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Imeglimin: a new antidiabetic drug with potential for the treatment of patients with type 2 diabetes

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Abstract

Imeglimin (IMEG) is the first drug of the "glimin" group. Glimin is a new group of hypoglycaemic drugs for the treatment of patients with type 2 diabetes mellitus (T2DM). The chemical structure and action mechanism of the drug are presented in the paper. Imeglimin is unique and different in action compared to other hypoglycaemic drugs. Imeglimin has been shown to have a beneficial effect on 3 key pathogenetic elements of T2DM, i.e., 1. increased gluconeogenesis, 2. inadequate glucose-induced insulin secretion by beta cells, and 3. peripheral insulin resistance. The peak effect on fasting plasma glucose (FPG) and glycated haemoglobin (HbA_{1c}) levels of IMEG is reached after 16 weeks of treatment. Subjects receiving IMEG at 1000- and 1500-mg doses twice daily also achieved significantly greater reductions in fasting plasma glucose (FPG) levels at week 24 compared to the placebo group (IMEG in humans causes increased insulin secretion as well as reductions in fasting plasma glucose and glycated haemoglobin). This paper also presents the pharmacokinetics of IMEG action, clinical evidence for its efficacy, results of phase II and III clinical trials, and drug tolerability. Our paper seems to show that IMEG, with its novel mechanism of action, has a chance to improve treatment results in a larger population of T2DM patients. **(Endokrynol Pol 2022; 73 (2): 361–370)**

Key words: *imeglimin; type 2 diabetes mellitus*

Introduction

Type 2 diabetes mellitus (T2DM), dubbed the epidemic of the 21st century, continues to pose a major medical, social, and economic challenge. The number of patients with disorders of carbohydrate metabolism is increasing steadily, and the problem is affecting younger and younger people [1]. According to the latest International Diabetes Federation (IDF) 2019 estimates, the number of people with diabetes worldwide will increase from 463 to 700 million by 2045 [1]. It is estimated that type 2 diabetes is diagnosed on average 10 years after the development of the disease, and a significant proportion of patients already have severe complications of micro- and/or macroangiopathy at the time of diagnosis [2]. The presence of chronic complications of diabetes is associated with a significant deterioration of quality of life and reduced survival time (higher mortality in this group of patients). The main cause of death in diabetic patients is cardiovascular disease. Microangiopathy-like complications lead to blindness, limb amputation, and kidney failure. Early detection of carbohydrate disturbances and intensive treatment are very important. The essence of diabetes treatment is multidirectional therapeutic intervention, including both carbohydrate and lipid control and normalization of blood pressure. This strategy has been shown to be beneficial for diabetic patients and contributes to the reduction of total mortality, cardiovascular deaths, and the risk of microangiopathy [3, 4].

In recent years, several new drugs have been added to the treatment of T2DM, and others are being intensively studied in experimental or clinical trials, producing not only hypoglycaemic effects but also affecting metabolic comorbidities. These include the following:

— type II activin receptor modulators (bimagrumab);
— amylin or dual amylin-calcitonin receptor agonists (pramlintide — amylin agonist);
— adenosine monophosphate-activated protein kinase (AMPK) activator (A-769,662, thienopyridone);
— fibroblast growth factor 21 analogues (pegbelfermin), fructose-1,6-bisphosphatase inhibitors (VK0612; MB07803);
— novel GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide, lyxisenatide, semaglutide, efpeglenatide, glutazumab, ITCA-650);
— sodium-glucose co-transporters (SGLT-1 and -2) (SGLT-1 — licogliflozin, sotagliflozin and LX2761;

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SGLT-2 — canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin and tofogliflozin) [5].

Imeglimin — the first oral glimin drug

Imeglimin (IMEG) is the first of the group of oral tetrahydrotriazine compounds, glimin, which has shown hypoglycaemic activity in several studies [6–13]. The chemical name of IMEG is (6R)-(+)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5-triazine hydrochloride. Imeglimin is an inhibitor of oxidative-phosphorylation chemical reactions taking place inside the mitochondria of cells. Thus, it exerts a strong metabolic effect in eukaryotic cells [7, 14, 15]. The molecular weight of IMEG is 155.2 Da. The chemical structure of IMEG is shown in Figure 1.

Imeglimin is a drug intended for oral administration. The half-life has been shown to be 10–20 hours in healthy volunteers [6, 16]. Until now, only a few studies that report on the absorption, metabolism, and elimination of IMEG from the body have been conducted. After oral administration of IMEG, its absorption occurs by both passive and active transport and lasts up to 6 hours [6]. The bioavailability after oral administration of IMEG drug ranges from 50 to 20%, and it depends on the dose of the drug administered (100–6000 mg) –it decreases with the drug dose increasing [16, 17]. Imeglimin bonds to plasma proteins only to a small extent (1–8%) [18]. Imeglimin is eliminated from the body in a biphasic manner with an initial rapid phase followed by a slower elimination phase. The hepatic metabolism of IMEG is very low, so it is excreted almost completely unchanged in urine [16]. The amount of IMEG excreted in the urine corresponds to the amount absorbed from the gastrointestinal tract. The pharmacokinetics of IMEG does not differ in Caucasian and Japanese individuals [19, 20].

