Clinical Review of Sitagliptin: A DPP-4 Inhibitor

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Abstract
Type 2 Diabetes Mellitus is most common form of diabetes. Oral agents are the mainstay of pharmacological treatment for type 2 diabetes mellitus. Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for type 2 diabetes. Sitagliptin is highly selective DPP-4 inhibitor that has been approved for type 2 diabetes therapy. It acts by increasing the levels of incretins by inhibiting their degradation by DPP-4. Sitagliptin has been shown to be effective, well tolerated and safe in the treatment of type 2 diabetes in monotherapy or in combination with metformin or thiazolidinediones with minimal side effects.

Introduction
In Type 2 Diabetes Mellitus (T2DM) patients, the evident metabolic abnormalities include obesity, insulin resistance, qualitative and quantitative abnormalities in insulin secretion, dysregulated secretion of other islet hormones such as amylin and glucagon and increased endogenous glucose production. In addition, there is the decreased incretin effect due to impairment in secretion and action of incretin hormones glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP).

In April 2005, the US Food and Drug Administration (US FDA) approved the first incretin mimetic, Exenatide, a GLP-1 receptor analogue resistant to Dipeptidyl peptidase-4 (DPP-4) degradation, as adjunctive therapy for patients with T2DM, but the use of this drug is limited by its parenteral route of administration. Therefore considerable efforts have been devoted for creating an oral hypoglycaemic drug targeting the incretin pathway. Inhibition of the enzyme DPP-4 extends the half life of native incretins, thereby prolonging their physiological effects. On October 17, 2006, the US FDA approved the first oral incretin enhancer, Sitagliptin, a selective DPP-4 inhibitor, for use as monotherapy or in combination with metformin or thiazolidinediones. In India, Sitagliptin (MK-O431) is approved and available for use as monotherapy under the brand name Januvia-Merck. Sitagliptin is used clinically in India as combination therapy with Metformin and is marketed as Janumet-Merck. Besides Sitagliptin, other drugs in the class of DPP-4 inhibitors include Vildagliptin, Saxagliptin, Alogliptin.

Physiological Role of Incretins
In 1932, the term “incretin” was used for the first time to refer to a substance derived from the gut presumably a hormone that regulates insulin secretion after eating. Thereafter in 1971, the first incretin GIP and in 1985, second incretin GLP-1 was described. GIP and GLP-1 are secreted by enteroendocrine K-cells in the proximal gut and L-cells in the distal gut respectively. Both GIP and GLP-1 are secreted into the circulation as active hormones within minutes in response to food consumption and are rapidly inactivated by the enzyme DPP-4, an ubiquitous serine protease. Both GIP and GLP-1 bind to specific G-protein coupled receptors present on β-cells and other target tissues. Activation of the incretin receptors on β-cells acutely enhances glucose dependent exocytosis of insulin and long term effects like stimulation of insulin synthesis, enhancement of β-cell proliferation and promotion of resistance to apoptosis. GLP-1 also lowers plasma glucose levels through inhibition of glucagon secretion, deceleration of gastric emptying and inhibition of food intake.

Role of Incretin Hormones in Pathophysiology of Type 2 Diabetes Mellitus
Recent improvement in understanding of the incretin effect on pathophysiology of T2DM has led to development of new hypoglycaemic agents. Studies have shown that in T2DM, there is deficient insulin as well as GLP-1 secretion after the injection of glucose or a meal, though biological effects of GLP-1 are preserved. In contrast, plasma levels of GIP are normal or slightly increased in T2DM, while its activity is defective or absent. This is clear that the incretin effect of GLP-1 in T2DM is better preserved in contrast to that of GIP. The incretin effect of GIP in stimulating insulin secretion is almost lost in T2DM and many studies indicate the existence of a specific defect in GIP action in these patients, may be due to chronic desensitization of GIPRs (Glucose dependent insulinotropic peptide receptors).

Pharmacological Profile of Sitagliptin
Mechanism of action
Sitagliptin is a highly selective DPP-4 inhibitor for the treatment of T2DM that was discovered through the optimisation of class of β-amino acids derived DPP4 inhibitors. DPP4 is a complex molecule that exists as membrane spanning cell anchored protein that is expressed on many cell types, and as soluble form in circulation both forms have proteolytic activity. It lowers DPP4 activity in dose dependent manner (50-200 mg/day), preserves the circulating levels of intact GIP and GLP-1 following meals and reduces blood glucose levels without causing significant hypoglycaemia.
fasting glucose concentration. Both GLP-1 and GIP are rapidly inactivated by an enzyme DPP-4. By blocking this inactivation, DPP-4 inhibitors increase the incretin levels, enhancing incretin effects and thereby offer a new therapeutic approach for management of patients of T2DM.8

