Gemigliptin: Newer Promising Gliptin for Type 2 Diabetes Mellitus

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Abstract

The dipeptidyl peptidase-4 (DPP-4) inhibitors have facilitated the management of type 2 diabetes mellitus (T2DM) owing to their superior efficacy and safety with low incidence of adverse effects. Gemigliptin is a new member of this family of drugs, and studies have revealed certain advantages of gemigliptin use compared to its previous congeners. Besides, this drug has also been studied for the treatment of T2DM as monotherapy, in combination with metformin or other oral antidiabetic drugs and in T2DM with moderate-to-severe renal failure. In this review, we explore the published data highlighting the pharmacology, efficacy, and safety of gemigliptin along with its recommendations for use in patients with T2DM.

Keywords: Dipeptidyl peptidase-4, gemigliptin, type 2 diabetes mellitus

Introduction

The optimal management of type 2 diabetes mellitus (T2DM) is a complex since it requires a large armamentarium of drugs acting on the various altered physiological mechanisms leading to hyperglycemia. Incretin-based therapy has developed as a useful component of modern day diabetic management. The dipeptidyl peptidase-4 (DPP-4) inhibitors have been recommended as a first-line or an add-on therapy after metformin due to their superior efficacy, weight-neutrality, low risk of hypoglycemia, and excellent tolerability.[¹⁻²] Although they have certain common benefits owing to their mechanism of action, the DPP-4 inhibitors vary considerably in terms of pharmacology and safety profiles.[³]

Gemigliptin was developed by LG Life Sciences (Seoul, Korea) and was approved by the Ministry of Food and Drug safety in June 2012 for the treatment of T2DM.[⁴] The company also signed licensing agreement with multinational pharmaceutical companies including Sanofi (Paris, France), and at present gemigliptin is approved in India, Columbia, Costa Rica, Panama, Ecuador and a few other countries. Registration studies are currently ongoing in several countries including Russia, Mexico and Thailand. Various studies have proven the efficacy and safety of gemigliptin for the treatment of T2DM, both as monotherapy as well as in combination with other anti-diabetic drugs. In this review, the recent updates pertaining to the clinical efficacy, safety, tolerability, adverse effects and approval of gemigliptin use in T2DM have been highlighted by going through the relevant published data.[⁴]

Chemical Structure of Gemigliptin

Gemigliptin (Zemiglo®, previously known as LC15-0444) has a different chemical structure compared to other DPP-4 inhibitors due to the presence of pyrimidine piperidine derivative as evident by X-ray crystallography.[⁵] Gemigliptin binds to the S1, S2, and S2' extensive subsites of the DPP-4 enzyme. The piperidinone group of gemigliptin binds to the S1 subsite, where the upside F atom on the piperidin ring forms a hydrogen bond with the side chain of Tyr631 and the downside...
F atom makes a hydrophobic interaction with the side chain of Tyr662 and Tyr666. In addition, the key interaction occurs between the CF3 groups on the pyrimidino piperidine and the S2 extensive subsite of the DPP-4 substrate, which enhances the potency of the drug and increases its selectivity as well.\[^5\]

**Pharmacology**

Gemigliptin is a reversible and competitive inhibitor of DPP-4 enzyme with a Ki value of 7.25 ± 0.67 nM. It acts as a long-acting DPP-4 inhibitor which inhibits DPP-4 in a dose-dependent manner. In addition, it showed at least >23,000 fold selectivity for proteases such as DPP-8, DPP-9, and fibroblast activating protein – α.\[^6-10\] By preventing degradation of GLP-1 by DPP-4 inhibition, it increases insulin secretion, reduces glucagon secretion, decreases HbA1c, and prevents β-cell damage.\[^6\]

Besides glucose lowering, gemigliptin has also been reported to have certain pleiotropic effects which were mostly observed in various animal models.\[^11,12\] These include reducing albuminuria, podocyte apoptosis, glomerular basement-membrane thickening, and retinal vascular leak. Some cardiovascular protective effects were also demonstrated in *in vitro* studies.\[^13,14\] However, further studies are needed to validate the role of gemigliptin in preventing micro- and macro-vascular complications of diabetes.

