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


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/m² and fasting plasma glucose (FPG) level < 15 mmol/L, who had type 2 diabetes with inadequate glycemic control (hemoglobin A1c [HbA₁c] ≥ 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 HbA₁c 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 HbA₁c 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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**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 HbA₁c 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**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Adjusted mean change from baseline‡</th>
<th>Difference in change between groups</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A₁c (%)</td>
<td>0.5</td>
<td>0.2</td>
<td>-0.7</td>
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<tr>
<td>FPG (mmol/L)</td>
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<td>0.2</td>
<td>0.7</td>
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<tr>
<td>Fasting triglycerides (%)</td>
<td>-1.0</td>
<td>0.7</td>
<td>-1.7</td>
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<tr>
<td>Body weight (kg)</td>
<td>-0.4</td>
<td>-1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

†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.