Review Article

Choosing a Gliptin

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ABSTRACT

The treatment of type 2 diabetes mellitus (T2DM) has included the use of metformin and sulfonylurea (SU) as first-line anti-diabetic therapies world over since years. This remains, despite the knowledge that the combination results in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an additional pharmacological agent to maintain the glycosylated hemoglobin (HbA1c) <7.0% (UKPDS). Gliptins represent a novel class of agents that improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. They function by augmenting the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4). Not only are they efficacious but also safe (weight neutral) and do not cause significant hypoglycemia, making it a unique class of drugs. This review focuses on gliptins (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin) discussing pharmacokinetics, pharmacodynamics, efficacy, and safety.

Key words: Diabetes mellitus, dipeptidyl-dipeptidase, dipeptidyl peptidase-4-inhibitors, gliptins, GLP, incretins

Introduction

The treatment of type 2 diabetes mellitus (T2DM) has included the use of metformin (particularly in the overweight patient) and sulfonyurea (SU) (in both lean and overweight patient), as first line anti-diabetic therapies world over. Prior to 1995, the use of SU was the most popular anti-diabetic therapy in the USA (United States). SU's act by increasing insulin secretion in a glucose-independent manner, thereby risking severe unpredictable hypoglycemia, particularly if the meal is delayed or if its carbohydrate quantity reduced. The use of metformin only became popular in the US post 1995. It only makes sense that they continue to remain mainstay therapy as despite their problems they are best suited to deal with the original pathogenic triumvirate theory for T2DM proposed by Ralf Defranzo, (qualitative and quantitative beta cell failure and insulin resistance at level of liver and peripheral tissue). This was particularly true since there was no agent that could help improve health of the beta cell and cause insulin release in a glucose dependant manner. This all changed once it was learnt that the incretin system was involved in the pathogenesis of T2DM. Failure of this incretin system has been implicated in progression of beta-cell failure and therefore any therapy that can augment this system has been shown to promote beta cell health and insulin release in a glucose-dependent manner.[1-5]

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Although the use of metformin therapy has been associated with several advantages (non-hypoglycemic, weight-loss promoting, anti-ischemic to cardiac tissue, improvement in non-alcoholic hepatosteatosis, anti-neoplastic etc), its use has been associated with gastrointestinal adverse effects, precluding or limiting its use, particularly in the non-overweight patient.[2,6] Use of SU's on the other hand although effective in lowering plasma glucose can be associated with variable severities of hypoglycemia, weight gain, beta-cell death, and possibly adverse cardiac outcomes as proposed originally by the UKPDS and later by other groups.[2,7]

The UKPDS was the first to show that the combination of SU and metformin resulted in a progressive decline in

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[beta]-cell function and by 3 years up to 50% of diabetic patients can require an additional pharmacological agent to maintain the glycosylated hemoglobin (HbA1c) <7.0%.[2,5] Moreover, the percentage of diabetic patients classified as adequately controlled while mostly on these therapies still remains a challenge with a majority (> 50%) of diabetic patients having a HbA1c > 7%.[8] From the above data it seems clear that existing popular therapies are not only ineffective but are associated with a significant amount of morbidity (weight gain and hypoglycemia). The need of the hour is a refreshing class of drugs whose effects on hyperglycemia can be sustained, without adversely affecting the survival of beta-cells, and are weight neutral and free of hypoglycemia, a true class of anti-hyperglycemics, a dream too good to be true. GLIPTINS might just fulfill that dream.

Pathogenesis of type 2 diabetes mellitus

The natural history of T2DM as proposed originally of Ralph Defranzo *(triumvirate theory)* involved[9]:

1. Insulin resistance at level of liver resulting in hepatic outpouring of glucose into the hepatic venous system
2. Insulin resistance at peripheral tissue (skeletal muscles) resulting in inability in uptake of glucose
3. Beta-cell failure (five stages) resulting in declining insulin secretion capacity[1]

Beta cells failure can be described in five stages:

Stage 1: Beta-cell compensation, where the beta cell mass increases. This causes increased basal insulin release so that plasma glucose can be kept within the normal range. This beta-cell compensation occurs because of increasing insulin resistance (obesity and genetic factors). At this stage, people are usually obese with normal glucose tolerance and reduced insulin sensitivity by approximately 29%. It has been shown that 66% of beta-cell function is lost when the 2-hour post-meal plasma glucose is between 120 and 139 mg/dl (normal glucose tolerance) suggesting that beta cell dysfunction starts very early .

