Review Article

Imeglimin in Type 2 Diabetes: A Comprehensive Review of Clinical Trials, Mechanistic Insights, and Safety Advantages

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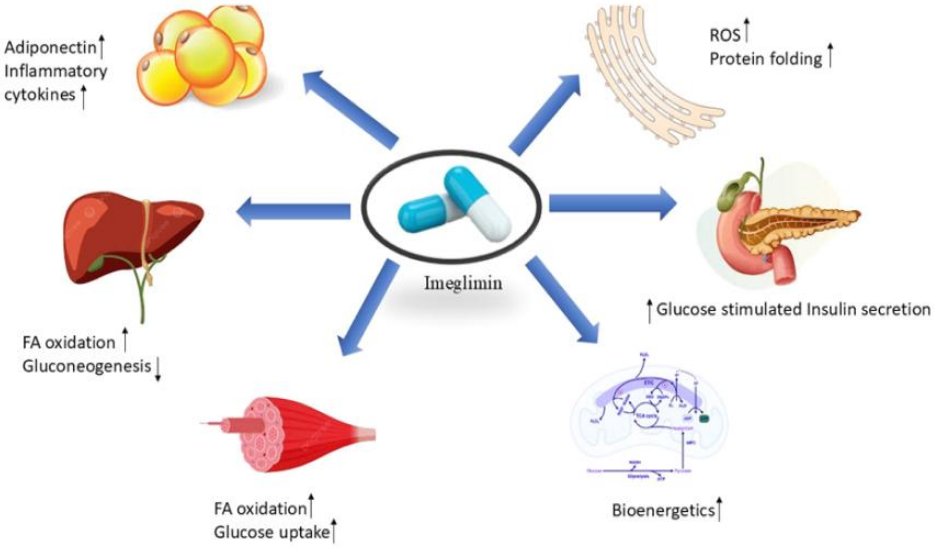
ABSTRACT

Imeglimin is a new molecule, which is in the category of therapeutic agents for type 2 diabetes and seems to have a favourable risk/benefit profile. Randomized, controlled studies of imeglimin in phase I prove that it has mild side effects, not different from those of a placebo. This places imeglimin as a safe and effective option to manage type 2 diabetes mellitus either as a first-line therapy or as add-on therapy to other antidiabetic medications including metformin, sitagliptin and insulin. Notably, its safety profile offsets some shortcomings characteristic of current treatments, such as the potential for lactic acidosis. Unlike metformin, which is known to have a very high predisposition to causing lactic acidosis especially in the circumstances involving renal impairment or major surgery, imeglimin has been notably demonstrated to reduce the risk of lactic acidosis in the susceptible. Besides, it also has a favourable tolerability effect within individuals with moderate hepatic or renal impairment, provided that the dosage adjustment is made. This characteristic further operationalizes the model and makes it particularly valuable in clinical matrices where traditional treatments could be contraindicated. This additional activity for the drug being discussed, adding up to its selectivity to the mitochondrial targeting profile, continues to set it apart from other treatments. Further study is needed to conclusively prove the safety and effectiveness of imeglimin over the long-term and in specific patients – those who have cardiovascular complications. Further, these studies should also compare its additive/synergistic benefits in combination with other favourable novel antidiabetic agents. The improvement of these aspects should provide a solid foundation for further popularization of imeglimin as one of the key drugs in managing type 2 diabetes for patients with different comorbidities.

Keywords: Imeglimin, Type 2 Diabetes, Metformin, Sitagliptin.



Graphical Abstract

INTRODUCTION

Diabetes is a chronic health condition that has a detrimental influence on people around the world. From 1990 to 2022, the number of diabetics increased to 630 million, with low- and middle-income nations experiencing the highest frequency.[1]

According to the 2021 IDF Diabetes Atlas, the overall number of persons with diabetes is expected to reach 643 million (1 in 9 adults) by 2030 and 784 million (1 in 8 adults) by 2045. In 2021, diabetes claimed the lives of almost one person every five seconds (6.7 million). [2]Diabetes is a significant health concern due to its rising incidence, high avoidable morbidity and mortality from diabetes and diabetic complications, and the associated enormous economic cost.[3]

