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Mini-review: Pharmacokinetics of Omarigliptin, a Once-weekly Dipeptidyl Peptidase-4 Inhibitor

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ABSTRACT

The dipeptidyl peptidase-4 (DPP-4) inhibitors are novel oral hypoglycemic drugs which have been in clinical use for the past 10 years. The drugs are safe, weight neutral and widely prescribed. There are currently many gliptins approved by FDA, namely sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin with several more in advanced stages of development. The gliptins may possess cardiovascular protective effects and their administration may promote β-cell survival; claims currently being evaluated in clinical and preclinical studies. The gliptins are an optional second-line therapy after metformin; they are generally well tolerated with low risk of hypoglycemia. The various compounds differ with respect to their pharmacokinetic properties; however, their clinical efficacy appears to be similar. The clinical differences between the various compounds stem from effects other than hypoglycemic effects, their safety and side effects profile. The currently registered compounds appear to have maximized the clinical potential of DPP-4 inhibition, and the new compounds in the companies' pipelines seem to be as effective as the ones presently in use. In our effort to review and evaluate DPP-4 inhibitors with added benefits over currently commercially available DPP-4 inhibitors, omarigliptin was selected for this review article as a potent and selective dipeptidyl peptidase 4 (DPP-4) inhibitor with an excellent pharmacokinetic profile amenable for once-weekly human dosing. Omarigliptin is a potent, oral, long-acting (DPP)-4 inhibitor approved in Japan and in global development as a once-weekly treatment for type 2 diabetes mellitus. The aim of this review was to investigate the different pharmacokinetic studies of omarigliptin in a concise way in the form of tables.

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors occupy an increasing place in the armamentarium of drugs used for the management of hyperglycaemia and offer new opportunities for a personalized medicine in patients with Type 2 diabetes [1]. DPP-4 inhibitors offer various advantages when compared to other glucose-lowering agents. Despite they have been commercialized since a few years only, available data obtained in randomized controlled trials are of better quality compared to those available with ancient classical glucose-lowering agents, especially in more fragile populations such as elderly people, individuals with renal impairment or at high cardiovascular risk and patients at higher risk of hypoglycemia [1]. Such incretin-based therapies offer advantages over other glucose-lowering agents. An extensive literature search was performed to analyze clinical cases of acute pancreatitis reported in the literature or to the Food and Drug Administration (FDA), in randomized clinical trials, and in observational studies with five DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin and confirmed that increased risk of pancreatitis has been reported in diabetic versus nondiabetic patients [2]. In rather short-term clinical trials with well-selected diabetic patients, no increased risk of acute pancreatitis has been observed with any of the five commercialized FDA approved DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin [2]. Similarly, real-life cohort studies showed no increased incidence of pancreatitis with gliptins compared with other

glucose-lowering agents, a finding recently challenged by a case-control study. These results must be confirmed in postmarketing surveillance programs and in ongoing large prospective trials with cardiovascular outcomes [2].

Preclinical data indicated a beneficial action on blood vessels, via both glucagon-like peptide 1 (GLP-1)-dependent and GLP-1-independent effects. DPP-4 inhibition increases the concentration of many peptides with potential cardio protective effects. Clinically, DPP-4 inhibitors improve several risk factors in patients with type 2 diabetes mellitus [3]. They improve blood glucose control, are weight neutral, lower blood pressure, improve postprandial lipaemia, reduce inflammatory markers, diminish oxidative stress, and improve endothelial function. Some positive effects on the heart have also been described in patients with ischemic heart disease or congestive heart failure, although their clinical relevance requires further investigation. Post-hoc analyses of phase II-III, controlled trials suggest a possible cardio protective effect with a trend for a lower incidence of major cardiovascular events with gliptins than with placebo or active agents. However, the actual relationship between DPP-4 inhibition and cardiovascular outcomes remains to be proven [3]. Omarigliptin is a new once-weekly (DPP-4) inhibitor developed for the treatment of type 2 diabetes. It is indicated to have favorable effects on glycosylated hemoglobin (HbA_{1c}), fasting and postmeal plasma glucose. It potently but reversibly inhibits DPP-4 enzyme, which prolongs the circulating half-life of glucagon-like peptide-1 that increases insulin secretion in a glucose-dependent manner [4]. Benefiting from glucose-dependent insulin secretion, omarigliptin is associated with low risk of hypoglycemia. In contrast to the once-daily DPP-4 inhibitors, once-weekly omarigliptin can improve patients' adherence and thus achieve optimal therapeutic efficacy [4]. Omarigliptin was selected for this review article to investigate different pharmacokinetic studies in the form of concise tables. In comparison to the literature of the analytical methods described for once daily previously FDA approved gliptin, linagliptin [5-23], many analytical and bio-analytical procedures should be developed for omarigliptin to enable the development of new dosage forms and further pharmacological and clinical applications.

