original article

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ORIGINAL ARTICLE

Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea

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Aim: The broadly used combination of metformin and sulphonylurea (SU) often fails to bring patients to glycaemic goal. This study assessed the efficacy and safety of vildagliptin as add-on therapy to metformin plus glimepiride combination in patients with type 2 diabetes mellitus (T2DM) who had inadequate glycaemic control.

Methods: A multicentre, double-blind, placebo-controlled study randomized patients to receive treatment with vildagliptin 50 mg bid (n = 158) or placebo (n = 160) for 24 weeks.

Results: After 24 weeks, the adjusted mean change in haemoglobin A1c (HbA1c) was −1.01% with vildagliptin (baseline 8.75%) and −0.25% with placebo (baseline 8.80%), with a between-treatment difference of −0.76% (p < 0.001). Significantly more patients on vildagliptin achieved the HbA1c target <7% (28.3% vs. 5.6%; p < 0.001). The difference in fasting plasma glucose reduction between vildagliptin and placebo was −1.13 mmol/l (p < 0.001). In subgroup of patients with baseline HbA1c ≤8%, vildagliptin reduced HbA1c by 0.74% from baseline 7.82% (between-treatment difference: −0.97%; p < 0.001) with significantly more patients achieving the HbA1c target <7% (38.6% vs. 13.9%; p = 0.014). Vildagliptin was well tolerated with low incidence of hypoglycaemia, slightly higher than with placebo (5.1% vs. 1.9%) and no clinically relevant weight gain.

Conclusions: Vildagliptin significantly improved glycaemic control in patients with T2DM inadequately controlled with metformin plus glimepiride combination. The addition of vildagliptin was well tolerated with low risk of hypoglycaemia and weight gain. This makes vildagliptin an attractive treatment option for patients failing on metformin plus SU particularly in patients with baseline HbA1c ≤8%.

Keywords: DPP-4 inhibitor, glimepiride, metformin, oral antidiabetic drug, type 2 diabetes, vildagliptin

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease that often requires combination of antidiabetic drugs with different mechanisms of action to achieve glycaemic targets [1–3]. The broadly used combination of metformin and a sulphonylurea (SU) fails to maintain glycaemic control over time [4] and the addition of a third antihyperglycaemic agent is required.

When choosing options for the third agent, physicians should consider improvement of glycaemic control without additional risks such as hypoglycaemia and weight gain [5]. While insulin is recommended as a preferred next step by many international and local guidelines in patients failing on dual therapy [1–3], parenteral administration, increased

risk of hypoglycaemia and weight gain may limit the use of insulin. Negative attitudes towards initiation of insulin and a preference for oral therapies by many patients should also be taken into account. Hence, a third oral agent that provides sustained glycaemic control and delays the time to permanent use of insulin could benefit patients who are reluctant to start injectable therapy [1,6].

Vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), improves glycaemic control by increasing the availability of endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [7,8]. Complementing the pharmacological effect of metformin, vildagliptin enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby improving glycaemic control, and contributing to weight-neutrality and reduced hypoglycaemia [9]. Vildagliptin has demonstrated similar efficacy as an add-on to metformin when compared to SU with markedly reduced hypoglycaemia risk and no weight gain [10,11].

This study evaluated the efficacy and safety of vildagliptin 50 mg bid as an add-on therapy in patients with T2DM inadequately controlled with dual therapy of metformin

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(≥1500 mg) and glimepiride (≥4 mg). Of particular interest was whether and which patient population could achieve glycaemic control with such a triple combination.