Type 2 Diabetes Mellitus (T2DM) is described as a condition of impaired glycaemic regulation due to insulin resistance in small blood vessels and impaired functionality in the Isles of Langerhans producing insulin. [4] It remains difficult to handle this condition as its progress is linked to the dysfunction of most organ systems. These include augmented β-cell death and augmented hepatic glucose output and diminished peripheral utilization of glucose. Therefore, the fact that the different aspects of the disease are targeted by current treatments could be the major reason as to why treatments are developed. T2DM has been demonstrating clinical care over decades, and this growth has been characterized by multiple therapies. But T2DM is a chronic relapsing disease, which means that its management at the later stages means administration of several medications to sustain efficiency.[5] This, in consequence, may lead to the enhancement of side effect profile, which, in turn, may restrict therapeutic possibilities. But even in this case, there may be numerous challenges in the treatment of T2DM The presence of other diseases or complications makes the situation even worse. For instance, insulin, metformin, sulfonylureas and SGLT2 might have risks in patients with CKD, thiazolidinediones—in patient with heart failure. Since metabolic syndrome is closely associated with T2DM and is a major factor affecting heart health, and furthermore, diabetic nephropathy is one of the largest contributors to CKD in the United States, such therapies should be safe and efficient for treating these diseases. This is important in actually advancing the different treatments needed in T2DM at different points in the disease.[6]

Imeglimin is the first in a new tetrahydro triazine-containing class of oral antidiabetic agents, the glimins. Imeglimin decreases hepatic glucose production, increases muscle glucose uptake, and improves pancreatic glucose-dependent insulin secretion. [7]

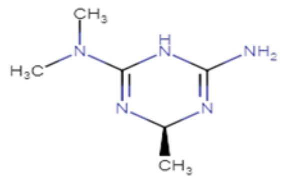
Imeglimin is a new type of oral antidiabetic drug in phase III clinical trial for type 2 diabetic patients. It has a different mode of action to other antihyperglycemic agents and seeks to optimise mitochondrial function by manipulating mitochondrial bioenergetics. In particular, imeglimin regulates the activities of the complexes of the mitochondrial respiratory chain and decreases generation of ROS (Reactive Oxygen Species). ROS have a strong correlation to imeglimin as this research proved that the compound improves glucose stimulated insulin secretion through expanding β cell glucose sensitivity about type 2 diabetes patients. It has also been shown to enhance insulin sensitivity in rodent models and to help to correct glucose tolerance back to normal. In the last two years, imeglimin was shown to protect human endothelial cells from death by blocking a known mechanism of cell death – the opening of the mitochondrial permeability transition pore, while not affecting the functioning of mitochondria. This finding also implies that imeglimin may possess beneficial effects for the end organs, including kidneys and heart.[8]

T2DM is characterized by extensive cardiovascular morbidity and mortality and is the leading etiology of end-stage renal disease in the United States. One of the complexities in managing T2DM is working with patients with moderate to severe renal disease because many antidiabetic therapies are contraindicated in patients with severe renal impairment, including insulin, metformin, DPP-4 receptor agonists, and some second-generation sulfonylureas. However, publications established clinical trials and pointed to the fact that imeglimin is a safe drug when used as monotherapy and in combination with other popular T2DM therapies.[9] It has also proved its safety in patients with comorbidities, including chronic kidney disease (CKD) which is a central concern for therapies of T2DM. Furthermore, preliminary data from animal studies indicated that imeglimin may enhance renal function, which, in turn, might be helpful for those patients who have renal constraints against the use of other diabetes medications and for those patients who may benefit from the potential reno-protective effect of imeglimin. Nonetheless, this is still a pilot finding and additional research has to be conducted to establish the extent of how imeglimin can shield the renal troubles in diabetics. These and other derived properties may, if substantiated, alter the management of T2DM and that of patients with kidney disease in particular.[10]

Pharmacokinetic profile [11]

Table 1 below highlights the details of the pharmacokinetic studies of Imeglimin with regards to its absorption, metabolism and site of action.

Table 1: Pharmacokinetic profile of Imeglimin

Parameter	Details
Chemical Structure	Tetrahydrotriazine compound: (6R)-(+)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5-triazine hydrochloride 
Site of Action	Mitochondria (aerobic cells), impacting oxidative phosphorylation and serving as a substrate for organic cation transporters
Absorption	Moderate intestinal absorption (50–80%) via active paracellular mechanism; decreased absorption at higher doses due to transport saturation
Distribution	Rapid distribution through the bloodstream; low plasma protein binding
Metabolism	No evidence of cytochrome P450 inhibition or induction
Excretion	Primarily excreted unchanged through the kidneys
Effect of Hepatic Impairment	Safe and well tolerated in moderate hepatic impairment; no clinically significant increase in Cmax or AU
Liver	Inhibits mitochondrial complex I (competitive inhibition). Rebalances pathways favouring complex II and restoring complex III function.

	Reduces liver steatosis and reactive oxygen species (ROS). Increases hepatic 3-hydroxyacetyl-CoA dehydrogenase activity.
Muscle Cells	Induces insulin-dependent protein kinase B phosphorylation.