Literature review

Table 1: Study design and major outcomes of different studies evaluating omarigliptin as a once weekly Dipeptidyl Peptidase-4 Inhibitor

Study design	Major outcomes
This double-blind, randomized, placebo-controlled study evaluated the effects of age, sex, and obesity on the pharmacokinetics of omarigliptin in healthy subjects. A single oral dose of omarigliptin 10 mg (n = 6/panel) or placebo (n = 2/panel) was administered in the fasted state to elderly non-obese men and women, young obese ($30 \leq$ body mass index [BMI] ≤ 35 kg/m^2) men and women, and young non obese women of non-childbearing potential. Plasma was collected at selected post-dose times for evaluation of omarigliptin concentrations. Pharmacokinetic parameters were compared with historical data from a previously-conducted single-dose study in young, healthy, non-obese men [24].	There were no clinically significant differences in omarigliptin $AUC_{0-\infty}$, the primary pharmacokinetic parameter for assessing efficacy and safety, based on age, sex, or BMI (pooled non obese elderly versus pooled non obese young, young non obese female versus young non obese male, and pooled young obese versus pooled young non obese). There were no serious adverse events or hypoglycemic events attributable to omarigliptin administration. Demographic factors and BMI had no meaningful effect on omarigliptin pharmacokinetics, suggesting that dose adjustment based on age, sex, or obesity is not required [24].
This was a two-part, double-blind, randomized, placebo-controlled study in healthy Japanese male subjects (n = 6) to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of omarigliptin after single dose (5-100 mg) and multiple dose (1-50 mg for 3 weeks) administration [25].	The results of this study in healthy young Japanese male subjects demonstrated that omarigliptin was well tolerated and had a pharmacokinetic and DPP-4 inhibition profile that supports once-weekly dosing in Japanese patients with T2DM [25].
Pharmacokinetics of omarigliptin were assessed following single and multiple doses in healthy subjects. Absorption was rapid, and food did not influence pharmacokinetics. Accumulation was minimal, and steady state was reached after 2 to 3 weeks. Weekly (area under the curve) AUC and C_{max} displayed dose proportionality within the dose range studied at steady state. DPP-4 inhibition ranged from ~77% to 89% at 168 hours following the last of 3 once weekly doses over the dose range studied [26].	Omarigliptin resulted in ~2-fold increases in weighted average postprandial active GLP-1.Omarigliptin acts by stabilizing active GLP-1, which is consistent with its mechanism of action as a DPP-4 inhibitor. Administration of omarigliptin was generally well tolerated in healthy subjects, and the PK profiles support once-weekly dosing [26].
This was a Phase I, randomized, double-blind, placebo-controlled, multiple-dose study of 50 mg omarigliptin administered once weekly for 4 weeks. Participants included 24 obese but otherwise healthy subjects (panel A; omarigliptin, n = 18; placebo, n = 6) and 8 obese patients with T2DM (treatment naive, hemoglobin A1c $\geq 6.5\%$ and $\leq 10.0\%$ [panel B]; omarigliptin, n = 6; placebo, n = 2). Participants were 45 to 65 years of age with a body mass index of ≥ 30 and ≤ 40 kg/m^2. Blood sampling occurred at select time points, depending on the study panel. Body weight was an exploratory endpoint. Due to sparse sampling in panel A, a thorough PK analysis was performed in obese patients with T2DM (panel B) only [27].	The administration of omarigliptin was generally well-tolerated in obese participants with and without T2DM, and the favorable PK profiles support once-weekly dosing. Omarigliptin may provide an important once-weekly treatment option for patients with T2DM [27].

Table 2: Summary of the pharmacokinetic parameters of omarigliptin following single and multiple oral doses in healthy and diabetic subjects

