Imeglimin: Finding a Place in Modern Diabetes Pharmacotherapeutics

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A B S T R A C T

Type 2 diabetes mellitus (T2DM) is a multifactorial disease. Newer facets of its causation, clinical course, complications and therapy are being unraveled regularly. This editorial describes imeglimin, a first-of-class oxidative phosphorylation inhibitor, that has been approved for T2DM in Japan and India.

Keywords: Gluconeogenesis, imeglimin, oxidative phosphorylation inhibitor, mitochondria, pharmacotherapeutics, type 2 diabetes mellitus

Introduction

Newer facets of the pathophysiology of diabetes are being recognized by researchers. This has opened up novel possibilities and avenues for the treatment of this syndrome. Oxidative phosphorylation is a key biochemical reaction, which occurs in our cells, and ensures energy homeostasis. Modification of the pathways of oxidative phosphorylation is a promising therapeutic target for diabetes, and imeglimin, a novel drug, utilizes this mechanism. The clinical trial program of imeglimin has shown favorable results. This editorial analyzes this new molecule as a potential treatment of diabetes.

Table 1. Mechanism of Action of Imeglimin

Biochemical
• Inhibition of oxidative phosphorylation
• Modulation of mitochondrial function and structure
Physiological
• Increase in insulin sensitivity (muscle uptake of glucose)
• Reduction of hepatic gluconeogenesis
• Increase in insulin secretion
Downstream
• Reduction in formation of reactive oxygen species (antioxidant effect)

Mechanism of Action

Imeglimin has a dual mechanism of action. It acts simultaneously to increase insulin sensitivity as well as insulin secretion. Both these mechanisms are mediated through separate biochemical pathways (Table 1).[1]

Insulin secretagogue

Imeglimin enhances insulin secretion of nicotinamide phosphoribosyltransferase (NAMPT). NAMPT is the rate-limiting enzyme for nicotinamide adenine dinucleotide (NAD) synthesis. If expressed properly, it increases intracellular NAD^+ concentration, which in turn optimizes the efficiency of the mitochondrial electron transport chain, and increases mitochondrial adenosine triphosphate (ATP) content in the beta cells. This inhibits ATP-sensitive potassium (K_{ATP}) channel activity, encourages calcium influx into the beta cells, and promotes insulin secretion. A NAD^+ metabolic known as cyclic ADP-ribose (cADPR) also increases glucose-stimulated release from the beta cells.[1]

Insulin sensitization

Imeglimin also optimizes mitochondrial function in hepatocytes. It inhibits complex I activity, restores complex III activity and suppresses formation of

reactive oxygen species (ROS). In the muscle, it improves uptake of glucose by increasing the expression of a transcriptional coactivator termed as peroxisome proliferator-activated receptor-γ coactivator 1α (PgC1α).[1]

Imeglimin vs. Metformin

Imeglimin differs from metformin in that it is a competitive inhibitor of complex I activity and balances complex III: I function. Its insulinotropic effect also sets it apart from metformin. There is no risk of lactic acidosis with imeglimin. Metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPDH) and causes pyruvic acid to be converted to lactic acid, which may accumulate to toxic levels. However, imeglimin is not an mGPDH inhibitor and therefore this safety concern does not arise with its use.[2]

Place in Taxonomy

Imeglimin is the first of its class of oxidative phosphorylation inhibitors. It is thought to act by increasing the mitochondrial bioenergetic efficiency of cells in the pancreas, liver and skeletal muscle. Imeglimin does not find mention in contemporary classifications of glucose-lowering therapy,[3,4] though it is listed in a classification of obesity-lowering drugs.[5] However, it can be comfortably placed along with other insulin secretagogues as well as insulin sensitizers. Imeglimin does not lead to hepatic AMP kinase activation in murine models.[6]

