The Journey of Vildagliptin: From Bench to Bedside

Manish Maladkar[1], Srividya Sankar[2], Mahesh Darshanwad[3]

Abstract

Vildagliptin, a DPP-4 inhibitor has been available for the management of type 2 diabetes mellitus for more than a decade. The extensive clinical data support from several vildagliptin clinical trials and real-world studies provided the clinicians with an effective treatment option for lowering blood glucose, which neither causes weight gain nor increased the risk of hypoglycemia and cardiovascular events. This article reviews the development journey of vildagliptin from the proof-of-concept of DPP-4 inhibition from its earlystages in the 1990s to the present, being an extensively studied, well-established DPP-4 inhibitor. The article highlights the clinical effectiveness, safety, and tolerability studies of vildagliptin, which proved vildagliptin as an effective and safe option in the armamentarium of type 2 diabetes mellitus management in this era of evidence-based medical practice. This vildagliptin journey, from proof-of-concept to a very well-established molecule gives a lesson that a novel concept takes time and requires focused efforts, persistence, and long-term perseverance for bringing it into clinical practice.

Keywords: **Vildagliptin, gliptins, DPP-4 inhibitor, diabetes, glucose lowering therapy**

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitor therapy is the established glucose-lowering therapy in type 2 diabetes mellitus (T2DM). It has low risk of hypoglycaemia and is not associated with weight gain. It is used mainly as an add-on to metformin when metformin alone is insufficient for glycemic control. It is also used as initial monotherapy when metformin is not tolerated, in subjects with renal insufficiency and as combination therapy with thiazolidinediones (TZDs), sodium-glucose transport protein 2 (SGLT2) inhibitors, sulfonylureas (SUs), and insulin. It may also be a possibility for DPP-4 inhibitors as first-line glucose-lowering therapy when an islet-directed approach is desirable.[1]

Any therapy grows and gains trust over time through its benefits in clinical studies. Vildagliptin is one of the most extensively studied DPP-4 inhibitors in terms of its clinical utility. Over the last decade, a vast panorama of evidence on the benefit-risk profile of vildagliptin has been generated in patients with T2DM.[2] This article reviews the journey of vildagliptin from a proof-of-concept of DPP-4 inhibition to an extensively studied DPP-4 inhibitor standing strong in the type 2 diabetes management armamentarium.

Vildagliptin Journey

Proof-of-Concept and Discovery

In 1990, at the European Association for the Study of Diabetes (EASD) it was first reported that GLP-1 was a useful tool in the treatment of T2DM in humans, and in subsequent years, the data was published. In 1993, after an aggressive but failed attempt over 2 years to make a non-peptide GLP-1 a peptide mimetic, attention moved towards inactivating dipeptidyl peptidase-4 (DPP-4) when it was reported that GLP-1 was inactivated solely by the DPP-4 enzyme. The same is true for the inactivation of the other incretin hormone glucose-dependent insulinotropic polypeptide (GIP), but this was not in focus at that time. The DPP-4 program was accelerated in 1995 after it was reported that DPP-4 inhibition raised GLP-1 *in-vitro*. By the end of 1995, using valine pyrrolidide, a known orally active DPP-4 inhibitor from the Sandoz library, it was shown that a DPP-4 inhibitor could lower blood glucose levels in rodents and non-human primates. In 1996, using combinatorial chemistry and valine pyrrolidide as a starting point DPP-728 was discovered. Kinetic studies of DPP-728 determined that it was a slow substrate for the catalytic site of the DPP-4 enzyme, rather than a simple competitive inhibitor, thereby blocking GLP-1 and GIP inactivation than simply slowing these rates of inactivation. By 1999, DPP-728 was evaluated in patients, which provided the first human proof-of-concept that a DPP-4 inhibitor could improve glycaemic control in patients with T2DM.[3,4]

Initial Clinical Study

The first clinical study of DPP-4 inhibitor, NVP DPP728 was carried out in Sweden at five centers and involved 93 drug-naive patients with mild type 2 diabetes (HbA1c, 7.4%). After four weeks of treatment with NVP DPP728 (100mg TID or 150mg BID), HbA1c was reduced by 0.5% from baseline. Furthermore, despite the lower glucose levels, insulin levels were sustained. There were no safety issues and tolerability was good.[5]

This was the breakthrough study in the development of DPP-4 inhibitors as it ended the 10-year development from the concept of using DPP-4 inhibition for glucose-lowering action in T2DM with a clear proof-of-concept study.

