REVIEW ARTICLE

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SAFETY AND EFFICACY OF VILDAGLIPTIN: DIPEPTIDYL PEPTIDASE-4 INHIBITOR

***BHOOMIKA PATEL[1], JIGNA SHAH [1]**

1. Department of Clinical Pharmacy, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

Corresponding Author Email: ph.bhoomika@gmail.com

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Abstract: Diabetes mellitus (DM) is one of the most common chronic disorders, with increasing prevalence worldwide. Vildagliptin is a drug from a new class of medications called dipeptidyl peptidase IV (DPP4) inhibitors. Several studies have found that certain diabetes drugs may carry increased cardiovascular (CV) risks compared to others. The new approach in management of T2DM based upon the effects of incretin hormones; Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic peptide (GIP). Clinical trials have shown that vildagliptin is effective in significantly lowering glycosylated hemoglobin (HbA1c), fasting plasma glucose, and prandial glucose levels. β-cell function may also be improved. The pharmacology, efficacy and safety of vildagliptin, a novel DPP-4 inhibitor, are also discussed.

Keywords: Diabetes, Vildagliptin, incretin, DPP-4 inhibitor, Glucagon-like peptide

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a dual disease, characterized by islet (beta- and alpha-) cell dysfunction in the setting of insulin resistance. Moreover, ample clinical evidence, such as data from the landmark UK Prospective Diabetes Study (UKPDS), indicates that loss of beta-cell function is progressive. This progressive decline leads to the clinical impression of failure of therapy in T2DM patients and is the main reason why so many patients with T2DM are not within target ranges of glycemic control. Moreover, the clear alpha-cell dysfunction that is also present in T2DM has been disregarded in previous years, mainly because therapeutic interventions were lacking. The need to address this underlying islet cell deficit led to a search for therapeutic alternatives and has led to the rediscovery of the incretin hormones and their role in glucose homeostasis. Improved understanding of their potential has led in turn to the development of incretin analogs and incretin enhancers for treatment of T2DM.[1-4]

The present review discusses the data available on the incretin enhancer vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for the rapid degradation of the incretin hormones glucagons like peptide-1 (GLP-1) and glucose-dependent insulin tropic peptide (GIP).[5-10]

Vildagliptin

The DPP-4 inhibitor vildagliptin is approved in Europe for the treatment of T2DM. It is a potent, selective and orally active second generation inhibitor of DPP-4, with a reversible and competitive mechanism of action that binds and forms a complex with DPP-4, causing its inhibition.[11] This results in improved glycemic control as determined by glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels plus an enhancement of pancreatic α-and β-cell function. Structurally, vildagliptin is 1-([(3-hydroxy-1-adamantyl) amino] acetyl)-2-cyano-[S]-pyrrolidine. Its molecular weight is around 303.41 gm. (Figure: 1)

Pharmacology

The pharmacokinetics of vildagliptin has been studied in healthy subjects and people with type 2 diabetes.[12, 13] Oral doses of 25–100 mg administered once or twice daily were used. Vildagliptin is rapidly absorbed and is not subject to significant first-pass metabolism; resulting in 85% oral

bioavailability.[12] Administration of vildagliptin with food has no clinically relevant effect on bioavailability.[14] Maximal concentration occurs one hour after administration regardless of the dose. Its elimination half-life in plasma is short (average 2.8 hrs), yet its effects on DPP-4 inhibition are long lasting with 86% and 95% 24-hour inhibitory effect at 25 mg twice daily and 100 mg twice daily doses, respectively.[13] This is likely related to the extensive distribution of the drug into the tissue: the volume of distribution in the steady state is 71 L.[15] Vildagliptin undergoes hydrolysis in the liver, with a smaller (20%) contribution from the DPP-4 enzyme itself.[12] The principle hydrolysis reaction yields the major carboxylic metabolite which is inactive. This does not involve the p450 system, making the potential for drug–drug interactions low. When vildagliptin was studied specifically in combination with commonly used antihypertensive medications (amlodipine, valsartan, and ramipril) no significant interactions were found.[16] Final elimination of vildagliptin metabolites is via kidney, where one third of the drug is excreted in an unchanged form. [12]

