Vildagliptin was effective as add-on therapy in type 2 diabetes inadequately controlled with metformin monotherapy

Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. **Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin.** Diabetes Care. 2007;30:890-5.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Endocrinology ★★★★★★☆

QUESTION

In patients with type 2 diabetes inadequately controlled with metformin monotherapy, is vildagliptin (VDGP) effective as add-on therapy for 24 weeks?

METHODS

Design: Randomized placebo-controlled trial.
Allocation: Unclear allocation concealment.*
Blinding: Blinded (clinicians and patients).*
Follow-up period: 24 weeks.
Setting: 79 centers in the United States, 8 in France, 6 in Italy, and 16 in Sweden.
Patients: 544 patients 18 to 78 years of age with a body mass index 22 to 45 kg/m^2 and fasting plasma glucose (FPG) level < 15 mmol/L, who had type 2 diabetes with inadequate glycemic control (hemoglobin A_{1c} [HbA_{1c}] 7.5% to 11%) with metformin monotherapy for ≥ 3 months. Patients had to be receiving a stable dose of metformin ≥ 1500 mg/d for ≥ 4 weeks before the first screening visit; those not taking the maximum-tolerated dose agreed to increase the dose to 2000 mg/d. Exclusion criteria were type 1 or secondary forms of diabetes, complications of acute metabolic diabetes in the past 6 months, congestive heart failure requiring pharmacologic treatment, myocardial infarction, unstable angina, coronary artery bypass surgery in the past 6 months, liver disease, or renal disease or dysfunction.
Intervention: VDGP, 50 mg/d (n = 177) or 100 mg/d (n = 185), or placebo (n = 182) for 24 weeks.
Outcomes: Mean change from baseline in HbA_{1c} level. Secondary outcomes were mean change from baseline in FPG, fasting lipids (triglycerides and low-, high-, non-high-, and very-low-density lipoprotein cholesterol), and body weight.
Patient follow-up: 85% completed the study; 416 patients (mean age 54 y, 57% men) were included in the primary intention-to-treat analysis.

MAIN RESULTS

At 24 weeks, both doses of VDGP led to greater decreases from baseline in HbA_{1c} and FPG levels than did placebo (Table). VDGP 50 mg/d led to a smaller increase in fasting triglyceride level than did placebo, but VDGP 100 mg/d and placebo did not differ (Table). Groups did not differ for change in any other fasting lipid level. VDGP 100 mg/d led to a greater increase in body weight than did placebo, but VDGP 50 mg/d and placebo did not differ (Table).

CONCLUSION

Vildagliptin was effective as add-on therapy for 24 weeks in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

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*See Glossary.

Vildagliptin (VDGP), 50 mg/d or 100 mg/d, vs placebo (PLAC) as add-on therapy in type 2 diabetes inadequately controlled with metformin monotherapy at 24 weeks†

Outcomes	Adjusted mean change from baseline‡			Difference in change between groups	*P* value
	VDGP, 50 mg/d	VDGP, 100 mg/d	PLAC		
Hemoglobin A_{1c} level (%)	–0.5	—	0.2	–0.7	< 0.001
	—	–0.9	0.2	–1.1	< 0.001
FPG (mmol/L)	–0.1	—	0.7	–0.8	0.003
	—	–1.0	0.7	–1.7	< 0.001
Fasting triglycerides (%)	1	—	19	–18	0.014
	—	5	19	–14	NS
Body weight (kg)	–0.4	—	–1	0.6	NS
	—	0.2	–1	1.2	< 0.05

†Results based on primary intention-to-treat analysis (n = 416). Similar results were found for the intention-to-treat analysis (n = 520) (data not reported in article). FPG = fasting plasma glucose; NS = not significant.
‡Adjusted using Hochberg's multiple testing step-up procedure to maintain an overall 2-sided significance level of 0.05.

COMMENTARY

The multicenter study by Bosi and colleagues is one of several recently published clinical trials (1) showing efficacy of dipeptidyl peptidase (DPP)-4 inhibitors in improving glycemic control in type 2 diabetes. These studies have examined effects of DPP-4 inhibitors independently and in combination with metformin, sulphonylurea, or pioglitazone and have shown up to a 1% decline in HbA_{1c} levels. However, hard clinical endpoints, such as changes in incidence of diabetic microvascular and macrovascular complications, are clearly lacking, and further long-term randomized trials are needed.

The physiologic basis for use of DPP-4 inhibitors appears sound. Doubling the levels of native glucagon-like peptide (GLP)-1 postprandially enhances glucose-mediated insulin secretion and inhibits glucagon secretion. This leads to a favorable insulin–glucagon ratio and improved postprandial glucose and FPG. Furthermore, animal studies with DPP-4 inhibitors suggest preservation of β-cell mass by preventing apoptosis and stimulating proliferation. The achieved level of endogenous GLP-1 is insufficient to slow gastric motility, thus preventing the nausea and vomiting that occasionally occur with GLP-1 analogues. Although GLP-1 analogue therapy—unlike DPP-4 inhibition—leads to weight loss, the oral route of administration of the latter provides an advantage (2).

As a word of caution: The DPP-IV system (or CD26) has an immunomodulatory role on T-cell activation. Whether longer-term DPP-IV inhibition perturbs biological activities of T-lymphocytes or various peptides remains unknown. It is also important that DPP-IV inhibitors be highly specific for DPP-4 with minimal or no effect on DPP-8 or 9 because inhibition of DPP-8 or 9 has led to multiorgan toxicities in animal studies (3).

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References

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