The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials


CRD summary
The authors concluded that vildagliptin at daily doses of 50 or 100mg was effective in glycaemic control for patients with type 2 diabetes, with a low risk of hypoglycaemia and other adverse reactions. Substantial heterogeneity and lack of trial quality information mean that the reliability of the authors’ conclusions is uncertain.

Authors’ objectives
To provide an update on the clinical efficacy and safety of vildagliptin in patients with type 2 diabetes.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to December 2010, for articles published in English. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) with duration of 12 weeks or more that compared vildagliptin versus a placebo or other active drugs (oral hypoglycaemic agents and/or insulin) were eligible for inclusion. Eligible trials had populations of adult patients (at least 18 years of age) with type 2 diabetes. Outcomes of interest were: glycaemic efficacy measured by mean changes in levels of glycated haemoglobin (HbA1c), fasting plasma glucose and body weight; and safety evaluation (hypoglycaemia and other main adverse events reported).

Mean patient age ranged from 51 to 70.9 years. Duration of diabetes ranged from one to 14.7 years (where reported). In intervention groups, daily dose of vildagliptin ranged from 20mg to 100mg; control treatments included placebo and other active drugs.

Two reviewers independently selected studies for inclusion; any discrepancies were resolved by a third reviewer.

Assessment of study quality
The authors did not state whether they assessed study quality.

Data extraction
Data were extracted to calculate weighted mean differences (WMD) for continuous outcomes, and risk ratios (RRs) for dichotomous outcomes; all calculations were estimated using 95% confidence intervals (CI).

Data were extracted by one reviewer and checked by a second reviewer.

Methods of synthesis
Effect sizes were pooled in a fixed-effect or random-effects meta-analysis, according to the level of statistical heterogeneity indicated by $I^2$. The inverse variance method was used for pooling mean differences and the Mantel-Haenszel method was used to pool risk ratios. Data from 100mg and 50mg regimens of vildagliptin were used for meta-analyses of dose-dependent outcomes.

Results of the review
Thirty RCTs were included in the review (18,022 patients).

Glycaemic efficacy
By endpoint, vildagliptin was statistically significantly more effective at reducing mean HbA1c levels than control treatments (WMD -32%, 95% CI -0.44 to -0.19; 30 trials; $I^2$=96%), particularly when placebo was compared with daily vildagliptin regimens of 50mg (WMD -0.58%, 95% CI -0.72 to -0.44; 11 trials; $I^2$=63%) and 100mg (WMD -0.77%, 95% CI -0.96 to -0.58; 10 trials; $I^2$=82%). Compared with metformin, daily vildagliptin regimens of 100mg were
statistically significantly less effective for reducing HbA1c levels (WMD 0.30, 95% CI 0.15 to 0.46; four trials; I²=51%). Other comparisons revealed 100mg vildagliptin regimens to have been less effective than thiazolidinediones or sulphonylureas, but more effective than α-glucosidase inhibitors for reducing HbA1c levels. None of these differences were statistically significant.

Statistically significant increases in body weight were observed when vildagliptin regimens of 100mg/day were compared with placebo (WMD 0.95 kg, 95% CI 0.73 to 1.17; ten trials; I²=0%), metformin (WMD 1.54 kg, 95% CI 0.73 to 2.36; four trials; I²=78%) and α-glucosidase inhibitors (WMD 1.19, 95% CI 0.84 to 1.55; two trials; I²=94%). Statistically significant reductions in body weight were observed when vildagliptin regimens of 100mg were compared with thiazolidinediones (WMD -1.55, 95% CI -2.10 to -1.01; five trials; I²=76%) and sulphonylureas (WMD -1.40, 95% CI -1.78 to -1.02; four trials; I²=69%). Body weight was increased with 100mg vildagliptin compared with α-glucosidase inhibitors but the difference was not statistically significant.

Compared with placebo, mean fasting plasma glucose was statistically significantly reduced with daily vildagliptin regimens of 50mg (WMD -0.57, 95% CI -0.76 to -0.38; ten trials; I²=12%) and 100mg (WMD -0.96, 95% CI -1.26 to -0.65; nine trials; I²=49%). A reduction was also demonstrated when vildagliptin (100mg/day) was compared with α-glucosidase inhibitors but this difference was not statistically significant. Statistically significant increases in mean fasting plasma glucose was observed for vildagliptin (100mg/day) in comparison with thiazolidinediones (WMD 0.75, 95% CI 0.45 to 1.05; six trials; I²=74%), metformin (WMD 0.69, 95% CI 0.41 to 0.96; three trials; I²=40%), and sulphonylureas (WMD 0.17, 95% CI 0.04 to 0.30; four trials; I²=0%).

**Safety**

Borderline statistically significant reductions in overall risk of adverse events were found for vildagliptin compared with α-glucosidase inhibitors (RR 0.77, 95% CI 0.61 to 0.97; two trials), sulphonylureas (RR 0.95, 95% CI 0.91 to 0.99; three trials), and metformin (RR 0.92, 95% CI 0.88 to 0.97; four trials). Similar results were found when vildagliptin was compared with sulphonylureas for incidence of serious adverse events (RR 0.85, 95% CI 0.73 to 0.99; three trials), and with metformin for discontinuation due to adverse events (RR 0.61, 95% CI 0.40 to 0.92; four trials). Risk of hypoglycaemia was significantly lower for vildagliptin over sulphonylureas (RR 0.25, 0.10 to 0.64; four trials), but no statistically significant differences in risk were observed between both regimen of vildagliptin (50mg/day and 100mg/day) and placebo.

**Authors' conclusions**

Vildagliptin at daily doses of 50 or 100mg was moderately effective in glycaemic control in patients with type 2 diabetes, with a low risk of hypoglycaemia and other adverse reactions.

**CRD commentary**

The review question was clear and inclusion criteria appeared sufficiently replicable. Relevant databases were searched but the restriction to studies published in English increased the likelihood of publication and language biases. Efforts were made to minimised error and bias during study selection and data extraction. It was unclear whether any quality assessment of trials was performed. Study details were presented, which revealed some clinical and methodological differences between the trials. Methods of synthesis seemed appropriate, but substantial statistical heterogeneity was not explored. Lack of quality information also meant that influence of confounding biases within the trials could not be ruled out.

Substantial heterogeneity and lack of trial quality information mean that the reliability of the authors' conclusion is uncertain.

**Implications of the review for practice and research**

**Practice:** The authors stated that daily vildagliptin doses of 50mg resulted in overall neutral effects on weight, but that daily doses of 100mg resulted in slight weight gain compared with placebo. It was suggested that vildagliptin was suitable for individuals with mild diabetes, who were at risk of hypoglycaemic sequelae.

**Research:** The authors stated that further research on outcomes with varying vildagliptin dose may provide more information, particularly on the benefit of 100mg/day vildagliptin balanced with increased weight gain versus 50mg/day vildagliptin. More direct comparisons of vildagliptin with thiazolidinediones and sulphonylureas may provide further
evidence regarding its efficacy.

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