This study was followed by a rapid development process. Engineering of the DPP-728 structure by Ed Villhauer and colleagues to attenuate the dissociation rate further led to the discovery of vildagliptin (LAF237) in 1998. The 'vil' in vildagliptin was in recognition of Ed Villhauer's contribution.[1]

First Animal Study of Vildagliptin

The first animal study of vildagliptin was published in 2004 in high-fat, diet-fed mouse, which demonstrated its efficacy in improving glucose tolerance after gastric glucose administration in mice.[6]

First Clinical Study of Vildagliptin

The first clinical study of vildagliptin was conducted in drug naïve T2DM patients who were on a controlled diet. Four-week treatment with vildagliptin was found to reduce fasting glucose, 4-h prandial glucose excursion, and mean 24-hr glucose by ~18 mg/dl and HbA1c by 0.4%. This was observed with increased post-prandial intact GLP-1 concentration from baseline, reduced post-prandial glucagon levels, and sustained insulin levels (Figure 1).[7]

These results indicating an increase in the insulinogenic index as a sign of stimulated β-cell function provided the first insight into the mechanism of action of DPP-4 inhibition in T2DM.[7]

The initial study with vildagliptin in drug-naïve patients was followed by a 12-week study with a 40-week extension phase in 107 T2DM patients who

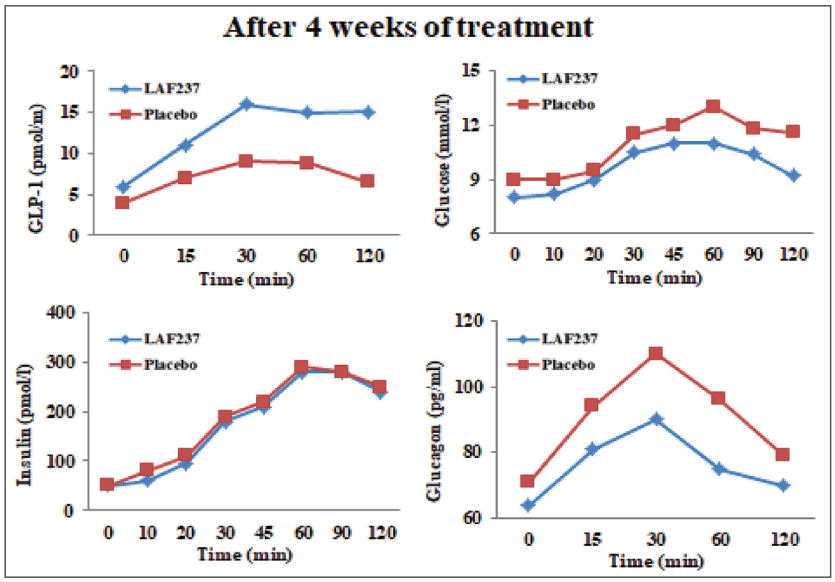

Figure 1: Active GLP-1, glucose, insulin, and glucagon levels after intake of breakfast (performed at time 0) after 4 wk of treatment with placebo (n=19) or Vildagliptin (LAF237) at 100 mg daily (n=18) in subjects with T2DM.

