Emerging Role of Dipeptidyl Peptidase-IV (DPP-4) Inhibitor Vildagliptin in the Management of Type 2 Diabetes

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Abstract

Diabetes mellitus (DM) is one of the most common chronic disorders, with increasing prevalence worldwide. Type 2 diabetes (T2DM), a multifaceted disease involving multiple pathophysiological defects, accounts for nearly 85–95% of total reported cases of DM. Chances of developing T2DM are increased by obesity and physical inactivity and are augmented further with age. Two most important unmet needs associated with the management of T2DM are the lack of lasting efficacy in reducing hyperglycemia and failure to target primary causes. Different classes of Oral Hypoglycemic Agents (OHA’s) with nearly equipotent efficacy are now available targeting the different pathophysiologic factors contributing to T2DM; however, almost all of them are associated with one or the other kind of adverse effect. 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 insulinotropic peptide (GIP). Vildagliptin is a drug from a new class of medications called dipeptidyl peptidase IV (DPP4) inhibitors. By inhibiting DPP-4, vildagliptin causes an increase in GLP-1, an intestinal hormone that aids in glucose homeostasis and insulin secretion. Vildagliptin has a half-life of about 90 minutes; however, ≥50% of DPP4 inhibition continues for more than 10 hours, allowing for once- or twice-daily dosing. 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 drug has placebo like tolerability and rate of hypoglycemia events. Vildagliptin expands non-injectable treatment options available for management of T2DM patients, who are poorly controlled with monotherapy.

Introduction

Diabetes mellitus (DM) is one of the most common chronic disorders attaining epidemic proportions worldwide. The prevalence of diabetes is rapidly rising globally at a distressing rate, affecting both developed and developing countries alike. Worldwide DM is currently estimated to affect 285 million (6.4%) adults aged 20–79 years and this number is projected to increase to 439 million (7.7%) adults by the year 2030.1 Diabetes Atlas 2009 published by the International Diabetes Federation estimated diabetic population in India to around 50.8 million, which is expected to rise to 87 million by 2030, earning India the dubious distinction of being called the “diabetes capital of the world”. Type 2 diabetes (T2DM) accounts for nearly 85–95% of total reported cases of diabetes.2 T2DM is a multifaceted disease involving multiple pathophysiological defects, including impaired islet function and insulin resistance, which results in impaired glucose tolerance and inappropriately high fasting hepatic glucose production. Chances of developing T2DM are increased by obesity and physical inactivity and are further augmented with age.

Two most important unmet needs associated with the management of T2DM are the lack of lasting efficacy in reducing hyperglycemia and failure to target primary causes. Poor glycemic control accounts for much of the morbidity, mortality and economics associated with T2DM.3,5 Though Lifestyle modification (Exercise, dietary management) provides the basis for metabolic control of patients with T2DM, but with course of time this approach alone is insufficient to attain glycemic control, calling for introduction anti-hyperglycemic pharmacotherapy.

Different classes of Oral Hypoglycemic Agents (OHA’s) are now available that target the different pathophysiologic factors contributing to T2DM:α-glucosidase inhibitors to delay intestinal carbohydrate absorption, biguanides to target hepatic insulin resistance, insulin sensitizers or thiazolidinediones (TZDs) to target adipocyte and muscle insulin resistance and insulin secretagogues or sulfonylureas (SU) to increase pancreatic insulin secretion.6 These compounds have nearly equipotent efficacy; however, almost all of them are associated with one or the other kind of adverse effect.7

An alternative approach based on targeting incretin hormones, founded on better understanding of their potential has in turn led to the development of incretin analogs and incretin enhancers for treatment of T2DM. In this article we will review the pharmacology, clinical efficacy and role of incretin enhancer vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4) in the management of T2DM.