Methods

Study Design and Patients

This was a 24-week, multicentre, randomized, double-blind, placebo-controlled study in patients with T2DM. Eligible patients were 18–80 years of age, had body mass index (BMI) ≥22 to ≤45 kg/m^2, and were inadequately controlled on a stable dose of oral antidiabetic drugs (OADs) for at least 12 weeks prior to the screening visit. Acceptable background therapy prior to enrollment included metformin ≥1500 mg as monotherapy [haemoglobin A1c (HbA1c) ≥8.5 and ≤11%] or dual combination of metformin ≥1500 mg with SU, thiazolidinedione (TZD) or glinide (HbA1c ≥7.5 and ≤11%). Eligible patients continued their current metformin treatment ≥1500 mg throughout the study. Patients were excluded if they had fasting plasma glucose (FPG) ≥15.0 mmol/l; significant hepatic, renal or cardiovascular medical conditions; significant laboratory abnormalities; and pregnant or lactating females.

The study consisted of a 1–2 week screening period, an up to 12-week titration and/or stabilization period (depending on the type and dose of background OAD at study entry) and a 24-week double-blind treatment period. After screening, eligible patients who were (i) on metformin ≥1500 mg plus glimepiride ≥4 mg for at least 12 weeks proceeded directly to randomization; (ii) on metformin monotherapy ≥1500 mg entered a titration and stabilization period for glimepiride up to 4 mg; (iii) on any other combination with metformin discontinued their SU, TZD or glinide therapy, and entered titration and/or stabilization for glimepiride up to 4 mg. Patients were discontinued from the study if they could not tolerate the prescribed dose of metformin ≥1500 mg or glimepiride ≥4 mg during stabilization period. Eligible patients with HbA1c ≥7.5 and ≤11% at the end of stabilization period were randomized (1 : 1) to receive either vildagliptin 50 mg bid or placebo in addition to their metformin ≥1500 mg plus glimepiride ≥4 mg therapy for 24 weeks.

After randomization, the dose of metformin (≥1500 mg) was kept stable. The dose of glimepiride, however, could be adjusted downward for safety reasons at the investigators' discretion. Rescue medication (insulin or pioglitazone, per investigator discretion) was prescribed if the patient had FPG >13.3 mmol/l between week 6 and 12, FPG >11.1 mmol/l between week 12 and 24 or symptoms of worsening of hyperglycaemia at any visit.

Study Assessments and Endpoints

The primary endpoint was change in HbA1c from baseline to week 24 or to the final visit. Secondary efficacy assessments included change in FPG from baseline to week 24 endpoint and responder rates achieving HbA1c targets of <7 or ≤6.5%. Safety assessments included recording and monitoring of treatment-emergent adverse events (AEs); biochemistry and haematology laboratory test results; electrocardiogram (ECG) findings

and vital signs. Hypoglycaemia was defined by symptoms suggestive of hypoglycaemia and a self-monitored plasma glucose measurement <3.1 mmol/l. Severe hypoglycaemia was defined as an episode that required assistance of another person or hospitalization with or without a plasma glucose measurement <3.1 mmol/l.

Statistical Analysis

A sample size of 246 completed patients (123 per arm) would ensure 90% power with a one-sided significance level of 2.5% to declare superiority of vildagliptin 50 mg bid over placebo in HbA1c reduction (%) from baseline after 24 weeks of treatment, assuming a clinically relevant difference of 0.5 absolute units between treatments and a standard deviation of 1.2%. Assuming a drop-out rate of 15%, about 290 patients (145 patients per arm) were to be randomized with an equal randomization ratio 1 : 1 to the two treatment groups.

The adjusted mean changes in HbA1c and FPG from baseline to week 24 were compared between vildagliptin and placebo using an analysis of covariance model with treatment and pooled centre as a classification factor and baseline HbA1c as a covariate. This comparison was performed on full analysis set (FAS) consisting of all randomized patients who received at least one dose of the study drug and had at least one post-randomization efficacy parameter measurement. In addition, responder rates (percentage of patients achieving endpoint HbA1c <7.0 or ≤6.5%) were compared between treatments using a chi-squared test.

Efficacy data used in the analyses were censored at the start of rescue medication. The last observation carried forward (LOCF) method was used to handle missing data because of early discontinuation or data censoring. Safety data were summarized descriptively by treatment. All data of patients who received at least one dose of study medication were included in analysis for safety assessment.