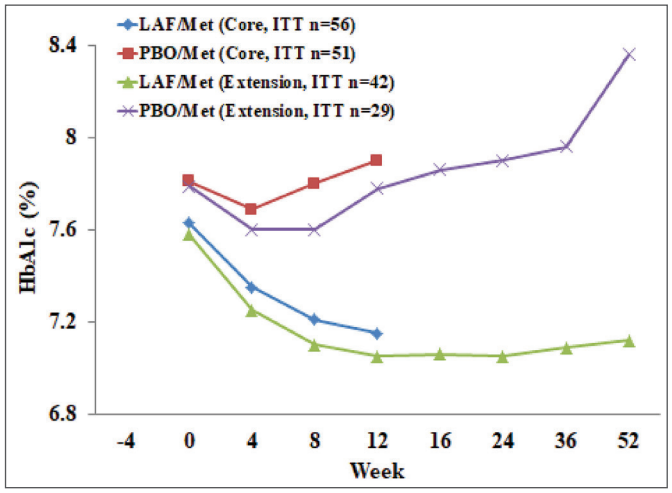

Figure 2: Time course of HbA1c in a core study (open circles) and an extension study (closed circles) in 56 subjects with type 2 diabetes treated with the DPP-4 inhibitor vildagliptin (LAF237) and metformin (Met) and 51 subjects treated with placebo (PBO) and metformin. Forty-two subjects with vildagliptin plus metformin and 29 subjects with placebo plus metformin participated in the extension. Data are means ± S.E.M.

were on metformin monotherapy.[8] The study showed that vildagliptin reduced HbA1c by around 0.6% from a mean baseline of 7.7% to 7.1% after12 weeks. Thereafter, throughout the 40-week extension, HbA1c was stable during DPP-4 inhibition, whereas in placebo-treated patients, HbA1c increased throughout the study period, resulting in a difference in HbA1c between the groups after 52 weeks of 1.1% (Figure 2).[8]

Furthermore, standardized meal tests were performed before and after the study period. The results of these tests revealed that vildagliptin stimulated beta-cell function and improved insulin resistance after 52 weeks (Figure 3).[9]

Entry into the Market

The vildagliptin clinical registration program started in 2002 and ended in 2006 with new drug application submissions in several countries. It was first approved in the European Union (EU) market by the European Medicines Agency (EMA) in September 2007.[10] The fixed-dose combination of vildagliptin with metformin was approved in November 2007.[10] Vildagliptin was approved by the Central Drugs Standard Control Organisation (CDSCO) of India in 2008, just a few months after the EMA clearance.[11] Vildagliptin is indicated as an adjunct to diet and exercises to improve glycaemic control in adults with type 2 diabetes mellitus; as monotherapy in patients in whom metformin is inappropriate due to contraindications or intolerance, and in combination with other medicinal products for the treatment of diabetes, including insulin, when monotherapy does not provide adequate glycaemic control.

The introduction of vildagliptin in the market provided clinicians with a novel and effective glucose-lowering therapy alternative that neither causes weight

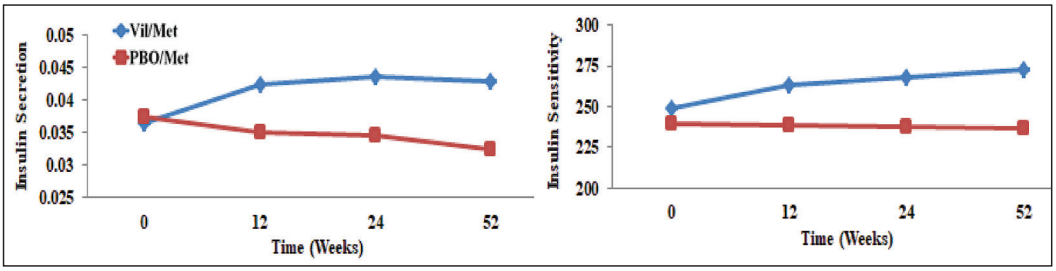

Figure 3: Insulin secretion (pmol/l 30min)/(mmol/l) (left) and dynamic insulin sensitivity (oral glucose insulin sensitivity index, ml • min−1 • m−2) (right) at baseline (week 0) and after 12, 24, and 52 weeks of treatment with the DPP-4 inhibitor vildagliptin (n=31) or placebo (n=26) in metformin-treated subjects with T2DM. Means ± S.E.M. are shown. *P < 0.05 between the groups.

gain nor raises the risk of hypoglycemia. It is currently used in more than 130 countries around the world.[12] Since it entered the market, vildagliptin has been exposed to more than 17 million patients.

