World Applied Sciences Journal 7 (1): 01-06, 2009
ISSN 1818-4952

REVIEW ARTICLE

Clinical Efficacy of Gliptins for Glycemic Control in Type 2 Diabeties Mellitus

[1]*Atif Sitwat Hayat,* [2]*Naila Shaikh,* [3]*Pyar Ali,* [1]*Tariq Zaffar Shaikh and* [2]*Abdul Haque Khan*

[1]Registrar Medicine, Liaquat University Hospital, Jamshoro/Hyderabad, Sindh, Pakistan
[2]Liaquat University of Medical and Health Sciences, Jamshoro, Sind, Pakistan
[3]Assistant Professor of Medicine, Dow University of Health Sciences, Karachi, Pakistan

Abstract: The *Gliptins*, a new class of oral anti-diabetic drugs for type 2 diabetes mellitus, lower blood glucose by inhibiting the enzyme dipeptidyl peptidase 4 and hence increasing the circulating levels of incretins (i.e gut hormones which can boost insulin levels). This article reviews the current evidence on the effectiveness of *gliptins* and suggest several ways in which these drugs could be used in type 2 diabetes mellitus treatment.

Key Points:

- Gliptins effectively lower blood glucose levels and do not require dose titration. They are well tolerated, neither cause weight gain or loss and unlikely to cause hypoglycemia.
- Gliptins can be used alone or in combination with metformin or a thiazolidinedione. Preliminary studies also show evidence of benefit when they are used in combination with insulin.
- Comparative studies show that *gliptins* lower blood glucose levels by about the same amount as other oral hypoglycemic agents.
- Sitagliptin is now available in US and Europe but *vildagliptin* is awaiting approval.

Abbreviations: DPP-4 inhibitors (Dipeptidyl peptidase 4 inhibitors), FPG (Fasting plasma glucose), PPG (Plasma Postprandial glucose), OAH (Oral anti-hyperglycemic agents), HbA_{1c} (Hemoglobin A_{1c}), TZD (Thiazolidinedione),FDA(Food and Drug Administration)

Key words: Gliptins · Type 2 diabetes mellitus · Incretins · Hemoglobin A_{1c} · Glucagon-like peptide 1 (GLP-1) · Glucose-dependent insulinotropic peptide (GIP)

INTRODUCTION

The *Gliptins- Dipeptidyl peptidase 4 (DPP-4) inhibitors,* are one of the newest anti-diabetic drugs for the treatment of type 2 diabetes mellitus. *Sitagliptin* has been approved by the Food and Drug Administration (FDA) and is currently in clinical use in USA, while *Vildagliptin* awaits FDA approval. Other *gliptins* are under development.

The *Gliptins* act by prolonging the action of gut hormones called Incretins, which boost insulin levels. They stimulate insulin production with little risk of associated hypoglycemia. As the number of patients with type 2 diabetes mellitus continues to rise steadily [1,2], a lot of work has gone into studying treatment goals and how to achieve them. Although most experts generally agree on glycemic goals [3], we currently fail to achieve those goals in close to two-thirds of patients; only 37% have a hemoglobin A_{1c} (Hb A_{1c}) value at or below the goal of 7% and the same number have levels exceeding 8% [4]. Secondly, treatment regimens are not adjusted in a timely fashion. In a prescribing database of almost 4,000 patients with type 2 diabetes mellitus [5], the mean time from the first HbA_{1c} reading above 8% to an actual change in therapy was about 15 months for those taking metformin alone and 21 months for those taking a sulfonylurea alone. Thirdly, on average, patients with HbA_{1c} of 8.0% to 8.9% can expect only a 0.6% lowering with the

Corresponding Author: Dr. Atif Sitwat Hayat, 78/ A Block E unit no 6 Latifabad, Hyderabad, Sind, Pakistan
Tel: +92-223-869661

addition of one agent [6]. This clearly show, we need new pharmacologic approaches and new management paradigms. One new approach is the use of *gliptins*.

In this review article, we will discuss the rationale behind *gliptins* drugs, their use alone or in combination with current oral hypoglycemic drugs (and even with insulin) and when and how to use them in daily practice.

Pharmacodynamics of Gliptins: There are two main mechanism of actions for *gliptins*:

- Direct action of Incretins stimulating endogenous insulin secretion and
- Inhibition of DPP-4 which indirectly boosts incretin action.