Ethical Statement

This trial was conducted in accordance with the Declaration of Helsinki. An independent ethics committee or institutional review board at each research site reviewed the study protocol. Each patient gave written informed consent before randomization.

Results

Patient Disposition and Baseline Characteristics

The disposition of patients from screening to study endpoint is depicted in figure 1. Of the 564 patients screened, 318 were randomized to vildagliptin (n = 158) and placebo (n = 160). The most common reason for screen failure was having not met the diagnostic/severity criteria (66.8%) and unacceptable laboratory values (55.7%). The percentage of randomized patients who discontinued the study was overall low and slightly higher in the vildagliptin group (8.9%) than in the placebo group (3.1%) mainly due to a greater percentage of patients who withdrew consent (4.4% vs. 1.3%, respectively).
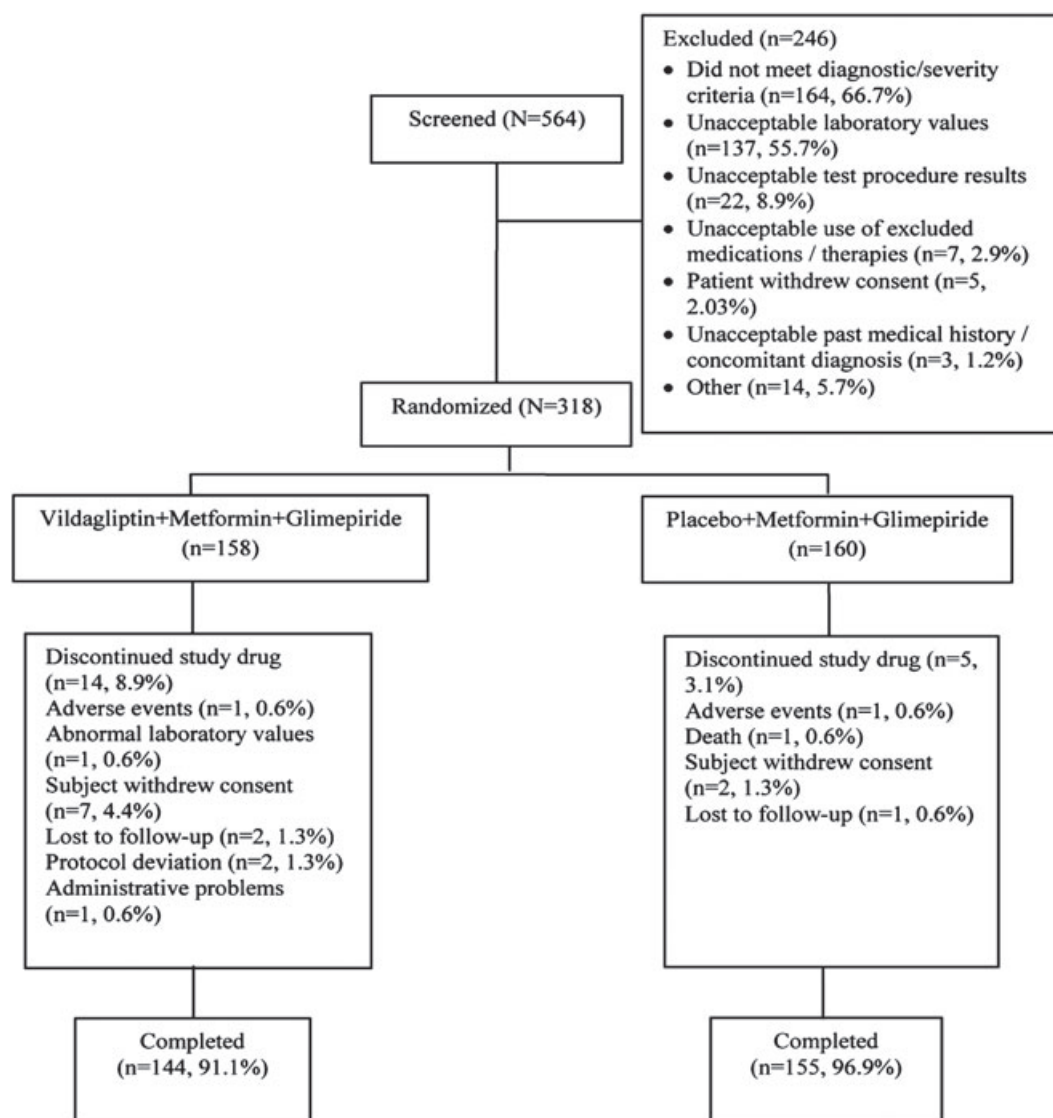
Figure 1. Patient disposition.