Mechanism of Action

Imeglimin has a unique method of action that improves insulin sensitivity while also restoring pancreatic β-cell activity. This manner of action is consistent with the present understanding of type 2 diabetes (T2D) pathogenesis. T2D is often caused by a mix of genetic and environmental factors, including excessive eating and inadequate physical exercise. These factors cause insulin resistance and β-cell malfunction, resulting in glucose intolerance and diabetes. Mitochondrial dysfunction is a significant factor in the pathophysiology of type 2 diabetes (T2D), leading to β-cell malfunction and insulin resistance. Rare inherited forms of type 2 diabetes, caused by abnormalities in mitochondrial DNA, highlight the importance of mitochondrial function. [8]

Imeglimin's dual method of action most likely stems from its ability to selectively target critical molecular elements of diabetes pathogenesis. Reversing β-cell dysfunction involves increasing glucose-stimulated insulin secretion (GSIS) and boosting insulin sensitivity in the liver and skeletal muscles. These effects are primarily caused by improved mitochondrial function, which has been reported in a variety of cell types. Imeglimin also enhances the cellular NAD+ pool in pancreatic islets, which has been associated to better calcium mobilisation and GSIS. While there are various types of treatment medications available for controlling type 2 diabetes (T2D), they are sometimes only partially successful and may cause safety or tolerability difficulties in some patients. As a result, there is an ongoing need for novel medicines that target the basic processes of T2D while also addressing unmet medical requirements. Imeglimin's specific method of action is consistent with its clinical profile, suggesting that it could be a valuable therapy option in the future of diabetes care.[12]

Imeglimin, β-Cell Function, and Insulin Secretion.

Imeglimin has been shown to improve β-cell function and glucose-induced insulin production. Perry et al. (2016) discovered that Imeglimin restores glucose homeostasis and lowers HbA1c in diabetic mice by directly increasing insulin production and restoring pancreatic islet function.[13] Hallakou-Bozec et al. (2016) found that Imeglimin enhances postprandial insulin secretion in diabetic rats via a nicotinamide adenine dinucleotide (NAD)-dependent mechanism, activating the salvage pathway in a dose-dependent manner.[8] In 2015, Pacini and colleagues discovered that Imeglimin protects β-cells and improves islet activity, leading to improved glucose homeostasis in diabetic circumstances.[14] Lablanche et al. (2018) found that Imeglimin inhibits β-cell apoptosis by reducing glucotoxicity through a mitochondrial-dependent mechanism. Imeglimin may boost β-cell mass by blocking mitochondrial permeability transition pores. Imeglimin's protective effect in β-cells and ability to improve glucose homeostasis through β-cell function are supported by emerging research.[15]

Imeglimin and Mitochondrial Function

Mitochondrial dysfunction has been reported to be linked to diabetes mellitus (DM) and in particular, insulin-sensitive cells, including adipocytes, cardiomyocytes and myocytes are impaired in their ability to respond to circulating insulin. This malfunction can affect pancreatic β-cells functioning and ability to produce and secrete insulin in relation to blood glucose concentrations. Hence, preservation of the mitochondrial function becomes part of management of diabetes.[16] Studies show that Imeglimin could possibly help increase mitochondria activity to diabetics. Vial et al. (2015) have reported that Imeglimin enhances mice heart mitochondria, complex I and III activity, increases fatty acid oxidation in diabetes animal mitochondria, and corrects the altered phospholipid composition with better glucose metabolism.[17] In addition, Detaille et al. (2016) did show that Imeglimin prevents the opening of permeability transition pores (PTPs) which is associated with the activity of the mitochondria in cultured human endothelial cells.[18]

Imeglimin and Oxidative Stress.

The pathogenesis and complications of diabetes mellitus (DM) are closely associated with oxidative stress, which is an increase in free radical production and the free radical/antioxidant ratio. It tends to impair the pathways of insulin signalling by as much as 50 percent and thus leads to insulin resistance. New studies to the existing have indicated that Imeglimin has antioxidative properties that makes it reduce formation of free radicals and help to achieve redox equilibrium. For instance, Vial et al. (2015) toe the line with their discovery that Imeglimin reduced oxidative stress through the inability of mitochondria to generate free radicals.[17] Just as Detaille et al. (2016) ascertained, Imeglimin lowered the indices of mitochondrial free radicals in the KEBS human endothelial culture.[18] Lablanche et al. 2018 studied Imeglimin's effect on inflammation and oxidative stress markers in INS-1; they identified that Imeglimin helped to combat hyperglycaemia-induced oxidative damage. These works show the antioxidative effects of Imeglimin.[15,19]

Clinical Evidence and Trials

In Table 2, the overview of major clinical trials aimed at exposing antihyperglycemic efficacy of Imeglimin is presented, proving that Imeglimin helps to decrease HbA1c and FPG levels in patients throughout all phases of clinical trials and in different populations.