Therapeutic Efficacy

The therapeutic efficacy of oral vildagliptin once-daily (OD) or twice-daily (BID) has been investigated as monotherapy, in placebo-controlled or active comparator-controlled trials in drug naive patients or in combination with metformin, pioglitazone, glimepiride or insulin in treatment-experienced patients. The trials were randomised, double-blind, placebo or active comparator controlled, multicentre studies in patients with T2DM (n =71–780).[17] The mean age of the patients was 53–59 years. Mean duration of diabetes, where stated, was 2.0–4.7 years in the monotherapy trials and 4.6–6.2 years in the combination studies.[18] BID dosages where stated were administered at breakfast and dinner, whereas as OD dosage was administered before breakfast.[19] Mean baseline HbA1c of patients considered for monotherapy was between 6.2–7.5%.[17] FPG baseline means were 8.8–10.3 mmol/L in all studies.[18] The primary efficacy endpoint for all trials was change in HbA1c levels. Other endpoints included FPG, PPG, bodyweight and blood lipids.

Vildagliptin: clinical program

Most data available on vildagliptin until now have come from company-sponsored studies designed for registration purposes. The drug has been evaluated in an extensive, ongoing clinical program, involving approximately 22,000 treated patients overall and 14,200 vildagliptin-

treated patients representing approximately 7000 subject-years of vildagliptin exposure as of April 2008 (data on file, Novartis). It is approved for use in treatment of T2DM in the European Union, Latin America (Brazil, Mexico), and Asia (Korea, Singapore, Philippines). As reviewed herein, clinical trials have shown that vildagliptin improves glycemic control in patients with T2DM as monotherapy[20-24] and as add-on or initial combination therapy with other oral antidiabetic agents and insulin[25-30], as well as in patients with impaired glucose tolerance (IGT).[31, 32] Recent evidence from T2DM patients with mild hyperglycemia indicates that vildagliptin attenuates deterioration of β-cell function over long-term treatment.[33-35] Vildagliptin treatment is characterized by weight-neutral and lipid-neutral effects, very low risk of edema, and very low risk of hypoglycemia. T2DM is characterized by continual loss of glycemic control despite treatment, with few patients achieving and maintaining treatment goals and combination treatment typically becoming unavoidable.[36-38] Current guidelines encourage a prompt move to combination treatment when initial metformin treatment fails to achieve glycaemic goals.[39] The primary utility of vildagliptin is likely to be as add-on treatment or in initial combination with metformin. These agents have complementary effects in improving glycemic control, potential mechanistic synergy, and a favourable interaction of tolerability profiles, including absence of risk for weight gain, edema, and hypoglycaemia.

Monotherapy

In one randomized, placebo-controlled study, 37 drug-naive patients (mean baseline HbA_{1c}, 6.3%–10%) with type 2 diabetes received vildagliptin 100 mg once daily or placebo.[40] This 4-week study assessed the effect of vildagliptin on glycemic control, plasma glucagon, and insulin levels. Vildagliptin significantly reduced fasting glucose and postprandial glucose (PPG) versus placebo (P<.037 and P<.001, respectively); vildagliptin also reduced HbA_{1c} by 0.38% versus placebo (P<.001). Glucagon levels were decreased with vildagliptin versus placebo, whereas insulin levels were not significantly altered versus placebo. Hypoglycemia did not occur in either group. Body weight increased by 0.12 kg in the placebo group and by 0.21 kg in the vildagliptin group, a nonsignificant difference. The authors concluded that vildagliptin improve metabolic control in association with reduced glucagon levels, improved glycemia, and unaltered insulin levels.