Pharmacokinetics

The pharmacokinetics of Sitagliptin is similar in healthy individuals and in T2DM patients. It is well absorbed orally with an 87% bioavailability. In human beings, the protein binding of Sitagliptin, as determined by ultracentrifugation, is 34-46%. In healthy volunteers and in patients with T2DM of different ethnic background, the tolerability of different doses as once or twice daily is good. The main pharmacokinetic parameters (Tmax, Cmax and t1/2) measured in studies were similar at baseline and in the steady state after longer administration. Steady state plasma concentration of Sitagliptin is reached after 3 days with terminal half-life of 10-12 hours at doses of 25-100 mg. The elimination and excretion is mainly renal (75-80% of an oral drug is found in urine as unchanged drug) and the rest is metabolised via cytochrome CYP3A4 and CYP2C8.3,4,9

Safety Profile of Sitagliptin

Few adverse effects reported with Sitagliptin are nasopharyngitis, upper respiratory tract infections, headache, back pain, osteoarthritis, and pain in extremities. In Laboratory parameters, small increase in white blood cells, serum uric acid and small decrease in alkaline phosphatase is reported. Treatment with Sitagliptin is having neutral effect on body weight.6,10

Sitagliptin in Renal / Hepatic Insufficiency Patients

As Sitagliptin is primarily secreted via renal elimination, therefore, the dosage must be adjusted in patients with moderate-to-severe renal impairment or end stage renal disease. Dose is decreased by two fold in moderate (Creatinine Clearance 30-50 ml/min) renal insufficiency and four fold in severe (Creatinine clearance < 30 ml/min) renal insufficiency patients. There is no need of dose adjustment in patients of mild (Creatinine clearance 50-80 ml/min) renal insufficiency.11

Studies have shown that moderate hepatic insufficiency (Child-Pugh classification scores 7 to 9) have no clinical effect on pharmacokinetics of Sitagliptin. The single 100 mg dose of the Sitagliptin was well tolerated with no meaningful changes observed in liver function tests. Therefore, no dosage adjustments of Sitagliptin are required in patients with mild to moderate hepatic insufficiency.12 There are no clinical studies on humans in literature to demonstrate the effects of Sitagliptin in severe hepatic insufficiency patients.

Role of DPP-4 Inhibitors in Malignancy

DPP-4, the cell surface protease is expressed in various normal tissues and functions as tumour suppressor. DPP-4 expression is lost in many types of human cancers like non small cell lung carcinoma (NSCLC) and prostate cancer. Therefore, DPP-4 inhibitors are associated with risk of NSCLC and prostate cancer. In a study, DPP-4 inhibitors have shown to promote already existing intestinal tumours and may support the potential of colon cancer cells to metastasise.13-15

Clinical Data

There are 13 published double-blind trials (n = 4780) (age range, 18-80 years) in which Sitagliptin was compared with a DPP-4 inhibitor given as monotherapy, or as add-on therapy to oral hypoglycaemic agents or insulin, of which a few have been shown in Table I. In trials lasting for 18-52 weeks, various doses of Sitagliptin were utilised with once or twice daily dosing.1

Raz et al (2006) demonstrated that Sitagliptin at doses of 100 mg and 200 mg provided clinically meaningful and statistically significant (p < 0.001) reduction in glycosylated haemoglobin HbA1c fasting plasma glucose (FPG) and post prandial glucose (PPG) levels over 18 weeks compared to placebo in patients of T2DM with mild to moderate hyperglycaemia (baseline HbA1c equivalent to 8%) inadequately controlled on diet and exercise. Sitagliptin, at both doses also led to a significantly (p < 0.001) higher proportion (35.8% with 100 mg and 28.6% with 200 mg) of patients achieving an HbA1c < 7% after 18 weeks compared with placebo (15.5%).10

In a similar study, Ascher et al (2006) studied that after 24 weeks, Sitagliptin 100 and 200 mg significantly (p < 0.001) reduced HbA1c, FPG and PPG levels as compared with placebo without deterioration in Sitagliptin effect throughout 24 weeks. The percentage of patients achieving HbA1c < 7% was 41% with 100 mg and 45% with 200 mg versus 17% for placebo (p < 0.001). A significant (p < 0.001) interaction between baseline HbA1c and treatment was observed with the finding of great efficacy in patients with higher baseline HbA1c.16