The demographic and baseline characteristics of the randomized patients were generally similar between the treatment groups (Table 1). The mean dose of metformin at screening was 1810 mg/day with 43.7% of patients receiving ≥2000 mg daily dose. Approximately 80% of patients (n = 254) were already treated with metformin plus glimepiride with a mean daily glimepiride dose of 4.4 mg; 35 of those patients who were on glimepiride <4 mg were up-titrated to 4 mg. Besides glimepiride, 59 (18.5%) patients were receiving other SUs, 1 (0.3%) patient was on a TZD and 4 (1.2%) patients were on metformin monotherapy at screening; all these patients were switched and up-titrated to glimepiride 4 mg as per protocol.

Efficacy

Vildagliptin had a sustained glucose-lowering effect during 24 weeks of treatment (figure 2A). The adjusted mean change in HbA1c at study end point in the vildagliptin group of −1.01% (baseline 8.75%) was significantly different from the 0.25% reduction in the placebo group (baseline 8.80%) with a between-treatment difference of −0.76% (p < 0.001) (figure 2B). Changes in HbA1c in subgroup analyses by baseline HbA1c, BMI, age, gender and race were in line with the overall study results.

After 24 weeks of treatment, a significantly higher percentage of patients on vildagliptin achieved HbA1c targets compared with placebo (HbA1c <7%: 28.3% vs. 5.6%, or HbA1c ≤6.5%: 13.2% vs. 1.3%, respectively; p < 0.001).

Vildagliptin demonstrated a clinically relevant reduction in FPG of 1.11 mmol/l (baseline 9.34 mmol/l) compared with nearly no change in the placebo group of +0.02 mmol/l (baseline 9.52 mmol/l). The difference versus placebo of −1.13 mmol/l was clinically and statistically significant (p < 0.001). Rescue medication was used by fewer patients in the vildagliptin group (n = 6/158, 3.8%) compared with the placebo group (n = 22/160, 13.8%).

Table 1. Patient baseline demographic and background characteristics (randomized set).

	Vildagliptin + Metformin + Glimepiride N = 158	Placebo + Metformin + Glimepiride N = 160	Total N = 318
Age, years	55.3 (10.2)	55.0 (11.1)	55.1 (10.6)
≥65, n (%)	29 (18.4)	38 (23.8)	67 (21.1)
Gender, female, n (%)	78 (49.4)	88 (55.0)	166 (52.2)
Race, n (%)			
Asian	116 (73.4)	116 (72.5)	232 (73.0)
Indian	81 (51.3)	77 (48.1)	158 (49.7)
Chinese	12 (7.6)	21 (13.1)	33 (10.4)
Caucasian	34 (21.5)	38 (23.8)	72 (22.6)
Other	8 (5.1)	6 (3.8)	14 (4.4)
BMI, kg/m^2	27.9 (4.6)	28.0 (4.5)	28.0 (4.5)
HbA1c, %	8.7 (0.9)	8.8 (0.9)	8.8 (0.9)
≤8%, n (%)	48 (30.4)	36 (22.5)	84 (26.4)
≤9%, n (%)	99 (62.7)	102 (63.8)	201 (63.2)
FPG, mmol/l	9.3 (2.4)	9.5 (2.1)	9.4 (2.3)
Duration of T2DM, years	7.1 (6.2)	7.5 (6.1)	7.3 (6.1)
GFR (MDRD), ml/min/1.73 m^2, n (%)			
Normal, >80	99 (62.7)	104 (65.0)	203 (63.8)
Mild, ≥50 to ≤80	55 (34.8)	50 (31.3)	105 (33.0)
Moderate, ≥30 to <50	4 (2.5)	6 (3.8)	10 (3.1)