Incretins are peptides, have a high degree of homology and both promote insulin secretion. GLP-1 is produced by the L-cells of the ileum and colon, inhibits glucagon secretion and slows gastric emptying, whereas GIP, secreted from the K-cells of the duodenum, has no effect on glucagon secretion and little effect on gastric emptying. Both peptides appear to promote pancreatic beta cell growth and survival [7,8], an effect that might allow us to slow progressive loss of insulin secretory capacity in type 2 diabetes mellitus.

In addition, the effect of GLP-1 on insulin secretion depends on the plasma glucose concentration, with a greater insulin secretory effect at higher glucose level and minimal effect at euglycemic levels [9]. This mechanism suggests that drugs that boost GLP-1 activity should not cause hypoglycemia typically seen in patients taking insulin, insulin secretagogues, sulfonylureas, or the meglitinides (i.e repaglinide or nateglinide). Studies of combined treatment with metformin and GLP-1 receptor agonist exenatide have shown little risk of hypoglycemia [10], offering evidence for their combined treatment. Furthermore, GLP-1 and GIP have very short half -lives in the circulation, i.e, less than ten minutes. GLP-1 and GIP both have two N-terminal amino acids that are quickly cleaved by DPP-4 [11], an enzyme present in the circulation [12] and on endothelial cells [13].

Currently, there are two classes of drugs based on incretins. Class I, the incretin mimetics or GLP-1 receptor agonists, include drugs that mimic the effect of GLP-1 but are not so quickly degraded by DPP-4 enzyme. The GLP-1 receptor agonists act directly on GLP-1 receptors located in pancreatic alpha and beta cells and other tissues [14], thereby regulating insulin and glucagon secretion in a glucose-dependent manner. Examples of these drugs are exenatide and liraglutide. Class II, on the other hand act indirectly to increase the levels of endogenous GLP-1 by inhibiting the enzyme DPP-4, which inactivates GLP-1 in vivo [15]. Hence, their effects are limited by the patient's GLP-1 and GIP levels. Unlike most anti-hyperglycemic drugs, the risk of hypoglycemia is very low with either GLP-1 receptor agonists or DPP-4 inhibitors. The glucose- lowering effects of DPP-4 inhibitors are observed to be less than those of the GLP-1 receptor agonists. GLP-1 receptor agonists delay gastric emptying hence reduce body-weight and decrease Hb A_{1c} from 0.5% to 1.6%. Similarly, DPP-4 inhibitors are weight- neutral and HbA_{1c} is generally lowered from 0.5% to 0.8%. Greater reductions typically occur with a higher baseline HbA_{1c} and longer duration of treatment. Finally, incretins can also improve beta cell function and reduce glucagon secretion.

The DPP-4 inhibitors (*Gliptins*) have been used as mono-therapy in patients naïve to drug treatment with comparison to placebo.In addition, they have been compared alone or in combination with one or two oral anti-hyperglycemic(OAH) agents.

Randomized Clinical Trials of Sitagliptin: S*itagliptin* alone and in combination with other anti-hyperglycemic agents has been shown to reduce the Hb A_{1c} from 0.2 to 0.9% and fasting plasma glucose (FPG) levels by 11 to 18 mg/dl. A 24- weeks mono-therapy study in patients treated with or without an OAH showed that *sitagliptin* 100mg once daily[16]:

- Reduced Hb A_{1c} from 8.0% at baseline to 7.4% compared to an increase from 8.0% to 8.2% for placebo (p-value = 0.001)
- FPG levels were reduced 13 mg/dl in the *sitagliptin* group and 5mg/dl in the placebo group (p-value = 0.001) and
- Plasma postprandial glucose (PPG) levels were reduced 49 and 2mg/dl in the *sitagliptin* and placebo groups (p-value < 0.001) respectively.

Similar results were observed in an 18- week trial comparing *sitagliptin* 100mg or placebo once daily in patients inadequately controlled with diet and exercise [17]. The addition of *sitagliptin* to existing OAH therapy further improves glycemic control. *Sitagliptin* 100mg once daily combined with metformin 1500 mg or more[18]:

- Caused the Hb A_{1c} to decrease from 8.0% at baseline to 7.3% at 24 weeks compared to no change with the addition of placebo to metformin (p-value < 0.001).
- Whereas the FPG level was increased 5mg/dl in the placebo group, it was reduced 18mg/dl in the *sitagliptin* group (p-value < 0.001) and
- The PPG level was significantly reduced in the *sitagliptin* group compared with placebo (p-value < 0.001)

The addition of *sitagliptin* to a thiazolidinedione (TZD) also provides further benefit [19]. *Sitagliptin* 100mg once daily added to pioglitazone 30mg or 45mg daily for 24 weeks led to a reduction in the:-

- Hb A_{1c} from 8.1% to 7.2% compared with 8.0% to 7.8% for the addition of placebo to pioglitazone (p-value < 0.001) and
- FPG levels from 168mg/dl to 150mg/dl in the *sitagliptin* group, but did not change in the placebo group (p-value < 0.001).