A thorough literature search was carried out using PubMed, ClinicalTrials.gov, and the Cochrane Library to discover papers evaluating Imeglimin as a therapy for T2DM. The search, which was limited to English-language articles until September 2023, included keywords such as "Imeglimin," "Metformin," "type 2 diabetes," and "glycaemic control."

Imeglimin, a new tetrahydro triazine chemical, works in a unique way by targeting mitochondrial bioenergetics to improve insulin secretion and sensitivity while decreasing hepatic gluconeogenesis. This technique addresses insulin resistance and β-cell dysfunction, providing a multimodal glycaemic management strategy.[12,20]

The TIMES program (Trials of Imeglimin for Efficacy and Safety) found that Imeglimin effectively lowers glycated haemoglobin (HbA1c) and fasting blood sugar (FBS), with a favourable safety profile and little gastrointestinal side effects. While trials have looked into its efficacy as a monotherapy or in combination with insulin, there have been no direct head-to-head comparisons with Metformin, the current first-line treatment for T2DM. Furthermore, the long-term effects of Imeglimin on weight management and metabolic markers such as body mass index (BMI) and waist-to-hip ratio, especially when combined with dipeptidyl peptidase-4 (DPP-4) inhibitors such as Sitagliptin, have yet to be completely explored. [21–23].

Table 2: Some Clinical Evidence on Antihyperglycemic Effects of Imeglimin

Study Phase	Study Population	Treatment	Duration	Key Findings	Reference
Phase 2	156 patients with type 2 diabetes (T2D)	Imeglimin monotherapy	12 weeks	Significant reduction in HbA1c (0.6% from baseline) compared to placebo; fasting plasma glucose reduction	24
Phase 2	T2D patients as add-on to metformin	Imeglimin + metformin	12 weeks	Additional HbA1c reduction (0.5%) vs. metformin alone; well tolerated with minimal side effects	25
Phase 3	Japanese patients with T2D (n = 215)	Imeglimin monotherapy	24 weeks	HbA1c reduced by 0.87% from baseline; significant improvement in fasting glucose and postprandial glucose	11
Phase 3	Japanese patients with T2D on insulin therapy	Imeglimin + insulin	24 weeks	HbA1c reduced by 0.64% from baseline; incidence of hypoglycaemia comparable to placebo	26
Long-term Study	T2D patients	Imeglimin monotherapy (long-term)	52 weeks	Sustained HbA1c reduction; no serious drug-related treatment-emergent adverse events	27

Comparative Effectiveness

Imeglimin enhances β-cell activity, and thus, is preferred to Metformin. Imeglimin ameliorates and restores the pancreatic β-cells responsible for the manufacture of insulin. This leads to increased stomach natural insulin release and increased blood glucose level management. Imeglimin replenishes a primary deficit in type 2 diabetes mellitus by enhancing β-cell mass and function. This tends to make it a far more complete therapy methodology because it not only raises sensitivity to insulin that is already present, but it also stimulates the manufacture of much more insulin within a person's body. Thus, the therapeutic effects of Imeglimin transcend simple glycaemic control for the metabolic alteration. It enhances heart performance by reducing oxidize stress and enhance the endothelial health, within the cardiovascular system. Imeglimin also exerts renal-protective effects originated from the augmentation of mitochondrial biogenesis and the attenuation of oxidative stress, two factors that are critical to diabetic nephropathy development. Because Imeglimin represents an SGLT inhibitor, it may also be a potential drug for managing diabetes' systemic effects.[28,29]

In a 24-week randomised controlled trial, Dev Sudersan V et al efficacy and safety of Imeglimin accompanied with Sitagliptin to Metformin/Sitagliptin in 103 patients with T2DM. This is a randomised, open-label controlled trial that revealed a superior glycaemic control by Imeglimin with a greater percentage reduction in HbA1c by -1.3% as compared to Metformin, -0.6%. Imeglimin was also shown to bring about greater reductions in fasting blood sugar (FBS) and postprandial blood sugar (PPBS). The results displayed enhancements in insulin sensitivity and a reduction in the BMI of all patients in both treatment groups the treatment group administered Imeglimin had slightly more weight loss outcomes than the control treatment.[21]

