Efficacy of vildagliptin and sitagliptin in lowering fasting plasma glucose: Results of a randomized controlled trial

R. Göke \(^a\), P. Eschenbach \(^b\), E.D. Dütting \(^b, *\)

\(^a\) Diabetes Center, Marburg-Cappel, Germany

\(^b\) Novartis Pharma GmbH, Nuremberg, Germany

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Abstract

**Aim.** – This study compared the efficacy of vildagliptin and sitagliptin in lowering fasting plasma glucose (FPG) as single-pill combinations (SPCs) with metformin.

**Methods.** – The randomized crossover, open-label, active-controlled study design assessed the FPG-lowering abilities of a vildagliptin/metformin (50/1000 mg twice daily) SPC compared with a sitagliptin/metformin (50/1000 mg twice daily) SPC after 2 weeks of treatment in 99 type 2 diabetes patients uncontrolled by stable metformin therapy (1000–2000 mg/day).

**Results.** – The change in FPG from baseline to day 14 was significantly greater (\(P < 0.02\), Wilcoxon) with vildagliptin [–21.9 mg/dL (SD 27.0)] than with sitagliptin [–14.5 mg/dL (SD 23.0)]. After 14 days of treatment, the mean FPG was 137.8 mg/dL (SD 28.5) with vildagliptin and 140.1 mg/dL (SD 26.5) with sitagliptin (\(P < 0.05\), Wilcoxon).

**Conclusion.** – Both of these DPP-4 inhibitors, given as SPCs twice daily with metformin, lowered FPG after 14 days of treatment. However, vildagliptin produced a significantly greater reduction in FPG vs baseline compared with sitagliptin, which may translate into clinical relevance.

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**Keywords:** Type 2 diabetes mellitus; Vildagliptin; Sitagliptin; Fasting plasma glucose; Dipeptidyl peptidase inhibitors

1. Introduction

Dipeptidyl peptidase (DPP)-4 inhibitors such as vildagliptin and sitagliptin improve glycaemic control in patients with type 2 diabetes mellitus (T2DM) primarily by increasing both α- and β-cell sensitivity to glucose [1]. This is achieved by DPP-4 inhibition to prevent degradation of incretins glucagon-like peptide (GLP)-1 and gastric inhibitory polypeptide (GIP) [2]. The prolonged incretin effect results in improved glucose control [3].

Vildagliptin is a substrate enzyme blocker, which prevents incretin inactivation, whereas sitagliptin competitively inhibits DPP-4, which reduces the rate of inactivation. Treatment with vildagliptin therefore leads to prolonged meal-induced increases in GLP-1 and GIP levels [4].

Large-scale reviews evaluating DPP-4 inhibitors have revealed no substantial differences in their glucose-lowering potential when used on their own [5], although some data have indicated differences in fasting plasma glucose (FPG)-lowering potential [6] and glycaemic control [7].

In the present study, FPG was chosen as the parameter to define overnight glucose control, as FPG can be assessed acutely and new steady states achieved within 2 weeks.

This study is the first to directly compare the FPG-lowering potential of vildagliptin and sitagliptin in T2DM patients in the form of single-pill combinations (SPCs) with metformin in a twice-daily regimen.

2. Methods

2.1. Study design and procedures

This study (Clinicaltrials.gov identifier: NCT01398592) applied a crossover, open-label, active-controlled design to
to assess the FPG-lowering abilities of a vildagliptin/metformin (50/1000 mg twice daily) SPC vs a sitagliptin/metformin (50/1000 mg twice daily) SPC after a 2-week treatment in T2DM patients uncontrolled by stable metformin therapy (1000–2000 mg/day).

Patients were randomized after their FPG values were assessed by a central laboratory to receive either the vildagliptin/metformin SPC during period 1 and sitagliptin/metformin SPC during period 2, or vice versa, for 14 days, with a 14-day (up to 28-day) washout period using metformin as monotherapy (1000 mg twice daily). For the analysis, patients’ data from both periods (vildagliptin/metformin and sitagliptin/metformin) were pooled, and are henceforth referred to as the vildagliptin and sitagliptin groups, respectively.