Present Treatment Regimes and Cardiovascular Risks

In the past, several studies have found that certain diabetes drugs may carry increased cardiovascular (CV) risks compared to others. A recent study of over 90,000 T2DM patients compared the CV effects in individuals treated with either metformin or SU.
These researchers found an increased likelihood of death from any cause in the patients treated with SU (24-61% increased risk depending on the specific drug), along with an increased risk of congestive heart failure (18-30%). These results reinforced the similar findings of a 2006 study and an earlier 2009 study. Also concerns have been raised about CV risks associated withTZDs, which are increasingly being used to treat T2DM. Rosiglitazone monotherapy was found to be associated with higher risk for any CV event (HR 1.89; 95%CI 1.57, 2.28) and significant increase in the risk of myocardial infarction (43%). Moreover as add-on rosiglitazone and pioglitazone were associated with comparable CV risk. SU were the first widely used OHAs and have been available in the United States since 1954 and still remain a cornerstone of T2DM therapy. Second-generation SUs (glyburide, glipizide, and glimepiride) are more potent and probably safer than first-generation SUs (chlorpropamide, tolbutamide, acetohexamide and tolazamide) but essentially of equal efficacy. Unfortunately, SUs do not always succeed in controlling diabetes. With SU therapy, some 10%-20% of people will immediately fail to control their blood glucose levels adequately on the highest recommended dose (Primary failure). Another concern with SUs is their tendency to overwork the pancreas until it eventually “exhaust β-cell function” and is unable to secrete an adequate amount of insulin, so roughly 5% to 10% of people who initially respond to SU therapy will subsequently fail each year (Secondary failure).

The utmost practical concern of SU therapy is associated with two common adverse effects, weight gain and hypoglycemia. About 80% to 90% of people with diabetes are obese and SUs tend to make them gain even more weight, typically from 2 to 5 kg and SU associated hypoglycemia affects the elderly with worsening renal function and irregular meal schedules. Jennings et al demonstrated that up to 20% of patients taking oral SU agents experience symptoms consistent with hypoglycemia over a 6-month period. Seltzer et al in a comprehensive retrospectively review of 1418 cases of severe drug-induced hypoglycemia, identified SU ingestion, advanced age and fasting as the major risk factors for the development of hypoglycemia requiring hospitalization. Specifically, SU ingestion was a factor in 65% of adult cases and 86% of these cases were of patients older than 50 years. Hypoglycemia results in significant morbidity and in younger patients with T2DM (aged from 20–49 years), between 6 and 18% of deaths have been attributed to hypoglycemia. Case fatality rates of 4%-10% have been reported with SUs, with about 5% of survivors having permanent neurological impairment.

Although much attention has been paid to neurologic consequence of SUs induced hypoglycemia but its CV side effect can not be overlooked. In addition to this weight gain associated with SUs is also marker of increased CV risk, which is the main cause of death in people with T2DM. Ischemic preconditioning in human myocardium relies on KATP channels, which plays an important role in regulation of coronary blood flow but also protect cardiac cells from ischaemia/reperfusion injury. However in diabetic patients KATP channel function are already impaired and the long-term inhibition of KATP channels with KATP channel inhibitors like older generation SUs, especially the ones with less selectivity, may explain the excess CV mortality in these patients. The ACCORD study has reported an increased CV risk and total mortality associated with intensive glucose control, with an excess of fatal vascular events being associated with a higher frequency of severe hypoglycemia. Hypoglycemia secondary to insulin and SU therapy is often associated with serious morbidity; anecdotal evidence has long implicated hypoglycemia as a potential cause of myocardial ischaemia or a cardiac arrhythmia.