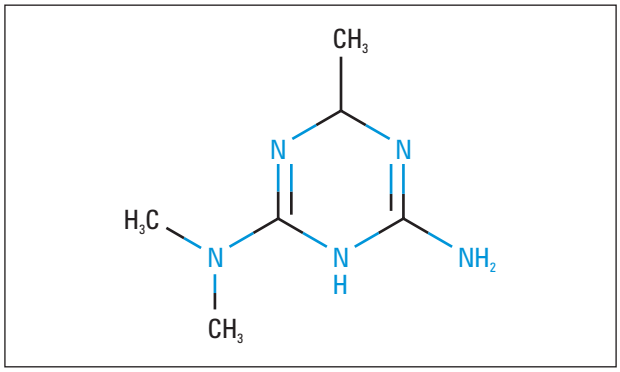

Figure 1. *Chemical structure of imeglimin (IMEG)*

IMEG — probable mechanism of action

Imeglimin is unique and different in action compared to other hypoglycaemic drugs. It acts by both improving insulin action and reversing pancreatic β-cell dysfunction [14, 15]. The results of this study suggest that IMEG exerts potent antihyperglycaemic effects and is able to normalize glucose homeostasis by affecting several metabolic pathways [21, 22, 8]. Among the actions of IMEG are the following:

— effects on insulin sensitivity;
— effects on gluconeogenesis;
— effects on mitochondrial function;
— effects on pancreatic function;
— antioxidant effects.

We will present the collected information in the text and in Figure 2.

Effects on insulin sensitivity

The mechanisms underlying the improvement in insulin sensitivity after IMEG administration are not well understood; they may be due to effects on glucose transporter-4 (Glut-4) and insulin receptor autophosphorylation (IRS). Pacini et al. [8] showed that IMEG has

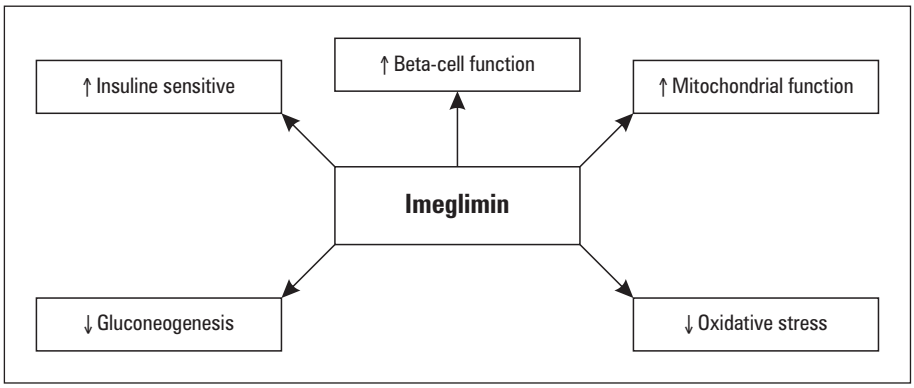

Figure 2. *Probable molecular mechanisms of the effects of imeglimin (IMEG) on glucose homeostasis (according to Yaribeygi et al. [15] with own modification).*

anti-apoptotic effects, stimulates function and insulin sensitivity in β-cells in T2DM patients. The mechanisms underlying the improvement in insulin sensitivity after IMEG administration are not well understood.

Vial et al. [23] in an experimental animal model showed that IMEG facilitates signal transduction through insulin by enhancing Akt (protein kinase B) phosphorylation and thereby increasing insulin sensitivity.

Lablanche et al. [24] showed that IMEG inhibits β-cell apoptosis by decreasing glucotoxicity through a mitochondrial-dependent mechanism and increases β-cell mass through an inhibitory effect on the permeability transition pore (PTP) of mitochondria. Imeglimin prevents PTP opening and cell death induced by high concentrations of glucose or fructose in both insulin cell line (INS-1) cells and human pancreatic islet cells. The authors assessed the status of PTPs in cells by confocal microscopy, measuring mitochondrial membrane potential (TMRM) and nicotinamide adenine dinucleotide phosphate hydrogen (NAD(P)H) by autofluorescence. Cell viability was measured by flow cytometry. Cell viability was significantly decreased ($p < 0.05$) in cells exposed for 72 h to glucose (30 mM) (76 ± 5% and 47 ± 18% in INS-1 cells and human pancreatic islet cells, respectively) and to fructose (2.5 mM) (78 ± 3% and 35 ± 11% in INS-1 cells and human pancreatic islet cells, respectively) but remained unchanged when cells were preincubated with 100 μM IMEG (in 30 mM glucose: 94 ± 3% and 98 ± 3%/in 2.5 mM fructose: 96 ± 4% and 79 ± 6% in INS-1 cells and human pancreatic islet cells, respectively).