Stage 2: Beta-cell adaptation, where in plasma glucose although higher than at stage 1 is associated with normal glucose tolerance, at the cost of increased workload. This stage is associated with a further decline in insulin sensitivity by 28% (as age advances and obesity worsens).

Stage 3: Beta-cell decompensation, where in glucose levels rise relatively rapidly. At this stage, 80% of [beta]-cell function is lost. Fasting hyperglycemia of approximately 140-200 mg/dl can result from basal hepatic glucose production of ~0.5 mg/kg/min due to associated insulin resistance. The liver of an 80-kg diabetic can add as much as 35 g of glucose to the systemic circulation following an overnight fast.[9-11]

Stage 4: Beta-cell decompensation (stable), once the plasma glucose rises it stays relatively stable.

Stage 5: Beta-cell failure, marked by severe hyperglycemia and progression to ketosis.[1,2,10-34]

Declining beta-cell function is the epitome phenomenon of worsening hyperglycemia over time.[2,4,25] Secretagogues (SU) have been shown to expedite beta-cell dysfunction. Defranzo in the Banting ADA lecture (2009) showed that after an initial decline of glycosylated hemoglobin (between 0.5% and 1.8%) in various studies using SU's (glyburide, glimerperide, gliclazide) time to failure of therapy (return of glycosylated hemoglobin to baseline) occurred as early as 1-2 years with glimerperide and 5-10 years with other SU's.[2] SU's have been shown to expedite beta-cell failure and induce apoptosis at rates greater by two- to fourfold.[24,35] Up to 80% of patients while on SU's, loose control of diabetes with need for insulin therapy, due to beta-cell exhaustion.[2]

Based on data from the UKPDS[25] and Weir[2] by the time patient develops impaired glucose tolerance, between 50% and 66% of [beta]-cell function is lost. Between 75% and 80% of beta-cell function is lost once hyperglycemia fulfilling the definition of diabetes mellitus develops. After 10–15 years of diabetes duration <10% of endogenous insulin is present and exogenous insulin therapy becomes necessary.

It therefore makes sense that a paradigm shift to newer therapies is required that can help conserve beta-cell function. Until a few years ago only thiazolidinedione (TZD) therapy was shown to conserve beta-cell function[26,27] apart from its overwhelming insulin sensitizing benefits (at the level of liver and periphery/skeletal muscle). Incretin-based therapies have been shown to outscore all other anti-diabetic therapies in that regard. Any therapeutic strategy that helps improve plasma incretin concentration following a carbohydrate meal, improves beta-cell function (increased insulin biosynthesis and secretion). It has also been shown by some studies that improvement in beta-cell health occurs more following a morning meal compared to an afternoon meal.[30]

From the triumvirate theory, Ralf Defranzo in the Banting and Best Lecture at the 2009 American Diabetes Association suggested there is much more to the pathogenesis of T2DM and proposed the "*ominous octet.*"[1,2,10-34]

Lipotoxicity (disharmonious quartet, fourth component)

Fat cells are resistant to the insulin's anti-lipolytic effect resulting in increased plasma free fatty acids (FFA). Increased FA have been shown to competitively inhibit insulin-mediated glucose uptake, transport and metabolism in muscle and liver, stimulate hepatic glucose production, impair first and second phases of insulin release, and reduce insulin secretory rate.[12,13]

Incretin (quintessential quintet, fifth component)

Glucose disposal is more efficient following an oral glucose meal as compared to an intravenous glucose infusion. This led some scientists to believe that the gastrointestinal tract was responsible for release of hormones that aided in glucose disposal. This theory was entertained more than 100 years ago.[14-19] These hormones were later identified as gut derived "incretins" (glucagons like peptide {GLP-1} and gastric insulotropic peptide {GIP}) which are responsible for > 99% of this incretin effect (enhanced glucose disposal following oral load). Out of the two hormones it is GLP-1 that is the more active peptide in human beings. Patients with T2DM experience a blunting or even total loss of this incretin effect. Amplification of this incretin effect forms the basis of several incretin-based therapies.[14-19]

GIP is secreted by neuro-endocrine K-cells present in stomach and proximal small intestine. It has an amino acid sequence that is highly conserved across species, with over 90% homology. It has a half life of approximately 7 min in healthy individuals and 5 min in patients with T2DM. GIP is cleared through the kidney.