2.2. Study patients

Female and male subjects (aged 18–85 years) diagnosed with T2DM at least 3 months prior to screening and stable while taking metformin monotherapy (for at least 4 weeks prior to screening) at 1000–2000 mg/day were eligible to participate. Subjects also had to have HbA1c levels of 7.0–9.5% (with metformin ≥ 1000 mg/day but < 2000 mg/day) or of 6.5–9.5% (with metformin 2000 mg/day) at screening, and FPG of 126–270 mg/dL (7–15 mmol/L) at screening and at randomization. Women of childbearing potential not using adequate contraception and pregnant or breastfeeding women were excluded. Further relevant exclusion criteria were FPG ≥ 270 mg/dL (15 mmol/L), use of any antidiabetic medication other than metformin within the last 12 weeks, clinically significant renal dysfunction (glomerular filtration rate < 60 mL/min/1.73 m²), acute metabolic conditions, congestive heart failure, myocardial infarction and hepatic disorders.

2.3. Efficacy and safety endpoints

The two efficacy endpoints of this study were the difference in FPG between vildagliptin and sitagliptin, additionally assessed as the decrease from baseline after 2 weeks and after a missed dose of either drug. The safety evaluation consisted of the adverse events (AEs) and serious AEs (SAEs) observed in each treatment group.

2.4. Statistical analyses

Treatment effects of vildagliptin and sitagliptin on FPG were compared with an analysis of variance (ANOVA) model, using centre, period, patients within centre and treatment as factors for endpoint FPG after 2 weeks. Raw as well as adjusted (least-squares) means were provided as point estimates for the pairwise contrast of treatments. A two-sided 95% confidence interval (CI) and P-value for the null hypothesis of no treatment difference were calculated. The significance level was 5% (two-sided). For all pairwise comparisons, a non-parametric (Wilcoxon signed-rank) test was calculated.

The difference in FPG between baseline and day 14 was descriptively analyzed post hoc. The study required 83 patients to achieve a power of 90% with a two-sided significance level of 5%, and a (within-patient) standard deviation (SD) of the difference in FPG of 0.83 and a true effect size of 0.3 mmol/L. To compensate for dropouts and other protocol deviations, 100 patients were randomized into the trial.

2.5. Ethics

The study protocol was approved by the ethics committee of Hessen (Germany) and conducted in accordance with good clinical practice guidelines and the declaration of Helsinki. Written informed consent was obtained from each participant.

3. Results

3.1. Patients’ demographic and disease characteristics

A total of 99 patients [mean (SD) age: 61.2 (10.1) years; 35.4% female] with T2DM [mean (SD) time since diagnosis: 6.33 (5.79) years] from 15 centres throughout Germany were enrolled. All patients completed the study except one who discontinued due to an AE (see Safety below).

3.2. Efficacy

Mean baseline FPG values in the vildagliptin and sitagliptin groups were 159.5 mg/dL (SD 31.2) and 154.4 mg/dL (SD 26.6), respectively. Mean FPG after 14 treatment days decreased in both groups, but favored vildagliptin: the change in FPG from baseline to day 14 was significantly greater with vildagliptin [−21.9 mg/dL (SD 27.0)] than with sitagliptin [−14.5 mg/dL (SD 23.0); P < 0.02, Wilcoxon]. The final FPG values and change in FPG from baseline to day 14 are presented in Table 1.

The post hoc analysis-defined subgroup with baseline HbA1c > 7.9% showed a mean change in FPG from baseline in the first treatment period of −27.45 mg/dL (SD 28.93) for vildagliptin (n = 11) and −12.09 mg/dL (SD 23.45) for sitagliptin (n = 11).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean fasting plasma glucose (FPG) and change in FPG after 14 days of treatment.</th>
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</thead>
<tbody>
<tr>
<td>FPG</td>
<td>Vildagliptin (n = 98)</td>
</tr>
<tr>
<td>Mean FPG [mg/dL (SD)]</td>
<td>137.8 (28.52)</td>
</tr>
<tr>
<td>Difference sitagliptin – vildagliptin [95% CI]</td>
<td>2.2 [–1.8; 6.2]</td>
</tr>
<tr>
<td>P-value (ANOVA/Wilcoxon)</td>
<td></td>
</tr>
<tr>
<td>Change in FPG</td>
<td>(n = 98)</td>
</tr>
<tr>
<td>Least-squares mean change (mg/dL)</td>
<td>–21.2</td>
</tr>
<tr>
<td>Difference sitagliptin – vildagliptin [95% CI]</td>
<td>7.0 [0.2; 13.7]</td>
</tr>
<tr>
<td>P-value (ANOVA/Wilcoxon)</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA model: FPG; Change in FPG: centre, period, patients within centre and treatment.
3.3. Safety