Effects on gluconeogenesis

Gluconeogenesis is the enzymatic process of converting non-sugar precursors, such as glucogenic amino acids, glycerol, or lactate into glucose. This process occurs mainly in hepatocytes. Hepatic gluconeogenesis is excessive in diabetic patients [25]. Imeglimin has been used to reduce hepatic gluconeogenesis [21]. Fouqueray et al. showed that IMEG inhibits gluconeogenesis by decreasing phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) activities in isolated rat hepatocytes [26], while Vial et al. showed that IMEG reduces hepatic gluconeogenesis by affecting a pathway dependent on mitochondrial function [27]. Also, Wagner et al. [28] showed that IMEG improves glucose homeostasis by modulating hepatic gluconeogenesis in diabetic mice. Imeglimin reduced blood glucose levels (165 *vs.* 192 mg/dL, $p = 0.007$) by increasing glucose oxidation, which coincided with partial restoration of gluconeogenesis (0.38 *vs.* 0.31 mg/hr, $p = 0.032$), hepatic mitochondrial activity (oxidative phosphorylation [136 *vs.* 116] pmol O_2/second/mg tissue, $p = 0.003$), and maximal oxidative capacity (166 *vs.* 147 pmol O_2/second/mg tissue, $p = 0.064$). Imeglimin increased hepatic expression of heme oxygenase 1 (HMOX1, HO-1, decreased hepatic expression of Bax protein and suppressed NF-κB activation (all $p < 0.001$).

Effects on mitochondrial function

At the molecular level, mitochondrial dysfunction is one of the main pathogenetic features of T2DM contributing to β-cell defect [29] and insulin resistance [30]. The role of mitochondria is highlighted by the existence of rare hereditary forms of DM that result from mutations in mitochondrial DNA [31]. Deficits in oxidative metabolism and reduced ATP production lead to impaired fatty acid oxidation, which causes lipid accumulation in cells [32]. Defects in mitochondrial respiratory chain function result in excessive reactive oxygen species (ROS) formation, which is one of the pathogenetic links of T2DM [33]. Nicotinamide adenine dinucleotide (NAD+) is essential for normal mitochondrial function [34], and metabolic disorders, including obesity and T2DM, are associated with altered NAD+ metabolism and decreased NAD+ levels [35]. Mitochondrial dysfunction occurring in DM impairs in an insulin-independent manner the function of cells including adipocytes, cardiomyocytes, and myocytes for an adequate insulin concentration-dependent response [36]. It also negatively affects pancreatic islet β-cells by reducing insulin production and release in response to glucose. Therefore, preserving mitochondrial function is an important aspect in the treatment of diabetes [37].

Imeglimin improves mitochondrial function by modulating the activity of the mitochondrial respiratory chain complex while reducing the production of ROS, and it delays the opening of mitochondrial PTPs under oxidative stress [23]. Vial et al. in an animal model showed that IMEG improved mitochondrial function by modulating the activity of complexes I and III, stimulating mitochondrial fatty acid oxidation, and by normalizing mitochondrial phospholipid composition, which affects glucose homeostasis [23]. In experimental studies, IMEG increased the activity of enzymes involved in fatty acid metabolism, such as cluster of diferentiation-36/fatty acid translocase and 3-hydroxyacylcoenzyme A (CoA) dehydrogenase (HAD). This indicates increased fatty acid oxidation. Increased fatty acid oxidation leads to the production of acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle and increases flux through complex II (CII) and complex III (CIII). Reverse electron transfer (RET) from CII to complex I (CI) is decreased, resulting in decreased production of reactive oxygen species (ROS) [38].

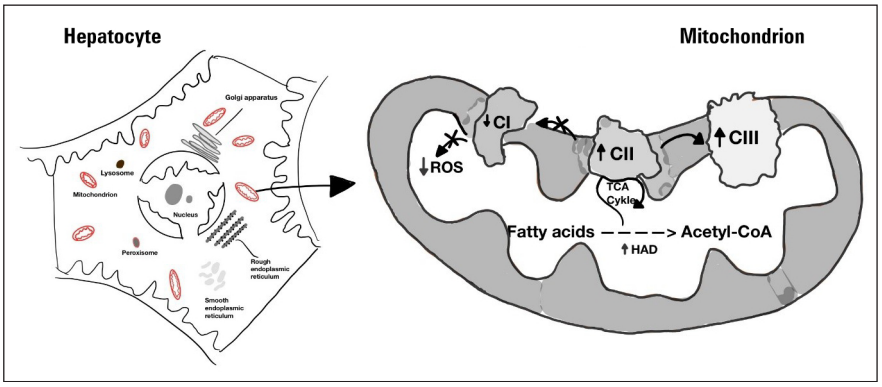

Figure 3. *Proposed mechanisms by which imeglimin (IMEG) improves mitochondrial bioenergetics (according to Konkwo et al. [38] with own modification)*

The proposed mechanism by which IMEG improves mitochondrial bioenergetics is presented in Figure 3.