A new study has found that SUs—the mainstay of glucose control in T2DM, increase the risk of both CV and all-cause mortality. The researchers found higher daily doses of first and second-generation SUs increased mortality risk by more than 200% and 30%-40%, respectively. Even though cardiotoxic effect of SUs therapy has been debated for long, studies have provided pathophysiological plausibility as SUs appear to aggravate the hypoaemic damage to the myocardium in the case of coronary occlusion or artery disease. Furthermore every SU drug needs to be studied individually for its effectiveness and safety vis-à-vis the relevant endpoints for T2DM, i.e. CV morbidity and mortality, rather than being limited to surrogate markers

**New Approach in Management of T2DM**

The new approach in management of T2DM is based upon the effects of incretin hormones; Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), gastrointestinal hormones released from β-cells of the islets of Langerhans into the bloodstream primarily in response to meal ingestion. They enhance meal-induced insulin secretion and play an important part in maintenance of normal glucose homeostasis by a process termed as incretin effect. GLP-1 has also shown to suppress glucagon secretion, slow gastric emptying, reduce food intake and body weight. In T2DM patients, reduced incretin effect combined with constant decline in pancreatic β and α-cell function leads to progressive loss of glucemic control. This decline in β and α-cell function is evident as progressive loss of glucose-dependent insulin release and as a progression to unregulated glucagon production, respectively.

In T2DM effects of GLP-1 functions are preserved and in contrast GIP secretion remains normal but with reduced incretinotropic effect, giving rise to hypothesis that reducing degradation of GLP-1 may compensate for its decreased secretion in T2DM. However the role of GLP-1 and GIP in glucose regulation is limited because of their short half life, since they are rapidly degraded and inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4), resulting in loss of their incretinotropic activity.

Two approaches have been developed to negate this problem and prolong duration of GLP-1 action. One is the development of long-acting stable analogues of GLP-1, which maintains the physiologic effect of native GLP-1 but is resistant to action of DPP-4, so-called “Incretin Mimetics” and second, inhibition of DPP-4 using low molecular weight inhibitors which decrease the inactivation of GLP-1, thereby increasing its concentration as well as its duration of action on target tissue, called “Incretin Enhancers”. This approach was first encapsulated by Holst and Deacon, who showed that DPP-4 inhibition increases circulating levels of GLP-1 in experimental animals and that the incretinotropic action of exogenously administered GLP-1 is augmented by DPP-4 inhibition. Later studies demonstrated that the prevention of inactivation of GLP-1 by DPP-4 inhibition markedly increases the active GLP-1 in the circulation.

As a therapeutic application in T2DM, the prolongation of the endogenous GLP-1 and GIP effect produced by DPP-4 inhibition has several advantages compared with conventional therapies and newer GLP-1 analogues. Also being small molecule DPP-4
Vildagliptin

The DPP-4 inhibitor vildagliptin is approved in the Europe for the treatment of T2DM. It is a potent, selective and orally active 2nd generation inhibitor of DPP-4, with a reversible and competitive mechanism of action (MOA) that binds and forms a complex with DPP-4, causing its inhibition.36 This results in improved glycemic control as determined by glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels or food intake.36 Vildagliptin is 1-[(3-hydroxy-1-adamantyl) amino]-2-cyano-[S]-pyrrolidine. Its molecular weight is around 303.41 gm.

Pharmacologic Overview

The effect of vildagliptin in humans is reflected by the 50% inhibitory constant (IC50 4.5 nmol/L) of DPP-4 inhibition, which is more potent than that reported for another DPP-4 inhibitor, sitagliptin (IC50 26 nmol/L).37,38 Vildagliptin has demonstrated the ability to inhibit DPP-4, increase plasma concentrations of intact GLP-1 and GIP, reduce FPG and postprandial glucose (PPG) and suppress plasma glucagon in clinical trials in T2DM patients.39-41 The drug improves hyperglycemia primarily by prolonging the half-lives of GLP-1 and GIP, thus enhancing their actions on islet cells and promoting glucose-dependent insulin secretion and suppression of inappropriate glucagon secretion. Vildagliptin appears to attenuate the decline in glucose-dependent β-cell function and improve insulin sensitivity, and also to enhance the sensitivity of α-cells to glucose.42

Drug is quickly absorbed after oral administration, reaching peak plasma concentrations (Cmax) achieved in a time (tmax) of 1.5-1.7 hours after administration.43,44 Although the tmax is delayed to 2.5 hours and Cmax reduced by 19% when drug is administered with a high-fat meal, however these effects are not thought to be of any clinical significance and drug can be taken with any type of meal.43

