Sitagliptin improved glycemic control and β-cell function in type 2 diabetes

Aschner P, Kipnes MS, Lunceford JK, et al. **Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes.** Diabetes Care. 2006;29:2632-7.

Clinical impact ratings: Endocrinology ★★★★★★★

QUESTION

In patients with type 2 diabetes, is sitagliptin (a dipeptidyl peptidase-4 inhibitor) more effective than placebo for glycemic control?

METHODS

Design: Randomized placebo-controlled trial.
Allocation: Unclear allocation concealment.*
Blinding: Blinded (clinicians and patients).*
Follow-up period: 24 weeks.
Setting: Centers worldwide.
Patients: 741 patients 18 to 75 years of age (mean age 54 y, 52% men) who had type 2 diabetes mellitus with inadequate glycemic control on diet and exercise, had mean hemoglobin (Hb) A_{1c} 8.0% (range 6.3% to 10.9%), and had adequate compliance (≥ 75%) during the placebo run-in period. Exclusion criteria were type 1 diabetes; unstable cardiac disease; significant renal impairment (creatinine clearance < 50 mL/min); or elevated alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase levels (> 2 times the upper limit of normal).
Intervention: Sitagliptin, 100 mg/d (n = 238); sitagliptin, 200 mg/d (n = 250); or placebo (n = 253). Patients who did not meet glycemic goals received rescue therapy (metformin). Glycemic rescue criteria were fasting plasma glucose (FPG) > 15 mmol/L (270 mg/dL) from randomization to week 6, FPG > 13.3 mmol/L (240 mg/dL) from week 6 to 12, or FPG > 11.1 mmol/L (200 mg/dL) from week 12 to 24.
Outcomes: Change from baseline in HbA_{1c}, FPG, insulin, proinsulin, fasting lipids, proinsulin-to-insulin (PTI) ratio, and homeostasis model assessment of β-cell function (HOMA-β); HOMA of insulin resistance (HOMA-IR); quantitative insulin sensitivity check index (QUICKI); and adverse effects.
Patient follow-up: 86% of patients completed the study (96% were included in the analysis).

MAIN RESULTS

Both 100 and 200 mg of sitagliptin were better than placebo for reducing HbA_{1c}, FPG, PTI ratio, and HOMA-β (Table). Patients with baseline HbA_{1c} ≥ 9.0% had greater reductions in placebo-subtracted HbA_{1c} with sitagliptin at 100 and 200 mg (–1.52% and –1.50%, respectively) than did those with baseline HbA_{1c} < 8.0% (–0.57% and –0.65%) or ≥ 8.0% to < 9.0% (–0.8% and –1.13%). Sitagliptin at 100 or 200 mg did not differ from placebo for insulin, proinsulin, or fasting lipid levels; HOMA-IR; QUICKI; and adverse effects. Sitagliptin at 100 and 200 mg did not differ for any outcomes.

CONCLUSION

In patients with type 2 diabetes, sitagliptin is more effective than placebo for improving glycemic control and β-cell function.

Source of funding: Merck.

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*See Glossary.

Sitagliptin, 100 mg or 200 mg, vs placebo for type 2 diabetes at 24 weeks†

Outcomes	Comparisons	Difference in least-squares mean change between groups (95% CI)
Hemoglobin A_{1c} (%)	Sitagliptin 100 vs placebo	–0.79 (–0.96 to –0.62)
	Sitagliptin 200 vs placebo	–0.94 (–1.11 to –0.77)
Fasting plasma glucose (mmol/L)	Sitagliptin 100 vs placebo	–1.0 (–1.3 to –0.6)
	Sitagliptin 200 vs placebo	–1.2 (–1.6 to –0.8)
Proinsulin-to-insulin ratio	Sitagliptin 100 vs placebo	–0.07 (–0.11 to –0.02)
	Sitagliptin 200 vs placebo	–0.10 (–0.14 to –0.05)
Homeostasis model assessment of β-cell function	Sitagliptin 100 vs placebo	12.9 (3.9 to 21.9)
	Sitagliptin 200 vs placebo	12.8 (3.9 to 21.7)

†CI defined in Glossary and provided by author.

COMMENTARY

Having practiced at a time when the only drugs available in the United States to treat type 2 diabetes were sulfonylureas and insulin, I welcome the attention of scientists and drug companies to the development of totally new classes of drugs to treat this devastating disease. Sitagliptin is a member of the dipeptidyl peptidase-4 inhibitor class of oral agents that blocks the degradation of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. Both of these are released in response to food intake, and both in turn stimulate insulin and suppress glucagon release. Sitagliptin improves insulin secretion but does not change insulin resistance.

Nevertheless, we should proceed cautiously. The study by Aschner and colleagues was only 24 weeks in duration, whereas long-term studies examining important morbidity and mortality outcomes or incidence of rare side effects are not yet available. We learned a hard lesson about the need for postmarketing surveillance with troglitazone (1). Direct comparisons with other oral agents also need to be done.

The patient population in this study is not really the population for whom we need new options. Sitagliptin was tested in patients with short duration of type 2 diabetes who were able to live for 2 months without any antidiabetic medications and had no unstable cardiac disease or significant renal or liver disease. But the patients we have problems treating are those who cannot take metformin because of renal disease or cannot tolerate glitazones because of fluid retention. From the results of this study, we do not know if sitagliptin is safe for them.

As with almost every drug tested, about a 1% reduction in HbA_{1c} was achieved. But the cost will be $5/d for sitagliptin compared with either $4/mo for metformin or no cost to go outside and walk briskly for 45 min/d. Sitagliptin should not be the first-line agent to treat type 2 diabetes because of current limited evidence of both its effects and its cost.

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Reference

1. Rezulin to be withdrawn from the market. U.S. Department of Health and Human Services NEWS. 21 March 2000. http://www.fda.gov/bbs/topics/NEWS/NEW00721.html (accessed 30 January 2007).