Clinical Efficacy Studies

Various randomized controlled studies have shown the effectiveness and safety of vildagliptin alone or in combination with metformin.[13]

There is a vast panorama of studies of vildagliptin which prove its efficacy in clinical settings compared with placebo or in comparison with other antidiabetic agents. It has been studied as initial monotherapy, dual or triple combination therapy. This review summarises the major studies of vildagliptin in Tables 1, 2, and 3.

A. Monotherapy studies

a. Comparison with Placebo

Vildagliptin monotherapy (50mg once or twice daily) reduced HbA1c from baseline to a significantly greater extent than placebo, according to the results of 12- to 52-week trials in patients with type 2 diabetes. Few studies were extended up to 104 weeks. This section presents the findings of three randomized, double-blind, multicenter monotherapy studies in adults with type 2 diabetes that compared vildagliptin 50 mg twice daily to a placebo.[14]

The average baseline HbA1c values were 7.4% to 8.6%. Vildagliptin 50 mg twice daily monotherapy lowered mean HbA1c from baseline substantially more than placebo (-0.7 to -0.9 percent vs. -0.3 to +0.3 percent; p<0.01).[14]

b. Comparison with other Oral Antihyperglycemic Drugs (OAD)

Vildagliptin has been studied as monotherapy in comparison with other antihyperglycemic agents such as metformin (MET), sulfonylureas (SUs), thiazolidinediones (TZDs), and alpha-glucosidase inhibitors (AGIs).

Table 1 summarises the results of vildagliptin monotherapy studies compared with placebo and active control (MET, SUs, TZDs, and AGIs).

Overall, vildagliptin monotherapy studies have shown that vildagliptin treatment results in persistent and clinically substantial reductions in HbA1c from baseline levels, with no weight gain and hypoglycemia.[4] The pooled analysis data of these studies found a relationship between baseline HbA1c and the drop from baseline HbA1c; with vildagliptin treatment, the higher the baseline, the greater the reduction. Vildagliptin therapy showed a mean change in HbA1c of -2.1% from a baseline of 10.6%, -1.8% from 9.5%, -1.2% from 8.5%, -0.7% from 7.7% and -0.5% from 6.9%.[4]

Table 1. Efficacy of vildagliptin monotherapy compared with monotherapy of other antihyperglycemic drugs or placebo in T2DM patients.[14]

Study [Year]	Treatment (dose in mg) [no. of patients]	Study duration	Mean change from baseline in HbA1c (%)
Comparison with Placebo			
Pi-Suniyer *et al.* [2007]	VIL 50 BID – 100 OD [262]	24 weeks	-0.7%
	Placebo [92]	24 weeks	-0.0%
Dejager *et al.* [2007]	VIL 50 BID – 100 OD [472]	24 weeks	-0.8%
	Placebo [92]	24 weeks	-0.3%
Kikuchi *et al.* [2009]	VIL 50 BID – 100 OD [219]	12 weeks	-1.1%
	Placebo [72]	12 weeks	+0.28
Comparisons with MET monotherapy			
Schweizer *et al.* [2007]	VIL 50 BID [511]	1 year	-1.0%
	MET 2000 daily [249]	1 year	-1.4%
Goke *et al.* (extension of above study) [2008]	VIL 50 BID [305]	2 years	-1.0%
	MET 2,000 daily [158]	2 years	-1.5%
Comparisons with SUs monotherapy			
Foley and Sreenan [2009]	VIL 50 BID [546]	2 years	-0.5%
	GCZ up to 320 daily [546]	2 years	-0.6%
Comparison with AGIs monotherapy			
Iwamoto *et al.* [2010]	VIL 50 BID [188]	12 weeks	-0.95%
	VOG 0.2 TID [192]	12 weeks	-0.38%
Pan *et al.* [2008]	VIL 50 BID [431]	24 weeks	-1.4%
	ACA 100 TID [216]	24 weeks	-1.3%
Comparison with TZDs monotherapy			
Rosenstock *et al.* [2007]	VIL 50 BID [519]	24 weeks	-1.1%
	ROS 8 OD [267]	24 weeks	-1.3%
Rosenstock *et al.* (extension of above study) [2009]	VIL 50 BID [396]	104 weeks	-0.82%
	ROS 8 OD [202]	104 weeks	-1.44