Plasma concentrations of vildagliptin increase in an approximately dose-dependent manner; the absolute bioavailability of the drug is 85%. Vildagliptin is primarily metabolized in the kidney to inactive cyano and amide metabolites and approximately 85% of the drug is eliminated in the urine (21-23% as the unchanged drug) and 15% into the faeces,45,46 with a terminal elimination half life of approximately 3 hours following oral administration, irrespective of drug dosage or food intake.41

Therapeutic Efficacy

The unique action of Vildagliptin, a second member of DPP-IV inhibitor class of drugs, has encouraged new outlook in treatment and pathobiology of T2DM. 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).42 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.46 BID dosages where stated were administered at breakfast and dinner, whereas as OD dosage was administered before breakfast.49 Mean baseline HbA1c of patients considered for monotherapy was between 6.2–7.5%.42 FPG baseline means were 8.8–10.3 mmol/L in all studies.46 The primary efficacy endpoint for all trials was change in HbA1c levels. Other endpoints included FPG, PPG, bodyweight and blood lipids

Monotherapy

In a randomised, placebo-controlled, phase II trials (n=27949 and 986), considerably greater reduction in HbA1c levels from baseline was seen with Vildagliptin 50mg (between-group
In one of the dose-finding study in Japanese patients (n=291), 12 weeks of vildagliptin 10, 25 or 50mg BID treatment significantly reduced HbA1c levels by 0.53%, 0.67% and 0.92% respectively (p<0.001 vs. placebo) from baseline levels of 7.4%. Similarly, plasma FPG and 2-hour PPG levels were significantly reduced with all vildagliptin dosages. Furthermore, 12 weeks vildagliptin 50mg BID (n=188) was shown to be more effective than Voglibose 0.2mg three times daily (TID) (n=192) in reducing HbA1c levels in Japanese patients, with a mean between-group difference of −0.6% (95% CI:−0.68 to −0.46%; p=0.001) amid this vildagliptin provided a significantly greater response rate in achieving HbA1c levels of ≤6.5% compared with voglibose (50.8% vs. 24.2%; p<0.001).

In study of diet-treated T2DM subjects, monotherapy with vildagliptin 25mg BID (n=70) was well tolerated and significantly improved glycemic control in comparison to placebo (n=28). Between-group difference in adjusted mean change in HbA1c from baseline to endpoint was −0.6±0.2% (p=0.0012) for the whole cohort (baseline HbA1c 8.0%) and −1.2% for subjects with baseline HbA1c of 8.0-9.5%. Associated improvements in β-cell function were also observed with vildagliptin 25mg.

In the active comparator trials, the reduction from baseline mean HbA1c levels with vildagliptin 50mg BID in drug-naive T2DM patients was non-inferior to that with acarbose 300mg/day or rosiglitazone 8mg OD, after 24 weeks of treatment. A pooled analysis of five trials further confirmed that dosages of vildagliptin 50mg BID (n=1338) provides a significant (p<0.05) reduction of 1.0% from a mean baseline HbA1c of 8.7% after 24 weeks.

In a 52 week study conducted to evaluate efficacy and tolerability of vildagliptin 50mg OD in 306 drug-naive T2DM patients with mild hyperglycemia, vildagliptin 50mg OD significantly reduced HbA1c, FPG and PPG and improved β-cell function without weight gain or hypoglycemia. In patients with baseline HbA1c<8%, reductions in HbA1c was 1.1% with vildagliptin 50mg BID and 1.7% with metformin 200mg/day, whereas in patients with baseline HbA1c ≥8%, the reductions were 0.6% and 0.7% respectively. Also the effect of vildagliptin 50mg OD was shown to be dose-related in the higher baseline group (HbA1c >8%) in two placebo controlled trials.

