VIA MEDICA
EDITORIAL
ISSN 2450–7458
E-ISSN 2450–8187

This Editorial accompanies a Research Paper, see page 151

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Sojourn of Gemigliptin: A Hidden Gem?

Gemigliptin (LC15-0444) is a competitive, reversible (fast association and slow dissociation), selective (> 3000-fold against DPP-8/9), and long-acting (half-life 30.8 hours) dipeptidyl peptidase-4 (DPP-4) inhibitor, first approved for clinical use by the Korean Food and Drug Administration (FDA) in 2012. It has been approved to be taken orally, with or without food, at a dose of 50 mg once daily, either as monotherapy or in combination with other drugs, and no dose adjustment is required in patients with renal or hepatic impairment. While DPP-4 inhibition with gemigliptin in experimental animal studies was found to be 80%, the fast association and slow dissociation kinetics of DPP-4 inhibition with gemigliptin were found to be albeit different compared with sitagliptin (fast on and fast off rate) and vildagliptin (slow on and slow off rate). Although the originator LG Life Sciences initially signed a licensing agreement with developers such as Sanofi (France) and Stendhal (Mexico) for 104 countries, gemigliptin has been currently approved in 11 countries including India, Columbia, Costa Rica, Panama, Ecuador, Russia, Mexico, and Thailand beside South Korea.

In this issue of *Clinical Diabetology*, a real-world, 12-week, small study (n = 60), of gemigliptin by Sarkar et al. [1] from the Eastern part of India conducted during 2016–2017, reported a robust –1.25% (95% confidence interval, –1.59 to –0.92) HbA1c reduction with gemigliptin in people with type 2 diabetes (median age 52.2 years with a mean HbA1c of 9.5% and duration of diabetes of 8.6 years) on a background antidiabetic (mono, dual, triple combination) therapy but majorly (65%) on background metformin monotherapy. Moreover, 57% of patients achieved a target HbA1c of < 7% with the addition of gemigliptin. The larger HbA1c lowering effect of gemigliptin in this real-world study could be due to a higher baseline mean HbA1c of 9.5% but this appears to be > 2-fold higher than the HbA1c lowering effect observed in the randomized controlled trials (RCTs) conducted in Indian patients. In the subgroup analysis of a double-blind RCT [2], the HbA1c lowering effect of gemigliptin was lower in 108 Indian patients compared with 74 Korean patients (–0.55% vs. –0.94%, respectively) against placebo, despite a higher mean baseline HbA1c (including a higher percentage of patients with baseline HbA1c of > 8.5%) in Indians compared to the Koreans. This suggests real-world studies could often overestimate the effect size related to its inherent bias. Interestingly, the sojourn of gemigliptin did not last long (launched in India in April 2016) and it was withdrawn from India in July 2018 by the Sanofi for unknown or perhaps commercial reasons related to its cost. Notably, the cost of gemigliptin (not approved by the USA FDA and with no cardiovascular (CV) outcome trial (CVOT) conducted) was nearly similar to another DPP-4 inhibitor sitagliptin (US FDA-approved) with clean cardiovascular (CV) safety data shown in CV outcome trial TECOS (2015).

Nevertheless, from the glucose lowering efficacy perspective, eleven RCTs of gemigliptin have been conducted to date either against placebo or active

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Clinical Diabetology 2022, 11; 3: 131–134
DOI: 10.5603/DK.a2022.0027
Received: 25.06.2022 Accepted: 26.06.2022

Table 1: HbA1c Lowering with Gemigliptin Against Placebo or Active Comparator in Randomized Controlled Trials