Effects on pancreatic function

Perry et al. [7], conducting studies in an animal model, showed that IMEG improves glycaemia by directly stimulating insulin secretion and improving pancreatic function. In a metabolic cage study, the authors showed that IMEG does not alter body weight, basal energy expenditure, or food intake in animals. Rats treated with IMEG show improved glucose tolerance due to increased insulin secretion. Imeglimin enhances rather than triggers insulin secretion. The 2-week IMEG treatment significantly improved glucose tolerance and lowered plasma glucose levels during the oral glucose tolerance test (OGTT). The authors demonstrated a 30–100% increase in insulin secretion at each time point during OGTT, more than doubling the area under the insulin curve during the test. The improvement in glucose tolerance in IMEG-treated rats was not associated with hepatic AMP-activated protein kinase (AMPK) activation; however, they demonstrated a 50% reduction in acetyl-CoA carboxylase (ACC) phosphorylation, which was associated with higher plasma insulin levels.

However, Hallakou-Bozec et al. demonstrated that IMEG stimulates postprandial insulin secretion through a nicotinamide adenine dinucleotide (NAD)-dependent mechanism [18].

Imeglimin has been shown to lower blood glucose levels and increase glucose-stimulated insulin secretion (GSIS) in preclinical models and clinical trials in patients with T2DM. Hallakou-Bozec et al. [39] showed that IMEG directly enhances GSIS in islets isolated from rodents with T2DM. A mode of action that differs IMEG from other therapeutic approaches. The primary mechanism of action of IMEG is an increase in cellular nicotinamide adenine dinucleotide (NAD+). This action is exerted through the salvage pathway and induction of nicotinamide phosphoribosyltransferase (NAMPT) and by increasing glucose-induced ATP levels. The results of Hallakou-Bozec et al. [39] suggest that conversion of NAD+ to a second messenger, cyclic adenosine diphosphate (ADP) ribose (cADPR), by ADP ribosyl cyclase/ADP hydrolase (CD38) is required for the observed effects of IMEG in islets. These results suggest a potential link between increased NAD+ and glucose-induced increased Ca^{++} mobilization. Increased Ca^{++} mobilization is a factor that increases exocytosis of insulin granules from β-cells. The collected information on this subject is shown in Figure 4 [39]. In summary, the results presented here indicate a new mode of action of IMEG and gives a new approach to the treatment of patients suffering from T2DM.

Antioxidant effects

Increased ROS production increases PTP opening, leading to the release of proapoptotic proteins into the cytosol resulting in cell death [24]. Detaille et al. demonstrated that IMEG effectively prevented the opening of mitochondrial PTPs and maintained mitochondrial function in cultured human endothelial cells (HMEC-1) [36].

Imeglimin shows antioxidant potential and alleviates oxidative stress by suppressing mitochondrial free radical generation, which also improves glucose homeostasis [24]. Detaille et al. found that IMEG reduced mitochondrial ROS generation in HMEC-1 [36]. Imeglimin attenuated hyperglycaemia-induced oxidative damage in the rat insulinoma cell line INS-1 [25]. The above studies indicate the antioxidant potential of IMEG.

There is evidence to suggest that IMEG improves vascular endothelial dysfunction and thus may be a novel drug for diabetes-induced vascular disorders such as nephropathy and retinopathy [40, 41].

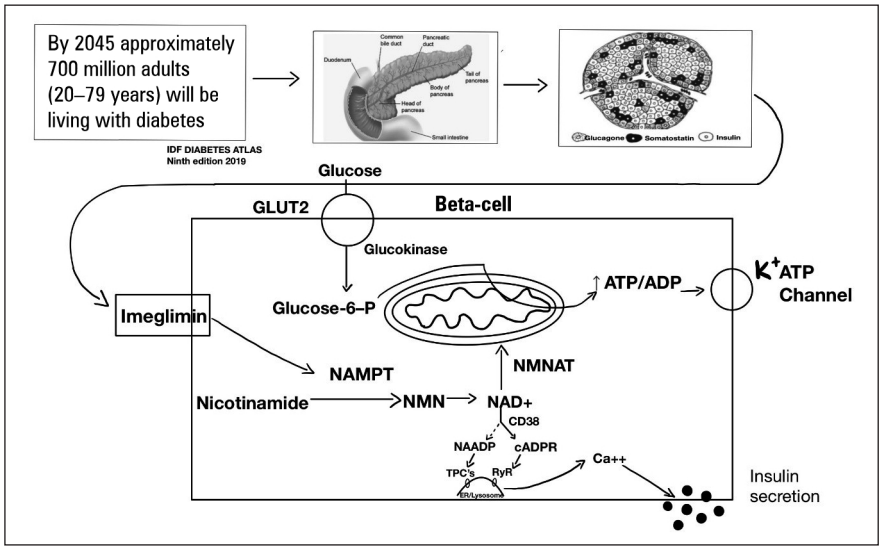

Figure 4. *Proposed mechanism of imeglimin (IMEG) action in islet β-cells (according to Hallakou-Bozec et al. [14] with own modification)*

In diabetic patients, there is an imbalance between free radicals and the antioxidant system [42]. The synthesis of free radicals is significantly higher than activity of the antioxidant system. Oxidative stress can significantly impair various insulin signalling pathways and induce insulin resistance [42]. Recent studies indicate that IMEG exerts antioxidant activity, which helps to reduce the generation of free radicals [23]. Vial et al. [23] demonstrated that IMEG alleviates oxidative stress by reducing mitochondrial free radical formation, which leads to improved glucose homeostasis [23]. Detaille et al. [36] showed that IMEG reduces free radical synthesis in mitochondria of human endothelial cells. Lablanche et al. [24] showed that IMEG reduces hyperglycaemia-induced oxidative damage in rat INS-1. The above studies indicate the antioxidant potential of IMEG.