Goldstein et al (2007) demonstrated the effect of Sitagliptin and Metformin as monotherapy and as combination therapies (at different doses) in T2DM patients who had inadequate glycaemic control with diet and exercise. It was found that all active treatment group produced statistically significant (p < 0.001) reduction in HbA1c, FPG and PPG levels compared to placebo and the co-administration groups provided greater reduction relative to the individual monotherapies. Patients with more severe baseline hyperglycaemia (HbA1c ≥ 9%) had the largest reduction with co-administration of Sitagliptin and Metformin.17

In another combination study by Cherbonnel et al (2006), in 701 patients of type T2DM who had inadequate glycaemic control with metformin alone, the addition of Sitagliptin 100 mg once daily was well tolerated and provided effective and sustained improvement in HbA1c, FPG and PPG levels. Nearly half of the patients receiving Sitagliptin 100 mg once daily achieved current American Diabetes Association glycaemic goal of HbA1c < 7% compared with less than one-fifth of placebo treated patients. Treatment with Sitagliptin was associated with low rate of hypoglycaemia that was similar to that seen with placebo as well as neutral effect on body weight.8

In a head-to-head comparison, Nauck et al (2007) found that Sitagliptin 100 mg once daily was non-inferior to Glipizide 20 mg once daily as an adjunct to Metformin ≥ 1500 mg once daily. 52-week mean reduction in HbA1c of 0.67% were achieved both in patients receiving Sitagliptin and those receiving Glipizide, with the added benefit of small weight losses with Sitagliptin (-1.5 kg) compared to small weight gain with Glipizide (+1.1 kg).18

Comparable results were observed in a study by Rosenstock et al (2006) with similar design with an add-on combination of Sitagliptin to an existing Pioglitazone therapy. The glycaemic parameters HbA1c, FPG and PPG levels improved. From baseline HbA1c of 7.9%, a significant percentage of patients reached a
**Table 1 : Sitagliptin in reducing Glycosylated Haemoglobin (HbA1c) and Fasting plasma glucose levels (FPG) and post-prandial glucose (PPG) levels in different clinical studies**

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Duration (weeks)</th>
<th>Dose (mg/day)</th>
<th>HbA1c reduction</th>
<th>FPG reduction(mg/dl)</th>
<th>PPG reduction(mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin Monotherapy10{2006}</td>
<td>18</td>
<td>100</td>
<td>0.60% (n=193)</td>
<td>19.8 (n=201)</td>
<td>46.8 (n=62)</td>
</tr>
<tr>
<td>Sitagliptin Monotherapy17{2007}</td>
<td>24</td>
<td>100</td>
<td>0.79% (n=229)</td>
<td>17.1 (n=234)</td>
<td>48.9 (n=202)</td>
</tr>
<tr>
<td>Sitagliptin + Metformin17{2006}</td>
<td>24</td>
<td>100+1500</td>
<td>0.65% (n=453)</td>
<td>25.2 (n=454)</td>
<td>50.4 (n=387)</td>
</tr>
<tr>
<td>Sitagliptin +Pioglitazone19{2006}</td>
<td>24</td>
<td>100+30-45</td>
<td>0.70% (n=163)</td>
<td>17.7 (n=163)</td>
<td>Not Available</td>
</tr>
<tr>
<td>Sitagliptin Monotherapy17{2007}</td>
<td>24</td>
<td>100</td>
<td>0.83% (n=175)</td>
<td>23.3 (n=178)</td>
<td>52.2 (n=236)</td>
</tr>
<tr>
<td>Metformin Monotherapy17{2007}</td>
<td>24</td>
<td>1000</td>
<td>0.99% (n=178)</td>
<td>33.1 (n=179)</td>
<td>53.7 (n=141)</td>
</tr>
<tr>
<td>Metformin Monotherapy17{2007}</td>
<td>24</td>
<td>2000</td>
<td>1.30% (n=177)</td>
<td>35.1 (n=179)</td>
<td>78.3 (n=138)</td>
</tr>
<tr>
<td>Sitagliptin +Metformin17{2007}</td>
<td>24</td>
<td>100+1000</td>
<td>1.57% (n=183)</td>
<td>52.9 (n=183)</td>
<td>92.8 (n=147)</td>
</tr>
<tr>
<td>Sitagliptin +Metformin17{2007}</td>
<td>24</td>
<td>100+2000</td>
<td>2.07% (n=178)</td>
<td>69.7 (n=180)</td>
<td>116.9 (n=152)</td>
</tr>
<tr>
<td>Sitagliptin +Metformin17{2007}</td>
<td>52</td>
<td>100+1500</td>
<td>0.67% (n=588)</td>
<td>10.1 (n=588)</td>
<td>Not Available</td>
</tr>
<tr>
<td>Sitagliptin +Glimepiride20{2007}</td>
<td>24</td>
<td>100+2 4-8</td>
<td>0.57% (n=102)</td>
<td>19.3</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

Values in parantheses: (n), { } indicate number of patients and year of the study respectively. All the figures of glycaemic parameters are statistically significant.