Clinical guidelines for the management of T2DM recommend target level of HbA1c to be between 6.5% and 7.5%, to reduce risk of CV complications. The overall population achieving HbA1c levels of <7% ranged from 30% to 46%, following treatment with vildagliptin 50mg. In addition, data from pooled monotherapy trials indicated that 65% of vildagliptin recipients achieved an HbA1c reduction of >0.7%. A double-blind, randomized, multicentre, active-controlled, parallel-group study evaluated comparative efficacy and tolerability of the vildagliptin (100mg daily, n=169) and metformin (titrated to 1500mg daily, n=166) in drug-naive elderly (≥65 yrs.) T2DM patients, with prime objective of demonstrating non-inferiority of vildagliptin vs. metformin in HbA1c reduction. Vildagliptin was as effective as metformin, improving HbA1c by −0.64±0.07% and −0.75±0.07% respectively, meeting the predefined statistical criterion for non-inferiority. This study established that the Vildagliptin is an effective and well-tolerated treatment option in elderly patients with T2DM, showing similar improvement in glycemic control as metformin, with superior Gastrointestinal (GI) tolerability.

Furthermore decrease in mean FPG levels after 24 week treatment with vildagliptin 50mg BID were -0.8±0.07 and -1.255 mmol/L and -1.06 and -0.526 mmol/L with vildagliptin 50mg OD, which were significantly greater compared to placebo. Data from the pooled analysis of vildagliptin 50mg BID (n=1135) indicated a significant (p<0.05) reduction of 1.08 mmol/L from a mean baseline FPG of 10.3 mmol/L after 24 weeks. However in active comparator trials reduction in baseline FPG were significantly greater with rosiglitazone or metformin, than with vildagliptin 50mg BID though it significantly reduced FPG levels from baseline. But noninferiority of vildagliptin 50mg BID when compared to acarbose 300 mg/day in reducing FPG levels was not established after 24 weeks of treatment.

**Combination Therapy**

Vildagliptin has been evaluated in randomized, double-blind trials as add-on therapy to metformin, SU, TZDs and insulin treatment and in initial combination with pioglitazone.

The mean age of enrolled patients across all combination trial was 54–60 years with a mean BMI of 31–33 kg/m², mean duration of T2DM 4.6–14.9 years and mean HbA1c and FPG levels at baseline ranging between 6.5-10% and 8.7–11.0mmol/L respectively. Vildagliptin and metformin were administered as separate agents in all the trials. Out of this Four trial were placebo controlled and one each had pioglitazone and TZD as comparative agent. In T2DM patients Vildagliptin achieved greater glycemic control as compared with placebo, as an add-on to metformin, pioglitazone and glimepiride therapy and was as effective as pioglitazone (noninferiority established), when added to metformin but without weight gain as associated with pioglitazone therapy.

In a comparative trial evaluating effect of vildagliptin 50mg BID to glimepiride up to 6mg OD on prandial glucagon levels, as add on to therapy to metformin in T2DM patients inadequately controlled by metformin mono therapy. Prandial glucagon levels decreased by 3.4±1.6 pmol/L by vildagliptin (n=137) and increased by 3.8±1.7 pmol/L by glimepiride (n=121), with between-group difference of 7.3±2.1 pmol/L (P=0.001). This established that vildagliptin 50mg significantly improves postprandial alpha-cell function when compared to SU glimepiride. Another trial evaluated non-inferiority of vildagliptin vis-à-vis glimepiride in reducing HbA1c levels as add-on to metformin over the period of 2 years. Result from study showed that Vildagliptin as add-on to metformin had similar efficacy as that of glimepiride, but with markedly reduced hypoglycemia risk and no weight gain, with more patient on vildagliptin therapy reaching target (HbA1c<7%) without hypoglycemia when compared to glimepiride (36.0% vs. 28.8%; p=0.004). Similar results were shown in a 52-week, randomized, double-blind, active-controlled study demonstrating non-inferiority of vildagliptin in comparison with gliclazide, as an add-on therapy in T2DM patients inadequately controlled with metformin. Similar proportion of patients reached HbA1c <7.0%, but the total number of hypoglycemic events were lower in the vildagliptin group (6 vs. 11 events); moreover vildagliptin did not induce weight gain. Also the number of AEs were similar in both groups but the number of SAEs was higher in the gliclazide group (8.7 vs. 6.7%).

