Imeglimin

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Glycemic control for type 2 diabetes continues to be a global concern, with diabetes entering the top 10 causes of death globally, at number nine, in 2020 (1). Studies have found that glycemic control has declined in the last several years, with <60% of patients meeting their A1C goal in 2014 (2). A more recent review found that young adults with type 2 diabetes have worse glycemic control than past cohorts, with an average A1C of 8.5% (3). There are many challenges to the management of diabetes, including high health care costs, poor patient adherence, and contraindications to and side effect profiles of available drug classes that limit their use.

Imeglimin is a novel antidiabetic agent for the treatment of type 2 diabetes. It is the first in a new tetrahydrotriazine-containing class of oral antidiabetic agents referred to as glimins (4). Imeglimin works by multiple mechanisms of action and has been shown to increase insulin secretion, reverse pancreatic β-cell dysfunction, and prevent death of human epithelial cells, suggesting the potential for end-organ protection. Although not yet approved by the U.S. Food and Drug Administration (FDA), imeglimin may provide a valuable new treatment option in the future.

Expected Indications

If FDA approval is obtained, imeglimin will most likely be indicated for patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control. It should also be approved as an add-on therapy in patients who are taking metformin or a dipeptidyl peptide 4 (DPP-4) inhibitor.

Mechanism of Action

Imeglimin has many purposed mechanisms of action that are not fully understood. Possible benefits of these mechanisms to improve glucose homeostasis include increasing insulin sensitivity, decreasing gluconeogenesis, increasing β-cell function, increasing mitochondrial function, and decreasing oxidative stress. Imeglimin has several documented effects on mitochondrial function. It has been found to enhance generation of adenosine triphosphate (ATP) and increase the ATP/adenosine diphosphate ratio, resulting in improvement of mitochondrial function. In addition, imeglimin amplifies glucose-stimulated insulin secretion. It improves β-cell function by increasing nicotinamide phosphoribosyltransferase, which leads to increased nictotinamide adenine dinucleotide and ultimately contributes to calcium mobilization in the insulin secretion amplification pathway (5). Enhanced insulin effects can be seen in both the liver and skeletal muscle. Recently, imeglimin was found to prevent endothelial cell death in human cells by inhibiting the opening of the mitochondrial permeability transition pore without inhibiting mitochondrial respiration.

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% (6,7). 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 (8). The safety profile is also promising, with no major adverse events, cardiovascular events, or increased incidence of hypoglycemia in patients treated with imeglimin (7–9).

Potential Disadvantages

Imeglimin is associated with gastrointestinal adverse reactions such as nausea, abdominal pain, and vomiting. The incidence of gastrointestinal disorders increased as the dose increased and was better tolerated at a dose of 1,000 mg twice daily than at a dose of 1,500 mg twice daily (6). Ongoing and future studies of imeglimin will continue to evaluate and shed light on

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the tolerability and safety of this agent. Furthermore, imeglimin has not been fully studied in patients with hepatic dysfunction and chronic kidney disease.

Cost

The likely cost of imeglimin is not yet known. It is being developed in Japan by Poxel, together with their partner Sumitomo Dainippon Pharma (10). In the United States, Europe, and other areas not covered by that partnership, Poxel will maintain the rights to this medication.

Commentary

In addition to lowering A1C, imeglimin has been found to decrease fasting plasma glucose when given at a dose of 1,000 or 1,500 mg twice daily (6–9). Additionally, discontinuation rates were similar to those occurring with placebo and those of the monotherapy group when studied as an add-on therapy (6–9), showing further promise for imeglimin as a potential add-on agent. Although its place in diabetes therapy is not yet known, this novel treatment offers a new option for patients and clinicians when trying to optimize glycemic control.

Bottom Line

Imeglimin's unique mechanism may provide it a new niche for the treatment of type 2 diabetes if it attains FDA approval. Although its mechanism is not fully understood, this agent has been found to be well tolerated and an effective treatment option for lowering A1C, both as monotherapy and in combination with other antihyperglycemic agents, in phase 2 and phase 3 trials.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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