Gastrointestinal disturbances occur in 9% to 16% of patients treated with *sitagliptin* compared with 6% to 14% for placebo. Hypoglycemia, which is usually mild to moderate, occurs in 0% to 4% and 0% to 2%, respectively [16-20]. There have been post-marketing reports of serious hypersensitivity reactions, i.e anaphylaxis, angioedema and exfoliative dermatitis, occurring within three months of initiating *sitagliptin* therapy. These reactions sometime occur after the first dose [21].

Renal Insufficiency Slows Sitagliptin Clearence: Lower doses and periodic monitoring of renal function are recommended in patients taking *sitagliptin* who have some degree of renal insufficiency. Clearance of *sitagliptin* is delayed in patients with renal insufficiency (Creatinine clearance < 50ml/minute).

In a placebo-controlled study of *sitagliptin* safety, Scott et al [22] found that the area under the *sitagliptin* concentration-time curve was 2.3 times greater in patients with moderate renal insufficiency (Creatinine clearance rate 30-49.9 ml/minute), 3.8 times greater in those with severe renal insufficiency (15-29.9 ml/minute) and 4.5 times greater in those with end- stage renal disease (< 15 ml/minute).

The Januvia Package Insert [23] recommends that the daily dose be decreased to 50mg in patients with creatinine clearance rates of 30 to 49.9 ml/minute (Serum creatinine>1.7 mg/dl in men,and >1.5 mg/dl in women) and that the dose be decreased to 25mg per day in those with creatinine clearance rates below 30ml/minute (Creatinine>3.0/2.5 mg/dl).

Randomized Clinical Trials of Vildagliptin: *Vildagliptin* has been approved in Europe but not the United States. *Vildagliptin* mono-therapy for 24- weeks has been shown to significantly lower blood glucose levels in drug-naïve patients in two studies. In the first study, patients were randomized to *vildagliptin* 50mg once daily, 50mg twice daily, 100mg once daily or placebo [24]:

- The HbA_{1c} decreased in all groups; 8.3% to 7.9% (p-value = 0.011 vs placebo), 8.4% to 7.7% (p-value < 0.001 vs placebo), 8.3% to 7.5% (p-value < 0.001 vs placebo) and 8.5% to 8.4% respectively and
- The respective changes in FPG levels from baseline to 24- weeks were 187mg/dl to 178mg/dl (p-value= not significant [ns] vs placebo), 196mg/dl to 173mg/dl (p-value = 0.001 vs placebo) and 180mg/dl to 162mg/dl (p-value = 0.001 vs placebo), but no change in the placebo group.

A comparison of *vildagliptin* 50mg twice daily with rosiglitazone 8mg once daily provided further support for the efficacy of *vildagliptin* mono-therapy [25]:

- From a baseline of 8.7%, HbA_{1c} decreased to 7.6% in the *vildagliptin* and 7.4% in the rosiglitazone groups (p-value = not significant)
- Corresponding changes in the FPG levels were 186mg/dl to 162mg/dl and 186mg/dl to 144mg/dl in the *vildagliptin* and rosiglitazone groups (p-value < 0.001), respectively

The efficacy of *vildagliptin* in combination with other OAH therapy further improves glycemic control. In patients uncontrolled with metformin in doses up to 3000mg/day, the addition of *vildagliptin* 50mg once daily for 12- weeks reduced the [26]:

- HbA_{1c} from 7.7% to 7.1% compared with no change for the addition of placebo (p-value < 0.001)
- FPG levels from 177mg/dl to 166mg/dl in the *vildagliptin* group but increased from 184mg/dl to 187mg/dl in the placebo group (p-value = 0.0057)

- An extension phase to 52-weeks was completed by 75% and 57% of patients, respectively:
- At the end of 52- weeks, HbA_{1c} remained relatively constant in the *vildagliptin* group (7.2%), but increased in the placebo group to 8.3% (p-value < 0.001).
- Similarly, FPG levels decreased an additional 11mg/dl in the *vildagliptin* group, but increased 9mg/dl in the placebo group.

