing insulin resistance, from Trials of IMeglimin for Efficacy and Safety (TIMES) 1-3. For basic medicine, imeglimin revealed reduction of apoptotic  $\beta$ -cell death with reduced expression for inflammation. Thus, imeglimin may increase insulin granules, bring beneficial efficacy on  $\beta$ -cell mitochondrial morphology and enhance directly insulin secretion from  $\beta$ -cell of the pancreas. Imeglimin has chemical moiety for metformin. Compared with both agents using experiments of dog and mice, lactic acidosis would be lower in imeglimin group.

**Keywords:** Imeglimin (Twymeeeg); Oral hypoglycemic agent (OHA); Trials of IMeglimin for Efficacy and Safety (TIMES); Mitochondrial morphology; Lactic acidosis

## Commentary Article

In the light of common disease across the world, non-communicable diseases (NCDs) have become crucial problems [1]. Among them, type 2 diabetes (T2D) has brought medical, social and pharmacological practice and research [2]. American Diabetes Association (ADA) has announced standard guideline for diabetes in 2022 [3]. For the development of oral hypoglycemic agents (OHAs) for T2D, effective kinds of meds are found such as glucagon-like-peptide 1 receptor agonist (GLP1-RA) [4] and also sodium-glucose cotransporter 2 inhibitor (SGLT2i) [5]. Recent topics of OHA would be novel introduction of imeglimin as brand name of Twymeeeg [6]. In this article, latest information of imeglimin will be described.

Imeglimin has been recently developed as OHA in Japan. Several large clinical trials of imeglimin were reported for human subjects. They include Trials of IMeglimin for Efficacy and Safety (TIMES) 1-3 [7]. A series of TIMES have shown clinical effect and safety of long-term treatment and also its effectiveness of combined therapy of other OHAs and insulin treatment [8,9]. The difference between imeglimin and previous OHAs may be

the existence of various mechanism of imeglimin. From clinical point of view, imeglimin has clinically dual efficacy of increasing insulin secretion function in response to glucose situation [10], and decreasing insulin resistance that is similar to metformin [11]. It also shows the preservation of the  $\beta$ -cell mass and reduction of  $\beta$ -cell apoptosis through modulating the pathway of ER stress [12,13].

Furthermore, imeglimin leads improving insulin sensitivity and also inhibiting glycogenesis [14]. As a matter of fact, imeglimin was reported to prevent heart failure associated with preserving the degree of ejection fraction [15], and to improve cardiac impaired function in the case of rat experiment [16]. Concerning the function of pancreas and liver, imeglimin can alleviate impaired function of mitochondria in  $\beta$ -cell and hepatocyte [14]. However, these phenomena are not always observed, and then these mechanisms have been not fully apparent yet.

In actual medical practice, imeglimin has been introduced for treating T2D patients and it has been drawing most attention in also diabetic research. For recent report, fundamental efficacy of imeglimin on  $\beta$ -cell of pancreas was evaluated [17]. Firstly, single administration of imeglimin has strengthened insulin secretory

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degree from  $\beta$ -cell and reduced blood glucose in T2D mice (db/db). Moreover, single imeglimin administration has augmented significant insulin secretion that was responsive to glucose stimuli from  $\beta$ -cell in non-diabetic mice (db/m). Secondly, it enhanced insulin secretion and improved blood glucose variability in diabetic mice (db/db) during GTT associated with imeglimin for 4 weeks. Using electron microscope, imeglimin has brought beneficial efficacy on morphological image of  $\beta$ -cell mitochondria and more insulin granules in T2D and KK-Ay mice [17]. For surprising results, imeglimin revealed reduction of apoptotic  $\beta$ -cell death that was found with reduced expression related with inflammation and apoptosis of  $\beta$ -cell. From mentioned above, imeglimin may enhance directly insulin secretion from  $\beta$ -cell, increase insulin granules, bring beneficial efficacy on  $\beta$ -cell mitochondrial morphology and decrease apoptotic  $\beta$ -cell death in T2D mice.

From pharmacological action point of view, the detail mechanism of imeglimin was not completely clear. However, it seems to be involved in the enhanced situation of glucose-stimulated insulin secretion (GSIS). During the GSIS process, transient receptor potential melastatin 2 (TRPM2) channel can be activated, and it can promote the depolarization of plasma membrane as a non-selective cation channel (NSCCs) in  $\beta$ -cell of the pancreas [18]. In the experiments of wild-type and TRPM2-knockout (KO) mice, imeglimin can promote the function through NSCC. This is related to the releasing efficacy of insulin from  $\beta$ -cell. Imeglimin causes the activation of TRPM2 channels of  $\beta$ -cell through the mechanism of  $\text{NAD}^+$  /cADPR production that leads to GSIS potentiation. In addition, imeglimin contributes to calcium mobilization through the amplified pathway for insulin secretion from  $\beta$ - cell [14]. Concerning the categorization of OHAs, imeglimin become the first agent for tetrahydrotriazine-containing class as glimins [19].

In the actual diabetic practice, clinical efficacy of imeglimin was recently investigated [20]. The protocol included 32 cases of T2D and detail measurement of blood glucose using continuous glucose monitoring (CGM). These data were gathered for more than 4 weeks. As a result, imeglimin has improved significantly mean glucose levels (from 159 mg/dL to 142 mg/dL,  $p < 0.001$ ), TIR (67.9% to 79.5%,  $p < 0.001$  and TAR (29.4% to 17.9%,  $p < 0.001$ ). Consequently, imeglimin can apparently shift daily glucose profile to appropriate range in T2D cases, which indicates better glycemic variability in a short period [20].

From pharmacokinetic point of view, detail blood concentration of imeglimin was measured in two groups of Japanese and Caucasian healthy individuals [21]. The methods included two randomized placebo-controlled phase 1 clinical studies, in which single for 250-8000mg and multiple administration (500-2000mg twice a day) were included. The half-lives ( $t_{1/2}$ ) showed dose-dependent manner and their means were 4.5-12 h in Japanese and

9.0-20 h for Caucasians. Exposures were similar between two groups with  $< 20\%$  difference, but Japanese tended to have slightly higher exposure value. From these results, imeglimin showed acceptable tolerability profile and safety, associated with mild gastrointestinal adverse events (GIAEs).

Imeglimin has molecular similarity and chemical moiety for metformin, and has modulated the activity of mitochondrial complex I [22]. Then, it may show a potential mechanism concerning metformin-related lactate accumulation. Comparative studies were conducted between imeglimin and metformin for experiments. For dog model with major surgery, both agents were provided. As a result, only metformin caused lactate accumulation with pH decrease leading to lactic acidosis with severe state. For rat model with gentamycin-induced renal failure, only metformin brought high lactatemia with high h+ concentrations leading to mortality of higher amounts. Consequently, the results supposed that lactic acidosis by imeglimin may be lower than that of metformin [22].

In summary, latest information concerning imeglimin has been described for basic medicine and clinical practice. Imeglimin as brand name Twymeeeg may become a first-line agent for T2D because of its dual mechanism and safety. This article becomes hopefully a reference for future diabetic practice and research.

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