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IMEGLIMIN: A REVIEW

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ABSTRACT

Imeglimin is a novel molecule currently under development for the treatment of type 2 diabetes mellitus, and is the first agent of the 'glimin' class of glucose-lowering medication. It has a unique mechanism of action that targets the three main pathophysiologic components of type 2 diabetes: impaired glucose uptake by muscle tissue, excess hepatic gluconeogenesis and increased β-cell apoptosis. To date, imeglimin has been evaluated in many preclinical and clinical trials and has shown to have notable antihyperglycaemic effects, such as statistically significant reductions in glycated haemoglobin, fasting plasma glucose and other glycaemic parameters. The encouraging tolerability profile, combined with its efficacy, could make it suitable as a monotherapy or in combination with other classes of antidiabetic agents, hopefully in the near future.

KEY WORDS: *Type 2 diabetes mellitus, imeglimin, mechanism of action, clinical trials*

INTRODUCTION

Imeglimin is an oral antidiabetic drug. Approved for use in Japan in June 2021. It is an oxidative phosphorylation blocker that inhibits hepatic gluconeogenesis, increases glucose uptake into muscle, and restores normal insulin secretion. It is the first approved drug in this class of antidiabetic agents.Type 2 diabetes (T2DM) is a widespread disease that affects more than 380 million people worldwide and is projected to affect more than 590 million people worldwide by 2035. Addressing this global problem requires enormous amounts of time, effort, and funding that many organizations, including private and public agencies, have devoted to treatment, prevention, and education. Despite our best efforts, the prevalence of type 2 diabetes continues to rise, especially given an aging population, rising obesity rates, and an increase in at-risk ethnic groups. Furthermore, the physiological and progressive nature of diabetes requires a combination of lifestyle modifications and pharmacotherapy to achieve and maintain long-term glycemic control. The major physiological defects of type 2 diabetes include excessive hepatic glucose production, decreased peripheral glucose uptake by insulin-sensitive tissues, and insufficient insulin secretion. This article introduces a potential new pharmacological agent, imeglimin, and reviews its basic and clinical activities in comparison with other widely used drugs.

I. MECHANISM OF ACTION

Imeglimin exhibits a unique mechanism of action that targets the three major pathophysiological components of type 2 diabetes: impaired glucose uptake by muscle tissue, excessive hepatic gluconeogenesis, and increased β-cell apoptosis. The use of imeglimin to improve fasting glycated hemoglobin (HbA1c) and plasma glucose (FPG) levels, either as monotherapy or in combination with other hypoglycemic agents, has been shown to improve type 2 diabetes mellitus at all stages of the disease spectrum. It is a promising candidate for treatment. For the sake of brevity, this review will focus on the effects of imeglimin on HbA1c and FPG.

II. PHARMACOKINETICS

Imeglimin is a tetrahydrotriazine compound. Its chemical name is (6R)-(+)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5-triazine hydrochloride, and its primary site of action is the mitochondria of the aerobic cells, where it alters the oxidative phosphorylation, serving also as a substrate for organic cation transporters.3 There are signs to suggest that imeglimin induces an insulin-dependent protein kinase B phosphorylation increase, in both liver and muscle cells. In the liver, imeglimin changes the flow of substrates and rebalances the pathways, favouring complex II, inhibiting complex I (competitive mitochondrial inhibition) and restoring complex III functions. As a result, it reduces liver steatosis and reactive oxygen species (ROS) produced in mitochondria, and increases hepatic 3-hydroxyacetyl-CoA dehydrogenase activity.