Values are mean (s.d.) unless indicated otherwise. BMI, body mass index; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, haemoglobin A1c; MDRD, modification of diet in renal disease; T2DM, type 2 diabetes mellitus.

Table 2. Overall summary of adverse events (AEs) by treatment group (safety set).

Event	Vildagliptin + Metformin + Glimepiride N = 157, n (%)	Placebo + Metformin + Glimepiride N = 160, n (%)
AEs	79 (50.3)	76 (47.5)
SAEs	3 (1.9)	2 (1.3)
Discontinuation due to AEs	1 (0.6)	2 (1.3)
Deaths	0 (0.0)	1 (0.6)
Hypoglycaemic events	8 (5.1)	3 (1.9)
Severe hypoglycaemia	1 (0.6)	0 (0.0)
Discontinuation due to hypoglycaemia	0 (0.0)	0 (0.0)

In a subgroup of patients with baseline HbA1c ≤8% (n = 80, 44 patients on vildagliptin and 36 patients on placebo), vildagliptin provided a significant HbA1c reduction of 0.74% from baseline HbA1c 7.82% compared with an increase of 0.23% in the placebo group from baseline HbA1c 7.67%; the between-treatment difference was −0.97% (p < 0.001). The responder analysis demonstrated that significantly more patients receiving vildagliptin (38.6%) achieved an HbA1c target of <7.0% vs. placebo (13.9%) (p = 0.014) in this subgroup (figure 3).

Safety

The overall safety and tolerability of vildagliptin was similar to placebo when used in triple combination with metformin and SU (Table 2). The overall incidence of AEs was comparable between treatments, 50.3% vs. 47.5% in the vildagliptin and the placebo groups, respectively. Serious AEs and discontinuations due to AEs were similarly low in both treatment groups. There were no deaths in the vildagliptin group, one placebo-treated patient died due to suicide.

Urinary tract infection was the most frequent AE in both groups (vildagliptin: 6.4% and placebo: 8.1%). Slightly more vildagliptin-treated patients reported dizziness (7.0% vs. 1.9% with placebo) and hyperhidrosis (6.4% vs. 0.6% with placebo), which could be symptoms of hypoglycaemia.

The incidence of hypoglycaemia was overall low with both treatments; however, it was slightly higher in the vildagliptin group (n = 8, 5.1%) than in the placebo group (n = 3, 1.9%). Most of these patients had a single episode of hypoglycaemia; multiple hypoglycaemic events were only reported for one patient in each treatment group. The majority of the hypoglycaemic events were mild and none of them led to the discontinuation from the study. One patient in the vildagliptin group experienced a grade 2 hypoglycaemic event that was not study drug-suspected, but considered due to decreased food intake after a surgery.

No clinically relevant changes in the mean body weight from baseline to week 24 were observed: 73.1 kg at baseline vs. 73.6 kg at study endpoint in the vildagliptin group and 72.4 kg vs. 72.3 kg in the placebo group, respectively. There were no meaningful changes in laboratory values, physical examination results or ECGs between treatment groups. No patients receiving vildagliptin had a treatment emergent alanine aminotransferase or aspartate aminotransferase elevation ≥3x upper limit of normal.

