INTENSIFICATION AFTER BASAL INSULIN IN TYPE 2 DIABETES

Introduction

“It is vital to advise the type 2 diabetic patient from the outset of the progressive nature of this condition, which will over time require insulin therapy and intensification of therapy,” Professor Martin Pfahl, chief physician at Bethesda Hospital, Duisburg, pointed out at the start of his presentation to delegates attending the Sanofi-sponsored Intensification Summit held in Cape Town recently.

Lowering HbA₁c in type 2 diabetes reduces the relative risk of complications (Figure 1). While the current focus of diabetic discussion is the reduction of macrovascular disease, over the longer term the consequences of microvascular disease, such as nephropathy, are debilitating. “Currently, two-thirds of our renal dialysis patients in Germany are type 2 diabetes patients with disease of longstanding duration – in fact, achieving and maintaining glucose control in type 2 diabetes over 20-30 years is much more challenging than glucose control in type 1 diabetes.”

KEY MESSAGES

• Type 2 diabetes is a progressive disease that requires insulin intensification after several years of evolution of the condition

• The dose of basal insulin should be titrated for maximum efficacy before prandial insulin is introduced

• If, despite adequate titration, the patient is still not at target, addition of one dose of postprandial insulin at the main meal should be considered

• ‘Basal plus’, i.e. glargine once daily with glulisine once daily, demonstrates combined efficacy and safety

• As the disease progresses, a second injection of prandial insulin at the second main meal can be considered

• For patients with advanced type 2 diabetes who are still not at target, a basal bolus regimen should be considered

• Basal bolus has superior efficacy to premixed insulin regimens.
Efficacy of basal insulin as intensification therapy

It is important to note that each individual patient has his own insulin need. A number of pivotal trials of basal insulin analogues, conducted more than 10 years ago, have shown the glucose-lowering effectiveness of these insulins when titration is optimised to deliver a fasting blood glucose (FBG) below 6mmol/l.\(^{2-4}\) A variety of algorithms of intensification of basal insulin was used in these studies to reach an HbA\(_{1c}\) <7%, which was achieved in the majority of patients (Table 1). While the insulin dosages of glargine in randomised clinical trials were quite high, a recent ‘real-world’ study showed that these can be much lower in everyday practice. This multicentre study of more than 50 000 patients from the German/Austrian DPV-wiss database showed that a mean daily basal insulin glargine dose of 0.29IU/kg achieved HbA\(_{1c}\) levels around 7%.\(^{5}\) Lower daily insulin dosages in modern therapy are also as a result of continued concomitant therapy with metformin, DPP-4 inhibitors and GLP-1 receptor agonists.

One of the first real-world studies with global input, involving patients from three continents, including some from South Africa, produced some interesting insights into how insulin therapy has evolved in clinical practice. This global study was of physician-selected therapy and was not randomised. The reduction in HbA\(_{1c}\) on insulin therapy was similar over the four years, regardless of whether patients were given basal, basal plus mealtime insulin, mealtime insulin or premixed insulin alone.\(^{6}\) (HbA\(_{1c}\) dropped by about 2%.) Basal insulin alone resulted in less hypoglycaemia over three years of treatment than other regimens and persistence rates with insulin glargine were higher than with NPH or insulin detemir.\(^{7}\) It’s important to note that achieving a mean HbA\(_{1c}\) of 7% still means that approximately 50% of patients will be above target and will require intensification of insulin therapy with either a mealtime insulin added or a switch to premixed insulin.

**Table 1. Maximum insulin glargine efficacy is obtained following optimised titration**

<table>
<thead>
<tr>
<th>Studies based upon commonly used glargine treatment algorithms</th>
<th>Treat-To-Target(^{2})</th>
<th>LANMET(^{3})</th>
<th>INSIGHT(^{4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target FBG</td>
<td>≤5.6mmol/l</td>
<td>≤5.6mmol/l</td>
<td>≤5.6mmol/l</td>
</tr>
<tr>
<td>Algorithm</td>
<td>+2 to +8 IU every week</td>
<td>+2 IU or +4 IU every three days</td>
<td>+1 IU every day</td>
</tr>
<tr>
<td>HbA(_{1c}), reached</td>
<td>6.96</td>
<td>7.14</td>
<td>7.0</td>
</tr>
<tr>
<td>Final insulin glargine dose (IU)</td>
<td>47</td>
<td>68</td>
<td>38</td>
</tr>
</tbody>
</table>

**Figure 1. Lowering HbA\(_{1c}\) reduces the relative risk of complications**
Insulin intensification

In the face of progressive deterioration of β-cell function, the ‘basal plus’ approach is suitable for patients whose HbA1c control has slipped to between 7% and 9%, despite optimal titration of the basal insulin, and whose FBG is controlled close to, or at target of, 6mmol/l (Figure 2). The excess hyperglycaemia in these patients is largely due to postprandial hyperglycaemia.