ACA- acarbose, BID- twice daily, GCZ- gliclazide, HbA1c- glycated hemoglobin, MET- metformin, OD- once daily, ROS- rosiglitazone, TID- three times daily, VIL- vildagliptin, VOG- voglibose

Table 2. Efficacy of combination therapy with vildagliptin plus metformin in patients with T2DM inadequately controlled with metformin or who were treatment naïve.[14]

Study [Year]	Treatment (dose in mg) [no. of patients]	Study duration	Mean change from baseline in HbA1c (%)
Ahrén *et al.* [2004]	VIL 50 OD + MET 1500 – 3000/day [56]	52 week	-0.6 %
	MET 1500 – 3000/day [51]	52 week	+0.1%
Bosi *et al.* [2007]	VIL 50 OD + MET (≥1500/day) [177]	24 weeks	-0.5%
	VIL 50 BID + MET (≥1500/day)[185]	24 weeks	-0.9%
	MET (≥1500/day) [182]	24 weeks	+0.2%
Bosi *et al.* [2009]	VIL 50 BID + MET 500 BID [290]	24 weeks	-1.6%
	VIL 50 BID + MET 1000 BID [295]	24 weeks	-1.8%
	VIL 50 BID [300]	24 weeks	-1.1%
	MET 1000 BID [294]	24 weeks	-1.4%
Kim *et al.* [2012]	VIL 50 BID + MET 1500 daily [132]	24 weeks	-1.25%
	MET 2000 or 2500 daily [125]	24 weeks	-0.9%
Pan *et al.* [2012]	VIL 50 OD + MET (≥1500/day) [148]	24 weeks	-0.92%
	VIL 50 BID + MET (≥1500/day) [146]	24 weeks	-1.05%
	MET (≥1500/day) [144]	24 weeks	-0.54%

BID- twice daily, HbA1c- glycated hemoglobin, MET- metformin, OD- once daily, VIL- vildagliptin

Table 3. Efficacy of vildagliptin plus metformin vs. a sulfonylurea or a thiazolidinedione plus metformin in type 2 diabetes mellitus. Trials in patients inadequately controlled with metformin or who had received oral antihyperglycaemic drugs for <6 months or were treatment-naïve[14]

Study [Year]	Treatment (dose in mg) [no. of patients]	Study duration	Mean change from baseline in HbA1c (%)
Comparison with a Sulfonylurea plus Metformin			
Ferrannini *et al.* [2009]	VIL 50 BID + MET (≥1500/day) [1396]	52 weeks	-0.44 %
	GMP upto 6 daily + MET (≥1500/day) [1393]	52 weeks	-053%
Filozof and Gautier [2010]	VIL 50 BID + MET (≥1500/day) [513]	52 weeks	-0.81%
	GCZ up to 320 daily + MET (≥1500/day) [494]	52 weeks	-0.85%
Jeon and Oh [2011]	VIL 50 BID + MET 500 BID [51]	32 weeks	-0.94%
	GMP 2 BID + MET 500 BID [51]	32 weeks	-1.0%
Comparison with a TZD plus Metformin			
Blonde *et al.* [2009]	VIL 100 OD + MET (≥1000/day) [1653]	12 weeks	-0.68%
	TZD + MET (≥1000/day) [825]	12 weeks	-0.57%
Bolli *et al.* [2008]	VIL 50 BID + MET (≥2000/day) [295]	24 weeks	-0.88%
	PIO 30 OD + MET (≥2000/day) [281]	24 weeks	-0.98%