Addition of Vildagliptin 50mg OD or BID to existing oral therapy or insulin therapy produced significantly greater reduction in HbA1c baseline levels as compared to placebo;
which were −0.5,39–0.840 and −0.663 for Vildagliptin 50mg OD and −0.9,39–1.060 and −0.662 for Vildagliptin 50mg BID. In an extension of the vildagliptin plus insulin trial60 the reduction in HbA1c seen with vildagliptin at 24th week was sustained at week 52.62 When added to metformin, the reduction in mean baseline HbA1c with Vildagliptin 50mg BID (+0.9±0.1%) was noninferior to pioglitazone 30mg OD (-1.0±0.1%), after 24 weeks of treatment.62 The mean HbA1c of <7% was achieved in considerably more recipients of vildagliptin 50mg OD or BID than placebo recipients when administered as adjuvant therapy to pioglitazone (28.7% or 36.4% vs 14.8%)99 or glimepiride (21.2% or 24.8% vs 12%)60 (all p < 0.05).

Galiant trial compared efficacy and tolerability of vildagliptin 100mg with TZDs (agent and dose at the investigators discretion) as add on therapy to stable dose of metformin (≥1000 mg/day), in T2DM patients with inadequately controlled HbA1c (7-10%). The mean change in HbA1c from baseline was -0.68±0.02% and -0.57±0.03% in vildagliptin and TZD group respectively. Between the groups difference was -0.11% (95%CI:-0.17% and -0.04%), establishing the non-inferiority of vildagliptin (p=0.001) after 3 months of treatment.67 In a 52 week interim analysis of large randomized, double-blind, multicentre study, examining the efficacy and safety of vildagliptin vs. glimepiride as add-on therapy in patients inadequately controlled on metformin monotherapy (HbA1c 6.5-8.5%). Mean change from baseline HbA1c (7.3%) at week 52 endpoint was -0.44% (0.02%) and -0.53% (0.02%) with vildagliptin and glimepiride respectively, demonstrating non-inferiority of vildagliptin (97.5% CI; 0.02%, 0.16%), but a greater proportion of patients reached this target without hypoglycemia in the vildagliptin group (50.9 vs. 44.3%; p<0.01).68

In vildagliptin plus insulin trial, subgroup analysis showed that patient age was an important factor in achieving glycemic control. Patients aged >65 years had a significant lowering of adjusted mean HbA1c levels (between-group difference vildagliptin 50mg BID vs. placebo −0.6% [95% CI −1.0, −0.3; p=0.001]) unlike patients aged <65 years (−0.1% [95% CI −0.4, 0.1; p=0.361])99 and this effect was sustained in extension trial at week 52.62 Similarly in combination with glimepiride, vildagliptin showed greater lowering of adjusted mean HbA1c levels in the older patients.63

Vildagliptin 50mg OD or BID showed significantly greater reduction in baseline FPG levels as add on therapy to metformin when compared with placebo39 at 24th week. However reduction in baseline FPG levels compared to placebo, when evaluated as add-on therapy to pioglitazone,60 glimepiride61 or insulin62 was not significant. However in comparator trial of Vildagliptin 50mg BID daily, drug failed to establish the noninferiority to pioglitazone 30mg OD in reducing mean FPG, levels when added to metformin.62

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 utmost importance for treatment of chronic and progressive disease like T2DM. The tolerability profile of oral vildagliptin has been reviewed previously,67 drug 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,53-54,57-62 with rare treatment related discontinuations.53

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 36–69% of vildagliptin plus active comparator (metformin, pioglitazone and insulin) recipients.46 The most common AEs reported in patients receiving vildagliptin during clinical trials included headache, nasopharyngitis, cough, constipation, dizziness, and increased sweating.