Cultural and personal lifestyles are different and the clinician should assess the patient’s mealtime routine and add prandial insulin at the main meal. If this is not possible, select breakfast as a target of postprandial control. Tips for the introduction of basal plus are summarised in Table 2.

The effectiveness of the basal plus approach in patients on insulin glargine, with a regular lifestyle and the introduction of insulin glulisine at either breakfast or the main meal, was seen in the OPAL study. Thirty-three percent of patients in this study reached a strict target HbA1c of less than 6.5%, although initial HbA1c levels were not greatly elevated (a mean of 7.3%).

An interesting study of basal plus control with insulin glargine plus glulisine, the ELEONOR trial, evaluated a ‘telecare’ support approach compared to standard patient blood glucose monitoring and failed to show any benefit of a more intensive ‘at-a-distance’ approach. “I am a great believer in the self-awareness and self-responsibility of patients to monitor and control their glucose levels after appropriate education,” Professor Pfohl noted.

In this study more than 50% of patients achieved an HbA1c ≤7% with standard blood glucose monitoring.
Transitioning from basal plus to basal bolus

It is important to note that early in an individual’s progression of type 2 diabetes (first 10 years), the stepwise addition of prandial insulin glulisine is an effective transition to the full basal bolus regimen frequently required in late-stage type 2 diabetes (20-30 years’ duration).

In this early stage, the 1.2.3 study11 and the AT.LANTUS study12 showed that the addition of a third prandial insulin injection achieved very little further benefit in HbA1c reduction, as compared to two prandial injections (Figure 3) over a six-month period. In advanced type 2 diabetes, the basal bolus regimen is the most physiological insulin regimen. “These patients with advanced type 2 diabetes are becoming fragile; they have frequently had at least one or two late diabetic complications and therefore the HbA1c target range should be between 7% and 8.5% to reduce the risk of hypoglycaemia.” Patients in this category of advanced disease require more precise basal bolus approaches. However, the prescribed prandial insulin dosage should not seek to cover the glucose excursion of the whole meal, but aim to cover about 70-80% of the postprandial blood glucose in order to limit the risk of hypoglycaemia.

![Figure 3. The 1.2.3 study](image)

*Stepwise addition of insulin glulisine to insulin glargine improves glycaemic control over 24 weeks*

- **Insulin glargine + OHAs + insulin glulisine ×1 (n = 64)**
- **Insulin glargine + OHAs + insulin glulisine ×2 (n = 68)**
- **Insulin glargine + OHAs + prandial insulin ×3 (n = 68)**

*HbA1c (%)*

-0.08
-0.06
-0.04
-0.02
0

-0.46
-0.48
0.58

*p < 0.001 from baseline to endpoint (week 24)*

1Per protocol population
The role of premixed insulin in intensification strategies

Premixed insulin also provides an effective strategy for both insulin initiation and intensification. The use of premixed insulin in intensification strategies does, however, suffer from poor flexibility with an increased risk of hypoglycaemia when planned meal times are not adhered to.

A recent open-label multicentre trial of patients with inadequately controlled type 2 diabetes (HbA1c 7.5-11%) on premixed insulins requiring intensification were randomised to insulin glargine and three daily doses of insulin glulisine (basal bolus) or twice-daily premixed insulin.13 “These intensification regimens achieved similar glucose control and the difference was not very significant,” Professor Pfohl noted. “Symptomatic hypoglycaemia was, however, lower on the basal bolus regimen. The choice of which of these regimens is most suitable rests with the individual patient and the clinician.

Switching from a premix-based insulin regimen to basal bolus

The effect of switching from premixed insulin to basal bolus has been evaluated in the everyday clinical situation in primary care in the United Kingdom.15 The HbA1c of these patients was above 9% at the switch and after one year of insulin glargine and postprandial insulin glulisine, in the patients whose HbA1c was above 10%, a reduction of 1.2% had been achieved with little change in body weight.

A real-life clinical study in the USA looked at the efficacy and cost-effectiveness of the basal bolus approach relative to that of premixed insulin in type 2 diabetes patients requiring intensification therapy.16 While the basal bolus approach resulted in better HbA1c reduction, there was little difference in hypoglycaemia in these patients who were not too strictly controlled (i.e. who achieved an HbA1c between 7% and 8%).

“It is important for the clinician to accept that insulin regimens can be switched and that this does not imply initial poor clinical judgement, but rather that patients’ needs change over time,” Professor Pfohl concluded.
TYPE 2 DIABETES

References


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