Individual Population	$AUC_{0-\infty}$ (μM-h)	C_{max} (nM)	AUC_{0-168} (μM-h)	C_{168} (nM)	$T_{1/2}$ (h)	Renal Clearance (L/h)	Creatinine Clearance (L/h)	Tmax (h)
Elderly nonobese male, Elderly nonobese female, Young nonobese female, Young obese male, Young obese female, [24].	M range 10.2-13.4	M range 197-303	M range 9.34-11.3	M range 7.96-13.1	M range 69.6-134	M range 1.39-2.01	GM range 4.02-9.16	MD 1.0-2.0
Subjects received single doses of 5^a, 25^b or 100^c mg omarigliptin in the fasted state [25].	BM 6.27^a 25.13^b 98.87^c	BM 141.51^a 749.54^b 2709.59^c	BM 5.34^a 23.81^b 94.83^c	BM 7.55^a 19.98^b 54.49^c	GM 66.65^a 38.89^b 43.41^c	N.D.	N.D.	MD: 1.5^a 1.0^b 2.0^c
Subjects received single doses of 10^d mg and 50^e mg omarigliptin in the fasted state, subjects received 10^f mg omarigliptin after breakfast [25].	BM 9.78^d 50.54^e 10.07^f	BM 297.84^d 1712.32^e 223.03^f	BM 9.07^d 48.66^e 8.75^f	BM 8.10^d 23.62^e 9.16^f	GM 49.91^d 33.43^e 89.45^f	N.D.	N.D.	MD: 1.00^d 1.00^e 4.0^f
Multiple oral doses of omarigliptin (1^g, 10^h, 25^i, or 50^j mg) under the fasted state for three weeks (a total of 3 doses to be given on Days 1, 15*), [25].	N.D.	BM 15.66^g 21.25^{g*} 236.65^h 278.21^{h*} 802.60^i 700.63^{i*} 1083.59^j 1305.97^{j*}	BM 1.03^g 1.40^{g*} 8.92^h 9.75^{h*} 21.19^i 22.31^{i*} 40.32^j 41.56^{j*}	N.D.	GM 144.88^{g*} 143.52^{h*} 82.48^{i*} 73.73^{j*}	N.D.	N.D.	MD 2.00^g 2.00^{g*} 1.50^h 1.00^{h*} 0.5^i 1.5^{i*} 1.58^j 1.00^{j*}
Healthy male subjects received single doses of 0.5^k, 1.5^L, 5^M, 12.5^N, 25^O, 50^P, 100^Q, 200^R and 400^S mg omarigliptin following an overnight Fast [26].	GM $N.D.^k$ 1.7^L 5.3^M 12^N 22.5^O 41.6^P 86.9^Q 162^R 335^S	GM 6.5^k 20.7^L 88.2^M 219^N 484^O 904^P 2210^Q 3850^R 9290^S	GM $N.D.^k$ 1.2^L 4.1^M 10.6^N 20.9^O 39.4^P 82.5^Q 155^R 323^S	GM $N.D.^k$ 3.3^L 6.75^M 10.8^N 20.6^O 26.7^P 54.3^Q 79.5^R 174^S	GM $N.D.^k$ 93.3^L 115.9^M 68.9^N 49.5^O 47.7^P 42.6^Q 45.2^R 42.5^S	GM $N.D.^k$ 1.6^L 2.1^M 2.3^N 2.2^O 2.4^P 2.1^Q 2.7^R 2.7^S	N.D.	MD 0.75^k 1.0^L 2.0^M 4.0^N 0.75^O 1.5^P 0.75^Q 1.5^R 1.0^S
Healthy male subjects received multiple doses of 10^T, 25^U, 50^V and 100^W mg omarigliptin once-weekly (Days 1, 8, and 15*) after an overnight fast [26].	N.D.	GM: 184^T 195^{T*} 610^U 565^{U*} 988^V 1080^{V*} 2320^W 2400^{W*}	GM: 7.4^T 8.8^{T*} 22.0^U 22.0^{U*} 40.7^V 47.8^{V*} 82.3^W 87.8^{W*}	GM: 8.8^T 11.9^{T*} 18.8^U 17.1^{U*} 26.5^V 32.8^{V*} 51.5^W 61.1^{W*}	GM: $N.D.^T$ 83.2^{T*} $N.D.^U$ 66.7^{U*} $N.D.^V$ 48.3^{V*} $N.D.^W$ 41.7^{W*}	GM $N.D.^T$ 2.0^{T*} $N.D.^U$ 1.6^{U*} $N.D.^V$ 1.9^{V*} $N.D.^W$ 2.1^{W*}	N.D.	GM 3.0^T 4.0^{T*} 1.0^U 1.5^{U*} 4.0^V 4.0^{V*} 2.5^W 1.0^{W*}
Administration of multiple dose omarigliptin 50 mg in obese diabetic patients on days 1*, 8, 15, and 22**and in healthy non obese volunteers on days 1*, 8, and 15** [27]. N.B. ** (last dose).	N.D.	955* 1170**	37.4* 38.2**	27.2* 28.3**	N.D.* 58.71**	N.D.	N.D.	2.5* 1.0**

M: mean, BM: Back-transformed least squares mean, GM: Geometric least-squares mean, MD: Median, N.D.: Not determined

CONCLUSION

After the literature review, omarigliptin absorption was found to be rapid, and food did not influence single-dose pharmacokinetic parameters, accumulation was minimal, and steady state was reached after 2 to 3 weeks. Administration of omarigliptin was generally well tolerated in healthy subjects, and the pharmacokinetic profiles support once-weekly dosing. Consistent with other DPP-4 inhibitors, omarigliptin had no effect on body weight in this short-duration study. The administration of omarigliptin was generally well-tolerated in obese participants with and without type 2 diabetes mellitus. A thorough QTc study confirms early pharmacokinetics/QTc modeling that a supratherapeutic dose of omarigliptin, a Once-Weekly DPP-4 Inhibitor, does not prolong the QTc interval. There were no serious adverse events or hypoglycemic events attributable to omarigliptin administration. Demographic factors and BMI had no meaningful effect on omarigliptin pharmacokinetics, suggesting that dose adjustment based on age, sex, or obesity is not required.

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