In a 24- week study [27],256 patients with type 2 diabetes mellitus who had a mean body mass index of $33kg/m^2$ and who were taking more than 30 units of insulin daily (an average of 82 units) were randomized to additionally receive either *v ildagliptin* 50mg twice daily or placebo. The HbA_{1c} decreased by 0.5% with *vildagliptin* and by 0.2% with placebo, from a baseline level of 8.5%. Of interest, 33 patients receiving *vildagliptin* had a hypoglycemic episode (a total of 113 events), compared with 45 patients in the placebo group (185 events). None of the episodes in the *vildagliptin* group was classified as severe, whereas six episodes in the placebo group were classified as severe. This suggests that adding *vildagliptin* in patients taking insulin can improve glycemia without causing excessive hypoglycemia.

A weakness of the design of this study is that it did not include patients who were receiving an insulin sensitizer, an approach that is typically taken. Given this, it is understandable that overall glycemic control was relatively poor. More effort is needed to explore the use of *gliptins* with insulin.

Headache, dizziness and nasopharyngitis have been the adverse events most commonly reported in clinical trials, with an incidence similar to placebo [24,27,28]. Hypoglycemia occurred in less than 1% of patients treated with *vildagliptin* [27]. Perhaps of greatest concern with *vildagliptin* are adverse skin effects and elevated liver enzymes, which are a focus of the FDA during it's review of the *vildagliptin* new drug application [29].

Randomized Clinical Trials of Alogliptin: Alogliptin is currently under review by the FDA. The short term efficacy of *alogliptin* mono-therapy has been demonstrated in doses ranging from 25 to 400mg once daily [30]. A total of 14 days of *alogliptin* reduced HbA_{1c} 0.2% to 0.4% compared with no change for placebo. PPG levels also were reduced ranging from 22mg/dl to 40mg/dl with *alogliptin* compared with an increase of 13mg/dl for placebo.

A 24-week study further demonstrated the efficacy of *alogliptin* mono-therapy in patients in-adequately controlled with diet and exercise [31]. The addition of *alogliptin* 12.5 or 25mg once daily reduced HbA_{1c} 0.6% in both groups compared with no change for placebo (p-value < 0.001 for both groups vs placebo). The FPG levels were significantly reduced from baseline with *alogliptin* 12.5mg (10mg/dl) and 25mg (16mg/dl) compared with an increase of 11mg/dl in the placebo group (p-value < 0.001 for both groups vs placebo).

Headache, dizziness and constipation have been the most commonly reported adverse effects in clinical trials, occurring in slightly more *alogliptin*-treated patients than in placebo-treated patients [31]. The incidence of hypoglycemia is 3% in patients treated with *alogliptin* compared with 2% in placebo-treated patients [31].

CONCLUSION

Evidence from the studies reviewed in this article suggests that *gliptins* can play an important role in the treatment of type 2 diabetes mellitus. In elderly patients, in whom concerns about hypoglycemia are greatest and who cannot take either metformin or a thiazolidinedione, thus precluding sulfonylurea therapy, *gliptins* may be the agent of choice.

The clinical trials reviewed here suggest that *gliptins* have glucose-lowering efficacy similar to that of other oral anti-hyperglycemic therapies, with minimal risk of hypoglycemia, with few immediate adverse effects and without requiring dose-titration. These characteristics suggest that *gliptins* should be considered useful agents in mono-therapy and combination therapy with either metformin, thiazolidinedione or insulin for the treatment of type 2 diabetes mellitus.

In summary, *gliptins* are variably effective in reducing HbA_{1c},FPG and PPG levels in patients with type 2 diabetes mellitus due to their unique mechanisms of action. Used alone, *gliptins* generally lowers HbA_{1c} from 0.5% to 0.8%. *Gliptins* generally possess good safety profiles and addition to existing anti-hyperglycemic therapy provides similar additional improvement in glycemic control. Infrequent adverse effects, such as hypersensitivity reactions with *sitagliptin* and skin reactions and elevated liver enzymes with *vildagliptin*, also have been observed.