BID- twice daily, HbA1c- glycated hemoglobin, GCZ- gliclazide, GMP- glimepiride, MET- metformin, OD- once daily, PIO- pioglitazone, TZD- thiazolidinediones, VIL- vildagliptin

B. Combination therapy

Vildagliptin is typically used in combination with metformin; in people with T2DM who are already taking metformin, adding vildagliptin once or twice daily to their treatment regimen effectively reduces HbA1c levels further. One trial included patients who were treatment naïve and another trial included patients who had received OADs for <6 months or who were treatment-naïve.

The results of combination therapy with vildagliptin (50 mg OD or BID) plus metformin in patients with T2DM inadequately controlled with metformin or who were treatment naïve are summarised in Table 2.

Most of the combination studies of vildagliptin are as second-line agent add-on in patients who were inadequately controlled with metformin monotherapy. Other trials were vildagliptin plus metformin compared with vildagliptin and/or metformin alone, with a sulfonylurea plus metforminor with a thiazolidinedione plus metformin (Table 3).

Other studies are of combination therapy with vildagliptin plus pioglitazone vs pioglitazone[15,16] and vildagliptin alone[16], vildagliptin plus glimepiride vs glimepiride[15,17], vildagliptin plus glimepiride plus metformin vs glimepiride plus metformin[18] and vildagliptin plus pioglitazone vs vildagliptin plus glimepiride[19] in patients with type 2 diabetes mellitus.

Glycaemic control was significantly improved by the addition of vildagliptin 50 mg twice daily to pioglitazone 45 mg once daily or vildagliptin once daily to glimepiride in patients with T2DM inadequately controlled by a thiazolidinedione or a sulfonylurea alone. Twice-daily vildagliptin 50 mg was more effective than once-daily vildagliptin 50 mg when administered in combination with glimepiride or pioglitazone.

Triple therapy of vildagliptin plus glimepiride plus metformin was significantly more effective than dual therapy of glimepiride plus metformin in reducing HbA1c from baseline. In addition, significantly more patients receiving triple therapy achieved HbA1c target of <7% than patients receiving dual therapy.

Vildagliptin Studies in High-Risk Populations

Over the last two decades, the safety and efficacy of vildagliptin have been tested in many clinical conditions with particular references to patients at higher risk, including the elderly, those with impaired kidney

function, and those on insulin treatment.

A 24-week, multicentre, randomized, double-blind, placebo-controlled trial was conducted to evaluate the treatment effect of vildagliptin 50 mg once daily compared to placebo in 515 patients with T2DM and moderate renal impairment (n=294) or severe renal impairment (n=221).[20] 68.8% and 80.5% of the patients with moderate and severe renal impairment respectively were treated with insulin (mean daily dose of 56 units and 51.6 units respectively) at baseline. In patients with moderate renal impairment vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.53%) from a mean baseline of 7.9%. In patients with severe renal impairment, vildagliptin significantly decreased HbA1c compared with placebo (difference of -0.56%) from a mean baseline of 7.7%.[20]

Two randomized, double-blind, multicentre, 24-week trials examined the efficacy of vildagliptin in elderly patients (aged ≥65[21] or ≥70[22] years) with type 2 diabetes.

The INTERVAL (Individualised treatment targets for elderly patients [≥70 years] with type 2 diabetes using vildagliptin add-on or lone therapy) study firstly introduce and showed the feasibility of using individualized HbA1c targets as an endpoint in any type 2 diabetes population. Individualized glycaemic target levels were achievable with vildagliptin without any tolerability issues in the elderly type 2 diabetes population.[22]

The overall safety and tolerability were similar in the vildagliptin and placebo groups, with a low incidence of hypoglycemia and no emergence of new safety signals.[22]

Another double-blind, randomized, multicentre, active-controlled, parallel-group study of 24-week treatment with vildagliptin (100 mg daily; n=169) or metformin (titrated to 1500 mg daily, n=166) was conducted in drug-naïve patients with type 2 diabetes aged ≥65 years (baseline HbA1c 7-9%) demonstrated similar improvement in glycaemic control as metformin, with superior GI tolerability.[21]

