SHORT COMMENT FOR THE LANCET DIABETES & ENDOCRINOLOGY

Once-weekly DPP-4 inhibitors: do they meet an unmet need?

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Dipeptidyl peptidase (DPP-4) inhibitors ("gliptins") are increasingly used in type 2 diabetes mellitus (T2DM) for treating hyperglycaemia. They offer the advantage of improving glucose control without weight gain and with a minimal risk of hypoglycaemia[1]. Randomised controlled trials have proven their efficacy and safety as monotherapy in patients on diet and exercise, as dual therapy in add-on to metformin, sulphonylurea, thiazolidinedione or insulin and in various triple therapies[1]. Commercialized DPP-4 inhibitors are used in once-daily administration (sitagliptin, saxagliptin, alogliptin, linagliptin), except vildagliptin that is given twice daily in absence of renal impairment.

Inagaki and colleagues report in the Lancet Diabetes Endocrinology the results of a first 24-week trial comparing the efficacy and safety profile of a once-weekly DPP-4 inhibitor (trelagliptin) with that of the once-daily DPP-4 inhibitor alogliptin in Japanese patients with T2DM treated with diet and exercise[2]. The study demonstrates that trelagliptin 100 mg once weekly is significantly more effective than placebo and non-inferior to alogliptin 25 mg once

daily in terms of reduction in glycated haemoglobin (HbA1c). The tolerance/safety profile was good and similar with the two DPP-4 inhibitors. These data should be confirmed in combined therapy, especially in patients not well controlled with metformin[3]. The comparator used in this Japanese study was alogliptin 25 mg whereas, in most comparative studies, the DPP-4 inhibitor used as reference is sitagliptin 100 mg. Although the two once daily DPP-4 inhibitors appear to have a comparable efficacy, no head-to-head trial compared alogliptin and sitagliptin. In a mixed treatment comparison of randomised controlled trials, the weighted absolute HbA1c change from baseline averaged -0.58% (95% confidence interval or CI -0.83, -0.33) with alogliptin and -0.59% (-0.75, -0.43) with sitagliptin[4]. In fact, rather few studies directly compared the efficacy of two different DPP-4 inhibitors[4]. In patients with T2DM inadequately controlled by metformin alone, saxagliptin 5 mg was noninferior to sitagliptin 100 mg regarding the reduction in HbA1c, although sitagliptin exerted a slightly stronger effect on fasting glucose than saxagliptin[5], probably because of a more prolonged inhibition of DPP-4 enzyme[6]. Vildagliptin 50 mg twice daily was also associated with a more sustained DPP-4 inhibition over 24 hours, which may contribute to a better control of fasting glucose levels[6]. Here, the reduction in fasting plasma glucose was lower with trelagliptin once weekly than with alogliptin once daily (-0.36 versus -0.83 mmol/l; point estimate 0.48, 95% CI 0.095, 0.858)[2]. A detailed comparison of the kinetics of DPP-4 inhibition with the two compounds would be of interest.

MK-3102 (omarigliptin) is another potent and selective DPP-4 inhibitor with an excellent pharmacokinetic profile amenable for once-weekly human dosing[7]. A 24-week head-to-head trial (reported as abstract only) compared the efficacy of omarigliptin 25 mg once weekly with sitagliptin 50 mg once daily (the classical dose used in Japan) and with placebo in Japanese patients with T2DM [8]. This study also reported better efficacy of omarigliptin once weekly than placebo and non-inferiority versus sitagliptin once daily (Table 1). The results of these two studies obtained in Japanese patients should be replicated in other ethnic groups, especially because DPP-4 inhibitors were shown to exhibit a better glucose-lowering efficacy in Asian than in Caucasian people and because doses of DPP-4 inhibitors may also differ[9].

Treatment of hyperglycaemia in T2DM with once weekly therapy started with the development of long-acting glucagon-like peptide-1 (GLP-1) receptor agonists. Extended-release exenatide was the first one commercialized but several others are now available or in late phase of development (dulaglutide, albiglutide, semaglutide)[10]. They have a better gastrointestinal tolerance and should improve ease of use and patient's compliance compared with once or twice daily GLP-1 receptor agonists. Whereas the advantage of a once-weekly

administration appears obvious for an injectable compound, it is less evident for orally administered medications such as DPP-4 inhibitors. Nevertheless, a majority of patients with T2DM require numerous drugs to tackle hyperglycaemia, hypertension, dyslipidaemia and other comorbidities. Thus, although questions remain over the extent to which once-weekly DPP-4 inhibitor administration is an unmet need, simplifying therapy may be well received from a patient perspective at a time when a patient-centered approach is recommended for the management of T2DM. Further real-life studies should demonstrate whether once-weekly DPP-4 inhibitors may contribute to improve patient's satisfaction and compliance and as a consequence help to better and safely control T2DM on a long-term basis.

I have received lecture, adviser's or investigator's fees from AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, NovoNordisk, Sanofi and Takeda.

Table 1 : Comparison of the results of to head-to-head 24-week trials comparing the efficacy of a once-weekly DPP-4 inhibitor with that of a once-daily DPP-4 inhibitor in Japanese patients treated with diet and exercise.

	n	Δ HbA1c %	Δ FPG mmol/l	Δ 2h post-meal glucose mmol/l	% patients with HbA1c <7%
Inagaki et al 2014[2]					
Placebo	50	+0.24	-0.31	-0.12	4.3
Alogliptin 25 mg once daily	92	-0.46	-0.83	-1.62	36.1
Tetragliptin 100mg once weekly	101	-0.32	-0.36	-0.96	29.2
	LSMD	0.11% (-0.054, 0.281)			
Gantz et al 2014[8]					
Placebo	82	+0.13	-0.35	-0.30	7.3
Sitagliptin 50 mg once daily	164	-0.65	-1.15	-2.51	37.8
Omarigliptin 25mg once weekly	166	-0.66	-1.03	-2.35	47.0
	LSMD	-0.02% (-0.15, 0.12)			

CI : confidence interval. Δ : change versus baseline FPG : fasting plasma glucose. HbA1c : glycated haemoglobin. LSMD : Least square mean difference (once-weekly versus once-daily administration).

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