Target HbA1c < 7.0% (45%) in Sitagliptin group compared with placebo (23%).

Hermansen et al (2007) found that Sitagliptin 100 mg once daily significantly improved glycaemic control and β-cell function in patients with T2DM, who had inadequate glycaemic control with Glimepiride or Glimepiride plus Metformin therapy. The addition of Sitagliptin was generally well tolerated.

Most trials of Sitagliptin in combination with oral anti-diabetic drugs (OADs) indicated that DPP-4 inhibitors produce incremental or sometimes additive improvement in glycaemic parameters. Clinical data suggest that Sitagliptin is a moderately effective anti-diabetic drug, providing reduction in HbA1c, up to 0.94%, when used as monotherapy and additional reduction in HbA1c when used as a part of combination. Unlike majority of OADs, these incremental reductions in HbA1c are not associated with significant weight gain and hypoglycaemia.

**Precautions and Drug interactions**

Due to a lack of safety and efficacy data, Sitagliptin is not recommended for use in children under 18 years of age and caution is advised in patients > 75 years old. Sitagliptin has shown reproductive toxicity at high doses and has been detected in high amounts in the milk of lactating animals. Because of a lack of human data this drug should not be used during pregnancy or breast feeding.

Sitagliptin have shown to have a few drug-drug interactions. Sitagliptin is metabolised by CYP3A4 but it does not appear to induce or inhibit cytochrome P450 isoenzymes and does not show interactions with inducers or inhibitors of cytochromes. Clinically important CYP3A4 inhibitors mainly include macrolide antibiotics (e.g. clarithromycin, and erythromycin), anti-HIV agents (e.g., ritonavir and delavirdine), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers (e.g. verapamil and diltiazem), steroids and their modulators (e.g., gestodene and mifepristone), and several herbal and dietary components. A small number of drugs such as rifampin, phenytoin and ritonavir are identified as inducers of CYP3A4. In phase I drug interaction studies, Sitagliptin did not meaningfully alter the pharmacokinetics of other oral hypoglycaemic agents, including metformin, rosiglitazone or glyburide. Sitagliptin concomitant administration with digoxin (0.25 mg) for ten days increased plasma digoxin concentration; therefore monitoring is advisable to avoid digoxin toxicity but dose adjustment is not recommended.

**Dose**

The maximum approved and recommended dose for Sitagliptin is 100 mg daily and this is the most effective dose for various glycaemic parameters. The administration of Sitagliptin is independent of meals.

**Clinical Use**

Sitagliptin phosphate was approved by the United States FDA for the treatment in October 2006 as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM either as monotherapy or in combination with metformin or thiazolidinediones, when the single agent does not provide adequate glycaemic control.

**Comparison of Sitagliptin with Other DPP-4 Inhibitors**

The comparison of Sitagliptin with other DPP-4 inhibitors has been shown in Table 2. Vildagliptin (Glavus- Novartis) has been approved for use in the European Union and is under regulatory review in United states. The FDA has granted an approval letter for Vildagliptin but require additional safety data prior to final approval. Saxagliptin (Onglyza-BMS and Astra Zeneca) is approved and recently marketed in India for the treatment of T2DM. Clinical trials have demonstrated that Saxagliptin (in doses 2.5, 5, 10, 20, 40 mg once daily) is non inferior to Sitagliptin in monotherapy and in combination therapy with metformin. It has also been observed that when saxagliptin is used as an add on combination therapy with thiazolidinedione, the incidence of peripheral oedema is increased. Alogliptin, a highly selective DPP-4 inhibitor, being developed by Takeda Pharmaceutical Company is currently in phase three clinical trials. Alogliptin in dose range of 25-400 mg causes significant reduction in HbA1c when used alone or in combination with other oral agents in patients with T2DM similar to Sitagliptin. However, long-term studies are necessary before the place of Alogliptin in the management of type 2 diabetes can be established.
Sitagliptin Versus Other Oral Hypoglycaemic Agents

Metformin, a sulphonylurea is widely viewed as the initial drug of choice for treatment of type 2 DM owing to its 30 year track record, efficacy, safety and low cost. There are now at least seven different classes of agents that can be used in combination with metformin including sulphonylureas, glitindes, α-glucosidase inhibitors, thiazolidinediones, insulin (injected/inhaled), the GLPR agonist exenatide and DPP-4 inhibitor, Sitagliptin. Sulphonylureas and glitindes are inexpensive but are associated with weight gain and hypoglycaemia, which can be problematic in elderly. The α-glucosidase inhibitors are effective and safe but frequently associated with gastrointestinal side effects that limit their tolerability. Thiazolidinediones improve insulin action with low risk of hypoglycaemia and have appealing long durability but side effects like fluid retention and weight gain might be a problem for many patients.

