SUNTEXT REVIEWS

SunText Review of Pharmaceutical Sciences
ISSN: 2766-5232

Open Access
Commentary Article
Volume 3:1

Pharmacological Characteristic of Imeglimin (Twymeeg) For Dual Mechanism to Insulin Secretion and Resistance

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Received date: 14 January 2022; **Accepted date:** 17 January 2022; **Published date:** 23 January 2022

Citation: Iwatsuki N, Bando H, Okada M (2022). Pharmacological Characteristic of Imeglimin (Twymeeg) For Dual Mechanism to Insulin Secretion and Resistance. SunText Rev Pharm Sci 3(1): 113.

DOI: https://doi.org/10.51737/2766-5232.2022.013

Abstract

Latest Standards of Medical Care in Diabetes was presented in January 2022. Among oral hypoglycemic agents (OHAs), imeglimin has been topic for a novel agent for type 2 diabetes mellitus (T2DM). Pharmacologically, imeglimin is a cyclic molecule including triazine ring. It has both pharmacological mechanism of increased insulin action and elevation of glucose-stimulated insulin secretion (GSIS). Clinically, it showed HbA1c reduction for 0.46% by monotherapy and 0.56-0.92% by combined therapy with other OHAs. From compared administration of 500mg, 1000mg and 1500mg, 1000mg twice doses would be adequate. No remarkable treatment-emergent adverse events (TEAEs) were found for treatment of imeglimin.

Keywords: Oral hypoglycemic agents (OHAs); Imeglimin; type 2 diabetes mellitus (T2DM); Glucose-stimulated insulin secretion (GSIS); Treatment-emergent adverse events (TEAEs); American Diabetes Association (ADA)

Introduction

For useful guideline, the Standards of Medical Care in Diabetes was presented on Jan 1, 2022 from American Diabetes Association (ADA) [1]. The number of patients with diabetes mellitus (DM) has been increasing, particularly in developing countries compared with developed countries [2]. DM has brought various impaired function including microvascular and macrovascular angiopathy. These chronic multifaced situation will give many patients remarkable physical detriment. From recent statistics, 463 million diabetic patients have been present in the world, and 90% of them show T2DM [3]. Concerning the pathophysiology of T2DM, both of decreased insulin secretion and increased insulin resistance (IR) are involved in the onset and exacerbation. IR means the impairment of adequate response to insulin leading to disturbed metabolic homeostasis. For these pathologies, mitochondria in the cell are involved in the impaired mechanisms of T2DM and IR. IR may affect mitochondrial function, and liver and skeletal muscle have high impact on glucose homeostasis for whole body [4].

From pharmacological point of view, some anti-diabetic agents for improving IR have been used until now. Phenformin and metformin are well-known biguanide agents which were provided to T2DM for reducing IR [5]. Phenformin was withdrawn from the market due to lactic acidosis. In contrast, metformin has been still widely prescribed as first-in-class agent for T2DM. It is one of the most prevalent oral hypoglycemic agents (OHAs), and it seems to have desirable pharmacokinetics. Metformin-induced lactic acidosis has been very rare, unless the patient has severe impaired renal or hepatic function. As related to metformin, a novel molecule for OHA has been produced for imeglimin by Poxel and Sumitomo Dainippon Pharma in Japan [6]. It is fundamentally basic small molecule like metformin. In contrast, it is a cyclic molecule including a triazine ring, which is unlike metformin. For the product of imeglimin, it can be synthesized from metformin as a precursor agent through single step chemical reaction [5]. From recent report, imeglimin improve the function of mitochondria. When provided by combined these two agents, it will contribute better glycemic control for T2DM [7].