Pharmacokinetics studies showed that absorption of imeglimin occurs in the stomach. The distribution of the drug through the bloodstream is fast, and plasma protein binding is low. Furthermore, there is no evidence of cytochrome P450 inhibition or induction. Imeglimin is excreted through the kidneys and mostly remains unchanged. A recent study by Chevalier et al. has indicated that it is safe and well tolerated in patients with moderate hepatic impairment, as the increase in maximum plasma concentration and the area under the curve (AUC) of concentration/time was not reported as clinically significant. Inhibition of hepatic glucose production

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Imeglimin has shown an inhibitory effect in glucose production in both isolated rat liver cells and rat liver slices. Moreover, imeglimin elicited a reduction in glucose produced by the isolated cells in a concentration dependent pattern, with reductions ranging from 9% (for 0.25 mmol/L) to 80% (for 1.5 mmol/L), which is comparable to the results of metformin in its highest dosages. In liver slices, the inhibition of glucose production was also apparent; in a dose dependent pattern, the reduction ranged from 14% (for 2.5 mmol/L) to 84% (for 10 mmol/L).5 On a molecular level, imeglimin achieved these results by downregulating phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in isolated hepatocytes from rats, and by inhibiting lactic acidosis via the mitochondrial dependent pathway. In muscle cell cultures, imeglimin has shown effectiveness by inducing glucose uptake by the muscle cells, which was statistically significant at a dose of 0.5 mmol/L with up to a 3.3-fold increase at the maximum dose given (2 mmol/L), compared with control. In vivo, in soleus and gastrocnemius muscle from streptozotocin diabetic rats, imeglimin showed a statistically significant) increase in glucose uptake even at the lowest dose (25 mg/kg), restoring the uptake to normal for diabetic rats at 50 mg/kg and 100 mg/kg.

III. CLINICAL STUDIES

Metformin is the first-line agent in the treatment of type 2 diabetes, mainly due to its safety, efficacy and low cost. It does not cause hypoglycaemia, and offers an effective reduction in HbA1c as a monotherapy or in combination with other oral glucose-lowering agents. However, in some patients, the use of metformin is limited, mostly due to its gastrointestinal side effects. There are several phase II and phase III studies that demonstrate the effectiveness of imeglimin as an alternative option.

In a 4-week phase IIa, three-arm parallel group trial in 59 patients with type 2 diabetes by Pirags et al., imeglimin was compared with metformin and placebo based on safety profile and efficacy to reduce the plasma glucose concentration AUC (AUC_{PG}). The patients (HbA1c: 6.5–8.5%) either did not receive any treatment at all, or were treated with monotherapy sulfonylurea or metformin before the initiation of the study, and were randomized to imeglimin 2,000 mg once daily, imeglimin 1,000 mg twice daily (BID), metformin 850 mg BID (mean baseline HbA1c levels of 7.41, 7.07 and 7.27%, respectively), or placebo. Imeglimin BID presented the greatest reduction in AUC_{PG} from baseline, followed by metformin and imeglimin once daily dosing (-33%, -30% and -10%, respectively). The results of this trial indicated that imeglimin presented a similar efficacy to metformin.

In a second 8-week phase IIa, four-arm, controlled multicentre study by Pirags et al. in 128 patients with type 2 diabetes, patients who were treatment naïve or received a sulfonylurea or metformin as a monotherapy were randomized to imeglimin 500 mg BID, imeglimin 1,500 mg BID, metformin 850 mg BID or placebo. Imeglimin 1,500 mg BID and metformin BID were superior to placebo in the assessment of the AUC up to 6 hours ($AUC_{0\text{-}6h}$) for glucose during a prolonged meal, and both led to the reduction of FPG and HbA1c from baseline; imeglimin 500 mg BID was the least effective dosing, and led to an increase of FPG and HbA1c from the baseline across all imeglimin groups. Concerning the safety profile of imeglimin, only 16 patients experienced headache compared with 20 patients in the metformin group, and gastrointestinal side effects were mainly observed in the metformin group. Although these studies highlight the efficacy of imeglimin based on specific glycaemic parameters.