Pirags et al. (2012) performed two multicentre, randomized phase II studies to establish the superiority of Imeglimin over Metformin in one pill regimen for T2DM patients. The first study was a 4-week crossover trial with 59 patients with T2DM who were either novices to antidiabetic agents or treated only with sulfonylurea or metformin. They were divided into two groups based on their haemoglobin A1C level which fall between 6.5 percent and 8.5 percent. The participants were divided into three groups: Imeglimin 2,000 mg once daily, Imeglimin 1,000 mg twice day (BID), and Metformin 850 mg BID of the investigational medicinal products. The overall mean A1C at restudy in these groups of patients was 7.41%, 7.07% and 7.27% respectively. Imeglimin BID showed the biggest improvement on the OGTT AUCPG compared to baseline, with the Pro area of 33% in comparison with Metformin (30%) and Imeglimin once daily (10%). The findings of these data show that Imeglimin BID is as effective in managing blood glucose concentration as Metformin. The second research lasted 8 weeks and comprised 128 patients with haemoglobin A1C levels ≤10% (average A1C: 7.1-7.3%). Participants were randomly assigned to one of four groups: Imeglemine 500 mg BID vs Imeglimin 1,500 mg BID vs Metformin 850 mg BID, or placebo, with baseline mean A1C of 7.20%, 7.35%, 7.12% and 7.21% respectively. Compared with placebo, Imeglimin 1,500 mg BID was superior in reducing the mean AUC0-6h for glucose over a longer meal: Imeglimin 500 mg BID was not significantly different from placebo, indicating that the higher dose regimen is more effective. These doses of Imeglimin and Metformin significantly reduced FPG and haemoglobin A1C, although Imeglimin 500 mg BID exhibited minor increments in both parameters, demonstrating the efficacy of the 1,500 mg BID dose. In terms of safety information, it was found that patient in the Imeglimin groups claimed less adverse events compared to patient in the Metformin groups. According to the results, gastrointestinal disorder was significantly more frequent in the Metformin group with overall less than 5% while headaches were reported frequent in the Imeglimin group. However, disadvantages of mentioned trials include low number of participants, short duration of follow-up, and inadequate assessment of Imeglimin impact on haemoglobin A1C – 3-month blood glucose average. Concerning, these outcomes cast doubt into the clinical benefit of Imeglimin that displays longer ACTG1 efficacy to A1C. [30]

The published research by Fouqueray and others to fill the gap in knowledge on Imeglimin and its effect on the level of haemoglobin A1C was to compare its effects after treatment for three months. [24,25] The first, prospective, multicentre, randomized controlled trial enrolled 156 patients with A1C of ≥7.5%. Participants were randomised to placebo administered with metformin or Imeglimin 1,500 mg BID along with metformin. Baseline A1C levels were 8.5% (range: 7. Imeglimin: overall LLNR change from baseline 1–10.2%, Placebo: overall LLNR change from baseline 8.6% (range, 7.3–10.2%). A significantly superior reduction of A1C level was observed in the combination groups receiving metformin with Imeglimin from 8.5 ± 0.6% to 7.84 ± 0.34% compared with metformin-placebo group from 8.6 ± 0.42 to 8.31 ± 0.41% ($p = 0.001$). Also, fasting plasma glucose (FPG) level declined significantly in the metformin-Imeglimin group compared to placebo group ($p < 0.001$). Metformin-Imeglimin group had a numerically higher percentage of patients who attained A1C <7% than metformin-placebo group 14.3% vs 3.8% respectively (p value 0.04) With reference to intergroup comparison 63.6% of the patients in the metformin-Imeglimin group experienced an A1C reduction of ≥0.5% compared These outcomes support the use of Imeglimin as an adjunct treatment option for T2DM subjects who show insufficient glycaemic control when on metformin monotherapy. In addition, no signs of increased risk of adverse events were observed, thus the safety of a combination therapy is proved. However, like in the work of Pirags and colleagues, limited sample size was also an issue here. In the second study, another 170 patients with A1C ≥ 7.5% and on sitagliptin monotherapy were then assigned at random to recess sitagliptin plus placebo or sitagliptin in conjunction with Imeglimin 1,500 mg BID for 12 weeks. At baseline, A1C levels were also similar between both groups; patients in the placebo intake group had an average A1C score of 8.53%, while those in the intervention intake group had an A1C score of 8.47%.[25] The analysis also revealed that sitagliptin-Imeglimin had better efficacy than sitagliptin-placebo regimens. It was found that a significantly higher percentage of patients in the intervention group attained an A1C of ≤7% (19.8% vs 1.1%, $p = 0.004$), greater mean decrease in A1C compared with baseline ($p < 0.0001$) and at least 0.5% decrease in A1C (54.3% vs. 21.6%, p < 0. Moreover, no treatment-emergent adverse events were identified, and this result supports the favourable safety profile of the combination therapy. These results are aligned with a previous study performed on the combination of metformin and Imeglimin and can attest to using Imeglimin as a second line of therapy for T2DM. Although the subjects involved are few compared to larger population studies, both the studies have shown a marked rise in glycaemic responsibility of Imeglimin as a beneficial addition to combination regimes in T2DM.

