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In Diabetes

Dorzagliatin: Dual Acting Glucokinase Activator

As our knowledge and understanding of glucose metabolism improves, so does our ability to tackle the challenge of diabetes. The past 2 decades have witnessed the successful development of various glucose-lowering agents, including incretin-based therapies, sodium-glucose cotransporter 2 inhibitors, alpha glucosidase inhibitors, insulin analogues, and pramlintide. Many potential candidates, such as muraglitazar, have been unsuccessful, while others like rosiglitazone failed to live up to initial promise.

All new drugs have expanded the frontiers of diabetes pharmacology, by targeting novel receptors and processes. They have also enhanced the quality of clinical diabetes care, by allowing higher levels of safety and tolerability. Regulatory oversight has mandated cardiovascular outcome trials for newly developed molecules, thus facilitating focus on cardiovascular safety and benefit. In spite of these achievements, however, our average glycemic control is far from optimal. There are disturbing trends, in fact, which suggest that we our losing our grip on glycated hemoglobin (HbA1c) control.

It is this context that makes Zhu D et al's original article on dorzagliatin monotherapy in persons with type 2 diabetes interesting and exciting. In this multicentric phase 2 dose-ranging study, the authors studied four doses of dorzagliatin in a randomized, double-blind, placebo-controlled manner.

Mechanism of action

Dorzagliatin is a glucose-lowering drug with a novel mechanism of action. It acts as an activator of the enzyme glucokinase which is expressed chiefly in the pancreas and liver. The glucokinase activators are a novel class of glucose-lowering drugs which are still in development. The enzyme glucokinase acts as a glucose sensor at the pancreas, and as a glucose processor in the liver. It increase the responsiveness of the beta cell, i.e, the ability to regulate insulin secretion in response to minor changes in ambient glycemia. It also facilitates processing of glucose in the liver, and suppresses hepatic gluconeogenesis.

Results of dorzagliatin

The drug was able to achieve effective glycemic control over 12 weeks at a dose of 50 mg twice daily and 75mg twice daily, without causing serious adverse events or severe hypoglycemia.

Dorzagliatin was able to achieve significant reductions in fasting and postprandial hyperglycemia, thus achieving a placebo-subtracted HbA1c reduction of 0.44% and 0.77% in the 50mg twice daily and 75 mg twice dosage groups respectively.

The percentage of participants achieving target HbA1c was 44% and 45% in these two groups respectively. Composite outcomes, predefined as an HbA1c <7.0% without weight gain and hypoglycemia, was achieved by 26% and 35% participants respectively. These figures, which compare favorably with results of other modern glucose-lowering drugs, build hope for the use of dorzagliatin in future.

One must be mindful of certain limitations, however. Only phase 2 results have been reported so far, and even those are limited to one particular ethnic group. The molecule has not been studied in combination with other glucose-lowering therapies. Long-term studies and cardiovascular outcome trials have not been conducted yet.

Placement in practice

Much more work needs to be done before dorzagliatin reaches clinical practice. However, data from initial randomized controlled trials suggest a few scenarios for the potential use of glucokinase activators. These includes persons with type 2 diabetes and:

1. Both fasting and post prandial hyperglycemia
2. Predominant fasting hyperglycemia (hepatic insulin receptor resistance)
3. High risk of hypoglycemia
4. Weight gain with other glucose-lowering drugs
5. Glycemic variability

We look forward to results of other glucokinase activators, and larger studies on dorzagliatin as well.

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