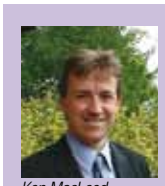
Can insulin glargine achieve target HbA_{1c} as well as insulin lispro?

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of an open, parallel randomised trial comparing the efficacy of two insulins when initiated in people with type 2 diabetes taking oral hypoglycaemic agents.



Ken MacLeod, Consultant Physician, Royal Devon and Exeter NHS Foundation Trust, and Reader in Medicine, Peninsula Medical School

One of the key advantages of this study is that it mirrors clinical practice and thus has considerable face value. It compares the addition of basal insulin glargine once daily to three pre-meal injections of insulin lispro in patients with type 2 diabetes failing to achieve optimal control on oral hypoglycaemic agents (OHAs).

The authors conclude that insulin glargine provides a simple and effective option that is more satisfactory for patients than is insulin lispro for early initiation of insulin. Insulin glargine was found to be associated with a lower risk of hypoglycaemia, fewer injections, less self-monitoring of blood glucose and greater patient satisfaction. Not surprisingly, given the pharmacokinetics, insulin glargine was more effective in lowering mean fasting blood glucose and insulin lispro was better at controlling postprandial glucose excursions.

Insulin glargine's trump card is obviously its long duration of action, boosting insulin levels and giving the compromised beta cells a helping hand. I think many of the advantages in terms of patient satisfaction follow from this once-daily injection. At least some of the increased frequency of mild hypoglycaemia with insulin lispro is, I suspect, a consequence of study design. If we correct for efficacy of glucose lowering (<38% of the insulin lispro group achieved an HbA_{1c} of <6.5% whereas only 30% of those on insulin glargine reached this target) and increased frequency of self-monitoring of blood glucose in the insulin lispro treated group (with consequent increased detection of asymptomatic hypoglycaemia), I suspect much of the difference would disappear. There were no differences in severe hypoglycaemia between the two groups. One of the key advantages of the study design is the intensification of treatment alogorithm which seems to outperform others available and could be directly implemented in practice.

Few could argue with the conclusions of the study: addition of a basal insulin to patients inadequately controlled on oral agents seems the logical next step, and insulin glargine is a reasonable choice. But caution is required. The initial efficacy of insulin glargine or other long-acting insulins should not lead to inappropriate fears about the use of soluble insulin, as with progressive beta-cell failure, it almost certainly will become a necessary, welcome and effective addition. In terms of soluble insulin, insulin lispro also lowers blood glucose, was well tolerated and improved patient satisfaction.

Many questions remain unanswered:

- What are the clinical advantages in achieving an HbA_{1c} <6.5% and do they justify the risks?
- Do the incretins and DPP-IV inhibitors offer additional advantages as third-line agents after metformin and sulphonylureas and before insulin? Or is the choice patient-specific and related to underlying aetiology?
- Would the same benefits be seen with standard isophane insulin and do the 'rehearsed' advantages of insulin glargine over standard NPH insulin, mentioned in the introduction to the paper, justify the additional costs?

As an aside, I also wonder in the interest of equity when a journal such as *The Lancet* agrees to publish a sponsored study reporting to show the superiority of one product over another, whether the manufacturer of the compared product should be offered access to the data and a right of reply.

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Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial

Bretzel RG, Nuber U, Landgraf W et al (2008) *Lancet* **371**: 1073–84

THE LANCET

Basal regimen 'more acceptable' for insulin initiation

1 This parallel, open randomised controlled trial investigated whether glycaemic control would improve more after the addition of once-daily insulin glargine, or after the addition of three-times daily prandial insulin lispro in adults with inadequately controlled type 2 diabetes taking oral hypoglycaemic agents.

2 The trial was undertaken in 69 centres across Europe and Australia for 44 weeks between June 2003 and May 2005.

3 A total of 418 people with diabetes were enrolled. Inclusion criteria were: age between 18 and 75 years; had type 2 diabetes for >1 year with an HbA_{1c} of 7.5%–10.5%; taking oral hypoglycaemic agents for at least

6 months with stable doses for 3 months or more before study entry; fasting blood glucose of ≥6.7mmol/l; BMI of ≤35kg/m^2.

