SHORT COMMENT FOR THE LANCET

Challenging incretin-based therapy selection in type 2 diabetes

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Incretin-based therapies, either incretin-enhancers as dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) or incretin-mimetics as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are increasingly used for the treatment of type 2 diabetes mellitus, essentially because of a good glucose-lowering activity without inducing hypoglycaemia or weight gain.[1] DPP-4 inhibitors and GLP-1 RAs are positioned, among other pharmacological options, as second line treatment after failure to metformin monotherapy or later on in triple therapy within various combinations.[2] One first challenge for the clinician is to decide whether a DPP-4 inhibitor or a GLP-1 RA should be preferred, for instance after metformin failure[3]. DPP-4 inhibitors have the advantage to be administered orally, to have an excellent tolerance profile and to be less expensive, but they are less potent and weight-neutral only. Alternatively, GLP-1 RAs offer a greater glycated haemoglobin (HbA1c) reduction and a significant weight loss, but they must be injected subcutaneously, may be associated with nausea and vomiting (especially during the first weeks after initiation of therapy) and are more expensive.[4] Consequently, the choice between a

DPP-4 inhibitor and a GLP-1 RA should be made on an individual basis according to physician's objectives and patient's preference.[2] However, the development of new once-weekly GLP-1 RAs may change the scene because of the lower burden imposed to the patient, especially if these agents are as (or even more) effective and better tolerated compared to once- or twice-daily GLP-1 RAs.[5]

If the clinician decides to prescribe a GLP-1 RA, another question arises: which one should be considered as the best option ? Indeed, an increasing number of GLP-1 RAs are already on the market (exenatide, exenatide LAR, liraglutide, lixisenatide) or will be available very soon (albiglutide, dulaglutide, semaglutide). Despite they share the same mechanism of action, consistent data suggest that they may differ, especially regarding their effect on gastric emptying resulting in different effects on postprandial versus fasting plasma glucose levels.[6] However, most of the classification between so-called short-acting GLP-1 RAs and long-acting GLP-1 RAs comes from indirect comparisons rather than from head-to-head trials, which remain rather scarce.[7] Furthermore, comparisons between once-weekly GLP-1 RAs and either twice-daily exenatide[8-10] or once-daily liraglutide[11, 12] gave controversial results regarding their respective efficacy in lowering HbA1c levels (Table 1). In this regard, the phase 3, randomised, open-label, parallel-group study by Dungan and colleagues comparing the newly developed once-weekly dulaglutide with the reference once-daily liraglutide at 62 sites in nine countries is of interest.[13] It showed that once-weekly dulaglutide **(**1·5 mg) is non-inferior to once-daily liraglutide **(**1·8 mg) in reducing HbA1c in 599 patients with inadequately controlled type 2 diabetes receiving metformin. Least-squares mean reduction in HbA1c after 26 weeks was –1・42% (SE 0・05) [-16 mmol/mol (0.55)] in the dulaglutide group and –1・36% (0・05) [-15 mmol/mol (0.55)] in the liraglutide group. Analysis of changes in fasting and postprandial plasma glucose levels confirmed the non-inferiority of dulaglutide versus liraglutide. Only a slightly smaller weight reduction was observed with dulaglutide compared to liraglutide [–2・90 kg (0・22) versus –3・61 kg (0・22); mean difference : 0・71 kg (0・17 to 1・26); p=0・011], but the clinically relevance of this slight difference remains doubtful. Finally, the safety and tolerability profile was similar with the two GLP-1 RAs regarding the incidence of gastrointestinal adverse events (nausea, diarrhoea, dyspepsia, vomiting) and the low hypoglycaemia rate [0・34 (SE 1・44) versus 0・52 (3・01) events per patient per year], with no severe hypoglycaemia in both groups.