GLP-1 is a peptide that is secreted by neuro-endocrine L-cells present in the distal small intestine. GLP-1 circulates as two equipotent forms, $GLP1_{7-37}$ and $GLP1_{7-36}$ amide. GLP-1 (7-36) constitutes 80% of circulating GLP-1. The half-life of circulating native bioactive GLP1 is less than 2 min mostly because it is cleared by the kidney and degraded by dipeptidyl peptidase (DPP)-4. DPP-4 represents a single polypeptide chain of 766 amino acids and consists of four domains: an N-terminal cytoplasmic domain, a trans-membrane domain, an [alpha]/[beta]-hydrolase domain, and a [beta]-propeller domain. It is also called adenosine deaminase (ADA) binding protein, or CD26 (T-cell activation antigen).[14–19,31]

GIP and GLP-1 have distinct yet overlapping actions and act through specific G-protein receptor complexes, gastric inhibitory peptide receptor (GIP-R), and GLP-1 receptor (GLP-1R), respectively. Both GLP-1 and GIP are susceptible to cleavage at amino-terminus, position 2 (alanine), by the DPP-4. DPP-4 is a type II membrane peptidase resembling CD26 (marker of activated T-lymphocyte). It is the canonical representative of a family of genetically related peptidases. The DPP-4 gene family includes four enzymes DPP-4, DPP-8, DPP-9, fibroblast activation protein (FAP) and catalytically inactive proteins DPP-6 and DPP-10. DPP-4 has a widespread organ distribution (liver; gut; endothelial capillaries; acinar cells of mucous and salivary glands, pancreas; uterus; and immune organs such as thymus, spleen and lymph node) with the highest levels found in the kidney. DPP-4 regulates the activity of secretory hormones glucagon-like peptide (GLP)-1, and glucose-dependent insulinotropic peptide (GIP) to maintain glucose homeostasis (enhanced insulin secretion and glucagons suppression), thereby improving post-prandial and fasting hyperglycemia.[14,18,19,29] Other physiological substrates of DPP-4 include neuropeptide-Y (NPY) (role in appetite, energy homeostasis, and blood pressure control), substance P (role in pain and inflammation).[33]

DPP-8 and DPP-9 enzyme levels are less well studied compared to DPP-4. Although DP8 and DP9 have no confirmed physiological substrates there is a growing body of evidence to suggest that they are actively involved in healing processes (skin, liver etc), play an important role in immune function (cleave chemokines), and hematopoiesis. They have been shown to predominate over DPP-4 in testis and brain tissue and have a wide area of organ distribution (gastrointestinal tract, skin, lymph node, spleen, liver and lung, as well as in pancreatic acinar cells, adrenal gland, spermatogonia and spermatids of testis, and in Purkinje cells and in the granular layer of cerebellum). Unlike DPP4, DPP8/9 are intracellular proteases responsible for T-cell activation and therefore off-target inhibition by selective DPP4 inhibitors can cause undesirable and serious side-effects (immune dysfunction, impaired healing, reticulocytopenias, skin manifestations).[33,34]

Following secretion, GLP-1 and GIP are both rapidly degraded by DPP-4. GLP-1 is degraded even before leaving the gut because of the presence of DPP-4 molecules anchored to the luminal surface of the endothelial cells of the mucosal capillaries. GIP is less susceptible to DPP-4 and leaves the gut un-degraded.

Hyperglucagonemia (setaceous sextet, sixth component)

The sixth member in the pathogenesis of T2DM is the pancreatic [alpha]-cell. Glucagon being a counter regulatory hormone contributes to fasting hyperglycemia via enhanced hepatic glucose production (neoglucogenesis) and to some extent via glycogenolysis. There is evidence that the liver may be hypersensitive to the stimulatory effect of glucagon. The incretins, particularly GLP-1, functions by augmenting insulin secretion and suppressing glucagon, thereby reducing post-prandial and fasting hyperglycemia. GIP on the other hand, although complementary to GLP-1 with regards insulin secretion, may antagonize GLP-1-mediated glucagon suppression.[2,20,22,23]

Kidney (septicidal septet, seventh component)