Safety and Tolerability

Katsuhiko Hagi et al., carried a Meta-analysis as first systematic review of Imeglimin's efficacy, safety, and tolerance in the treatment of T2DM, as applicable to RCTs. The outcome showed that Imeglimin significantly lower HbA1c, FBS, and other parameters they are alone or in combination with arms. The increase in treatment efficacy was noted two weeks after the beginning of the treatment, and the highest advantage was achieved with doses of 1000 Cubic mg, taken twice a day. With respect to safety, Imeglimin was reasonably safe treatment with no differences in the trend of early termination, serious adverse events, compared to placebo. The only side effect with a higher frequency was diarrhoea noted in the monotherapy group dosed at 1,500 mg b.i.d, and the authors considered it to be a minor concern. Slightly higher body weight, mean BMI, and mean LDL-C were also exteriorized; however, these were within the non-clinical values. A posteriori analysis of the results showed that Imeglimin could have a stronger positive effect on subjects that have a low BMI, particularly within Asian subjects, and efficacy in the medicine does not differ depending on the stage of chronic kidney disease. Even if the number of researches is still limited, and the treatments' duration is relatively short some of the meta-analysis results prove the effectiveness and safety of Imeglimin in T2DM management. [31]

Adverse Effects Profile

Imeglimin has always provided better safety signals to manage type 2 diabetes, giving it a therapeutic advantage in patients with such complications or in those patients who are at risk. Imeglimin was associated with similar adverse effect (AE) profiles as placebo and has no evidence of increased risk of serious AEs. For example, in the Phase 3 trial of Japanese patients, 44.3% of the imeglimin treated patients and 44.9% of the placebo group, reported AEs. Subcutaneous imeglimin was again proven to be safe and well tolerated in 52-week long term studies, The frequently reported Treatment-emergent adverse events being nasopharyngitis, pharyngitis and nausea experienced by the patients in the imeglimin arm in over 5% of the patients while the less frequently observed events were diarrhoea, constipation, hypoglycaemia and hyperglycaemia observed in the range of significant interest, no treatment emergent adverse event related to the use of any of the intent to treat drugs was considered serious. When combined with metformin, sitagliptin, or insulin as combination therapies, imeglimin had the similar tolerability profile to placebo plus other antidiabetic agents with regard to no clinically relevant effect on the pharmacokinetics of the combined medications. In the combination trials, hypoglycaemia was not severe and required no physiologically motivated intervention. On patients with moderate hepatic dysfunction, imeglimin was safe. In this group, the plasma concentrations of the drug were increased associated with reduced clearance and no adverse effects were reported but dose adjustment to 5 mg once daily was recommended for patients with an eGFR of 15– 45 mL/min/1.73 m^2 to avoid toxicity. In patients with severe renal impairment (eGFR < 15 mL/min/1.73 m^2), the extension of the dosing interval was recommended.[27]

Imeglimin on the other hand of this class offers special safety benefits where the risk of lactic acidosis associated with metformin is a major problem in renal failure patients or during major surgeries. In vitro and in vivo experiments on dogs and rats also revealed that imeglimin had minimal impact in inhibiting complex I and mGPDH, two critical mechanisms propounded for the generation of lactic acidosis with metformin. Regardless of its dose and independent of the stress factors, imeglimin did not cause lethal lactic acidosis as a marked departure from the metformin. These findings make imeglimin a safer option especially in patient with renal or hepatic compromise; they showed adequate glycaemic control together with low risk for severe metabolically associated complications. [32]

DISCUSSION

Imeglimin is apparently a new drug for the treatment of type 2 diabetes since the known efficacy and safety of metformin are proven. The clinical trials and pharmacokinetic studies also reveal its appropriateness for different patient categories – those with renal/ hepatic aliments or with lactic acidosis risk – a drawback of the metformin therapy. The AEs rated for imeglimin and placebo are almost similar in different studies which makes it safe to use. Compared to placebo, sitagliptin, metformin or insulin as monotherapy or when combined with imeglimin, imeglimin was not associated with any clinically significant AE. Notably, the rate of hypo-glycemia, a common problem contributing to undue morbidity in diabetes was moderate and was not associated with any need for help. The fact that no severe drug related Treatment-emergent adverse events were reported and this was over a 52-week course, accentuates the safety and possibly longevity of use of the drug in clinical practice. [27]The pharmacokinetics of Imeglimin are also beneficial making the drug even more attractive. No serious drug-drug interactions with inhibitors of transporter proteins including multidrug and toxin extrusion proteins (MATE) and organic cation transporters (OCT) makes its safe use alongside other medication possible as most patients with T2DM are on multiple medications. Moreover, it has shown favourable tolerability in moderate hepatic impairment and can be dose adjusted in patients with renal impairment, which can benefit by individualised therapy. Thus, the dose adjustments according to creatinine clearance were found to enhance the therapeutic efficacy while not worsening the adverse effects' profile, which makes imeglimin quite reasonable for chronic kidney disease patients.[33]