A few other trials directly compared the clinical efficacy and tolerance profile of a once-weekly GLP-1 RA and a once- or twice-daily GLP-1 RA (Table 1). All were

randomised, open-label, non-inferiority 24-32-week trials. However, they used different non-inferiority margins regarding differences in HbA1c reduction (0.25, 0.3 or 0.4%), which may affect the interpretation of the results. Once-weekly exenatide showed a better efficacy than twice-daily exenatide in two trials.[8, 9] Similarly, the newly developed once-weekly dulaglutide, whatever the dosage used (0.75 or 1.5 mg), also exerted a greater reduction in HbA1c than twice-daily exenatide.[10] However, as once-daily 1.8 mg liraglutide has been shown more potent than twice daily exenatide in a head-to-head trial[7], a direct comparison of once-weekly GLP-1 RAs with once-daily liraglutide used as reference seems more appropriate. To this respect, once-weekly exenatide showed a significantly lower HbA1c reduction compared with once-daily 1.8 mg liraglutide[11] and patients who received once-weekly albiglutide had also lower reductions in HbA1c than did those who received once-daily 1.8 mg liraglutide (Table 1).[12] However, no a-priori basis exists to explain why long-acting GLP-1 RAs might be inferior in terms of lowering HbA1c compared to short-acting GLP-1 RAs. Furthermore, liraglutide, despite its once-daily injection, is classified in the category of long-acting GLP-1 RAs, in contrast to twice-daily exenatide.[6] In the study by Dungan and colleagues, dulaglutide at a dose of 1.5 mg once weekly was non-inferior to once-daily 1.8 mg liraglutide. There is no obvious explanation for such differences between exenatide LAR, albiglutide and dulaglutide because sample size, demographic characteristics, background glucose-lowering therapies and baseline HbA1c were rather similar across the three studies (Table 1). Most likely, the apparent difference in efficacy derives from differences in dose estimations with the various once-weekly GLP-1 RAs, although fundamental differences in these agents' interactions with the GLP-1 receptor compared with liraglutide cannot be completely excluded. However, in absence of head-to-head trials, it is difficult to draw definite conclusion about a possible difference of efficacy between the various once-weekly GLP-1 RAs.

The obvious advantage of a once-weekly versus a once-daily injection concerns patient's acceptance and possibly compliance. However, compliance may be different in the clinical trial setting, where it is strictly controlled and regularly reinforced, and in real life where the patient is free to follow the prescription. Therefore, it is difficult to predict how short-term differences in compliance, balanced with potential improvement of patient's acceptance and compliance with the once-weekly medication, would impact glycaemic control in daily live conditions. This concern requires further study.

As for DPP-4 inhibitors, large, long-term prospective trials with cardiovascular outcomes are ongoing, comparing a GLP-1 RA (either once daily liraglutide or once weekly

GLP-1 RAs - exenatide LAR, dulaglutide, semaglutide, albiglutide -) with a placebo in patients with type 2 diabetes and a high cardiovascular risk profile. Although none of these trials will provide head-to-head comparisons, the huge amount of data they will offer to the medical community should help the physician's in the best choice of incretin-based therapies for the management of type 2 diabetes.

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Table 1 : Head-to-head trials of ≥ 24 weeks duration comparing a once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) with either twice-daily exenatide or once-daily liraglutide in patients with type 2 diabetes not well controlled with oral antihyperglycaemic medications. Data from the head-to-head trial comparing twice-daily exenatide and once-daily liraglutide (LEAD-6) are also mentioned for the purpose of comparison.

