DIABETES FFAR1 ACTIVATION IMPROVES GLYCEMIA

Activation of the free fatty acid receptor 1 (FFAR1), a G-protein-coupled receptor highly expressed in pancreatic β cells, might provide a novel clinical target for the treatment of type 2 diabetes mellitus.

In a phase II study, investigators from the University of Michigan and Takeda Global Research and Development Center randomly assigned 426 patients to receive either the FFAR1 agonist TAK-875 ($n=303$) at one of five doses (6.25, 25, 50, 100 or 200 mg), placebo ($n=61$) or the sulfonylurea glimepiride ($n=62$) for 12 weeks. Patients already receiving stable metformin therapy (76%) continued this treatment throughout the trial.

“The significance of the study is threefold,” explains lead investigator Charles F. Burant (University of Michigan). “First, the drug was effective in lowering glucose and HbA_{1c} levels, with no apparent tachyphylaxis. Second, TAK-875 did not appear to cause hypoglycemia, which supports the notion that it augments glucose-stimulated insulin secretion but by itself does not act as a direct insulin secretagogue. Finally, the drug seems to be relatively safe and leads to minimal weight gain.” However, as Burant readily acknowledges, studies of larger patient populations and of longer duration are needed to confirm these findings.

The insulinogenic index, a measure of β -cell function, was used to quantify the drug’s ability to augment insulin secretion. As the index was increased in patients taking TAK-875, the authors speculate that the improvement in glucose homeostasis is driven by glucose-dependent insulin secretion.

Burant and co-workers have begun *in vitro* studies to assess the effect of FFAR1 activation on β -cell metabolite levels and metabolite flux. “We’re using metabolomics and imaging to try to find out exactly how the clinical effects of this class of drugs arise on a molecular level,” comments Burant.

On the basis of the findings of the phase II trial, a phase III clinical study will be undertaken at Takeda. The results of this and future phase III studies should hopefully provide information on how FFAR1 agonists may fit into the clinical armamentarium for treating type 2 diabetes mellitus.

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