The seventh member in the pathogenesis of T2DM is the kidney. It filters approximately 162 g of plasma glucose of which 90% is reabsorbed by the high capacity SGLT2 (sodium-glucose like transporter type 2) transporter in the proximal convoluted and 10% is reabsorbed from the descending proximal tubule. Diabetic patients exhibit markedly up-regulated SGLT2 mRNA resulting in greater glucose reabsorption contributing to hyperglycemia so its exact importance in humans in not really known.[2,21]

Brain (ominous octet, eighth component)

The eighth member implicated in the pathogenesis of type 2 diabetes is the brain. GLP-1 is synthesized in the caudal part of the nucleus of the solitary tract and its receptors are widespread throughout the brain, particularly in the paraventricular nucleus of hypothalamus. The hypothalamus is the centre of feeding and satiety and it only seems logical that GLP-1 potentiation via any means will influence these responses of feeding. It has been shown that GLP-1 augmentation results in an anorexigenic effect. This occurs directly via its influence on the hypothalamus and indirectly via taste receptors. Humans GLP-1 is found in mammalian taste cells (type 2 and type 3). The weight loss observed with GLP receptor agonists have been associated with reduction in food intake and weight loss in rats. It has also been seen that GLP-1 helps modulate taste sensation, which might help with the possible anorexigenic effect of GLP-1 potentiation strategies. Obese subjects with T2DM have been associated with increased appetite, accounting for the usefulness of GLP-1 augmentation in this subset of patients.[2,36-38]

What Should be the Ideal Anti-Hyperglycemic Drug?

From the above pathogenetic discussion it would only seem logical that one chooses therapy that seems to address the ominous octet ie. a drug that can improve beta-cell health (TZD, incretin bases therapies {GLP analogues, DPP-4 inhibitors/Gliptins}, biguanides, alfa-glucosidase inhibitors), improve insulin resistance (biguanides, TZD's, possibly incretin based therapies) suppress glucagon secretion (incretin based therapies), suppress appetite (GLP-1 analogues, biguanides), improve lipid health (TZD), and suppress renal glucose reabsorption. The drug combination that seems most logical is incretin-based therapies (addressing 4 out of the 8 pathophysiological mechanisms) with biguanide (metformin) or TZD (addressing insulin resistance at liver and skeletal muscle).[2,26,27,39]

Dipeptidyl Peptidase-4 Inhibitors (Gliptins)

This new class of anti-diabetic agents seems like they have revolutionized the treatment of diabetes. Although various DPP-4 inhibitors have different pharmacokineic and pharmodynamic profiles, they are remarkably similar with regards anti-hyperglycemic properties with a very safe adverse effect profile (weight neutral without causing hypoglycemia).

A *list of available and expected gliptins* are as follows:

- Sitagliptin (Merck Sharp and Dohme Corp, approved as Januvia by US FDA in year 2006)
- Vidagliptin (Novartis, approved as Galvus by EU in year 2007)
- Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in 2010)
- Linagliptin (Boerhinger Ingelheim, approved as Tradjenta by US FDA in year 2011)
- Alogliptin (developed by Takeda Pharmaceutical Company Limited, approved for use in Japan)
- Dutogliptin (being developed by Phenomix Corporation)
- Gemiglaptin (being developed by LG Life Sciences)
- (Sitagliptin, Vidagliptin, Saxagliptin-are-approved-for-use-in-India)

The DPP-4 inhibitors based on their *structure* can be divided into those that mimic the DPP-4 molecule (peptidomimetics, vildagliptin and saxagliptin) and those that do not (non-peptidomimetics, sitagliptin, alogliptin, linagliptin) as shown in Tables 1 and 2. They are competitive reversible inhibitors of the DPP-4 substrate acting extra-cellularly. The molecules have varying affinities toward the DPP-4 substrate [Table 3]. In general, the peptidomimetics have lesser selectivity toward DPP-4 compared to DPP8/9. Lesser the relative selectivity toward DPP-4 and greater the relative inhibition of DPP8/9 greater is the possibility of side effects (allergic skin manifestations etc).[14-18,28-34,40-43]

The *mechanism of DPP-4 inhibition* differs from peptidomimetics (vildagliptin, saxagliptin) compared to non-peptidomimetics (sitagliptin, alogliptin, linagliptin). Non-peptidomimetics form non-covalent extra-cellular interactions with residues in the catalytic site of the DPP-4 substrate, thereby resulting in potent, immediate inhibition. In contrast, inhibition of the DPP-4 substrate by peptidomimetics occurs in a manner that involves formation of a reversible covalent enzyme–inhibitor complex. This complex binds and dissociates from the