The VIVIDD[23] (Vildagliptin in Ventricular Dysfunction Diabetes), a 52-week multicentre, randomized, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (NYHA functional class I-III) to evaluate the effect of vildagliptin 50 mg twice daily (50 mg once daily if treated with a sulfonylurea; n=128) compared to placebo (n=126) on left-ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) as compared to placebo. The main secondary endpoint that is the decrease in HbA1c from baseline to 16 weeks was greater in the vildagliptin group.[23]

Real-World Studies

Real-world studies demonstrate the picture of large data-sets from diverse patient populations. Additionally, studies of an observational nature, wherein data have been collected over a long period, provide an evaluation of the long-term safety and effectiveness of the drug in a large population, as well as information on utilization patterns. Thus, real-world studies have broader generalizability and are an effective tool to confirm the results of RCTs in clinical practice. Vildagliptin is the extensively studied DPP-4 inhibitor in RCTs as well as real-world studies. An enormous data support from real-world studies makes vildagliptin an effective and preferred antidiabetic agent for initial combination therapy as a second-line agent to metformin or first-line agent adjunct to diet and exercise.

EDGE[24] (Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin) is one of the largest T2DM observational studies ever conducted in a real-life setting. This was a prospective, 1-year, worldwide, observational study in which more than 45,000 patients seen in normal clinical practice demonstrated that vildagliptin was highly effective and well-tolerated, thus confirming results from a host of RCTs. Out of all selected patients, 11057 T2DM patients were enrolled from 472 sites in India. After 12 months of treatment, vildagliptin produced a greater reduction in HbA1c (-1.19%) as compared to the comparator group (-0.99%). Vildagliptin produced a greater HbA1c reduction in Indian population (-1.44%) as compared to the world (-1.19%). This provides a lot of confidence to Indian physicians to believe in vildagliptin as a second-line agent in patients on monotherapy with inadequate glycemic control.[24]

The GUARD[25] (The VildaGliptin clinical Use in the reAl woRlD) study evaluated the clinical effectiveness, safety, and tolerability of vildagliptin with or without metformin in >19000 adult patients with T2DM in routine clinical practice prospectively over 24 weeks. This was a large multi-ethnic study enrolling patients from Asia, the Middle East, Central America, and Africa. Of the total patients analysed, 82% of the patients received vildagliptin plus metformin therapy, and 18%

of the patients received vildagliptin monotherapy. At 24 weeks, both treatment groups significantly reduced HbA1c from baseline (Vildagliptin: -1.17%, Vildagliptin plus metformin: 1.29%). These reductions in HbA1c from baseline were observed regardless of patient age, BMI, or baseline HbA1c. Combination therapy provided clinically relevant glycemic and weight control and was well tolerated.[25]

The German PROVIL[26] (Pill Burden and Compliance in Type 2 Diabetic Patients Treated with Vildagliptin) study was a prospective, open, observational study, conducted in patients with T2DM previously on oral monotherapy. The selected patients were assigned to receive either vildagliptin add-on to metformin (cohort 1, n=603), vildagliptin + metformin single-pill combination (SPC) (cohort 2, n=2198) or another dual combination therapy with oral antidiabetic drugs (OADs) (cohort 3, SU- n=370, TZD- n=123, other DPP-4 inhibitor- n=99) according to treating physician's dissertation. After 6 months of treatment, the absolute reduction in HbA1c was significantly more pronounced in patients receiving vildagliptin add-on to metformin (-0.9%) and vildagliptin + metformin (SPC; -0.9) than in patients receiving other OADs (-0.6%). This study confirms that vildagliptin is an effective and well-tolerated treatment in combination with metformin in T2DM patients in real-world settings.[26]

A few real-world studies also evaluated the use of vildagliptin in T2DM patients who were fasting during Ramadan. The findings from the VIRTUE[27] study (Vildagliptin Experience Compared with Sulfonylurea Observed During Ramadan; n=1293), VERDI[28] study (Vildagliptin Experience During Ramadan in Patients with Diabetes; n=198),VECTOR[29] study (Vildagliptin Experience Compared to Gliclazide Observed During Ramadan; n=59) and one study conducted in India[30] (n=97) significantly favoured the use of vildagliptin over sulfonylurea in this patient population.