Pharmacokinetics of IMEG

The peak effect on glycated haemoglobin (HbA_{1c}) levels of IMEG appears to be reached after 16 weeks of treatment [11]. Subjects receiving IMEG at doses of 1000 and 1500 mg twice daily (BID) also achieved significantly greater reductions in fasting plasma glucose (FPG) levels at week 24 compared with the placebo group (–24.6 ± 4.45; –24.6 ± 4.46 *vs.* –8.6 ± 4.4 mg/dL, $p < 0.0001$) [12]. Fouqueray et al. published the results of a study evaluating the pharmacokinetics of IMEG in monotherapy and as supplementation to treatment with metformin (MET) or sitagliptin (SITA) [43]. T2DM patients received MET 850 mg BID with placebo (n = 16) or SITA 100 mg once a day (OD) with placebo (n = 16) on days 1-6 followed by MET 850 mg BID with IMEG 1500 mg BID or SITA 100 mg OD with IMEG 1500 mg BID on days 7–12. The authors demonstrated that concomitant administration of SITA with IMEG did not result in clinically significant changes in systemic availability for SITA. The slight reduction in MET bioavailability after concomitant IMEG administration was not clinically significant. The use of IMEG with MET or SITA was safe and well tolerated [43].

Studies suggest that IMEG prevents human endothelial cell death by inhibiting mitochondrial permeability without concomitant inhibition of mitochondrial respiration, which may reduce the risk of cardiovascular complications in T2DM [36].

Clinical evidence for the IMEG effects

There is increasing evidence that IMEG reduces postprandial hyperglycaemia, normalizes HbA_{1c} levels, and improves β-cell function in T2DM patients [6, 8, 44].

Imeglimin as add-on therapy to MET or SITA reduces placebo-adjusted HbA_{1c} levels by 4–8 mmol/mol (0.4–0.7%) [9, 10].

Pacini et al. [8] showed that after one week of treatment with IMEG (1500 mg/12 h), there was an improvement in β-cell function in T2DM patients. In the study group of 33 patients, GSIS was evaluated using a hyperglycaemic clamp. Total insulin secretory response [incremental area under the curve (iAUC) 0–45 min] and insulin secretion rate (ISR) calculated from C-peptide deconvolution were evaluated. Treatment with imeglimin for 7 days increased insulin secretion in response to glucose stimulation by +112% (iAUC0-45, $p = 0.035$), first phase ISR by +110% ($p = 0.034$), and second phase ISR by +29% ($p = 0.031$).

To date, the results from six phase II studies have been published [6, 8–12]. Imeglimin as monotherapy

has been studied in five trials [6, 8, 11, 12], one of which has only been published as a poster [11]. Two studies investigated IMEG as supplementation to the treatment with MET [9] or SITA [10]. Pirags et al. [6] published the results of 2 phase II trials conducted for 4 weeks and 8 weeks, respectively. In the first study, 60 T2DM patients received IMEG 2000 mg once a day (OD), IMEG 1000 mg twice a day (BID), or MET 850 mg BID. Imeglimin BID treatment was shown to be as effective as MET treatment as assessed by OGTT plasma glucose measurement (incremental reduction in OGTT AUC reduced by 33% and 30% for IMEG at 1000 mg BID and MET at 850 mg BID, respectively, ($p < 0.8$). Use of IMEG once daily at 2000 mg also reduced incremental AUC in OGTT but only by 10%, and it was less effective than IMEG and MET used BID ($p < 0.05$). Imeglimin 2000 mg OD and IMEG 1000 mg BID resulted in adverse events in 30% (n = 6) and 35% (n = 7) of patients, respectively, compared with 68% (n = 13) in the MET treatment group. The patients treated with IMEG BID reported headache more frequently (35%, n = 7) than those treated with IMEG OD or MET (15%, n = 3 in both groups). Gastrointestinal disorders were more common in MET users (75%, n = 16) compared with the IMEG OD and BID treatment groups (35%, n = 7 and 10%, n = 2, respectively).

In the second study on T2DM patients, these authors demonstrated no increase in insulin secretion after IMEG compared with placebo and no concomitant change in HbA_{1c} levels. Imeglimin 1500 mg BID and MET BID treatment resulted in a reduction in fasting plasma glucose compared to baseline, whereas IMEG 500 mg BID and placebo showed an unknown increase in fasting plasma glucose.