A 12-week study by Ristic et al[41] evaluated the effect of vildagliptin versus placebo in 279 patients with a baseline HbA_{1c} of 7.7%. Patients were treated with vildagliptin 25 mg twice daily or 25, 50, or 100 mg once daily or placebo. At study end, patients who were treated with vildagliptin 50 mg once daily experienced a 0.43% decrease in HbA_{1c} versus placebo (*P*=.003), and patients treated with vildagliptin 100 mg once daily experienced a 0.40% decrease in HbA_{1c} versus placebo (*P*=.004). A significant decrease in PPG levels was observed in patients treated with vildagliptin 50 mg once daily versus placebo (*P*=.012). Although a decrease in PPG levels was also noted in patients treated with vildagliptin 100 mg once daily versus placebo, this difference did not reach statistical significance. Hypoglycemic event rates were similar among all groups, including placebo, and rates were not dose related. Two cases of hypoglycemia were considered symptomatic, both of which occurred in patients taking vildagliptin. Treatment had a neutral effect on body weight throughout the trial.

In another 12-week study, the efficacy of vildagliptin versus placebo in medication-naïve patients was evaluated as the primary end point.[42] Patients (mean baseline HbA_{1c}, 8.0%) were randomized to receive vildagliptin 25 mg twice daily (n=70) or placebo (n=28). In patients treated with vildagliptin, both FPG and PPG levels were significantly reduced versus placebo (FPG, *P*=.0043; PPG, *P*<.001). HbA_{1c} was also reduced by 0.6%±0.2% with vildagliptin versus placebo (*P*=.0012). One episode of hypoglycemia occurred in the vildagliptin treatment arm; the study authors attributed this episode to a delayed meal. The between-group difference in adjusted mean change from baseline to end of study in body weight was 0.5 kg; this difference was not statistically significant.

Another study compared the efficacy and tolerability of vildagliptin with the efficacy and tolerability of rosiglitazone in a 24-week, double-blind, randomized trial.[43] Patients (N=786; baseline HbA_{1c}, 8.7%) received either vildagliptin 100 mg daily or rosiglitazone 8 mg once daily. HbA_{1c} levels decreased from baseline to a similar extent in the 2 groups. Vildagliptin decreased HbA_{1c} by 1.1%±0.1% (*P*<.001), and rosiglitazone decreased HbA_{1c} by 1.3%±0.1% (*P*<.001). These results demonstrated vildagliptin's noninferiority versus rosiglitazone. Patients in the rosiglitazone group were more likely to experience edema and increased body weight; these effects were not observed among patients in the vildagliptin group.

The authors concluded that vildagliptin was as effective as rosiglitazone in the treatment of patients with type 2-diabetes, with the added benefit of not causing weight gain. One patient in each group experienced 1 mild hypoglycemic episode; no serious hypoglycemic events were reported.

Combination therapy

In a clinical trial by Ahren et al,[44] patients (mean baseline HbA_{1c}, 7.7%±0.1%) currently taking metformin 1,500 to 3,000 mg/d were randomized to also receive treatment with vildagliptin 50 mg once daily (n=56) or placebo (n=51) for 12 weeks. The primary end point was change in HbA_{1c} from baseline. No change in HbA_{1c} was noted in the placebo group; however, a mean decrease of 0.7%±0.1% was noted in the combination group versus placebo (*P*<.0001). A 40-week, randomized, double-blind, placebo-controlled extension trial was then conducted.[44] At Week 52, HbA_{1c} had increased in both the vildagliptin plus metformin group (0.0128% per month) and the placebo plus metformin group (0.066% per month). The increase in HbA_{1c} was more pronounced in the placebo group, suggesting that the combination of vildagliptin and metformin may slow the rate of progressive deterioration in glycemic control. The difference in HbA_{1c} between the groups remained statistically significant throughout the trial (*P*=.0243). The between-group difference in HbA_{1c} was –1.1%±–0.2% at study end (*P*<.0001). No hypoglycemic episodes or significant changes in weight relative to placebo were observed in the extension trial.