The Practice-Changing Trials

The INITIAL[31] (The Initial combiNation therapy with vildagliptin plus metformin In drug-naïve T2DM patients In a reAlLife setting) was a 24-week prospective, observational study in T2DM patients with HbA1c ≥ 7.5%, and were prescribed vildagliptin/metformin as initial combination therapy. A total of 532 patients were enrolled in the study from four countries across Asia including India (n=200). Of enrolled T2DM patients, 30.1% of patients had dyslipidemia, 29.7% patients had hypertension and 20.9% of patients had obesity as a cardiovascular risk factor along with diabetes at baseline.

Significant HbA1c reductions were consistently seen from baseline to weeks 12 (-1.6%) and 24 (-1.9%) overall and in the various sub-groups. These findings were accompanied by good tolerability. The initial combination therapy showed clinically meaningful and consistent reductions in HbA1c regardless of baseline age, BMI, or associated co-morbidities (i.e. hypertension, dyslipidemia).[31]

The multinational VERIFY[32] (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) study was a randomized, double-blind, parallel-group study of newly diagnosed patients with type 2 diabetes conducted in 254 centers across 34 countries. Enrolled patients were randomized to receive either the early combination treatment group (n=998) or the initial metformin monotherapy group (n=1003).

Around 20% of all patients were enrolled from several centers in India. This provided evidence accrued over 5 years, demonstrating the potential of early combination therapy; time to loss of glycaemic control was nearly doubled. 62% of patients experienced initial treatment failure with metformin monotherapy; whereas only 44% of patients experienced initial treatment failure with combination therapy. There was around a 26% reduction in risk of time to secondary treatment failure following early combination therapy. More than twice the number of patients experienced extended glycaemic control, with avildagliptin–metformin combination therapy vs metformin monotherapy. This suggests a 'legacy effect' by which only the earlynormalization of blood glucose can help to attenuate diabetes progression. VERIFY is the first study to show the long-term benefits and glycaemic durability of an early combination treatment strategy with metformin and vildagliptin compared with the current standard-of-care, late combination strategy in patients with newly diagnosed type 2 diabetes.[33]

Another important feature of the VERIFY study was that it was designed to reflect the real-world clinical practice of managing treatment-naive patients with an initial standard-of-care monotherapy, and intensifying to late combination when initial treatment fails.[32]

Evidence from the VERIFY study has led to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) suggesting that healthcare providers engage their patients in

making shared decisions around using initial combination therapy when type 2 diabetes is diagnosed. This evidence, together with changes in management guidelines, will help physicians and multidisciplinary teams take the next steps in evolving the management of type 2 diabetes.[32]

Conclusion

The potential of DPP-4 inhibition as a glucose-lowering concept has now been explored for more than 25 years and it is now been around 15 years since the vildagliptin entry into the market. Several findings were revealed during this journey. The efficacy profile, together with a low risk of hypoglycemia, no weight gain, and no increased risk for CV events has established the clinical utility of vildagliptin, as an anti-diabetic agent for the treatment of patients with T2DM. Early studies of vildagliptin built up the foundation leading to the approval of vildagliptin. After its approval, a vast panorama of clinical trials and real-world studies has proved the efficacy and safety of vildagliptin.

An important lesson learned from the vildagliptin journey is that development of a proof-of-concept takes time and requires focused efforts with persistence and long-term perseverance. Finally, this type of effort in making a proof-of-concept to a very well-established molecule has indeed been fruitful not for only the generation of new agents to be introduced to the patients but also for the scientific field, since novel scientific discoveries have been made throughout these years of this journey.

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