A greater reduction in FPG was observed in subjects with HbA_{1c} levels ≥ 64 mmol/mol (8%). Imeglimin did not significantly reduce plasma glucose AUC 0–6 h as compared to the baseline during the extended meal test [6].

Fouqueray et al. conducted 2 studies evaluating the effects of IMEG on HbA_{1c} levels and FPG. Glycated haemoglobin levels were examined before and after 3 months of starting IMEG [33, 34]. The first study included T2DM patients (n = 156), aged ≥ 18 to ≤ 70 years, with inadequate glycaemic control ($HbA_{1C} \geq 7.5\%$). Subjects were randomized 1:1 to MET treatment in combination with IMEG at 1500 mg BID or placebo. Compared to baseline, after 12 weeks of treatment, subjects receiving combination MET and IMEG therapy had significant reductions in HbA_{1c} (8.5–7.84% *vs.* 8.6–8.31%, $p = 0.001$) and FPG (10.4–9.53 mg/dL *vs.* 10.28–10.59 mg/dL, $p < 0.001$) compared to the MET with placebo group. Significantly more subjects treated with MET with IMEG compared to those treated with MET with placebo achieved $HbA_{1c} < 7\%$ (14.3 *vs.* 3.8%, $p = 0.04$, respectively), as well as a reduction in $HbA_{1c} \geq 0.5\%$ (63.6% *vs.* 36.4%, respectively) [9].

In a second multicentre randomized clinical trial conducted in 170 T2DM patients [mean age — 56.8 years; body mass index (BMI) — 32.2 kg/m^2] with inadequate glycaemic control with SITA alone ($HbA_{1c} \geq 7.5\%$), Fouqueray et al. examined the effect of combination treatment of SITA with IMEG 1500 mg BID and SITA with placebo given for 12 weeks on HbA_{1c} levels. SITA-IMEG combination treatment compared to SITA-placebo treatment significantly increased the number of subjects achieving HbA_{1c} levels ≤ 7% (19.8 *vs.* 1.1%, respectively, $p = 0.004$), with a significant change in HbA_{1c} levels from the baseline (–0.6 *vs.* 0.12, respectively, $p < 0.001$) and a reduction in HbA_{1c} levels of at least 0.5% in 54.3% of subjects treated with SITA-IMEG *vs.* 21.6% in the SITA-placebo group. The SITA-IMEG combination treatment was well tolerated, and no significant treatment-related adverse events were reported [10].

Douborg et al. published the results of a phase II clinical trial evaluating the efficacy and safety of IMEG monotherapy versus placebo at 24-week follow-up in Japanese patients with T2DM [41]. The study included 299 patients who received BID oral placebo (n = 75) or IMEG in a dose of 500 mg (n = 75), 1000 mg (n = 74), or 1500 mg (n = 75). The effect of treatment on value-adjusted HbA_{1c} levels in the placebo group and the safety of the drug were evaluated. After 24 weeks of treatment with IMEG, there was a significant reduction in HbA_{1c} levels compared with the patients treated with placebo (difference *vs.* placebo: IMEG 500 mg –0.52% [95% CI: –0.77%, –0.27%], IMEG 1000 mg –0.94% [95% CI: –1.19%, –0.68%], IMEG 1500 mg –1.00% [95% CI: –1.26%, –0.75%], respectively). Treatment-related adverse events occurred in 68.0%, 62.2%, 73.3%, and 68.0% of patients receiving IMEG 500, 1000, 1500 mg, or placebo, respectively. A slight increase in the incidence of gastrointestinal side effects (e.g. diarrhoea) occurred at the 1500 mg dose. Given the marginal increase in efficacy with the 1500 mg dose compared to the 1000 mg dose (with a concomitant increase in gastrointestinal complications), the 1000 mg BID dose was selected for the subsequent phase 3 of the studies [12].

Pacini et al. [8] conducted a study of 33 T2DM patients using IMEG at a dose of 1500 mg BID. They showed that treatment for 7 days increased insulin secretion in response to glucose stimulation by +112% (iAUC0-45, $p = 0.035$), as well as the first ISR phase by +110% ($p = 0.034$) and the second ISR phase by +29% ($p = 0.031$).

In another multicentre randomized phase II clinical trial, Fouqueray et al. [11] investigated the effect of IMEG at doses of 500 mg, 1000 mg, 1500 mg, 2000 mg,

or placebo BID on HbA_{1c} levels and change in FPG levels. The study was conducted in a group of T2DM patients (n = 382, 60% female; mean age — 58 years; HbA_{1c} — 7.94%; BMI — 31.2 kg/m^2). Imeglimin reduced HbA_{1c} levels in a dose-dependent manner from the baseline, with the most effective dose being 1500 mg BID (placebo group-adjusted reduction in HbA_{1c} —0.63%, $p < 0.001$). Maximum efficacy for all IMEG drug doses tested was achieved after 18 weeks of treatment. After 24 weeks, significantly more subjects treated with IMEG at 1500 mg BID achieved HbA_{1c} levels ≤ 7% (33.3%) compared with the placebo group (12.5%) ($p = 0.005$). Fasting plasma glucose reductions were also the greatest with the treatment with IMEG at 1500 mg BID [placebo-adjusted reduction of 1.25 mmol/L (22.5 mg/dL) ($p = 0.001$)]. At 24-week follow-up, IMEG did not affect subjects' body weight, was well tolerated at all study doses, with no hypoglycaemia incidents, and no serious adverse events. The most commonly reported adverse events with IMEG drug at 1500 mg BID were gastrointestinal side effects. This study demonstrated that the IMEG drug 1500 mg BID is effective, does not affect body weight, and is well tolerated with no increased risk of hypoglycaemia.

