



Recent Research Development of Imeglimin as Oral Hypoglycemic Agent (OHA)

Hiroshi Bando^{1,2ID*}

¹Medical Research/Tokushima University, Tokushima, Japan

²Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan

Corresponding Author: **Hiroshi Bando** [ORCID iD](#)

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;

Email: pianomed@bronze.ocn.ne.jp

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Abstract

As a novel oral hypoglycemic agent (OHA), imeglimin (Twymeeeg) has recently been introduced into clinical practice. It has shown improved glucose variability via a mitochondrial mechanism. Adequate daily doses identified in several investigations are 1000 mg or 1500 mg twice a day (BID). Consequently, 1000 mg BID seems to be recommended in light of tolerability, safety, and gastrointestinal adverse effects (GI-AEs). For hemodialysis (HD) patients, 500 mg/day was tried with clinical effect. To minimize GI-AEs, novel research has explored the adaptation of nanofiber disintegration for the drug delivery system (DDS). This method takes only 2 +/- 1 seconds via buccal route administration.

Keywords

Oral Hypoglycemic Agent, Imeglimin, Twymeeeg, Gastrointestinal Adverse Effects, Hemodialysis, Drug Delivery System

Abbreviations

OHA: Oral Hypoglycemic Agent; GI-AEs: Gastrointestinal Adverse Effects; HD: Hemodialysis; DDS: Drug Delivery System

Commentary

From global and medical points of view, type 2 diabetes (T2D) has been a significant burden in every country [1]. Concerning the statistics of T2D, the age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), and other factors have increased. About 6% of the global population seems to be affected by T2D [2]. The global prevalence of T2D is expected to increase to 7% by 2030. Furthermore, the age-standardized mortality rate (ASMR) was 18.5 deaths per 100,000 [3].

Regarding the standard treatment of T2D, the American Diabetes Association (ADA) announced guidelines in January 2024 [4]. Among the treatments, several oral hypoglycemic agents (OHAs) have been introduced into clinical practice. As a novel OHA, imeglimin can stimulate both insulin secretion in a glucose-dependent manner and improve insulin sensitivity [5]. It targets mitochondrial bioenergetics, regulates respiratory chain complex activities, and reduces the production of reactive oxygen species (ROS) [6]. Additionally, it shows cell protective effects,

such as preservation of β -cell mass, increasing insulin granules, and ameliorating β -cell apoptosis, among others [7,8]. Previous randomized controlled trials (RCTs) have studied the efficacy and safety of imeglimin [9]. The dose-by-dose analyses revealed some limitations, as only twice-daily (BID) doses of 1000 mg or 1500 mg were evaluated. Some investigations studied monotherapy and combination trials, with the adequate dose still under discussion [10].

The purpose of the recent study was to evaluate the efficacy, tolerability, and safety of imeglimin [11]. It was administered as monotherapy and/or adjunctive treatment in T2D patients. Two groups were compared for risk ratios and/or weighted mean differences (WMD). The primary outcome showed changes in HbA_{1c}, and secondary outcomes showed other effects-related data, specific adverse events, body weight changes, and lipid changes. As a result, 9 RCTs were analyzed (n=1655). Analyses by dose in BID showed 1000 mg (517 cases, n=3), 1500 mg (448 cases, n=5), and 2000 mg (149 cases, n=1). Adjunctive imeglimin treatment significantly improved HbA_{1c} for 1000 mg and 1500 mg. For subgroup analysis, the primary outcome showed a clinical effect even if the case had CKD.

From several investigations of imeglimin, the standard dose seemed to be 1000 mg BID. Applying this dose of imeglimin, 24-week placebo-controlled, randomized, double-blind studies for T2D cases were conducted [12]. Outcomes were obtained as least squares mean (LSM) changes in HbA_{1c} for 6 months, associated with several factors including clinical characteristics, demographics, and comorbidities. As a result, a significant difference was found for LSM changes in HbA_{1c} between the imeglimin group and the placebo group. In detail, significant separation of HbA_{1c} in each group was found at 4 weeks, and it persisted through 24 weeks. Clinical effect and safety of imeglimin were observed across the groups, regardless of baseline clinical demographic characteristics.

Imeglimin is notable for its novel pharmacological mechanism via the mitochondrial pathway. It can target three organs related to diabetic pathogenesis:

the pancreas, skeletal muscles, and liver. Using several keywords, famous databases were investigated, including Medline, Scopus, CENTRAL, and ClinicalTrials.gov databases for adequate literature [13]. The study included the mean difference (MD) and dichotomous variables for odds ratio (OR). As a result, remarkable HbA_{1c} reduction was found in the case of 1000 mg and 1500 mg BID. These benefits continued when imeglimin was taken as combined treatment. When imeglimin doses were elevated, gastrointestinal adverse effects (GI-AEs) were found. Consequently, imeglimin 1000 mg BID would offer optimal efficacy for glucose variability associated with safety profiles.

For the latest report, an investigation to elucidate the efficacy and safety of imeglimin for HD cases was conducted [14]. The provided dose was 500 mg a day, a quarter of the usual amount. As a result, fasting blood glucose showed a significant decrease ($p=0.037$), and alanine aminotransferase (ALT) also showed a significant decrease ($p=0.006$). HbA_{1c} and TG tended to be lower without statistical difference. Consequently, imeglimin would be effective and well-tolerated, without GI-AEs. Thus, clinical response will become apparent concerning the pharmacological indication of imeglimin for T2D and HD cases.

In the latest review, imeglimin has recently become available and prevalent in East Asian countries as a novel class of OHA known as glimins, which include a tetrahydrotriazine ring [15]. It can intensify the insulin action mechanism by inhibiting hepatic glucose output and recovering altered insulin signaling in myocytes (skeletal muscle) and hepatocytes (liver). Additionally, it can preserve beta-cell mass and strengthen glucose-stimulated insulin secretion (GSIS). From several phase III trials, the recommended dose of imeglimin would be 1000 mg twice a day.

Regarding the latest case report of imeglimin, a T2D case showed a remarkable response of HbA_{1c} reduction from 8.4% to 6.5% over 5 months [16]. The pulse wave velocity (PWV) exam revealed stable values of the cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) for years. Thus, imeglimin may not only help maintain HbA_{1c} levels but also maintain arteriosclerosis by its mechanism of mitochondrial function.

Commentary

In the research of systematic data from PubMed, a meta-analysis was performed on the treatment of imeglimin for T2D [17]. The target was double-blind RCTs for imeglimin 1000 mg BID. As a result, 7 phase II and 3 phase III trials were found for analysis. By monotherapy investigation (n=360), imeglimin 1000 mg BID showed a -0.9% reduction in HbA_{1c} compared to the placebo group. When limited to pooled meta-analysis (n=574), significant HbA_{1c} reduction of 1000 mg BID was -0.79% compared to the placebo group.

However, imeglimin sometimes causes gastrointestinal adverse effects (GI-AEs). A novel investigation aimed to fabricate a formulation for imeglimin loaded into electrospun nanofibers [18]. It is delivered via the buccal cavity to overcome the current GI-AEs and provide a novel convenient route of administration. By X-ray diffraction (XRD) results, solid dispersion of imeglimin showed improved bioavailability. The nanofiber disintegration took only 2 +/- 1 seconds, indicating rapid disintegration ability. Consequently, nanofibers will potentially provide a novel buccal route of administration in the future.

In summary, the latest topics on imeglimin were described in this article. It is expected that these will contribute to further development in diabetic research and treatment.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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