**Pharmacokinetics, Dosage Modification, and Drug Interactions**

In both healthy controls and patients of T2DM, gemigliptin (50 mg) is rapidly absorbed and reaches a maximum plasma concentration of 62.7 ng/ml at about 1.8 h. The apparent half-life is 17.1 h.\[^6,7\]

In a study using \[^14\]C-gemigliptin in healthy male controls, a total of 90.5% of the administered dose was recovered, of which 63.4% was from urine and 27.1% from feces. Twenty-three metabolites were identified collectively in plasma, urine, and feces. The elimination of gemigliptin was found to be balanced between metabolism and excretion through urine and feces. The CYP3A4 enzyme was the dominant CYP isoenzyme involved in metabolism of gemigliptin.\[^15\]

**Renal Impairment**

In a study designed to assess the pharmacokinetics of gemigliptin in patients with renal impairment (RI),\[^16\] systemic exposure of the drug (in mild, moderate, severe RI, and end-stage renal disease) was within 2-fold of that seen with normal renal function, indicating that gemigliptin does not need any dose adjustment in RI. In addition, no significant pharmacokinetic difference was observed between dialysis and nondialysis periods. Less than 4% of the dose was removed by hemodialysis. Hence, RI seemed to have a moderate effect on gemigliptin disposition and impact of dialysis on the removal of gemigliptin was negligible.\[^16\]

**Hepatic Impairment**

The AUC of gemigliptin was increased 50% and 80% in patients with mild and moderate hepatic impairment as compared to healthy controls. These changes were not clinically significant; hence, gemigliptin can be safely used in such patients without dose modification.\[^17\]

Gemigliptin is unlikely to interact with drugs metabolized by most cytochrome P450 enzymes, neither does it have significant effect on p-glycoprotein and drugs metabolized by it. Studies also revealed that gemigliptin did not alter the pharmacokinetics of most commonly used antidiabetic agents (metformin, glimepiride, and pioglitazone), antihypertensives, and lipid lowering agents.\[^18-21\] Ketoconazole, a CYP3A4 inhibitor, moderately increased gemigliptin exposure while it was reduced when coadministered with rifampicin, a CYP3A4 inducer.\[^22\]

**Clinical Efficacy of Gemigliptin**

Gemigliptin has been evaluated in multiple studies, either as monotherapy or as add-on to other glucose lowering agents. Two of the multinational trials included patients from India as well.

**Glycemic Control (as Monotherapy)**

Gemigliptin as monotherapy for T2DM was evaluated in a Phase II study in a randomized, double-blinded, placebo-controlled, parallel group design involving 50, 100, and 200 mg oral dose (OD) doses of gemigliptin.\[^23\] Mean changes of HbA1c at 12 weeks were −0.98%, −0.74%, −0.78% with 50, 100, and 200 mg, respectively. The 50 mg dose proved to be equally efficacious compared to 100 and 200 mg doses along with the maximum safety margin.\[^23\]

In a Phase III trial, in which patients were randomized to receive gemigliptin 50 mg OD dose or placebo for 24 weeks,\[^24\] significant mean HbA1c reduction was noted in the gemigliptin treatment group (−0.71% adjusted after subtracting the placebo effect size). Further, the placebo subtracted fasting plasma glucose change from baseline was −19.80 mg/dl.\[^24\]

**Glycemic Control (in Combination with Metformin as Initial Therapy)**

Additive effects of gemigliptin were noted when combined with metformin in the form of increased plasma GLP-1 concentrations, lower serum glucose, and lower plasma glucagon levels.\[^20\] In a 24 weeks, randomized, double-blind, active-controlled, Phase III trial, patients with HbA1c >7.5% were randomized to gemigliptin 50 mg OD, metformin-slow release OD or combination of both.\[^25\] The mean HbA1c change from baseline was −2.06, −1.24, and −1.47% for gemigliptin/ metformin group, gemigliptin group, and metformin group, respectively. The differences in proportions of patients achieving HbA1c <7% were also statistically significant between the combination therapy and monotherapy groups, with >4/5th patients on the combination arm (82.4%), achieving the target HbA1c.\[^25\] The addition of gemigliptin to metformin...
and glimepiride significantly reduced HbA1c levels at week 24 compared with placebo (between-group difference in adjusted mean change −0.87%, 95% confidence interval [CI]: −1.09% to −0.64%). Fasting plasma glucose level was also significantly reduced with gemigliptin (−0.93 mmol/L, 95% CI: −1.50 to −0.35 mmol/L), and a higher proportion of participants achieved an HbA1c level of <7% (39.3% versus 5.5%; P < 0.001) in the gemigliptin group than in the placebo group.[26]

