SUNTEXT REVIEWS

SunText Review of Case Reports & Images
ISSN: 2766-4589

Open Access
Commentary Article
Volume 3:4

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

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Received date: 15 October 2022; **Accepted date:** 21 October 2022; **Published date:** 27 October 2022

Citation: Bando H (2022) Latest Topics on Novel Imeglimin with Various Mechanism and Safety for Oral Hypoglycemic Agent (OHA). SunText Rev Case Rep Image 3(4): 158.

DOI: https://doi.org/10.51737/2766-4589.2022.058

Abstract

A novel imeglimin (Twymeeg) 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 β-cell death with reduced expression for inflammation. Thus, imeglimin may increase insulin granules, bring beneficial efficacy on β-cell mitochondrial morphology and enhance directly insulin secretion from β-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 (Twymeeg); 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 Twymeeg [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 β-cell mass and reduction of β-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 β-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 β-cell of pancreas was evaluated [17]. Firstly, single administration of imeglimin has strengthened insulin secretory

degree from β-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 β-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 β-cell mitochondria and more insulin granules in T2D and KK-Ay mice [17]. For surprising results, imeglimin revealed reduction of apoptotic β-cell death that was found with reduced expression related with inflammation and apoptosis of β-cell. From mentioned above, imeglimin may enhance directly insulin secretion from β-cell, increase insulin granules, bring beneficial efficacy on β-cell mitochondrial morphology and decrease apoptotic β-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 β-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 β-cell. Imeglimin causes the activation of TRPM2 channels of β-cell through the mechanism of NAD+ /cADPR production that leads to GSIS potentiation. In addition, imeglimin contributes to calcium mobilization through the amplificated pathway for insulin secretion from β- 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 Jananese 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 (t1/2) 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 Twymeeg 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.

References

1. Yeung P, Severinsen C, Good G, O'Donoghue K. Social environment and quality of life among older people with diabetes and multiple chronic illnesses in New Zealand: Intermediary effects of psychosocial support and constraints. Disabil Rehabil. 2022; 44: 768-780.
2. Ogurtsova K, Guariguata L, Barengo NC, Ruiz PL, Sacre JW, Karuranga S, et al. IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. Diabetes Res Clin Pract. 2022; 183: 109118.
3. ADA Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 45: S125-S143.
4. Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingvay I, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. Diabetes Obes Metab. 2022; 24: 94-105.
5. American Diabetes Association; Standards of Medical Care in Diabetes - 2022 Abridged for Primary Care Providers. Clin Diabetes. 2022; 40: 10-38.
6. Le P, Ayers G, Misra-Hebert AD, Herzig SJ, Herman WH, Shaker VA, et al. Adherence to the ADA's Glycemic Goals in the Treatment of Diabetes among Older Americans, 2001-2018. Diabetes Care. 2022; 25: dc211507.
7. Dubourg J, Fouqueray P, Thang C, Grouin JM, Ueki K. Efficacy and Safety of Imeglimin Monotherapy Versus Placebo in Japanese Patients With Type 2 Diabetes (TIMES 1): A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Phase 3 Trial. Diabetes Care. 2021; 44: 952-959.

8. Dubourg J, Fouqueray P, Quinslot D, Grouin JM, Kaku K. Long-term safety and efficacy of imeglimin as monotherapy or in combination with existing antidiabetic agents in Japanese patients with type 2 diabetes (TIMES 2): A 52-week, open-label, multicentre phase 3 trial. Diabetes Obes Metab. 2022; 24: 609-619.
9. Reilhac C, Dubourg J, Thang C, Grouin JM, Fouqueray P, Watada H. Efficacy and safety of imeglimin add-on to insulin monotherapy in Japanese patients with type 2 diabetes (TIMES 3): A randomized, double-blind, placebo-controlled phase 3 trial with a 36-week open-label extension period. Diabetes Obes Metab. 2022; 24: 838-848.
10. Hallakou-Bozec S, Kergoat M, Fouqueray P, Bolze S, Moller DE. Imeglimin amplifies glucose-stimulated insulin release from diabetic islets via a distinct mechanism of action. PLoS One. 2021; 16: e0241651.
11. Shah N, Abdalla MA, Deshmukh H, Sathyapalan T. Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice. Ther Adv Endocrinol Metab. 2021; 12: 20420188211042145.
12. Hallakou-Bozec S, Kergoat M, Moller DE, Bolze S. Imeglimin preserves islet β-cell mass in Type 2 diabetic ZDF rats. Endocrinol Diabetes Metab. 2020; 4: e00193.
13. Li J, Inoue R, Togashi Y, Okuyama T, Satoh A, Kyohara M, et al. Imeglimin Ameliorates β-Cell Apoptosis by Modulating the Endoplasmic Reticulum Homeostasis Pathway. Diabetes. 2022; 71: 424-439.
14. Hallakou-Bozec S. Mechanism of action of Imeglimin: A novel therapeutic agent for type 2 diabetes. Diabetes Obes. Metab. 2021; 23: 664-673.
15. Kitakata H, Endo J, Hashimoto S, Mizuno E, Moriyama H, Shirakawa K, et al. Imeglimin prevents heart failure with preserved ejection fraction by recovering the impaired unfolded protein response in mice subjected to cardiometabolic stress. Biochem. Biophys. Res. Commun. 2021; 572: 185-190.
16. Lachaux M, Soulié M, Hamzaoui M, Bailly A, Nicol L, Rémy-Jouet I, et al. Short-and long-term administration of imeglimin counters cardiorenal dysfunction in a rat model of metabolic syndrome. Endocrinol. Diabetes Metab. 2020; 3: e00128.
17. Sanada J, Obata A, Fushimi Y, Kimura T, Shimoda M, Ikeda T, et al. Imeglimin exerts favorable effects on pancreatic β-cells by improving morphology in mitochondria and increasing the number of insulin granules. Sci Rep. 2022; 12: 13220.
18. Funazaki S, Yoshida M, Yamada H, Kakei M, Kawakami M, Nagashima S, et al. A novel mechanism of imeglimin-mediated insulin secretion via the cADPR-TRP channel pathway. J Diabetes Investig. 2021.
19. Giruzzi M. Imeglimin. Clin Diabetes; 39: 439-440.
20. Oda T, Satoh M, Nagasawa K, Sasaki A, Hasegawa Y, Takebe N, Ishigaki Y. The Effects of Imeglimin on the Daily Glycemic Profile Evaluated by Intermittently Scanned Continuous Glucose Monitoring: Retrospective, Single-Center, Observational Study. Diabetes Ther. 2022; 13: 1635-1643.
21. Fouqueray P, Chevalier C, Bolze S. Pharmacokinetics of Imeglimin in Caucasian and Japanese Healthy Subjects. Clin Drug Investig. 2022; 42: 721-732.
22. Theurey P, Vial G, Fontaine E, Monternier PA, Fouqueray P, Bolze S, et al. Reduced lactic acidosis risk with Imeglimin: Comparison with Metformin. Physiol Rep. 2022; 10: e15151.