CONCLUSION

In summary, imeglimin can be considered as one of the best options for patients with diabetes because it promotes efficacy, security, and tolerability. These features put it into a position of the needed component of the therapeutic strategy of diabetic patients because it reveals several threats in the diabetes management, including the possibilities of lactic acidosis and treatment-related complications. Subsequent research work will be of assistance in elaborating its application and usefulness in promoting patient favouring results in a type 2 diabetes population. Imeglimin assumes a benign safety profile and could be considered as a safe therapeutic agent for type 2 diabetes mellitus. Clinical trials continue to demonstrate that it has AE rates similar to placebo whether used as a monotherapy agent or in combination with other antidiabetic agents including metformin, sitagliptin or insulin. Overall, there are no changes in its pharmacokinetic profile across different categories of patients: mild, moderate or severe hepatic or renal impairment; With dose adjustments, further, it remains safe and effective in patients with renal issues. However, it is identified that imeglimin has lesser risk of lactic acidosis than metformin because according to preclinical data, there is no alteration in mitochondrial inhibition and lactic acid accumulation in normal and high-risk conditions such as renal failure or major surgical procedures. These findings fill a significant research gap in biguanide therapy to bring focus to imeglimin as a safer drug especially for the high-risk metabolic patients. On the safety side, there is no end in sight for possible side effects associated with imeglimin; however, from the perspective of combination therapy, imeglimin supplements seem promising for the treatment of type 2 diabetes. Subsequent studies involving larger cohorts, long term effects, and comparing the effects of this agent to other medication used in the management of diabetes will refine its application in managing diabetic patients.

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REFERENCES

1. World Health Organization. Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes. 2024.

2. IDF. Diabetes around the world in 2021. https://diabetesatlas.org/regional-factsheets/. 2021.

3. Jia W. Diabetes care in China: Innovations and implications. J Diabetes Investig. 2022 Nov 19;13(11):1795–7.

4. Dilworth L, Facey A, Omoruyi F. Diabetes Mellitus and Its Metabolic Complications: The Role of Adipose Tissues. Int J Mol Sci. 2021 Jul 16;22(14):7644.

5. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020 Aug 30;21(17).

6. Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, Cañizo-Gómez FJ del. Update on the treatment of type 2 diabetes mellitus. World J Diabetes. 2016;7(17):354.

7. Fouqueray P, Leverve X, Fontaine E, Baquié M, Wollheim C. Imeglimin - A New Oral Anti-Diabetic that Targets the Three Key Defects of type 2 Diabetes. J Diabetes Metab. 2011;02(04).

8. Hallakou-Bozec S, Vial G, Kergoat M, Fouqueray P, Bolze S, Borel A, et al. Mechanism of action of Imeglimin: A novel therapeutic agent for type 2 diabetes. Diabetes Obes Metab. 2021 Mar 29;23(3):664–73.

9. Schernthaner G, Brand K, Bailey CJ. Metformin and the heart: Update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure. Metabolism. 2022 May;130:155160.

10. MIMA A. Safety and Efficacy of Imeglimin for Type 2 Diabetes in Patients Undergoing Dialysis. In Vivo (Brooklyn). 2023;37(3):1334–8.

11. Doupis J, Baris N, Avramidis K. Imeglimin: A New Promising and Effective Weapon in the Treatment of Type 2 Diabetes. TouchREVIEWS in endocrinology. 2021 Nov;17(2):88–91.

12. Nowak M, Grzeszczak W. Imeglimin: a new antidiabetic drug with potential future in the treatment of patients with type 2 diabetes. Endokrynol Pol. 2022 Apr 27;73(2):361–70.

13. Perry RJ, Cardone RL, Petersen MC, Zhang D, Fouqueray P, Hallakou-Bozec S, et al. Imeglimin lowers glucose primarily by amplifying glucose-stimulated insulin secretion in high-fat-fed rodents. American Journal of Physiology-Endocrinology and Metabolism. 2016 Aug 1;311(2):E461–70.

14. Pacini G, Mari A, Fouqueray P, Bolze S, Roden M. Imeglimin increases glucose-dependent insulin secretion and improves β-cell function in patients with type 2 diabetes. Diabetes Obes Metab. 2015 Jun 25;17(6):541–5.