A larger study by Bosi et al[45] also evaluated vildagliptin in combination with metformin. Patients (mean baseline HbA_{1c}, 8.4%±1.0%) were randomized to receive vildagliptin 50 mg once daily (n=177), vildagliptin 100 mg once daily (n=185), or placebo (n=182) in addition to metformin ≥1,500 mg/d for 24 weeks. Patients treated with vildagliptin 50 mg plus metformin demonstrated a reduction in HbA_{1c} of 0.7%±0.1% versus placebo (*P*<.001), and patients treated with vildagliptin 100 mg plus metformin demonstrated a reduction of 1.1%±0.1% versus placebo (*P*<.001). The authors concluded that vildagliptin produced meaningful decreases in HbA_{1c} in patients whose diabetes was inadequately controlled with metformin. Body weight was unchanged relative to placebo in patients treated with vildagliptin 50 mg, but patients treated with vildagliptin 100 mg demonstrated an increase of 1.2 kg±0.4 kg relative to placebo. One patient

in each group experienced a mild hypoglycaemic event.

Vildagliptin was evaluated in combination with pioglitazone in a 6-month, randomized study of 592 treatment-naïve patients.[46] These results were presented at the 2006 ADA 66th Annual Scientific Sessions. Patients (mean baseline HbA_{1c}, 8.7%) were treated with pioglitazone 30 mg once daily, vildagliptin 100 mg once daily, vildagliptin 100 mg once daily plus pioglitazone 30 mg once daily, or vildagliptin 50 mg once daily plus pioglitazone 15 mg once daily. Vildagliptin 100 mg once daily plus pioglitazone 30 mg once daily resulted in a statistically significant reduction in HbA_{1c} levels compared with patients assigned to pioglitazone alone (1.9% vs 1.4%; $P<.001$). Although this abstract supports the efficacy of this combination, this information is limited by the inability to fully assess study quality and design.

Safety and Tolerability of Vildagliptin

T2DM itself is characterized by increased risk of organ specific complications like CV disease, hepatitis-C infection and pancreatitis and these complications could be aggravated by drug treatment. Subsequently alongside efficacy, the safety profile of any new OHA is of most importance for treatment of chronic and progressive disease like T2DM. The tolerability profile of oral vildagliptin has been reviewed previously,[18] drugs as monotherapy or in combination was well tolerated for periods up to 52 weeks. The majority of reported adverse events (AEs) were of mild to moderate severity and transient in nature[47-54] with rare treatment related discontinuations.[55] AEs were reported by 55–70% of vildagliptin recipients, 59–74% of placebo recipients, 34–75% of active comparator recipients (metformin, pioglitazone, rosiglitazone and insulin with or without matching placebo) and 26–69% of vildagliptin plus active comparator (metformin, pioglitazone and insulin) recipients.[18] The most common AEs reported in patients receiving vildagliptin during clinical trials included headache, nasopharyngitis, cough, constipation, dizziness, and increased sweating.

Cardio and Cerebrovascular Safety

Cardiovascular and cerebrovascular (CCV) events are highly prevalent co-morbidities of T2DM, over the past couple of years, the link between OHAs and CV disease has been a area of concern with some of new compounds have unexpectedly been linked with excess CV AEs. USFDA has issued guidance for industry with recommendations for methodology to show that a new therapy

does not cause any unacceptable increase in CV risk.[56] There is considerable preclinical evidence that DPP-4 inhibitors, which act by increasing plasma levels of active GLP-1, may actually exert cardio-protective effects, [57] also limited human studies that are available have suggested that GLP-1 may improve CV function.[58, 59] It is well known that hypoglycaemia is associated with increased CCV risk and as discussed in this article DPP-4 inhibitor vildagliptin has been associated with reduced incidence and severity of hypoglycemia. A study conducted as per Food and Drug Administration, USA (USFDA) guidance, showed that vildagliptin does not lead to an increase in CCV events in a T2DM population. This metaanalysis by Schweizer et al and colleagues,[60] pooled the data from 25 phase III vildagliptin trials lasting from 12 weeks to over 2 years, where the drug was used either alone or in combination with other therapies. Patients received either a 50-mg dose of vildagliptin once daily (OD) (n = 1,393), twice daily (BID) (n = 6,166) or active and placebo comparators (n=6,061), to evaluate CCV safety of vildagliptin. The RRs for both vildagliptin regimens were <1 (RR=0.88; 95% (CI) =0.37, 2.11 for 50 mg OD and RR=0.84; 95% CI=0.62, 1.14 for 50 mg BID). Similar results were seen across all subgroups including elderly patients (RR=1.04; 95% CI=0.62, 1.73), males (RR=0.87; 95% CI=0.60, 1.24) and those with higher CCV risk (RR=0.78; 95% CI=0.51, 1.19). The results of this meta-analysis established that vildagliptin was not associated with an increased risk of adjudicated CCV events in a T2DM population, including among those at most risk.