Table 1: Pharmacokinetic profile of DPP-4 inhibitors/gliptins[14-18,28-34,40-43]

	Chemistry	Metabolism	Elimination route
Sitagliptin (US, FDA approved)	Non-peptidomimetic (β-amino acid-based)	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin (EU, approved)	Peptide-like	Hepatically hydrolyzed to inactive metabolite	Renal (22% as parent, 55% as metabolite)
Alogliptin (Japan, approved)	Non-peptidomimetic (modified pyrimidinedione)	Not appreciably metabolized	Renal (>70% unchanged as parent)
Saxagliptin (US FDA approved)	Peptide-like	Some metabolism to active metabolite	Renal (12-29% as parent, 21-52% as metabolite)
Linagliptin (US, FDA approved)	Non-peptidomimetic (xanthine)	Not appreciably metabolized	Biliary (unchanged as parent); <6% via kidney

Table 2: Pharmacokinetic profile continued[14-18,28-34,40-43]

	Dosing	Compound t½ (half-life)	DPP-4 inhibition	Drug interactions
Sitagliptin (launched)	100 mg qd	8-24 h	Max ~97%; >80% 24 h post-dose	None known
Vildagliptin (launched)	50 mg bid	1½-4½ h	Max ~95%; >80% 12 h post dose	None known
Alogliptin (launched, Japan)	25 mg qd (anticipated)	12-21 h	Max ~90%; ~75% 24 h post-dose	None known
Saxagliptin (launched)	5 mg qd	2-4 h (parent) 3-7 h (metabolite)	Max ~80%; ~70% 24 h post-dose	Caution – with drugs metabolized by CYP3A4/5 system (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefaz odone, nelfinavir, ritonavir, saquinavir, and telithromycin)
Linagliptin (phase 3)	5 mg qd (anticipated)	10 – 40 h	Max ~80%; ~70% 24 h post-dose	

DPP-4: Dipeptidyl peptidase-4

Table 3: DPP-4 inhibitor *in vitro* selectivity, (fold selectivity for DPP-4 vs. other enzymes)[14-18,28-34,40-43]

	FAPα	DPP-8	DPP-9
Vildagliptin	285	270	32
Sitagliptin (highly selective)	>5 550	>2 660	>5 550
Saxagliptin	?	390	77
Alogliptin Highly selective)	>14 000	>14 000	>14 000
Linagliptin (highly selective)	89	40 000	>100 000

FAP: Fibroblast activating protein; DPP-8: Dipeptidyl peptidase-8; DPP-9: Dipeptidyl peptidase-9

catalytic site of the DPP-4 substrate very slowly resulting in persistent DPP-4 inhibition even after the drug has inactivated. This means that the catalytic activity remains inhibited even after the free drug has been cleared from the circulation and may help to explain why vildagliptin and saxagliptin inhibit DPP-4 activity for longer than their relatively short half-lives would suggest. DPP-4 inhibition by the specific DPP-4 inhibitors occurs extracellularly. Because the inactivation is extra-cellular the functioning of major intracellular proteins is preserved, accounting for the lack of immune dysfunction that could have otherwise resulted, should they have been affected.[14-18,28-34,40-43]

The *pharmocokinetic profile* of the drugs are mentioned in Tables 1 and 2. *DPP-4 inhibitor in vitro selectivity*, (fold selectivity for DPP-4 vs. other enzymes) has been mentioned in Table 3.

Efficacy Data Common to Gliptins

As "monotherapy"

Fasting glycemia reduction – approximately 18 mg/dl (10 – 35 mg/dl)

Post-prandial glycemia reduction – approximately 25 mg/dl (20 – 60 mg/dl)

HbA1c reduction – approximately 0.75% (0.4 – 1.2%)

When compared to metformin, SU (glimerperide, glipizisde), thiazolidinediones (rosiglitazone, pioglitazone), and alfa-glucosidase inhibitors (voglibose), the use of gliptin has shown to be equally efficacious and non-inferior. When compared to SU the incidence of hypoglycemia was near negligible with the added advantage of being weight neutral.[44-58]