Trial eponym; first author, year	Countries involved (n)	Background therapy	Duration of T2DM [yrs.]	Comparator groups	Each arm (n)	Baseline HbA1c [%]	Duration of study [weeks]	Primary outcome	Δ HbA1c [%]	Δ HbA1c (95% CI) between two groups, P value	Drug-related adverse event rates; Hypo's
HbA1c lowering studies											
Rhee et al. [3], 2010	Korea (145)	LSM	3	GEMI 50 mg	35	8.24	12	HbA1c change	–0.98	–0.92 (–1.29, –0.56), p < 0.0001	Similar in both groups including hypo's (0% in both groups)
				PBO	34	8.20			–0.06		
Yang et al. [2], 2013	Korea (74), India (108)	LSM	≈ 3	GEMI 50 mg	87	8.20	24	HbA1c change	NR	–0.71 (–1.04, –0.37), p < 0.0001	Similar; Hypo's: 2.3%
				PBO	87	8.30			NR		Hypo's: 0%
GUARD; Yoon et al. [4], 2017	Korea (132)	Renal impaired, INS ± SU	16.7	GEMI 50 mg	64	8.30	12	HbA1c change	–0.82	–1.20 (–1.53, –0.87), p < 0.001	Similar; Hypo's: 11%
			15.9	PBO	66	8.40			+0.38		Hypo's: 8%
GUARD Extension; Han et al. [5], 2018	Korea (102)	Renal impaired, INS ± SU	15.4	GEMI 50 mg	48	8.4	40	HbA1c change	–1.00	–0.35 (–0.84, 0.13), p = 0.15	Similar, including Hypo's
			16.5	LINA 5 mg	52	8.4			–0.65		
INICOM; Lim et al. [6], 2017	Korea (357) Thailand (76)	8–week wash out of prior 1 OAD	4.2	A. GEMI 50 mg + MET	136	8.65	24	HbA1c change	–2.06	*A minus B:* –0.62 (–0.82, –0.41), p < 0.001; *A minus C:* –0.82 (–1.02, –0.63), p <0.001	Similar; Hypo: 2.1%
			4.1	B. PBO + MET	148	8.73			–1.47		Hypo: 1.3%
			3.5	C. PBO + GEMI 50 mg	140	8.66			–1.24		Hypo: 0%
TROICA; Ahn et al. [7], 2017	Korea (219)	MET, GLIM	13.0	GEMI 50 mg	107	8.20	24	HbA1c change	–0.88	–0.87 (–1.09, –0.64), p < 0.001	Hypo: 9.4%
			12.8	PBO	109	8.20			–0.01		Hypo: 2.7%
ZEUS II; Cho et al. [8], 2020	Korea (44), Thailand (239)	INS ± MET	16.3	GEMI 50 mg	188	8.10	24	HbA1c change	–0.8	–0.7 (–0.9, –0.4), p < 0.0001	Similar including Hypo's: 5.7%
			16.5	PBO	95	8.10			–0.1		Hypo's: 5.2%
Rhee et al. [9], 2010	Korea (296), India (129)	MET	6.1	GEMI 50 mg	135	7.93	24	HbA1c change	–0.77	0.004 (–0.15, 0.16), p = NS	Similar, hypo's were not reported
			6.4	SITA 100 mg	133	8.05			–0.80		
Jung et al. [10], 2018	Korea (94), India (63)	MET	6.1	GEMI 50 mg	55	7.9	52	HbA1c change	–1.06	Groups not compared	Similar, hypo's were not reported
			6.4	SITA 100 mg switched to GEMI 50 mg	44	8.08			–0.99		
Glycemic variability studies								**Primary outcome**	**Δ MAGE (mg/dL)**	**Δ MAGE (95% CI) between two groups (mg/dL), P value**	**Drug–related adverse event rates; hypo's**
STABLE; Park et al. [11], 2017	Korea (69)	LSM	0.63	A. GEMI 50 mg	24	9.5	12	Change in MAGE	–42	*A minus B:* –0 (–20, 19), p = NR; *A minus C:* –20 (–39, –2), p = 0.03; *B minus C:* –20 (–38, –3), p = 0.02	Similar; hypo's: 0%
			2.0	B. SITA 100 mg	21	9.1			–42		Hypo's: 0%
			1.47	C. GLIM 2 mg	21	9.7			–21		Hypo's: 9.0%
STABLE II; Kwak et al. [12], 2020	Korea (71)	LSM or MET	2.2	GEMI 50 mg	34	7.9	12	Change in MAGE	–27.2	–19.2 (–31.3, –7.2), p = 0.002	Similar; hypo's 0% in both groups
			3.5	DAPA 10 mg	36	7.9			–7.9		

