Type 2 diabetes treatment pathways for patients failing oral therapy

People with type 2 diabetes are traditionally initiated onto oral therapy to improve their glycaemic control. Since the glycaemic benefits of oral antidiabetic agents (OADs) appear to be additive, patients are often prescribed two oral drugs as a combination therapy in an attempt to control their diabetes.

In those patients whose glycaemic control is not sufficiently improved using this approach, healthcare professionals may choose to prescribe a third oral agent or to initiate insulin therapy. Historically, the initiation of a twice-daily premixed insulin regimen, rather than a basal-bolus regimen, has been the preferred approach by healthcare professionals, however, over the last few years it has become increasingly common to add a basal insulin to the existing oral therapy.

The following commentary discusses the evidence behind the options mentioned above.

Adding a third oral agent versus premixed insulin

The evidence base for this approach includes a study by Schwartz et al (2003), which compared the safety, efficacy and cost implications of triple oral therapy versus twice-daily premixed insulin plus metformin in type 2 diabetes patients who showed an inadequate response to two OADs.

The study concluded that the two treatment approaches were as effective as each other (31 % of patients in the triple OAD group achieved an HbA_{1c} target of <7 %, compared with 32 % of patients taking premixed insulin plus metformin; p=0.898), but that triple oral therapy was less cost effective and some patients following this regimen did not complete the treatment due to side effects or a lack of efficacy.

Adding an analogue premixed insulin versus human premixed insulin

A study by Kilo et al (2003) compared the effects of initiating type 2 patients who had failed oral therapy onto a once-daily regimen of either analogue premixed insulin (biphasic insulin aspart 70/30), NPH insulin or human premixed insulin (biphasic human insulin 70/30). One-hundred-and-forty patients took metformin alone over a four week run-in period, followed by a 12-week period of insulin and metformin in combination.

Across the three treatment groups, the researchers found that HbA_{1c} levels were reduced by between 1.1 and 1.3 % from baseline, and that there were no significant differences between HbA_{1c} or fasting plasma glucose (FPG) at any timepoint in the investigation.

The investigators concluded that metformin in combination with either NPH insulin or premixed human or analogue insulin provides an efficient and safe way to begin insulin therapy.

Adding a basal insulin versus switching to premixed insulin

More evidence (Jänka et al, 2004) on the choice of treatment for type 2 diabetes patients failing to respond to two OADs was recently presented at the EASD Annual Meeting in Munich, Germany. The 24-week, multicentre, randomised, parallel-group LAPTOP (**L**antus® + **A**maryl® + metformin versus **P**remixed insulin in patients with **T**ype 2 diabetes mellitus after failing **O**ral treatment **P**athways) study compared the effects of adding once-daily basal insulin glargine (Lantus®) with continued OADs in these poorly controlled patients versus switching them to a traditional twice-daily premixed insulin regimen.

Three-hundred-and-sixty-four insulin-naïve patients with FPG ≥6.7 mmol/L and HbA_{1c} 7.5%–10.5% were included in the trial, which incorporated centres in the UK, Austria, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden and Switzerland.

Patients were randomised to receive once-daily Lantus® while continuing OADs (glimepiride [Amaryl®] or other sulphonylurea plus metformin) versus twice-daily premixed 30 % regular/70 % human NPH insulin monotherapy (OADs discontinued).

Insulin doses were titrated to a target FBP concentration of ≤5.6 mmol/L with Lantus®, or an FBP concentration of ≤5.6 mmol/L and a pre-dinner blood glucose concentration of ≤5.6 mmol/L with premixed insulin therapy. A weekly forced-titration algorithm was used.

Baseline characteristics (mean age, diabetes duration, BMI, HbA_{1c}) were well-matched between the two treatment groups. Mean insulin doses at the study endpoint were 28.2 U daily for the Lantus® plus OADs group and 64.5 U daily for the premixed insulin group.

On an intent-to-treat basis, the Lantus® plus OADs group exhibited a greater reduction in HbA_{1c} compared to the patients taking premixed insulin (-1.64 % from baseline versus -1.30 % respectively; p<0.0003). Furthermore, a greater proportion of patients achieved the target HbA_{1c} concentration of ≤7.0 % without documented nocturnal hypoglycaemia in the Lantus® plus OADs treatment group compared with the premixed insulin group (45 % versus 29 %, respectively; p<0.0013).

In addition, the Lantus® plus OADs treatment group exhibited a greater reduction in FPG compared with the monotherapy group (-3.1 mmol/L from baseline versus -2.2 mmol/L, respectively; p<0.0001).

The patients taking Lantus® plus OADs also exhibited fewer hypoglycaemic incidents compared with those taking premixed insulin (an average of 1.9 total events/patient versus 4.5, respectively; p<0.0001). Finally, the patients taking Lantus® plus OADs also exhibited a trend towards less weight gain compared with those taking premixed insulin (1.4 kg versus 2.1 kg, respectively; p=0.08), although this result was not statistically significant.

The investigators concluded that adding once-daily Lantus® to established OAD treatment offers greater glycaemic control with less risk of nocturnal hypoglycaemia compared with the usual practice of initiating a twice-daily premixed insulin regimen and discontinuing OADs in type 2 diabetes patients whose condition remains poorly controlled on oral therapy.

Conclusion

From the evidence presented above it is clear that there are a number of different approaches available for treating type 2 diabetes patients whose glycaemic control remains poor on two OADs. Healthcare professionals can therefore choose the approach they feel is best for particular patients.

Janka HU, Plewe G, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H (2004) Starting insulin for type 2 diabetes with insulin glargine added to oral agents versus twice-daily premixed insulin alone. *Diabetologia* **47**: [Suppl 1]: A269-70, Poster abstract 744

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Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P (2003) Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. *Diabetes Care* **26**(8): 2238-43