A meta-analysis comparing the efficacy of sitagliptin versus vildagliptin showed that the overall HbA1c reduction was ~0.74% and 0.73%, respectively. The glycemic outcomes were better if the initial HbA1c was higher >9% versus <8%.[40]

A recent meta-analysis suggested that using a gliptin (vildagliptin, sitagliptin, saxagliptin or alogliptin) in patients with T2DM was associated with a greater proportion of patients achieving their HbA1c goal of <7%, without any weight gain or hypoglycemia.[41]

As "add on therapy to metformin"

Data suggests that when a gliptin is added onto patients inadequately controlled with metformin there results a substantial improvement in HbA1c (range 0.50 – 0.75%) with as many twice as number of patients achieving an HbA1c of <7% compared to metformin alone. Furthermore, for the first time data has suggested that in patients with HbA1c between 7% and 8% while on metformin therapy, rather than optimizing the dose of metformin from 1 to 2 gm/day or greater, as most existing guidelines suggest, by adding a gliptin to an already existing dose of metformin the degree of HbA1c reduction is greater (additional HbA1c – 0.7% benefit) than that achieved by up-titrating the dose of metformin (additional HbA1c – 0.3% benefit), with far greater number of patients achieving HbA1c target of <7%..

The use of a gliptin compared to an SU as second line therapy added onto patients inadequately controlled on metformin therapy, provided non-inferiority data for use of gliptin suggesting that it might replace the use of traditionally used SU in the future.[5,50,52,56,58-67]

As "add on therapy to sulfonyureas"

Since the use of gliptin has shown to improve beta-cell health and promote insulin secretion in a glucose-dependent fashion, the concomitant use of SU can potentially be complicated by hypoglycemia. It is therefore suggested that the minimum possible dose of SU be started along with use of gliptin. If the patient is already on an SU and addition of gliptin is considered, the dose of SU should be halved and then up-titrated as required. Gliptins have been shown to non-inferior in efficacy to SU (glipizide, glimeperide, gliclazide) with the added advantage of being weight neutral and being virtually free of hypoglycemia. Whether compared head to head with an SU (HbA1c reduction of approximately 0.8% in both groups) or added to an SU (further HbA1c reduction of approximately a gliptin was found to be effective (HbA1c reduction 0.5-0.8%) with significantly greater number of patients achieving the HbA1c of <7%.[1,63,68-73]

As add "on therapy to thiazolidinedione"

The addition of a gliptin to TZD therapy in patients inadequately controlled have been associated with average HbA1c reduction of approximately 0.7-1%. On the other hand, the use of gliptin along with TZD in drug-naïve T2DM patients has been shown to reduce HbA1c by up to 2% after 24 weeks, compared with 1.1% with pioglitazone monotherapy. Besides the reduction in HbA1c there have been other beneficial effects seen with this combination such as improvement in inflammatory markers, beta-cell health (homeostasis model assessment-beta-cell, HOMA-beta and pro-insulin/insulin ratio) and markers of insulin resistance (homeostasis model of insulin resistance, homeostasis model assessment-IR). This combination has however been plagued by an average weight gain of 2.5 – 5 kg and peripheral edema. The weight gain can however be dealt with a comprehensive lifestyle-weight-management program.[61,64,70,73-80]

As "add on therapy to insulin"

The addition of gliptin to insulin (long-acting, intermediate-acting insulin or premixed) has been associated with an additional HbA1c reduction of approximately 0.6%. A greater proportion of patients were seen to achieve HbA1c level < 7. Fasting plasma glucose improved by approximately 15.0 mg/dl (0.8 mmol/l) and 2-h post-meal glucose improved by approximately 36.1 mg/dl (2.0 mmol/l). The presumed improvement in glycemia is because of improvement in beta-cell health and suppression of glucagon predominantly.[81-84]

Sitagliptin

This is the first gliptin to be US FDA approved (October 2006). The recommended dose is 100 mg once a day. Its absorption is unaffected by food. For patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) the recommended dose is 50 mg/day and for severe renal impairment (creatinine clearance is <30 mL/min) the recommended dose is 25 mg/day. In a meta-analysis[40] it was shown to be more effective at reducing fasting blood sugar compared to vildagliptin, but overall efficacy was similar. For patients with hepatic impairment no change in dose is recommended for Childs grade A or B, however for Child grade C sitagliptin use in not recommended. The Asian study (China India Korea study) suggested that sitagliptin was more effective in the Indian population with greater HbA1c reductions of approximately 1.3% compared to placebo. Recent data is emerging that in addition to improving beta-cell health, DPP-4 inhibitors also help improve insulin resistance and plasma levels of triglyceride-rich lipoproteins of both intestinal and hepatic origin (cardiovascular benefit).[14-16,18,28,29,32]