4 Individuals were randomly assigned to one of two groups: insulin glargine taken once-daily at the same time every day (n=205); or insulin lispro taken three times per day immediately before mealtimes (n=210).

5 Mean HbA_{1c} in the insulin glargine group decreased by 1.7% (from 8.7% [SD 1.0] to 7.0% [0.7]) and by 1.9% in the insulin lispro group (from 8.7% [1.0] to 6.8% [0.9]). The difference was within the predefined limit of 0.4 for non-inferiority.

6 In the insulin glargine group 106 people (57%) reached an HbA_{1c} of ≤7% and in the lispro group 131 (69%) reached an HbA_{1c} of ≤7%.

7 Insulin glargine lowered mean fasting blood glucose levels (-4.3 [SD 2.3] mmol/l vs -1.8 [2.3] mmol/l; *P*<0.0001) and nocturnal blood glucose levels (-3.3 [2.8] mmol/l vs -2.6 [2.9] mmol/l; *P*=0.0041) more than insulin lispro.

8 Insulin lispro better controlled postprandial blood glucose throughout the day (*P*<0.0001).

9 There were fewer hypoglycaemic events with insulin glargine than with insulin lispro (*P*<0.0001). Mean weight gain for the insulin glargine and insulin lispro groups were 3.01kg (SD 4.33) and 3.54kg (4.48) respectively.

10 Treatment satisfaction improved more for insulin glargine than insulin lispro (mean difference 3.13; 95%CI 2.04–4.22).

11 The authors conclude that overall glycaemic control with insulin glargine is non-inferior to that with insulin lispro.

12 The authors suggest that insulin glargine provides a more acceptable option to patients intiating insulin therapy than insulin lispro because insulin glargine was associated with a lower risk of hypoglycaemia, fewer injections, less self-monitoring of blood glucose and greater satisfaction.

Simon Heller, Reader in Medicine, University of Sheffield

The initiation of insulin for people with type 2 diabetes evokes strong opinions, yet like many aspects of diabetes care is not necessarily based on much reliable evidence. A few studies have provided clinical guidance but many clinical trials are sponsored by the pharmaceutical industry whose motivation may be influenced by their need to promote a new product rather than provide a totally objective evaluation of the most effective approach.

Two recent studies, the 4T (Holman et al, 2007) and APOLLO, have been published in *The New England Journal of Medicine* and *The Lancet,* respectively, suggesting that the quality of these trials is increasing. Yet, limitations of both studies show that clinicians need to be cautious when incorporating the results into their clinical practice.

The main finding of APOLLO was that both a basal insulin (glargine at bedtime) and pre-prandial fast-acting insulin analogue (lispro) lowered HbA_{1c} by similar amounts, with the basal approach, unsurprisingly, lowering fasting glucose more effectively, and prandial insulin controlling postprandial blood glucose more effectively. Hypoglycaemia was however, much more common in the prandial insulin group. Perhaps this was why treatment satisfaction was greater in the insulin glargine group. But before concluding that basal insulin can control blood glucose more safely, it is important to recognise that the study design mandated the continued use of a sulphonylurea (glimepiride) in both groups. This is a logical choice in those using basal insulin but might well be expected to result in more hypoglycaemia in those taking daytime insulin.

There are good reasons for choosing a basal insulin approach in people with type 2 diabetes, as this and the 4T trials (Holman et al, 2007) show: one injection a day is often more acceptable to the patient, appears to lead to less weight gain and the need for frequent adjustment of dose to lower fasting glucose values involves the patient in active self-management. However, those clinicians who believe that postprandial glucose 'spikes' lead to cardiovascular disease may prefer a prandial insulin regimen.

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The APOLLO study also provides no guidance as to the best insulin to use when initiating basal insulin therapy. The 'Treat to Target' trial indicated that NPH insulin could be used successfully to achieve tight glycaemic control with acceptable levels of symptomatic hypoglycaemia, even when compared to insulin glargine (Riddle et al, 2003).

Neither the 4T nor APOLLO trials have provided definitive proof in favour of any particular approach for new insulin starters in type 2 diabetes, with benefits and drawbacks for all of them. Clinicians still need to weigh the available evidence carefully (recognising the important limitations in study design) when deciding the most appropriate approach for their patients.

