What is the next treatment step in people with type 2 diabetes and poor glycaemic control despite optimised basal insulin?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we consider the addition of glucagon-like peptide-1 receptor agonists to insulin therapy.

Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes

Diamant M, Nauck MA, Shaginian R et al (2014) *Diabetes Care* **37**: 2763–73

Diabetes Care

Exenatide plus basal insulin in people with T2D

1 This open-centre, randomised, controlled, non-inferiority study compared twice-daily exenatide with titrated mealtime insulin lispro, both in conjunction with titrated insulin glargine and metformin, in people with T2D and poor glycaemic control despite 12 weeks of optimised treatment.

2 A total of 627 people with a BMI of 25–45 kg/m^2 and an HbA_{1c} of 53–86 mmol/mol (7.0–10.0%) underwent a 12-week basal insulin optimisation phase, followed by a 30-week intervention phase.

3 In the intervention phase, participants were randomised to receive exenatide 12–20 µg/day or mealtime lispro titrated according to self-monitored premeal glucose levels, as well as insulin glargine and metformin.

4 The cohort had a mean age of 59.8 years, a mean HbA_{1c} of 66 mmol/mol (8.2%) and a median diabetes duration of 12 years.

5 The primary outcome, change in HbA_{1c} from baseline, did not differ significantly between the groups, demonstrating the non-inferiority of exenatide.

6 A composite endpoint of weight gain ≤1 kg and HbA_{1c} ≤53 mmol/mol (≤7.0%) was achieved in more exenatide recipients than lispro recipients (44.6% vs 22.9%; $P<0.001$); however, the proportion of participants who achieved an HbA_{1c} of ≤7.0% or ≤6.5% (≤48 mmol/mol) was similar between the groups.

7 Mean weight decreased by approximately 1 kg in the exenatide group, whereas it increased by around the same amount in the lispro group ($P<0.001$).

8 Change in total cholesterol, LDL-cholesterol and triglyceride levels did not differ between the groups; however, HDL levels decreased in the exenatide group (least-squares mean difference −0.07 mmol/L; $P<0.001$).

9 Increased treatment satisfaction was observed in both groups; however, the improvements were greater in the exenatide group.

10 There were more gastrointestinal adverse events but fewer non-nocturnal hypoglycaemic events in the exenatide group.

11 The authors conclude that, in people with T2D who fail to achieve glycaemic control despite optimised basal insulin treatment, the addition of twice-daily exenatide is a valid treatment option.

Martin Hadley-Brown
GP, Thetford

Given the progressive nature of type 2 diabetes and the significant increase in its recorded UK prevalence over the last decade, clinicians are encountering increasing numbers of patients who require relatively complex treatment regimens to achieve target glycaemic control. In many areas, these patients remain under primary care rather than under specialist supervision. Currently there are at least two dilemmas arising from these realities.

Given the choices of agents now available for use once the potential of oral hypoglycaemic agents has been maximised, which approaches make the most sense? How can we optimise the performance of non-specialist practices in making the best choices with their patients and offering them appropriate support?

Given that this study by Diamant et al demonstrates the non-inferiority of exenatide compared to prandial insulin, both added to basal insulin, where does this leave practitioners making choices with their patients? We might wish that clear superiority had been demonstrated one way or the other to ease our choice, but such is not the case.

We must first consider the patients' needs and preferences. For some, the potential to control weight and minimise hypoglycaemia using a glucagon-like peptide-1 (GLP-1) receptor agonist will inform the choice. In many general practices, the facility or expertise to offer guidance

to patients regarding the flexible dosing of prandial insulin is lacking, making the GLP-1 option safer and more straightforward. For other patients, GLP-1-induced nausea will be unacceptable even with the hope of later resolution. It is also a reality that prescribing authorities will closely scrutinise the relative costs of adding GLP-1 agonists rather than prandial insulin to the regimen.