Glycemic control (as add-on therapy)

The efficacy and safety of gemigliptin 50 mg compared to active control (sitagliptin) added to patients with T2DM inadequately controlled with metformin alone (HbA1c 7% to 11%) was assessed in a 24 weeks, randomized, double-blind, active controlled study.[27] The reduction in HbA1c from baseline was 0.81% for gemigliptin 25 mg 2 times a day (BD) and 0.77% for gemigliptin 50 mg OD while the differences in the least square mean changes from baseline between groups (each group receiving either gemigliptin or sitagliptin) were −0.011% and −0.004% in gemigliptin 25 mg BD and gemigliptin 50 mg OD, respectively. In addition, patients in the gemigliptin group had a greater inhibition of plasma DPP-4 compared to sitagliptin.[27]

This study was extended by 28 weeks in which the subjects who had been treated with sitagliptin were switched over to gemigliptin, and hence, all subjects received gemigliptin at 50 mg OD dose for 28 weeks. The reduction in HbA1c from baseline was −1.06 in patients who continued to receive gemigliptin while an additional 0.1% reduction from baseline HbA1c was noted in those who were switched from sitagliptin to gemigliptin. Hence, switching from sitagliptin to gemigliptin facilitated sustained improvements in glycemic control in T2DM patients.[27]

In another randomized, double-blind, Phase III study, T2DM patients with inadequate glycemic control on metformin and glimepiride combination therapy (HbA1c 7% to 11%) were randomized to receive additional gemigliptin 50 mg or placebo.[28] At 24 weeks, adjusted mean change in HbA1c was −0.88% in the gemigliptin group compared to placebo. Gemigliptin was well tolerated, with the drug-related adverse effects being similar in both the treatment groups (3.7% in gemigliptin group vs. 2.7% in placebo group). In an recent study published by Park et al. which showed patients with T2DM who were treated with gemigliptin or sitagliptin had lower fluctuations in blood glucose levels than those in patients who were treated with glimepiride although there was no significant difference in HbA1c levels among the groups.[29]

Add-on therapy in patients with renal impairment

Owing to a balance between its urinary/fecal excretion and hepatic metabolism, gemigliptin does not require dose modification in patients with moderate to severe RI. Its efficacy and safety in RI patients was studied in a randomized, double blind, parallel group, Phase IIIb study.[30] A total of 132 patients with T2DM and moderate-to-severe renal insufficiency were randomized to receive gemigliptin or placebo while insulin was the predominant background therapy. The study comprised of 12 weeks placebo controlled period, followed by a 40 weeks, double-blind active controlled extension period (where placebo was switched to linagliptin). At 12 weeks, the placebo-adjusted mean decline in HbA1c from the baseline was −1.20% while at 52 weeks, the linagliptin-adjusted mean decline in HbA1c was −0.35%. In both groups with moderate and severe RI, gemigliptin showed greater albeit nonsignificant decline in HbA1c from baseline compared to linagliptin at 52 weeks. Other parameters such as fasting plasma glucose, glycated albumin, and fructosamine also showed similar declining trends. There was no significant change in estimated glomerular filtration rate in either of the groups. Hence, based on these results, gemigliptin may be considered a safe and effective treatment modality in T2DM patients with moderate-to-severe RI.

Head-to-head with other dipeptidyl peptidase-4 inhibitors

Gemigliptin has been directly compared with other DPP-4 inhibitors in a few randomized controlled studies for efficacy and safety. Head-to-head studies between gemigliptin and sitagliptin were conducted in T2DM patients both as an initial combination with metformin and as an add-on therapy to metformin. As noted above, the study showed gemigliptin was non inferior to sitagliptin when added on to metformin therapy as regards HbA1c reduction.[27] The results in Indian patients were similar to that of the overall study population (−0.83% HbA1c reduction with gemigliptin 50 mg OD vs. −0.6% with sitagliptin100 mg OD). Efficacy and safety of the DPP-4 inhibitor gemigliptin compared with sitagliptin as an add on to metformin in patients with type 2 diabetes inadequately controlled on metformin alone: India subgroup. In another study involving initial combination treatment with metformin of drug-naïve patients with HbA1c >7.5%, the mean HbA1c reduction from baseline at 12 weeks was 2.8%, 2.2%, and 2.8% for gemigliptin 50 mg OD, sitagliptin 100 mg OD and glimepiride 2 mg OD dosing, respectively. There was no significant difference in HbA1c reduction in between the three groups of patients.[31]