DAPA — dapagliflozin GEMI — gemigliptin; GLIM — glimepiride; hypo's — hypoglycemia; INS — insulin; LINA — linagliptin; LSM — lifestyle modifications; MAGE — mean amplitude of glucose excursion; MET — metformin; NR — not reported; PBO — placebo; SITA — sitagliptin; SU — sulfonylureas; T2DM — type 2 diabetes mellitus

comparators including two extension studies that varied in duration from 12 to 52 weeks (Tab. 1) [2–12]. Of the eleven RCTs, six were exclusively conducted in South Korea, three were conducted in India and two were conducted in Thailand in addition to South Korea. Change in HbA1c reduction was the primary objective in nine RCTs, whereas the change in glycemic variability [mean amplitude of glucose excursion (MAGE)] was the primary outcome in two RCTs. Gemigliptin was compared with placebo (six RCTs), sitagliptin 100 mg (3 RCTs), linagliptin 5 mg (1 RCT), glimepiride 2 mg (1 RCT), dapagliflozin 10 mg (1 RCT) and metformin up to 2000 mg (1 RCT). Summarily, in RCTs, gemigliptin was found to reduce HbA1c by –0.7 to –1.2% in monotherapy studies against placebo in a baseline HbA1c of mean 8–8.5%. A larger reduction of HbA1c of –2.0% was also observed with gemigliptin in combination with metformin in a mean baseline HbA1c of 8.7% in one RCT (INICOM). Similarly, the reduction of HbA1c was quite pronounced at the top of background metformin and sulfonylurea (SU) combination therapy (TROICA; –0.9%) or background insulin therapy (ZEUS II; –0.7%) even in a long-standing type 2 diabetes of >10 years duration. In a 24-week head-to-head study, HbA1c reduction with gemigliptin (–0.77%) was comparable to sitagliptin (–0.8%) with background metformin therapy and the 28-week extension of the same study showed switching to gemigliptin 50 mg from sitagliptin 100 mg yielded a similar efficacy outcome. Importantly, while gemigliptin was shown to reduce glycemic variability (MAGE) similar to the sitagliptin but significantly better than glimepiride, reduction in standard deviation (SD) of mean glucose was more effective with gemigliptin compared to both sitagliptin and glimepiride, in head-to-head RCT (STABLE). Interestingly, reduction in MAGE was significantly better with gemigliptin compared to dapagliflozin in a head-to-head RCT (STABLE II) of 12 weeks duration. Gemigliptin was also studied in patients with chronic renal disease (CKD, with a mean eGFR of 33.3 mL/min/1.73 m^2) in one RCT (GUARD) and was found to significantly lower HbA1c by –0.8% against placebo in background insulin (with or without SU) therapy, without provoking significant hypoglycemia. Moreover, the HbA1c lowering with gemigliptin was similar to linagliptin (–1.0% vs. –0.65%; Difference -0.35%; 95% CI, –0.84, 0.13; $p = 0.15$) in 28-week extension of GUARD study. Importantly, there was a significant decrease in urinary albumin creatine ratio (UACR) with gemigliptin at 12-weeks, in patients having both micro- and macro-albuminuria (–41.9 mg/g, $p = 0.03$; –528.9 mg/g, $p < 0.001$; respectively) regardless of the change in HbA1c, systolic blood pressure and use of renin-angiotensin system blockers. However, this reduction in albuminuria was no longer significant in a further 28-weeks extension of GUARD (40-week) study. Overall, gemigliptin was well tolerated in all RCTs and drug-related adverse events were similar compared to placebo or active comparators. Table 1 summarizes the glucose lowering potential of gemigliptin compared to placebo or active comparators.

Conflict of interest

None declared.

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