Vildagliptin

This is the second gliptin to be approved for commercial use although still not US FDA approved. The recommended dose is 50 mg twice a day. Its absorption is unaffected by food. It is extensively metabolized by the liver and has >90% bioavailability following a single oral dose. No dosage adjustment is required for liver disease although a greater amount of inactive metabolites (30% greater) are retained in patients with severe liver disease (Childs grade C). In patients with renal impairment no dose adjustment is required for mild renal insufficiency however for moderate renal insufficiency half the recommended dose of 50 mg is suggested.[14-16,18,28,29,32,47]

Saxagliptin

This is the third gliptin to be approved for commercial use, and US FDA approved. The recommended dose is 5 mg once a day. Its absorption is unaffected by food. Saxagliptin is metabolized mainly by cytochrome P450 (CYP) 3A4 to a major active monohydroxylated metabolite, 5-hydroxy saxagliptin which is half as potent as saxagliptin. Approximately 75% of the total dose of saxagliptin is renally excreted (comprising 24% saxagliptin, 36% 5-hydroxy saxagliptin and minor metabolites of saxagliptin), while 22% of a saxagliptin dose was eliminated in the feces, mainly as metabolites. One-half the usual dose of saxagliptin 5 mg (i.e. 2.5 mg orally once daily) is recommended for patients with moderate (CLCR 30-50 mL/min) or severe (CLCR<30 mL/min not on dialysis) renal impairment or ESRD, but no dose adjustment is recommended for those with mild renal impairment or any degree of hepatic impairment.[14-16,18,28,29,32,51,52]

Linagliptin

Linagliptin is a new agent in the DPP-4 inhibitor class that is currently undergoing regulatory review in Japan, the EU, and the USA. It is recommended in the dose of 5 mg once a day. It has a favorable pharmacokinetic profile has a potential advantage over currently approved gliptins in that it primarily undergoes non-renal elimination. Linagliptin is predominantly excreted via the enterohepatic system, with 84.7% of the drug eliminated in the feces and only 5% eliminated via the urine. It therefore appears to be safe in patients with renal failure.[15,16,18,28,29,32,54]

Linagliptin has been shown to hasten wound healing in preclinical studies with evidence of improvement in wound re-epithelialization.[56]

Alogliptin

Alogliptin is a dipeptidyl peptidase-4 inhibitor that is approved in Japan for the treatment of adult patients with T2DM. It is recommended in the dose of 25 mg once a day. It is unaffected by food. Its predominant route of excretion is the kidneys. Caution must be used in patients with renal impairment with need for appropriate dose adjustments. As most of it is eliminated through the kidney, it is unlikely that hepatic impairment will affect its dosage.[14-16,18,28,29,32]

Adverse effects

Dipeptidyl peptidase 4 inhibitors were generally well tolerated in most studies. Adverse reactions have been associated with non-selective inhibition of other members of the DPP-4 gene family (DPP-8/9). Since DPP-4/CD26 is a marker of activated T-cell, initial concerns were related to immune dysfunction associated with DPP-4/CD26 inactivation. DPP-4 inactivation by a gliptin occurs extra-cellularly in comparison to DPP-8/9 which is intracellular. As long as other members of the DPP-4 gene family remain un-affected immune dysfunction is not seen.[14-16,18,28,29,32,57]

Their strength lies in the fact that they are weight neutral and do not cause any significant hypoglycemia. A meta-analysis[40] suggested an increased risk of nasopharyngitis (6.4% for DPP4 inhibitor {sitagliptin>vildagliptin} vs. 6.1% for comparator) headache (5.1% for DPP4 inhibitor (vildagliptin>sitagliptin} vs 3.9% for comparator), urinary tract infection (3.2% for DPP4 inhibitor {sitagliptin = vildagliptin} vs 2.4% for comparator). Although rare an increased incidence of extremity pain was seen with DPP-4 inhibitors. No increased incidences in gastro-intestinal side-effects were observed. Saxagliptin use has been linked with a reduction in lymphocyte count.[14-16,18,28,29,32,57]