Imeglimin will become possibly a first-in-class OHA with higher evaluation. Some phase-3 trials were completed with satisfactory evidence of clinical efficacy and safety. It has dual action mechanism for its characteristics. They are i) increased insulin action associated with probable inhibition of hepatic glucose output and increase of insulin signaling in both of muscle and liver, ii) elevation of glucose-stimulated insulin secretion (GSIS) associated with beta-cell mass preservation [8]. From molecular and cellular points of view, its mechanism would involve the improvement of mitochondrial dysfunction, which are commonly found for pathogenesis of T2DM. As a whole, imeglimin seems to have a key for impaired cellular energy metabolism observed in T2DM. These potentials of action mode may be unique and different from previous categorization, such as sulphonylureas, biguanides and glucagon-like peptide-1 receptor agonists (GLP-1Ras). For the first agent in a novel category of OHA, the effect and safety of imeglimin was investigated. It was conducted for double-blind, randomized, parallel-group, placebo-controlled study as phase 3 trial in 30 multi-center research in Japan [9]. The subjects were patients with T2DM for HbA1c 7-10% (n=106), and control cases (n=107). Methods were randomly provided to either imeglimin or matched placebo for 6 months. As a result, the adjusted mean difference of change of HbA1c at 6 months was -0.87% (95% CI -1.04 to -0.69, $p<0.0001$). Regarding adverse effects associated with reports ≥1 adverse event, imeglimin group vs placebo group showed 44.3% vs 44.9%, respectively. From these, imeglimin significantly improved glucose variability with safety profile compared with placebo.

Concerning OHA for T2DM, it is important to investigate the pharmacokinetic (PK) characteristics for renal function, chronic kidney disease (CKD), diabetic kidney disease (DKD) and renal failure. Imeglimin has mainly excretion without changed metabolism through the kidneys [10]. The recommended dose was studied by area under the curve (AUC) for analyzed data of blood concentration. As a result, 500mg provided twice daily are adequate for patients with eGFR 15-45 mL/min/1.73 m^2, and 1000mg provided twice a daily are suitable for eGFR > 45 mL/min/1.73 m^2. Further investigation will be required in the case of 1500 mg twice daily in the future. By searching for randomized controlled trials (RCTs) of imeglimin studies, meta-analysis was conducted [11]. The method included the analysis of PubMed, Google Scholar, Cochrane Library Wiley and Scopus until April 2021. The report was summarized from 8 studies of 1555 subjects. Results included the comparison of imeglimin group and control group. Significantly lower values of HbA1c and blood glucose were found in imeglimin group. On the other hand, no significant differences were observed about LDL-C, HDL-C, TG and homeostasis model assessment-insulin resistance (HOMA-IR). Imeglimin will be widely used in clinical practice, where a several research would be necessary for monotherapy and combination therapy of imeglimin [9].

Clinical effect of imeglimin for lowering HbA1c was investigated for half year [12]. Subjects included 299 T2DM cases, they were divided into some groups with different doses. At 6 months, HbA1c decrease compared with that of placebo was -0.52%, -0.94% and -1.00% for imeglimin as 500mg x 2, 1000mg x 2, and 1500 mg x 2, respectively. From marginal increase between 1000mg and 1500mg, 1000mg administration twice a day was selected for subsequent phase studies. Regarding treatment-emergent adverse events (TEAEs), the result was 68.0%, 62.2%, 73.3%, 68.0% for subjects provided imeglimin as 500mg, 1000mg, 1500 mg and placebo, respectively. Successively, 52-week study was reported for efficacy of imeglimin for monotherapy and combined therapy with other agents [13]. The cases were 714 T2DM patients. Combined agents included biguanide, DPP4-I, GLP1-RA, SGLT2i, glinide and alfa-GI. No remarkable TEAEs, physical or laboratory exams were found. After 52 weeks, HbA1c was decreased 0.46% by monotherapy, and 0.56-0.92% by combined therapy. Most effective reduction of 0.92% was found by imeglimine and DPP4i. Thus, imeglimin of monotherapy and combined therapy seemed to be effective.

In summary, imeglimin as novel OHA category was described. It seems to be prescribed more in the diabetic practice. Further research will be expected for pharmacological mechanism and clinical efficacy.

Conflict of Interest

The author declares no conflict of interest.

Funding

There was no funding received for this paper.

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