Reference (trial name)	**GLP-1 RA**	**n**	**Follow up Weeks**	**Baseline HbA1c % or mmol/mol Mean (SE)**	**Δ HbA1c % or mmol/mol Mean (SE)**	**Δ HbA1c Treatment difference % Mean (95% CI)**	**P value (vs compa-rator)**	**HbA1c reduction Non-inferiority margin (%)**
Buse et al 2009[7] (LEAD-6)	Liraglutide 1.8 mg OD	233	26	8.2 (1.0) 66.1 (11.0)	-1.12 (0.08) -12 (0.9)	-0.33 (-0.47 to -0.18) -3.63 (-5.17 to -1.98)	<0.0001	0.4 (non-inferiority and subsequent superiority met)
	Exenatide 10 µg BID	231	26	8.1 (1.0) 65.0 (11.0)	-0.79 (0.08) -9 (0.9)			
Drucker et al 2008[8] (DURATION-1)	Exenatide 2 mg OW	148	30	8.3 (1.0) 67.2 (11.0)	-1.9 (0.1) -21 (1.1)	-0.33 (-0.54 to -0.12) -3.63 (-5.94 to -1.32)	0.0023	0.4 (non-inferiority and subsequent superiority met)
	Exenatide 10 µg BID	147	30	8.3 (1.0) 67.2 (11.0)	-1.5 (0.1) -16 (1.1)			
Blevins et al 2011[9] (DURATION-5)	Exenatide 2 mg OW	129	24	8.5 (1.1) 69.4	-1.6 (0.1) -18 (1.1)	-0.70 (-0.90 to -0.40) -7.7 (-9.9 to -4.4)	<0.0001	0.4 (non-inferiority and subsequent superiority met)
	Exenatide 10 µg BID	123	24	8.4 (1.2) 68.3 (12.1)	-0.9 (0.1) -10 (1.1)			
Wysham et al 2014[10] (AWARD-1) (*)	Dulaglutide 0.75 mg OW	280	26	8.1 (1.2) 65.0 (12.1)	-1.30 (0.06) -14 (0.7)	-0.31 (-0.44 to -0.18) -3.41 (-4.84 to -1.98)	<0.001	0.4 (non-inferiority and subsequent superiority met)
	Dulaglutide 1.5 mg OW	279	26	8.1 (1.3) 65.0 (14.3)	-1.51(0.06) -17 (0.7)	-0.52 (-0.66 to -0.39) -5.72 (-7.26 to -4.29)	<0.001	0.4 (non-inferiority and subsequent superiority met)
	Exenatide 10 µg BID	276	26	8.1 (1.3) 65.0 (14.3)	-0.99 (0.06) -11 (0.7)			
Buse et al 2013[11] (DURATION-6)	Exenatide 2 mg OW	461	26	8.5 (1.0) 69.4 (11.0)	-1.28 (0.05) -14 (0.55)	0.21 (0.08 to 0.33) 2.31 (0.88 to 3.63)	0.02	0.25 (non-inferiority not met, thus superiority not tested : p=NA)
	Liraglutide 1.8 mg OD	450	26	8.4 (1.0) 68.3 (11.0)	-1.48 (0.05) -16 (0.55)			
Pratley et al 2014[12] (HARMONY-7)	Albiglutide 30 mg OW	404	32	8.2 (0.9) 66.1 (9.9)	-0.78 (0.05) -8.58 (0.55)	0.21(0.08 to 0.34) 2.31 (0.88 to 3.74)	NA	0.3 (non-inferiority not met : p=0.086; thus superiority not tested)

	Liraglutide 1.8 mg OD	408	32	8.15 (0.8) 65.6 (8.8)	-0.99 (0.05) -11 (0.55)			
Dungan et al 2014[13] (AWARD-6)	Dulaglutide 1.5 mg OW	299	26	8.1 (0.8) 65.0 (8.8)	-1.42 (0.05) -16 (0.55)	-0.06 (-0.19 to 0.07) -0.66 (-2.08 to 0.77)	NS	0.4 (non-inferiority met : p<0.001; subsequent superiority not met)
	Liraglutide 1.8 mg OD	300	26	8.1 (0.8) 65.0 (8.8)	-1.36 (0.05) -15 (0.55)			

(*) Extension at 52 weeks confirming results at 26 weeks

Δ : change versus baseline. SE : standard error. OD : once-daily. OW : once-weekly. CI : confidence interval. NA : not available. NS : not significant.

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