Hepatic Safety Profile

To date, there is little evidence that vildagliptin or other DPP-4 inhibitors are associated with significant hepatic risk. Although cases of ALT elevations with concomitant increase in bilirubin have been reported recently for sitagliptin, these cases resolved on treatment and overall no increased risk of hepatic events was reported.[61]

The meta-analyses conducted by Kothny W et al and colleagues,[62] pooled the safety data from 36 phase 2 and 3 clinical trials to investigate hepatic safety profile vildagliptin. The results from this meta-analysis showed that the greater proportion of vildagliptin recipients had mild elevations in liver enzymes versus comparator recipients (ALT/AST levels >= 3 x upper limit of normal [ULN]).However, vildagliptin was not associated with an increased risk of having severely elevated liver enzymes (AST/ALT ≥10 x ULN, or AST/ALT ≥3 x

ULN and bilirubin ≥2x ULN). Nor was vildagliptin associated with an increased risk of hepatic AEs. Two patients experienced severe elevations in liver enzymes attributable to vildagliptin treatment. Both cases were asymptomatic and resolved upon discontinuation of treatment.

Pancreatic Safety Profile

T2DM has been associated with increased risk of pancreatitis, as cholelithiasis, hypertrygliceridaemia associated with disease are acknowledged risk factors for acute pancreatitis.[63] GLP-1 agonists such as exenatide[64] and sitagliptin[65] have been associated with some cases of acute pancreatitis. With aim of assessing whether treatment with vildagliptin is associated with an increased risk of pancreatitis, Ligueros-Saylan M et al,[66] pooled safety data from 24 phase 2 and 3 double-blind controlled clinical trials, to investigate its association with pancreatitis-related AEs. The odds ratio for pancreatitis-related AEs was <1 for vildagliptin 50mg OD and BID (OR = 0.90 and 0.78, respectively), indicating no increased risk relative to all comparators. The result from this meta-analysis established that there was no evidence of an increased risk of pancreatitis related AEs following treatment with vildagliptin at the marketed doses of 50mg OD and BID relative to the all comparators group. The safety of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function has been discussed in detail in metaanalysis by Ligueros-Saylan M and colleagues.[67]

SUMMARY AND CONCLUSIONS

Conventional treatments for T2DM do not address the progressive decline in β-cell function and as a result despite being on treatment, there is a continuous advance in disease state of patient. In clinical studies of T2DM patients, vildagliptin has been shown to reduce HbA1c, FPG, PPG and prandial glucagons secretion and improve β-cell function, both as monotherapy and in combination with other antidiabetic therapies. Theoretically DPP-4 inhibitor vildagliptin has shown promise β-cell protection in the long term and even reverse the progressive loss of insulin secretory capacity that is the primary cause of T2DM, although long-term studies will be required to demonstrate this and to rightly position vildagliptin vis-à-vis to other antihyperglycemic agents. Nevertheless, vildagliptin enlarges the treatment options available for management of T2DM patients, who are poorly controlled with monotherapy.

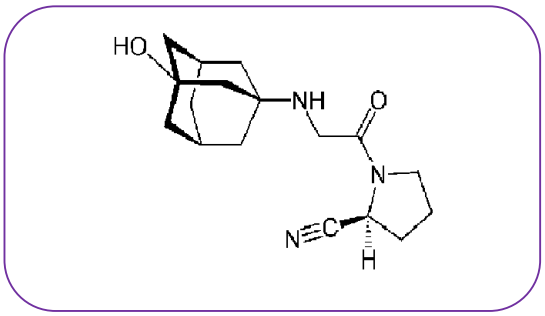

Figure 1. Structure of Vildagliptin

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