15. LABLANCHE S, TUBBS E, COTTET-ROUSSELLE C, LAMARCHE F, MOISAN A, PERSOONS V, et al. Imeglimin Protects INS-1 Cells and Human Islets against High Glucose– and High Fructose–Induced Cell Death by Inhibiting the Mitochondrial PTP Opening. Diabetes. 2018 Jul 1;67(Supplement_1).

16. Pinti M V., Fink GK, Hathaway QA, Durr AJ, Kunovac A, Hollander JM. Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. American Journal of Physiology-Endocrinology and Metabolism. 2019 Feb 1;316(2):E268–85.

17. Vial G, Chauvin MA, Bendridi N, Durand A, Meugnier E, Madec AM, et al. Imeglimin Normalizes Glucose Tolerance and Insulin Sensitivity and Improves Mitochondrial Function in Liver of a High-Fat, High-Sucrose Diet Mice Model. Diabetes. 2015 Jun 1;64(6):2254–64.

18. Detaille D, Vial G, Borel AL, Cottet-Rouselle C, Hallakou-Bozec S, Bolze S, et al. Imeglimin prevents human endothelial cell death by inhibiting mitochondrial permeability transition without inhibiting mitochondrial respiration. Cell Death Discov. 2016 Jan 18;2(1):15072.

19. Yaribeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Molecular Mechanisms by Which Imeglimin Improves Glucose Homeostasis. J Diabetes Res. 2020 Mar 6;2020:1–5.

20. Doupis J, Baris N, Avramidis K. Imeglimin: A New Promising and Effective Weapon in the Treatment of Type 2 Diabetes. touchREVIEWS in Endocrinology. 2021;17(2):88.

21. Venkatesan DS, Chandrasekaran A, Ramalingam D, Vijayakumar S, Ananthathandavan P, JS K. The Efficacy of Imeglimin Compared to Metformin in Dual Therapy with DPP-4 Inhibitor on Glycemic Control and Weight Management: A Randomized Controlled Trial. 2024.

22. Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, Del Cañizo-Gómez FJ. Update on the treatment of type 2 diabetes mellitus. World J Diabetes. 2016 Sep 15;7(17):354–95.

23. Nagendra L, Bhattacharya S, Bhat S, Dutta D, Kamrul-Hasan ABM, Kalra S. Comparative Analysis of Metformin and Imeglimin: Exploring Therapeutic Implications. Bangladesh Journal of Endocrinology and Metabolism. 2024 Jan;3(1):3–8.

24. Fouqueray P, Pirags V, Inzucchi SE, Bailey CJ, Schernthaner G, Diamant M, et al. The Efficacy and Safety of Imeglimin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy. Diabetes Care. 2013 Mar 1;36(3):565–8.

25. Fouqueray P, Pirags V, Diamant M, Schernthaner G, Lebovitz HE, Inzucchi SE, et al. The Efficacy and Safety of Imeglimin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Sitagliptin Monotherapy. Diabetes Care. 2014 Jul 1;37(7):1924–30.

26. Reilhac C, Dubourg J, Thang C, Grouin J, Fouqueray P, Watada H. Efficacy and safety of imeglimin add-on to insulin monotherapy in Japanese patients with type 2 diabetes (<scp>TIMES</scp> 3): A randomized, double-blind, placebo-controlled phase 3 trial with a 36-week open-label extension period. Diabetes Obes Metab. 2022 May 8;24(5):838–48.

27. Dubourg J, Fouqueray P, Quinslot D, Grouin J, 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 (<scp>TIMES</scp> 2): A 52-week, open-label, multicentre phase 3 trial. Diabetes Obes Metab. 2022 Apr 27;24(4):609–19.

28. 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 Aug 2;12(1):13220.

29. Nishiyama K, Ono M, Tsuno T, Inoue R, Fukunaka A, Okuyama T, et al. Protective Effects of Imeglimin and Metformin Combination Therapy on β-Cells in db/db Male Mice. Endocrinology. 2023 Jun 26;164(8).

30. Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel glimin oral antidiabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. Diabetes Obes Metab. 2012 Sep 16;14(9):852–8.

31. Hagi K, Nitta M, Watada H, Kaku K, Ueki K. Efficacy, safety and tolerability of imeglimin in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. J Diabetes Investig. 2023 Nov;14(11):1246–61.

32. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Glucose-Lowering Effects of Imeglimin and Its Possible Beneficial Effects on Diabetic Complications. Biology (Basel). 2023 May 16;12(5):726.

33. Chevalier C, Fouqueray P, Bolze S. Imeglimin: A Clinical Pharmacology Review. Clin Pharmacokinet. 2023 Oct 15;62(10):1393–411.