In a multicentre, randomized controlled trial, 156 patients (HbA1c >7.5%) were randomized 1:1 to receive imeglimin 1,500 mg BID or placebo, added to a stable dose of metformin (1,500–2,000 mg/day). In a second multicentre, randomized, placebo-controlled study, conducted by Fouqueray et al., 170 patients (HbA1c >7.5%) on sitagliptin monotherapy were randomized to receive sitagliptin + placebo or sitagliptin + imeglimin 1,500 mg BID for 12 weeks. The reported side effects in the imeglimin group were similar to those in the placebo group. There were also no significant differences in the mean changes from baseline to week 12 between treatment groups for triglyceride and C-reactive protein levels, as well as systolic blood pressure. Based on these studies, it may be concluded that imeglimin BID dosing is more effective than once-daily dosing, and can be used efficiently in combination with metformin or sitagliptin without any major side effects compared with placebo.

In a recent larger study that included 299 Japanese adults with diabetes who were treatment naïve or previously treated with only one oral antidiabetic medication, the efficacy and safety profile of imeglimin as a monotherapy was assessed compared with placebo. In this 24-week, randomized, double-blind, parallel group, dose-ranging, phase IIb clinical trial, the participants were randomized (1:1:1:1) to the following: imeglimin 500 mg, imeglimin 1,000 mg, imeglimin 1,500 mg or placebo BID. The most common adverse events were infections and infestations, with a slight increase over placebo in all imeglimin groups. The second most common adverse events were gastrointestinal disorders. Hypoglycaemic events were balanced between the groups. According to this trial, imeglimin was proven to be well tolerated as a monotherapy, significantly boosting glycaemic control by reducing HbA1c, compared with the placebo.

The approval of imeglimin in Japan is supported by a phase III clinical programme, which includes three trials: TIMES 1, TIMES 2 and TIMES 3 (Trials of imeglimin for efficacy and safety). In TIMES 1, which was a randomized, double-blind, placebo-controlled monotherapy study that included 213 Japanese patients (mean age 62 years) with type 2 diabetes, orally administered imeglimin (1,000 mg BID) was compared with placebo for 24 weeks. with an HbA1c placebo-corrected mean change from the baseline of -0.87%. The decrease in FPG level was also higher among patients who received imeglimin versus placebo (placebo-adjusted least

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squares [LS] mean decrease of 19 mg/dL in the imeglimin group). In TIMES 1, only 44.3% of the patients treated with imeglimin and 44.9% of those given placebo reported adverse effects, while 2.8% and 5.6%, respectively, experienced side effects resulting in treatment discontinuation.

In both TIMES 2 and TIMES 3, the adverse events were similar to previous clinical trials; overall, the safety profile of imeglimin was favourable and the adverse event incidence was similar to that of a placebo. Hypoglycaemic events reported during TIMES 3 were mild, and the number of patients receiving imeglimin who experienced hypoglycaemia was similar to the placebo group.

IV. POTENTIAL ADVANTAGES

The main advantage of imeglimin is its novel mechanism of action. As the first drug of its kind, it allows patients with type 2 diabetes the opportunity to try to optimize their therapy by targeting multiple mechanisms with one medication to ultimately improve insulin secretion and insulin sensitivity and decrease peripheral insulin resistance. Imeglimin has been shown to lower A1C in adults with type 2 diabetes. In recent phase 2 and phase 3 clinical trials, imeglimin 1,000 mg twice daily was found to lower A1C by 0.5–1%. Furthermore, imeglimin 1,500 mg twice daily, when added to the DPP-4 inhibitor sitagliptin or to metformin, resulted in A1C reductions of 0.6 and 0.65%, respectively. The safety profile is also promising, with no major adverse events, cardiovascular events, or increased incidence of hypoglycemia in patients treated with imeglimin.

V. DISCUSSION

The mechanisms by which imeglimin improves insulin sensitivity and β-cell function are not yet fully understood. The examination of imeglimin's effect on inflammatory responses, glucagon secretion and mitochondrial function may reveal other pharmacological aspects that demonstrate the potential of this promising new molecule. imeglimin has exhibited a good safety profile in most of the recent clinical trials; it has shown a lower frequency of gastrointestinal adverse effects than metformin. This review presents a general overview of imeglimin, including its mechanism of action, and the most important studies in the clinical development programme of this promising agent. In contrast with a systematic review, this paper aims to introduce this under-development agent to the medical community in a comprehensive, narrative way.

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