Discussion

In this study, vildagliptin 50 mg bid added as a third OAD to a stable combination of metformin (≥1500 mg) and glimepiride
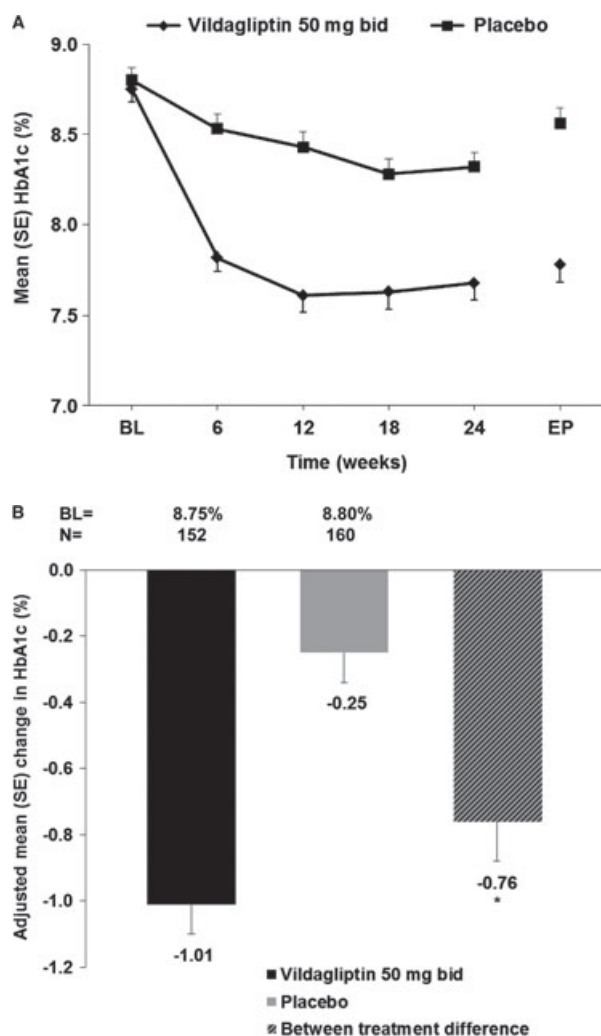
Figure 2. (A) Mean HbA1c (%) by treatment and visit (full analysis set). (B) Adjusted mean change in HbA1c from baseline to endpoint (full analysis set). BL, baseline; EP, endpoint; *p < 0.001.

Figure 3. Proportion of patients achieving haemoglobin A1c (HbA1c) <7% with baseline ≥7% in overall population and in subgroup of patients with baseline HbA1c ≤8% (full analysis set). *p = 0.014; **p < 0.001.

Considerable uncertainty exists regarding optimal treatment for patients in whom glycaemic targets cannot be met with metformin and a SU in combination. Recent meta-analyses conducted to evaluate the benefits of the third antihyperglycaemic agent added to metformin and SU in patients with T2DM inadequately controlled on dual therapy demonstrated statistically significant reductions in HbA1c with different drug classes, including insulin (basal, biphasic and bolus), DPP-4 inhibitors, GLP-1 analogues and TZDs (−0.89 to −1.17%), but not with meglitinides and alpha-glucosidase inhibitors [5,16]. In light of relatively minor differences in terms of the glucose lowering efficacy between these drug classes, tolerability and absence of weight gain are key factors in the choice of the drug to be added to existing metformin plus SU therapy.

The addition of a third glucose lowering agent to existing dual therapy with metformin and SU has been associated with an increased risk of hypoglycaemia. This has been demonstrated for TZDs, and GLP-1 analogues. Insulin in triple combination even doubled the incidence of severe hypoglycaemic events [5,16]. Although DPP-4 inhibitors typically do not increase the risk of hypoglycaemia; in triple combination with metformin plus SU, sitagliptin and linagliptin reported more hypoglycaemic events than placebo, 16.4% versus 0.9% and 22.7% versus 14.8%, respectively. Thus, a slightly higher rate of hypoglycaemia with vildagliptin (5.1%) compared to placebo (1.9%) in our study is consistent with the experience with other DPP-4 inhibitors [14,15].