No significant *drug-drug interaction* has been reported with DPP-4 inhibitors, except for saxagliptin where caution needs to be exercised when used along with drugs metabolized by hepatic CYP3A4/5 system (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). They are otherwise safe to use with commonly used anti-hyperglycemics (TZD, SU), anti-hypertensives, anti-hyperlipidemics, antibiotics, digoxin, warfarin, etc.[14-16,18,28,29,32,57]

The US FDA issued a warning in 2007 of risk of *pancreatitis* with use of drugs acting on the incretin system, following reports of pancreatitis with use of GLP-1 analogues (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm079781.htm). Post-marketing surveillance has identified isolated rare cases of pancreatitis with use of DPP-4 inhibitors. No direct cause and effect relationship has been found though between the two. It must be emphasized that diabetes and hypertriglyceridemia are itself independent risk factors for development of pancreatitis and an analysis of a US healthcare database showed that rates of pancreatitis with exenatide or sitagliptin were no different from metformin or glyburide.[85]

In preclinical studies an increased risk of *medullary carcinoma of the thyroid* was seen however as human thyroid has a low expression of GLP-1 receptors unlike the mice it is not surprising that it appears to be safe in human beings.[86,87]

Although clinical studies with DPP-4 inhibitors havn't shown any *adverse skin reactio*n, post-marketing survellance programs have suggested isolated rare cases of serious hypersensitivity skin reactions including Stevens–Johnson syndrome.[88]

Although not approved for use in *cardiovascular patients* there is some suggestion that DPP-4 inhibitors like GLP-1 analogues have a cardiovascular friendly profile Preclinical studies have suggested endothelial benefit, anti-atherosclerotic effects[89] and blood pressure lowering effects.[90] Several large cardiovascular outcome trials are currently underway which will specifically address the impact of the incretin-based therapies on macrovascular risk.

For patients with *hepatic insufficiency* except for vildagliptin no dose adjustment is necessary for gliptins. Vildagliptin is not recommended for patients with alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal.[32,91,92]

For patients with *renal insufficiency*, sitagliptin, vildagliptin, and saxagliptin can be used in patients with mild renal insufficiency without dose adjustment; however only sitagliptin and saxagliptin can be used in patients with moderate or severe renal insufficiency. In the European Union, however sitagliptin and saxagliptin is not currently recommended for use in patients with more moderate or severe renal impairment. Linagliptin appears to be safe in renal insufficiency.[32,47,61,92-94]

Current Position of Gliptins in Diabetes Management Guidelines

The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), European Society, and NICE (UK) guidelines suggest that gliptins should be considered over other anti-diabetic therapies especially if the patient is experiencing an increased incidence of hypoglycemias and/or weight gain. It is clear that even major guidelines appreciate their usefulness with the only apprehension being that they haven't withstood the test of time and therefore classified under less well-validated therapies. As data emerges suggesting sustained anit-hyperglycenic benefits they should replace current practices that include popular use of SU +/– insulin as second and third line agents to metformin.[95-97]

Current indications for use of gliptins are:
1. First line in T2DM with HbA1c <7%
2. Second line as add-on therapy in T2DM patients already on 1 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide})for uncontrolled T2DM with HbA1c >7%
3. Third line as add-on therapy in T2DM patients already on combination therapy (2 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide)

Contraindications or indication for stopping gliptin therapy includes previous or current adverse reaction to gliptins (hypersensitivity) or failure to achieve an HbA1c reduction of greater than 0.5% over a 6 month period.[95-97]

Conclusions

Gliptins have revolutionized the concept of diabetes management and have provided a breath of fresh air to healthcare professionals dealing with diabetes. They provide an effective and safe alternative to the management of diabetes. Shown to reduced HbA1c from 0.5 to up to 2% effectively and safely (weight neutral without any if at all hypoglycemia) this new class of drugs is here to stay. Even major diabetes management guidelines have acknowledged them for their safe adverse effect profile and urge healthcare professionals to use gliptins should they be struggling with regards weight or hypoglycemias with their patients. Recently, plagued with issues such as pancreatitis and cancer, these drugs need to stand the test of time and should they emerge victorious they will represent the only class of drugs that help improve beta-cell health, addressing the original triumvirate pathogenetic theory proposed for T2DM.

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