The pooled monotherapy data showed that frequency of AEs in patients with normal renal function compared to patients with mild renal impairment did not differ significantly in recipients of vildagliptin 50 mg OD (54.3% vs. 55.2%), vildagliptin 50 mg BID (60.3% vs. 65.3%) rosiglitazone 8 mg/day (64.9% vs. 61.5%), pioglitazone 30 mg/day (50.4% vs. 48%) or placebo (63.8% vs. 57.4%).20

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 OHA 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.71

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,72 also limited human studies that are available have suggested that GLP-1 may improve CV function.73-74 It is well known that hypoglycemia 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 CV events in a T2DM population. This meta-analysis by Schweizer et al and colleagues,75 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, 1.41 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.76
The meta-analyses conducted by Kothny W et al and colleagues, 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. Since a small number of these hepatic enzyme elevations were reported on vildagliptin as well, liver enzyme monitoring after initiation of therapy is prudent and consistent with the vildagliptin product information.

**Pancreatic Safety Profile**

As mentioned earlier T2DM has also been associated with increased risk of pancreatitis, as cholelithiasis, hypertriglyceridaemia associated with disease are acknowledged risk factors for acute pancreatitis. GLP-1 agonists such as exenatide and DPP-4 inhibitor sitagliptin have been associated with some cases of acute pancreatitis.

With aim of assessing whether treatment with the DPP-4 inhibitor vildagliptin is associated with an increased risk of pancreatitis, Ligueros-Saylan M et al., 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 meta-analysis by Ligueros-Saylan M and colleagues.

**Hypoglycemia**

The incidence of hypoglycemia reported by vildagliptin monotherapy were low and similar to that with metformin or rosiglitazone, (≤0.7%) vs. ≤0.4% in metformin, 0.04% in rosiglitazone and 0% in placebo recipients). In three trials, no hypoglycemic events were observed. Hypoglycemic events were rare (≤3.6%) in all combination therapy trials. In combination with metformin, one hypoglycemia event each was reported from vildagliptin 50mg OD and BID recipient and one recipient of vildagliptin 50mg BID experienced three hypoglycemic events (vs. no events with pioglitazone). Moreover, when used in combination with insulin, vildagliptin 50mg BID resulted in a significant (p<0.001) reduction in the frequency of hypoglycemic events compared with placebo.

**Gastrointestinal (GI) AEs**

The incidence of GI AEs reported with vildagliptin 50mg is comparable to placebo and is much less than in metformin or acarbose treated patients. The frequency of reported GI AEs with metformin 2000 mg daily were twice than that of recipients of vildagliptin 50mg BID (43.7% vs. 21.8%; p<0.001). This resulted in 3-4 times higher incidence of diarrhoea, nausea, abdominal pain, dyspepsia and flatulence with metformin than with vildagliptin. More notably, approximately five times as many patients withdrew because of AEs following treatment with metformin when compared with vildagliptin (4.4% vs. 0.8%). Also incidence of GI AEs was considerably lower in vildagliptin 50mg OD plus metformin (≥1500 mg/day) recipients (p=0.022), when compared to placebo plus metformin recipients. The occurrence of GI-related AEs in acarbose recipients was more than twice than that in vildagliptin recipients (25.5% vs. 12.3%; p < 0.001).

**Bodyweight**

The DPP-4 inhibitor vildagliptin appear to be bodyweight neutral, as change in bodyweight associated with vildagliptin treatment is neutral or modest in nature and not significantly different from placebo. However there was a tell apart difference in weight neutral effect of vildagliptin to weight gain effect of rosiglitazone, pioglitazone, in phase 3 comparator trial. All the same, vildagliptin treatment was not associated with the weight loss that is coupled with some other antidiabetic agents.

In addition to this, the occurrence of cardiac AEs (including arrhythmias and conduction abnormalities) and hypertension with vildagliptin was comparable to placebo and also less than with metformin.