In another head-to-head trial comparing gemigliptin and linagliptin in T2DM patients with RI (GUARD study), the placebo group was switched to linagliptin 5 mg OD dose after 12 weeks during the 40 weeks extension period. At 52 weeks, mean decline in HbA1c from baseline was-1.00% and-0.65% in the gemigliptin and placebo/linagliptin groups respectively. Hypoglycemic incidence was similar between the treatment groups, and there were no significant changes in body weight from baseline.[32]

Effect on glycemic variability and albuminuria

The variable pharmacodynamics profiles of DPP-4 inhibitors have been related to different effects on glycemic variability in patients with T2DM.[29,33,34] In the above-mentioned study (STABLE Study) comparing initial combination therapy of gemigliptin, sitagliptin and glimepiride with metformin
therapy, the mean amplitude of glycemic excursions (MAGE) and standard deviation (SD) of glucose were the parameters used to assess fluctuations in glucose levels. At 12 weeks of treatment, MAGE values were significantly lower in gemigliptin and sitagliptin groups compared with glimepiride; further the SD of mean glucose was significantly lower in the gemigliptin group as compared to sitagliptin and glimepiride.[32]

In the study comparing gemigliptin and linagliptin in T2DM patients with moderate-to-severe RI, the mean changes in the urinary albumin: creatinine ratio from baseline was −339 mg/g Cr in the gemigliptin group compared with 172 mg/g Cr in the placebo group after 12 weeks of therapy. Urinary nephrin values in the gemigliptin group were also significantly reduced compared to placebo group. This was observed regardless of blood pressure changes, glucose lowering effect, or the use of a renin-angiotensin-aldosterone system blocking drug.[32]

**Effect on Lipid Profiles**

Gemigliptinas mono- and combination therapy has also demonstrated its beneficial effects on the lipid profile, with slight lowering of the mean total cholesterol, low-density lipoprotein cholesterol, and triglycerides.[5] Total cholesterol and low density lipoprotein (LDL) cholesterol were modestly but significantly reduced in the gemigliptin group compared with the placebo group (−0.21 mmol/L, 95% CI: −0.38 to −0.03 mmol/L for total cholesterol, −0.18 mmol/L, 95% CI: −0.34 to −0.01 mmol/L for LDL cholesterol). The incidence of hypoglycemia was 9.4% in the gemigliptin group and 2.7% in the placebo group.[32]

**Safety and Tolerability of Gemigliptin**

To assess the safety of gemigliptin, a pooled safety analysis was undertaken with subjects who had been treated with the drug at least once in studies. One thousand eighty patients received gemigliptin 50 mg OD while 446 patients received other oral antidiabetic drugs. Upper respiratory tract infection, specifically nasopharyngitis, was the most common adverse effect reported in 5% of the subjects, and its incidence rate was similar between the two groups of patients. Other commonly reported adverse effects were urinary tract infection, diarrhea, headache, cough, arthralgia, and hypertension. Treatment with gemigliptin did not increase body weight while the incidence of hypoglycemia was similar to placebo or other control groups. Overall, gemigliptin demonstrated good tolerability with both monotherapy and combination therapy, with most adverse effects being mild-to-moderate in nature not requiring any additional intervention.[5]

**ongoing Trials**

Gemigliptin is being assessed for efficacy as safety as an add-on combination therapy with insulin (± metformin) (Clinical Trials. Gov registration number: NCT02831361). Further, a gemigliptin-rosuvastatin fixed dose combination is being studies in T2DM patients with dyslipidemia (ClinicalTrials. Gov registration number: NCT02126358). Gemigliptin is also being evaluated in Russian T2DM patients compared with vildagliptin. (ClinicalTrials. Gov registration number: NCT02343926).[5]

**Conclusion**

Based on the facts explored in this article, it is reasonable to conclude that gemigliptin is a potent, selective, long-acting DPP-4 inhibitor whose safety and tolerability has been proven in patients with T2DM, both with monotherapy and combination therapy with other oral antidiabetic drugs. It has an added on benefit in reducing glycemic variability and lowering albuminuria independent of its glucose lowering effects. This drug may also be useful for treating special populations affected with T2DM, especially the elderly and those with RI. The ongoing studies will provide further evidence for the utility of this drug in the treatment of patients with T2DM.

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**Conflicts of interest**

There are no conflicts of interest.

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