REFERENCES

1. National Diabetes Surveillance System. www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. Last accessed February 28, 2008.
2. Narayan, K.M., J.P. Boyle, L.S. Geiss, J.B. Saaddine and T.J. Thompson, 2006. Impact of recent increase in incidence on future diabetes burden: US, 2005-2050. Diabetes Care, 29: 2114-2116.
3. American Diabetes Association. Standards of medical care in diabetes—2007. Diabetes Care 2007; 30(suppl 1):S4–S41.
4. Saydah, S.H., J. Fradkin and C.C. Cowie, 2004. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA, 291: 335-342.
5. Brown, J.B., G.A. Nichols and A. Perry, 2004. The burden of treatment failure in type 2 diabetes. Diabetes Care, 27: 1535-1540.
6. Bloomgarden, Z.T., R. Dodis, C.M. Viscoli, E.S. Holmboe and S.E. Inzucchi, 2006. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care, 29: 2137-2139.
7. Drucker, D.J., 2003. Enhancing incretin action for the treatment of type 2diabetes. Diabetes Care, 26: 2929-2940.
8. Bloomgarden, Z.T., 2006. Gut hormones and related concepts. Diabetes Care, 29: 2319-2324.
9. Nauck, M.A., N. Kleine, C. Orskov, *et al*. 1993. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia, 36: 741-744.
10. DeFronzo, R.A., R.E. Ratner, J. Han, D.D. Kim, M.S. Fineman and A.D. Baron, 2005. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care, 28: 1092-1100.
11. Deacon, C.F., M.A. Nauck, M. Toft-Nielsen, L. Pridal, B. Willms and J.J. Holst, 1995. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. Diabetes, 44: 1126-1131.
12. Holst, J.J. and C.F. Deacon, 2005. Glucagon-like peptide-1 mediates the therapeutic actions of DPP-4 inhibitors. Diabetologia, 48: 612-615.
13. Hansen, L., C.F. Deacon, C. Orskov and J.J. Holst, 1999. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase-4 in the capillaries supplying the L cells of the porcine intestine. Endocrinology, 140: 5356-5363.
14. Drucker, D.J., 2006. The biology of incretin hormones. Cell Metab., 3: 153-165.
15. Deacon, C.F., T.E. Hughes and J.J. Holst, 1998. Dipeptidyl peptidase-4 inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. Diabetes, 47: 764-769.
16. Aschner, P., M.S. Kipnes, J.K. Lunceford, *et al*. 2006. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care, 29: 2632-2637.
17. Raz, I., M. Hanefeld, L. Xu, *et al*. 2006. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia, 49: 2564-2571.
18. Charbonnel, B., A. Karasik, J. Liu, *et al*. 2006. Efficacy and safety of the dipeptidyl peptidase- 4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care, 29: 2638-2643.
19. Rosenstock, J., R. Brazg, P.J. Andryuk, *et al*. 2006. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther., 28: 1556-1568.
20. Scott, R., M. Wu, M. Sanchez, *et al*. 2007. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract., 61: 171-180.
21. Januvia [package insert]. Whitehouse Station, NJ: Merck & Company, Inc; 2008.
22. Scott, R.S., P. Hartley, E. Luo, *et al*. 2006. Use of sitagliptin in patients with type 2 diabetes and renal insufficiency [abtract]. Diabetes, 55(suppl 1): A462.
23. Januvia prescribing information, 2008. www.merck.com/ product/ usa/ pi_circulars/j/ products_j.html. Last accessed February, 28.
24. Pi-Sunyer, F.X., A. Schweizer, D. Mills, *et al*. 2007. Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes. Diabetes Res Clin Pract., 76: 132-138.

25. Rosenstock, J., M.A. Baron, S. Dejager, *et al*. 2007. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. Diabetes Care, 30: 217-223.
26. Ahren, B., R. Gomis, E. Standl, *et al*. 2004. Twelve- and 52-week efficacy of the dipeptidyl Peptidase-4 inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care, 27: 2874-2880.
27. Fonseca, V., A. Schweizer, D. Albrecht, M.A. Baron, I. Chang and S. Dejager, 2007. Addition of vildagliptin to insulin improves glycemic control in type 2 diabetes. Diabetologia, 50: 1148-1155.
28. Garber, A.J., A. Schweizer, M.A. Baron, *et al*. 2007. Vildagliptin in combination with pioglitazone improves glycemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes Obes Metab., 9: 166-174.
29. Novartis Pharmaceuticals. 2008. New Galvus clinical data reinforces efficacy profile; safety updated provided to regulatory agencies. Available at: http://www.novartis. com/newsroom/media-releases/en/2007/1166139.shtml. Accessed October 6,
30. Covington, P., R. Christopher, M. Davenport *et al*. 2008. Pharmacokinetic, pharmacodynamic and tolerability profiles of the dipeptidyl peptidase-4 inhibitor alogliptin: A randomized, double-blind, placebo-controlled, multiple-dose study in adult patients with type 2 diabetes. Clin Ther., 30: 499-512.
31. DeFronzo, R., P. Fleck, C. Wilson, *et al*. 2008. Alogliptin monotherapy improves glycemic control in patients with type 2 diabetes. Paper presented at: American Diabetes Association 68th Scientific Session; June 6-10, San Francisco, Calif.