Median exposures to both treatments were 15 days. Compliance was over 98%. Treatment-related AEs were seldom seen and mainly of mild or moderate intensity. A total of 26 patients (26.3%) developed AEs with vildagliptin and 12 (12.2%) patients with sitagliptin. The majority of the AEs in vildagliptin patients were related to system organ class infections (nasopharyngitis) and nervous system disorders (headache). Only mild hypoglycaemic events occurred during the study (affecting one vildagliptin and two sitagliptin patients); all were thought to be related to the study medication, although none led to treatment discontinuation.

One patient discontinued the study due to moderate recurring skin disorders suspected of being related to vildagliptin. Also, three patients developed SAEs (anal abscess and mamma carcinoma with sitagliptin; urinary incontinence with vildagliptin) that were regarded as not drug-related and did not lead to study discontinuation. No patient died during the study.

4. Discussion

This comparative, active-controlled trial showed significant differences between vildagliptin and sitagliptin when added to metformin for FPG-lowering potential in T2DM patients. The current results confirm observations recently made by Guerci and co-workers [7], demonstrating a significant decrease in overall hyperglycaemia with vildagliptin vs sitagliptin using continuous glucose monitoring (CGM). The effect was mainly driven by a reduction in basal hyperglycaemia [7]. Earlier studies using CGM showed significantly lower mean amplitude of glycaemic excursions (MAGEs) [8] and significant declines in MAGEs with vildagliptin compared with sitagliptin treatment [9]. These studies also found small to no changes in FPG of no statistical significance, possibly because the patients were relatively well controlled (low baseline HbA1c/FPG) [8,9] and the sample size was relatively small [8]. The present study showed a significantly more pronounced FPG-lowering effect with vildagliptin than with sitagliptin, which confirms the findings in previous studies that vildagliptin leads to better glycaemic control than sitagliptin [8,9].

Our short-term study revealed no relevant novel safety findings. Interestingly, there was an imbalance in AEs, whereas no SAEs were seen. Due to the small patient numbers and low rates of AEs, this might be a chance finding; however, in general, no firm conclusions can be drawn. Nevertheless, this observation can clearly be put into perspective by the safety profile of vildagliptin in numerous higher-powered clinical trials [10] and in the 45,868-patient observational study EDGE [11,12], in which no differences in infections between comparator arms were reported.

Regarding disease status, an interesting finding was that the difference between sitagliptin and vildagliptin was most pronounced in patients with high baseline HbA1c levels, and favored vildagliptin. However, as the subgroup with a baseline HbA1c >7.9% included only a few patients, this finding needs to be interpreted with caution. As for sitagliptin, Aso and co-workers [13] found that baseline HbA1c and serum levels of DPP-4 were independent determinants of HbA1c reduction. Further investigations may elucidate whether the different binding modes of DPP-4 inhibitors might translate into clinically relevant effects. Also, the results of the subgroup analyses indicate the greater impact of overnight hepatic glucose production on FPG in progressive disease and the importance of sufficient overnight inhibition of DPP-4, although the small number of patients per subgroup limits these findings. Furthermore, the short study duration does not allow for conclusions regarding HbA1c reduction.

Considered as a whole, this study observed a more pronounced effect in reducing FPG by vildagliptin twice daily as a substrate enzyme blocker than sitagliptin twice daily as a competitive inhibitor, even after a skipped evening dose. However, given the small sample size and short trial duration, the present findings now have to be proven in larger and longer-term comparative randomized trials.

Contributions

Prof. Göke was the principle investigator and contributed to the overall clinical interpretation. Dr Eschenbach was the key contributor to the study design. Dr Dütting was the key contributor to initial data interpretation and drafting the manuscript. All authors were involved in manuscript revisions and are responsible for intellectual content.

Disclosure of interest

Prof. Göke has received fees for consultancy, advisory boards, speaking, travel or accommodation from AstraZeneca, Bayer, Berlin-Chemie, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis, Roche and UCB. Dr Eschenbach and Dr Dütting are employees of Novartis Pharma GmbH, Germany.

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Appendix A. Supplementary data

Supplementary data (French abstract) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2014.07.004.
References