Holman RR, Thorne KI, Farmer AJ et al (2007) Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. *New England Journal of Medicine* **357**: 1716–30

Riddle MC, Rosenstock J, Gerich J et al (2003) The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* **26**: 3080–86

'Clinicians still need to weigh the available evidence carefully (recognising the important limitations in study design) when deciding the most appropriate approach for their patients.'

Stephen Gough, Professor of Medicine and Honorary Consultant Physician, University of Birmingham

The addition of basal insulin to oral hypoglycaemic agents in patients with inadequately controlled type 2 diabetes is increasingly used as the first step in insulin initiation. Data from the recently published APOLLO study support the use of insulin glargine in this clinical scenario.

While the messages from the APOLLO study are clear and certainly reinforce the role of insulin glargine in insulin naive patients with type 2 diabetes, it is less clear whether the results are sufficiently novel or persuasive to impact further on current prescribing habits and address the ongoing debate as to which of several insulin initiation regimens should be used in type 2 diabetes and in which specific patient groups. Although the study achieved its primary objective of demonstrating non-inferiority compared to thrice-daily insulin lispro by achieving a similar mean decrease in HbA_{1c}, with a greater degree of patient satisfaction, it was unfortunately not powered to determine whether the increased number of patients achieving an HbA_{1c} <7.0% in those receiving insulin lispro was significant.

The observed differences between insulin glargine and insulin lispro including, for example, the relative changes in fasting and postprandial glucose were as expected. Consequently, although readers might hope that this study will provide further insight into the relative merits of targeting fasting or postprandial glucose, as outlined in the introduction to the paper, they may be disappointed. In addition, while many clinicians observe an initial improvement in HbA_{1c} when a basal insulin is added onto oral hypoglycaemic agents, this effect may be short-lived with further prandial insulin often required after 6 to 12 months. The 44-week duration of the study does not adequately address this issue.

The APOLLO study, therefore, adds to the body of evidence supporting the use of basal insulin in patients with type 2 diabetes, particularly when starting insulin for the first time. We will, however, have to wait for other longer term studies which address the relative roles of basal, prandial and premixed insulins beyond 12 months before we can answer some of the outstanding issues mentioned above. Ultimately, however, it is important that we have a range of insulin therapies that we are able to offer to our patients, in the hope that better-informed patient choice, based on good clinical evidence, allows more of them to achieve an improvement in glycaemic control.

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Roger Gadsby, GP and Associate Clinical Professor, Warwick Medical School, Warwick University

In the APOLLO study 415 people with type 2 diabetes on oral agents were randomised to receive once-daily insulin glargine or thrice-daily insulin lispro. There were robust titration processes to ensure that insulin doses were increased as necessary. Both regimens were equally effective at lowering HbA_{1c}. The insulin glargine group had less hypoglycaemia (5.2 vs 24 events per patient per year), fewer injections, less need for self monitoring of blood glucose and greater satisfaction (as measured using the diabetes treatment satisfaction questionnaire).

This paper adds to the growing literature base regarding which insulin and which insulin regimen is best to use when oral hypoglycaemic agent therapy alone is inadequate to control blood glucose levels in people with type 2 diabetes. It supports the view from the first year of the 4T trial (Holmann et al, 2007) that once-daily long-acting insulin has a similar effect on lowering HbA_{1c} as does 3 prandial injections of short-acting insulin. Similar HbA_{1c} reductions are obtained with lower rates of hypoglycaemia and fewer injections in the once-daily long acting insulin group.

Additionally, the findings add to the debate by looking at patient satisfaction using a validated questionnaire instrument. It is no surprise to read that patient satisfaction is greater with once-daily insulin as that regimen requires fewer injections, less need for self monitoring of blood glucose and less hypoglycaemia.

The data give further support to the concept that for many people with type 2 diabetes who are not adequately controlled on oral agents, the best way of initiating insulin is to use a once-daily long-acting insulin and continue oral agents.

This method of initiating insulin in type 2 diabetes is now being widely used across the UK. It is a method that trained and experienced primary care diabetes staff can initiate and supervise, so reducing the need for people with type 2 diabetes needing to initiate insulin therapy to be referred to hospital.

Holman RR, Thorne KI, Farmer AJ et al (2007) Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. *New England Journal of Medicine* **357**: 1716–30