**Role of Vildagliptin in T2DM Therapy**

The primary aim of T2DM therapy is a prompt and sustained lowering of elevated glucose levels, thereby reducing associated microvascular and vascular co-morbidities. The availability and accessibility of a new class of therapeutic agents is key to lessen burden of T2DM. In the last couple of years, a number of new medications have been approved by USFDA for treatment of diabetes. However with exception of inhaled insulin, no other recently approved medications are orally administrable. Despite the fact that injectable therapies like insulin and exenatide are effective treatments, but patient resistance and fear of needle, regimens complicatedness, inconvenience, time and cost are main barriers to patient non-compliance to these therapies.

In the new group of drugs orally administered DPP-4 inhibitor vildagliptin proves to be a very efficacious drug for improving glycemic control in a wide range of T2DM patients, ranging from the IGT population to patients with advanced disease on insulin. Vildagliptin is indicated as second-line therapy as part of an oral combination therapy regimen in T2DM patients whose hyperglycemia is poorly controlled by monotherapy with metformin, a SU or a TZDs. Existing data indicates that HbA1c lowering potential of Vildagliptin is in range of TZDs and acarbose, with sustained reductions to clinically significant levels for up to 2 years. When used as monotherapy or in combination with metformin or insulin, modest reductions in HbA1c values (0.4–1.1% reductions) have been observed in patients receiving vildagliptin.

T2DM is a disease associated with a progressive decline in β-cell function. Unlike many other antihyperglycemic medications, oral inhibitor of DPP-4 vildagliptin improves glycemic control in patients with T2DM through physiological mechanisms that result in an attenuation of β-cell decline and thus restoration of the incretin effect. As a result of their diverse mechanism of action, DPP-4 inhibitor such as
Vildagliptin presents several advantages over other antidiabetic medications. Vildagliptin enhances α-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia. These effects contribute to the efficacy of vildagliptin to improve glycemic control as well as to its low hypoglycemic potential. The effect of improving postprandial glycemia provides a good alternative for the up till now limited therapeutic options of affecting postprandial glycemia excursion.

Vildagliptin’s unique MOA permits a number of combination regimens for effective control of glucose levels. Combining drug with existing medications with complementary MOA, should be a welcome option to available treatment regimes for T2DM. Vildagliptin is particularly useful in combination with metformin or TZDs, with most appealing combination of drug being with metformin, since from a pathogenic point of view combining metformin principally targeting insulin resistance with vildagliptin primarily targeting the β-cell is a rational approach. As add-on therapy to metformin, vildagliptin provided better glycemic control than placebo and in an active comparator noninferiority trial; it was shown to be as effective as pioglitazone. Also in other combination trials, vildagliptin as add-on therapy to insulin, glimepiride and pioglitazone provided more effective glycemic control than placebo.

Vildagliptin was generally well tolerated as monotherapy or in combination with other antidiabetic agents, with a AEs event profile similar to placebo. AEs associated with Vildagliptin were generally of mild to moderate severity and transient in nature. The occurrence of hypoglycemic events during vildagliptin treatment were low and when added to other antidiabetic agents like metformin, pioglitazone or a SU, the risk of hypoglycemia was not aggravated. Moreover vildagliptin therapy has shown to be weight-neutral and does not aggravate this problem as many of the antihyperglycemic agents.

Vildagliptin is currently approved in Latin America, Asia & Asia pacific region, all countries of European Union (in combination with metformin, SUs and TZDs) for the treatment of T2D. The recommended daily dose of vildagliptin is 100mg, administered as one dose each of 50mg in morning and evening. When used in dual combination with a SU, the recommended dose of vildagliptin is 50mg OD administered in the morning. Drug can be administered with or without meals.

The preliminary evidence of beneficial effects of Vildagliptin, member of the novel class of DPP-4 inhibitors, presents it to be an effective and safe antihyperglycemic agent. It has the potential to significantly change the clinical management of diabetes and can be an effective strategy to prevent or delay progression from the prediabetic state to overt T2DM.

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 glucagon 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.

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Disclosures

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