The phase III TIMES (Trials of Imeglimin for Efficacy and Safety) study has recently been completed in Japan and consists of 3 separate studies (TIMES 1–3) involving a total of 1100 study patients with T2DM receiving IMEG at 1000 mg BID or placebo for 24 weeks.

The TIMES 1 phase III study included 213 Japanese T2DM patients aged 20 years or older treated with diet and exercise, with a stable course for the last 12 weeks before entering the study, with HbA_{1c} levels between 7.0 and 10.0% (53–86 mmol/mol). Compared with placebo, the adjusted mean difference in HbA_{1c} levels after 24 weeks of treatment was –0.87% [95% CI: –1.04, –0.69 (–9.5 mmol/mol; 95% CI : –11.4, –7.5); $p < 0.0001$] [13]. There was a significant increase (by 0.0093, $p = 0.005$) in the quantitative insulin sensitivity control index (QUICKI — insulin sensitivity index) [44]. Treatment in T2DM patients with IMEG resulted in a reduction in HbA_{1c} (adjusted for placebo group by 10 mmol/mol (0.9%), $p < 0.001$) as well as FPG (adjusted for placebo group by 1 mmol/l, $p < 0.001$). Forty-seven (44.3%) subjects reported > 1 adverse event in the IMEG-treated group compared with 48 adverse events (44.9%) in the placebo group [13]. TIMES 2 was a placebo-controlled, multicentre, 52-week study that evaluated the efficacy and safety of IMEG as monotherapy or in addition to other hypoglycaemic agents in 700 Japanese patients with T2DM. Adverse effects were mild and consistent with the known safety profile of IMEG — no cases of severe hypoglycaemia were observed. The change in HbA_{1c} levels from the baseline ranged from –0.56 ± 0.08 to –0.92 ± 0.11% in patients receiving IMEG in combination with other oral antidiabetic drugs [36].

In the TIMES 3 study, 215 T2DM patients with a mean HbA_{1c} level of 73 mmol/mol (8.8%) treated with insulin in monotherapy (81%) or insulin in combination with an oral antidiabetic drug (19%) were included in the study. The subjects received either 1000 mg BID or placebo in addition to their existing treatment with IMEG. Preliminary results showed that after 16 weeks of IMEG treatment as a supplement to insulin therapy, there was a significant reduction in HbA_{1c} level adjusted for in the placebo group (–7 mmol/mol [0.6%], $p < 0.0001$), which was maintained until week 52 of follow-up (difference from baseline: 20.64%). Switching from placebo to IMEG resulted in similarly lower HbA_{1c} levels (difference from the baseline: –0.54%) [18].

Depending on the dose of IMEG, the researchers achieved a reduction in HbA_{1c} of 0.52% to 1.0% after 3 months of therapy , which is comparable to the effect of other antidiabetic drugs [biguanides 7–12 mmol/mol (0.6–1.1%), sulphonylureas and glinides 7–10 mmol/mol (0.6–0.9%), DPP-4 inhibitors 7–12 mmol/mol (0.6–1.1%), GLP-1R agonists 12–18 mmol/mol (1.1–1.6%), SGLT-2 inhibitors 8 mmol/mol (0.7%), thiazolidinediones (PPAR-γ agonists) 11 mmol/mol (1%), α-glucosidase inhibitors (0.5–0.8%)] after 3 months of therapy [45–51].

Tolerability, interactions, and other potential beneficial effects of IMEG

Metformin is the first-line drug in T2DM. Gastrointestinal side effects limit its use in some patients, and IMEG may fill this gap [52]. Phase I and II clinical trials in Caucasian patients with T2DM have shown that IMEG is effective as monotherapy or as add-on therapy and has an adequate safety and tolerability profile [12, 18]. Dose-dependent side effects, mainly headache and gastrointestinal symptoms, have been demonstrated after IMEG use [11]. No serious adverse events have been reported, particularly no hypoglycaemia or cardiovascular events [9, 10, 12, 19].

In the TIMES 1 phase III study with 24 weeks of IMEG monotherapy, drug tolerability was good and consistent with the results of the phase II study. Treatment discontinuation due to adverse events was reported in 3% of IMEG-treated patients compared to 6% in the placebo group. No cases of severe hypoglycaemia were reported [13].