The risk of hypoglycaemia seen in this study slightly differs from the data recently reported with vildagliptin in combination with insulin. In patients with advanced T2DM not adequately controlled with metformin plus insulin, the addition of vildagliptin 50 mg bid provided robust reduction in HbA1c with an incidence of hypoglycaemia similar to placebo [17]. The generally low risk of hypoglycaemia in triple combinations might be due to vildagliptin's effect to increase GIP levels

(≥4 mg) provided a robust and clinically relevant reduction in HbA1c of 1.01% from a baseline of 8.75% in patients with T2DM not adequately controlled with dual therapy. The reduction in HbA1c observed in this study is similar to the reductions seen with vildagliptin when used in dual combination with metformin or SU from similar baseline [12,13]. About 30% of vildagliptin-treated patients (almost five-fold greater than in the placebo group) achieved HbA1c of <7% demonstrating that a significant proportion of patients who failed on broadly used dual combination could reach treatment target when vildagliptin was added as a third OAD. Other DPP-4 inhibitors have been studied as well in the combination with metformin and glimepiride. Both sitagliptin and linagliptin in combination with metformin and glimepiride decreased HbA1c by 0.6% compared with placebo from a similar baseline HbA1c of 8.3 and 8.2%, respectively [14,15], which appears slightly lower than the 0.8% difference versus placebo seen in our study.
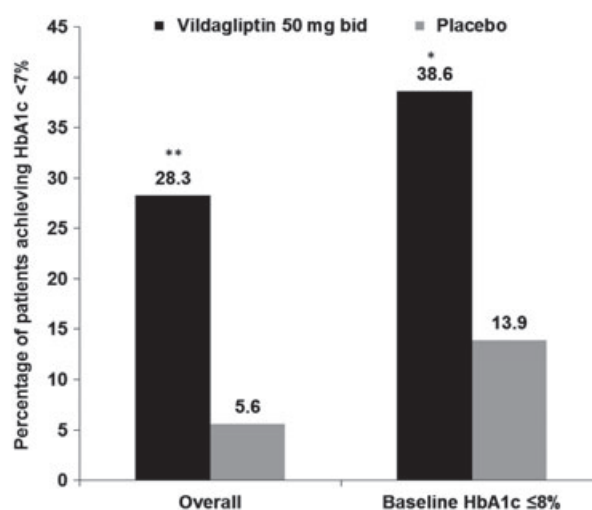
between meals and overnight when hypoglycaemia is most likely to occur [18], thereby increasing glucagon levels in hypoglycaemia [19]. The slightly greater risk of hypoglycaemia versus placebo with vildagliptin added to metformin plus SU compared to similar incidence of hypoglycaemic events with vildagliptin in combination with metformin and insulin might be due to uncoupling of the glucose-dependent insulinotropic effect of GLP-1 in the presence of SU [20].

Consistent with other findings from the DPP-4 inhibitors [21–23] the glucose-lowering effect of vildagliptin was not associated with an increase in weight. In contrast, TZDs or insulin added to metformin plus SU have been associated with an increase in body weight [24,25].

Ultimately, the clinical objective of treatment intensification is to achieve glycaemic control in as many patients as possible. We were therefore interested which patient group might get closest to this goal and analysed the efficacy and safety in patients having baseline HbA1c ≤8%. The results showed that approximately 40% of patients receiving vildagliptin responded to treatment demonstrating the benefit of triple therapy for this subgroup.

One limitation of our study is its relatively short 24-week duration. Longer study will be required to assess the durability effect of vildagliptin in triple combination as well as its potential in delaying the time to permanent use of insulin. However, durable glycaemic control with vildagliptin as monotherapy has been demonstrated previously [26].

In conclusion, vildagliptin in triple combination with metformin and SU demonstrated robust glucose-lowering efficacy and good safety with low risk of hypoglycaemia and weight gain. This makes vildagliptin an attractive treatment option for patients with T2DM failing on metformin and SU who require a third antihyperglycaemic agent and are not candidates for an insulin therapy, especially in patients with baseline HbA1c ≤8% as a substantial number of patients in this subgroup achieved treatment targets.

Acknowledgements

Conflict of Interest

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