The past few years have witnessed considerable progress in pharmacotherapy of T2DM and ease of use, favourable adverse event profile and lack of hypoglycaemia or weight gain are attractive features for the new class of DPP-4 inhibitors exemplified by Sitagliptin, though long term safety of prolonged DPP-4 inhibition in patients with T2DM is unknown. There is also no long term data available to inform the patients and physicians about Sitagliptin therapy to prevent progression of T2DM.7

Conclusion

It has been observed from various clinical studies (Table 1) that Sitagliptin is effective, well tolerated and safe in the treatment of T2DM as monotherapy or in the combination

<table>
<thead>
<tr>
<th>Pharmacological Name</th>
<th>Brand Name</th>
<th>Half life (hrs)</th>
<th>Daily dose (mg)</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>HbA1c reduction (%)</th>
<th>Adverse effects</th>
<th>Drug interactions</th>
<th>Status in hepatic/renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Januvia (Merck)</td>
<td>10-12</td>
<td>100</td>
<td>Hepatic (CYP3A4/5)</td>
<td>Renal</td>
<td>0.8</td>
<td>Abdominal pain, nausea, diarrhoea, nasopharyngitis, back pain, osteoarthritis</td>
<td>No drug-drug interactions are seen</td>
<td>No dose adjustments in mild to moderate hepatic impairment25/dose reduced to half and one-fourth in moderate and severe renal impairment respectively22</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Galvus (Novartis)</td>
<td>1.5-4.5</td>
<td>100</td>
<td>Hepatic (Hydrolysis)</td>
<td>Hepatic</td>
<td>0.5-1.0</td>
<td>Upper respiratory infection, dizziness, hypoglycaemia, headache</td>
<td>No drug-drug interactions are seen</td>
<td>No dose adjustment in hepatic impairment/under evaluation in patients of renal impairment6</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza (BMS &amp; Astra Zeneca)</td>
<td>2.5</td>
<td>2.5-5</td>
<td>Hepatic (CYP3A4/5)</td>
<td>Renal</td>
<td>0.7-0.9</td>
<td>Headache, upper respiratory infections, arthralgia, nausea, cough</td>
<td>Low risk of drug interactions, but dose is 2.5 mg in a patient taking strong inhibitor of CYP3A4/524,25</td>
<td>No dose adjustment in hepatic impairment/dose is 2.5 mg in renal impairment27</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>SYR-322 (Takeda)</td>
<td>12.5-21.1</td>
<td>25-50</td>
<td>Hepatic (CYP3A4/5)</td>
<td>Renal</td>
<td>0.6</td>
<td>Headache, dizziness, constipation</td>
<td>No drug-drug interactions are seen</td>
<td>No dose adjustments in mild to moderate hepatic impairment29/dose of 50 mg is reduced to half and one-fourth in moderate and severe renal impairment respectively4</td>
</tr>
</tbody>
</table>

Table 2: Comparison of sitagliptin with other DPP-4 inhibitors
with metformin or thiazolidinediones. Sitagliptin when used as monotherapy produces dose-dependent reduction in PPG levels but effect on HbA1c, and FPG levels is independent of dose. Sitagliptin when used in combination of Metformin or any other oral hypoglycaemic drug produces additive effect in reducing glycaemic parameters. Sitagliptin is weight neutral and does not increase the incidence of hypoglycaemic episodes or the occurrence of adverse events.

Sitagliptin and other DPP-4 inhibitors in general present a novel multimodal approach in treatment of T2DM. By preserving stimulated circulating plasma levels of incretin hormones, insulin secretion is stimulated under hyperglycaemic conditions and stimulated circulating plasma levels of incretin hormones, insulin secretion is stimulated under hyperglycaemic conditions and glucagon secretion is suppressed. Therefore, not only insulin secretion and insulin resistance are altered, as by previously used oral antihyperglycaemic agents, but also unmet needs of T2DM are covered by this novel therapeutic principle.3

References