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New drug improves glucose control without increasing risk of hypoglycemia in type 2 diabetes patients

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TAK-875, a new treatment for type 2 diabetes, improves glycaemic (blood sugar) control and is equally as effective as the sulphonylurea glimepiride (a common drug treatment) but has a significantly lower risk of hypoglycaemia (low blood sugar) and few side effects, according to the results of a phase 2 randomised trial published Online First in *The Lancet*.

Type 2 diabetes is the most common form of diabetes, accounting for 90% of the 285 million people worldwide currently living with the disease. It is primarily caused by a lack of response to insulin which leads to high blood sugar and a variety of chronic conditions.

Free fatty acid receptor 1 (FFA1), also known as G protein-coupled receptor 40 (GPR40), plays a vital role in stimulating and regulating the production of insulin. It works by boosting the release of insulin from pancreatic β-cells when glucose and fatty acids rise in the blood, such as after a meal. The release of insulin results in a fall in blood glucose levels. Drugs that activate the FFAR1 receptor have the potential to help diabetics release more insulin and improve control of blood glucose levels.

TAK-875 is a novel oral medication designed to enhance insulin secretion in a glucose-dependant manner, which means that it has no effect on insulin secretion when glucose levels are normal, and as such

has the potential to improve the control of blood sugar levels without the risk of hypoglycaemia.

In this study, Charles Burant from the University of Michigan Medical School, Michigan, USA, and colleagues randomly assigned 426 patients with type 2 diabetes who were not achieving adequate glucose control through diet, exercise, or metformin treatment to one of five doses of TAK-875 (303 patients), placebo (61), or glimepiride (62). The primary outcome was change in glycosylated haemoglobin (HbA1c) from the start of the study.

At 12 weeks, all doses of TAK-875 resulted in significant drops in HbA1c compared with placebo; a similar reduction occurred in patients given glimepiride.

At a TAK-875 dose of 25 mg or higher, about twice as many patients (33-48%) reached the American Diabetics Association target of HbA1c less than 7% within 12 weeks, compared with placebo (19%) and was similar to glyburide (40%).

TAK-875 was generally well-tolerated. The incidence of hypoglycaemia was significantly lower for all doses of TAK-875 compared with glimepiride (2% vs 19%), and was similar to placebo (2%). The overall incidence of treatment-related side effects was similar for the TAK-875 groups and placebo groups (49%; all TAK-875 groups vs 48%), but higher in the glimepiride group (61%) because of the increased risk of hypoglycaemia.

The authors say: "In view of the frequent hypoglycaemia after treatment with sulfonylureas, the low risk of hypoglycaemia after treatment with TAK-875 suggests that there may be therapeutic advantage of targeting FFAR1 in treating people with type 2 diabetes."

They conclude: "We are truly excited about the potential of TAK-875 and are eager to conduct larger trials to find out how well this drug works, how safe it is and what its place is in the treatment of diabetes."

In an accompanying Comment, Clifford Bailey from Aston University, Birmingham, UK, remarks: "On the journey to approval of a new class of treatment for type 2 diabetes, many questions will be asked of the FFAR1 agonists. Can they unlock the secretion-shy β cells, provide durable efficacy, and avoid off-target safety issues?"

Provided by Lancet