On the horizon lie even more choices. Biosimilar insulins will, if they are to make any impact, need to reduce the cost of prescribing insulin – basal initially but also short-acting insulins in the future. The combination of insulin with a GLP-1 receptor agonist in a single fixed-proportion device will also be on offer from at least two manufacturers imminently.

All this assumes, of course, that the patient commenced basal insulin whilst not using a GLP-1 agent. If cost were not an issue, would that be the best choice, given that most people with advanced type 2 diabetes are significantly overweight? I might argue that, in a majority of cases, a trial of a GLP-1 agent prior to the use of basal insulin would be more logical and probably more popular with patients given that choice.

The trend amongst "guideline algorithms" such as those from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) is now to lay out all available options but not to specify preferences. This contrasts with, for example, the NICE guideline CG87, which laid out "standard treatments," alongside which were presented other options and guidance as to when these might be appropriate. Given that "guidelines" are intended to assist decision making, and that generalists in the community may struggle to keep abreast of the continually changing options for T2D, such guidance may be more useful than the newer algorithms. It remains to be seen whether the updated NICE guideline for type 2 diabetes, expected in 2015, will follow a similar format to its predecessor or mimic the ADA/EASD approach.

For now, though, there are plenty of choices but no single best solution. It remains the case that individually chosen care, backed up by the rapport and support developed between clinician and patient, and built upon the efforts of the patients themselves, is the "best" option. ■

Jiten Vora
Professor of Diabetes, Royal Liverpool University Hospital, Liverpool

It is, of course, well recognised that the prevalence of type 2 diabetes is increasing worldwide. However, it is encouraging that the choice of available therapies, both oral and injectable, is also increasing. Consequently, healthcare professionals are now more able to individualise therapy for people with this condition. A large proportion of individuals will require treatment escalation, initially with increases in the number of oral agents but subsequently with injectable therapies, due to the well-recognised progressive nature of type 2 diabetes with declining beta-cell function.

The study by Diamant et al provides evidence to extend these choices in patients who have already reached a stage where they require basal insulin. More people achieved HbA_{1c} targets, without weight gain, in the group who received additional exenatide compared with those who received additional doses of prandial fast-acting insulin. Thus, whilst exenatide demonstrated non-inferiority in terms of glycaemic parameters, the clinically important composite endpoint of achieving glycaemic control without weight gain was also more likely to be met by those who received this agent. Most importantly, confirmed hypoglycaemia was considerably less frequent in the exenatide group. The three factors of achieving glycaemic targets, absence of weight gain and reduced hypoglycaemia may well explain the improved quality of life reported by those receiving exenatide compared with those receiving prandial insulin.

There is now further choice for people who are currently receiving optimally titrated basal insulin but have not achieved glycaemic targets. As is well recognised, the failure of such people to achieve glycaemic targets may relate more to the lack of control of postprandial glycaemic excursions (Soonthornpun et al, 1999). Diamant et al demonstrated equivalent glycaemic control with exenatide and with prandial insulin. Thus, whilst it may well prove to be the natural choice to add exenatide to basal insulin, the further management of such patients over the long term, particularly those who lose glycaemic control as diabetes progresses, remains to be established.

Glucagon-like peptide-1 (GLP-1) receptor agonists continue to modify treatment algorithms and choices for individual patients. There remains debate as to whether people who fail to achieve glycaemic control on oral hypoglycaemic agents should receive GLP-1 analogues or basal insulin as the next step. This will, of course, depend on individual patients, and particularly their levels of glycaemia and symptoms. However, in those people who have been optimally titrated with basal insulin and achieve appropriate control of fasting plasma glucose but poor HbA_{1c} levels, this study emphasises a further choice of adding a GLP-1 receptor agonist to the treatment regimen. Alternative therapies that could be utilised in this scenario include dipeptidyl peptidase-4 inhibitors and sodium–glucose co-transporter 2 inhibitors. ■

Soonthornpun S, Rattarasarn C, Leelawattana R, Setasuban W (1999) Postprandial plasma glucose: a good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. *Diabetes Res Clin Pract* **46**: 23–7