Clinical Trial Program

A robust clinical trial program has been conducted using imeglimin as monotherapy as well as in combination with other glucose-lowering drugs in Caucasian and Japanese participants. A recent meta-analysis of 8 studies involving 1,555 participants with type 2 diabetes mellitus (T2DM) reported a statistically significant reduction in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) as compared to the control group.[7] The Trials of Imeglimin for Efficacy and Safety (TIMES) 1 study compared imeglimin monotherapy with placebo in 213 Japanese participants over 24 weeks. It demonstrated a 0.87% reduction in HbA1c with a safety profile similar to that of placebo.[8] The open-label TIMES 2 study, assessed imeglimin in 714 participants, both as monotherapy and in combination with other glucose-lowering drugs (acarbose [n = 64], metformin [n = 64], dipeptidyl peptidase-4 inhibitors [n = 63], glinide [n = 64] glucagon-like peptide-1 receptor agonist [n = 70], sodium-glucose co-transporter 2 inhibitor [n = 63], sulfonylurea [n = 127] and glitazone [n = 65]). This Japanese study lasted 52 weeks, and showed an HbA1c reduction of 0.92%. Most adverse events were mild or moderate in nature.[9]

TIMES 3 was a 16-week long study with a 36-week open-label extension period conducted in 215 Japanese participants. It assessed the safety and efficacy of imeglimin in combination with insulin. An HbA1c reduction of 0.60% and 0.64% was noted at 16 and 52 weeks, respectively, with a satisfactory safety profile. Imeglimin use did not increase the risk of hypoglycemia.[10]

Safety

Imeglimin has shown a good safety and tolerability profile in both animal models and clinical studies. Angiomatous hyperplasia leading to development of hemangioma and possibly hemangiosarcoma has been observed in the small intestine of rats, but this appears less relevant to humans considering the relative dose used.[1] In clinical trials, no major safety or tolerability issue has been flagged. Imeglimin is well-absorbed orally, and is excreted through the kidney. The drug is safe for use even in severe renal insufficiency, albeit in reduced doses, though it has not been studied in severe hepatic impairment.

Place in Treatment Algorithms

The drug should be a welcome addition to our existing choice of glucose-lowering drugs. A rational approach incorporating both nonpharmacological and pharmacological modes of treatment is the way to successful diabetes management. Table 2 lists the

Table 2. Potential Indications for Imeglimin

Initiation
- If other drugs are contraindicated or considered to have averse risk-benefit ratio, e.g.;
  - Elderly
  - Renal insufficiency
- Isolated fasting hyperglycemia

Interchange
- If other drugs are not well-tolerated, e.g.;
  - Gastrointestinal effects
  - Risk of acidosis
  - Weight gain
  - Hypoglycemia

Intensification
- If other drugs are insufficient in achieving euglycemia

Table 3. Posology of Imeglimin

- Available as 500 mg tablets
- Dose 1000 mg twice a day post-meal
- Indication: type 2 diabetes
- Contraindications:
  - Pregnancy, lactation, preconception
  - Childhood
  - Intensive muscle exercise
  - Excessive alcohol intake
  - Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 [for full dosage]
  - Significant hepatic dysfunction
  - Pituitary or adrenal dysfunction
- Dose 500 mg if eGFR 15-45 mL/min/1.73 m^2
- Dose 500 mg OD if eGFR <15 mL/min/1.73 m^2
- No clinically significant drug-drug or drug-food interactions

potential position for imeglimin in T2DM, and suggests some specific indications for its use. Table 3 highlights the important posological considerations, caveats and contraindications which must be kept in mind while prescribing the drug.

We take this opportunity to reiterate, however, that no drug, singly or in combination can address the wide spectrum of pathophysiological abnormalities that lead to and are associated with type 2 diabetes. We also iterate that a balanced lifestyle and mind style including focus on diet, exercise, stress and sleep management are integral to diabetes care.

Summary

Imeglimin is now approved in India. The basic and clinical pharmacology of the molecule is encouraging and we hope that it will prove its mettle in the fight against diabetes.

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