However, no conclusions can be drawn about long-term safety because the longest clinical trial lasted 52 weeks [53]. It should be noted that preclinical studies have demonstrated a glucose-independent insulinotropic effect of IMEG at supratherapeutic doses, which raises concerns about overdosing and the associated risk of hypoglycaemia if dosing is inappropriate, in patients

with renal (or hepatic) impairment and in patients with increased sensitivity to IMEG [7].

In vitro studies have shown IMEG to be a substrate of the renal multidrug and toxic extrusion transporters (MATE): MATE1 and MATE2-K, and the organic cation transporters (OCT): OCT1 and OCT2, and a weak cometic inhibitor of MATE1, OCT1, and OCT2 [17]. In drug-drug interaction studies in healthy volunteers, it was shown that IMEG had no clinically relevant effect on the pharmacokinetics of metformin, which is also a substrate for MATE1, MATE-2K, and OCT2 transporters [52]. The effects of cimetidine, a reference inhibitor of MATE1, MATE-2K, OCT1, and OCT2 transporters, on the pharmacokinetics and safety of IMEG were also investigated. No clinically significant interactions between IMEG and cimetidine were observed. Single doses of 1500 mg IMEG were well tolerated when taken alone or in combination with a twice-daily dose of 400 mg cimetidine [20]. Because there is a higher risk of hepatic impairment in T2DM compared to the general population, Chevalier et al. investigated the effect of hepatic impairment on IMEG pharmacokinetics [43]. Because IMEG is a substrate of OCT1 and 2, which are expressed in the liver and kidney, liver dysfunction may affect its distribution and pharmacokinetics (PK). The authors evaluated the PK as well as safety of IMEG after oral administration of a single 1000 mg dose in subjects with moderate hepatic impairment and in a control group with normal liver function. The results of the control group of this study were consistent with the results of the previous PK studies after a single administration of IMEG, which strengthens the reliability of this study. There was a 1.3-fold increase in plasma concentration (Cmax) and a 1.5-fold increase in the area under the plasma concentration-time curve (AUC) in the subjects with moderate hepatic impairment compared to the control group, but this was not considered clinically significant. The study authors conclude that a single dose of IMEG 1000 mg is well tolerated in patients with moderate hepatic impairment [43].

The results of the study suggest that IMEG prevents endothelial cell apoptosis by inhibiting mitochondrial permeability without inhibiting mitochondrial respiration, which may reduce the risk of cardiovascular complications in T2DM. Dubourg et al. studied the effect of a single therapeutic dose (2250 mg) and a single supratherapeutic dose (6000 mg) of IMEG on the QT/QTc interval in electrocardiography (ECG) [52].

This study is consistent with current recommendations (ICH E14) requiring all non-antiarrhythmic compounds to undergo this type of evaluation [54]. This recommendation is because drug-induced delays in myocardial repolarization potentially increase the likelihood of fatal cardiac arrhythmias (torsades de pointes).

Cardiac repolarization is determined by the QT interval corrected by changes in heart rate. This study evaluates QTc interval prolongation and its possible relationship to a IMEG dose. The researchers did not demonstrate a dose dependence of IMEG used on the QTc interval, and there were no QTcF thresholds above 500 ms or QTc prolongation of more than 60 ms. Imeglimin also had no significant effect on heart rate, PR, or QRS intervals. The authors concluded that IMEG does not affect ventricular repolarization [52].

One of the major causes of mortality in T2DM is heart disease; therefore, improving cardiovascular outcomes has become an increasingly important feature of new T2DM therapies, such as certain SGLT2 inhibitors and GLP-1 receptor agonists (GLP-1 Ras) [55].

In an animal experimental model, IMEG has been shown to improve many of the cardiac indices [56]. Imeglimin treatment reduced left ventricular (LV) end-diastolic pressure and LV end-systolic volume, increased LV tissue perfusion, and reduced LV ROS production. Simultaneously, IMEG restored acetylcholine-mediated coronary relaxation and flow-mediated mesenteric vasodilation. One hour after IMEG administration, when plasma glucose levels were still unchanged, there was a reduction in LV mitochondrial ROS production and improvement in LV function. A 90-day treatment with IMEG reduces LV and renal fibrosis and improves LV function. The improvement in cardiac function was probably, at least in part, due to an increase in nitric oxide levels assessed by plasma nitrite levels (a marker of nitric oxide levels) as well as reduced collagen deposition in the LV [38].

Conclusions

Diabetes is the scourge of the early 21st century. This disease causes significant deterioration in life quality and shortened survival of patients. Development of more effective therapies targeting at the key pathophysiology of the disease is becoming increasingly important. This paper reports the results of the study of a new oral drug for the treatment of T2DM: imeglimin. Imeglimin acts on 3 key pathophysiological mechanisms found in T2DM. This feature is found in few drug classes used to treat this disease. Its true effect on peripheral organ glucose utilization and its dependence on insulin should be further studied. Imeglimin is effective in people with T2DM in whom other antidiabetic therapies have failed.

Imeglimin's unique mechanism of action and safety profile compared to currently available antidiabetic therapies potentially fills important gaps in the current treatment of T2DM.

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