NEW SIT2MIX TRIAL PROVIDES FIRST GLOBAL EVIDENCE

An important trial using a premix insulin (BIAsp 30) as the initial insulin in type 2 diabetes patients uncontrolled on oral agents provides evidence on the use of this type of insulin with (or without) a DPP-4 inhibitor.

Dr Duma Khutsoane, specialist endocrinologist at Bloemfontein Medi-Clinic, provides clinical insight and interprets the results of this trial for application in everyday practice in South Africa.

KEY MESSAGES

- In selected type 2 diabetes patients, biphasic insulin aspart 30 (BIAsp 30) can be safely combined with DPP-4 inhibitors and metformin to lower blood glucose levels.
- This combination offers benefits for patients who can accommodate a daily routine of at least two main meals and are willing to administer injections subcutaneously.
- Using either once- or twice-daily BIAsp 30 with a DPP-4 inhibitor and metformin allows more patients to reach target HbA1c levels (<7%) without hypoglycaemic events.
- These findings are relevant and important for type 2 diabetes patients for whom pre-mix insulin has been selected by the clinician as the starting insulin of choice.
- The addition of these evidence-supported regimens as intensification therapy adds to the clinician’s armamentarium when considering different approaches for individual patients. The three regimens (BIAsp 30 BID + sitagliptin, BIAsp 30 QD + sitagliptin, BIAsp 30 BID replacing sitagliptin) are not burdensome; neither are compliance and convenience compromised.
- This trial provides, for the first time, clear evidence that the combination of BIAsp 30 + sitagliptin is efficacious and well tolerated.

The Sit2Mix trial

This trial was conducted over six months in centres in Europe, Asia, South America and Australia, reflecting a bias towards middle-income countries and emerging economies (India, Brazil). Sit2Mix included a relatively homogenous population at baseline and investigated three distinct intensification regimens in patients with type 2 diabetes not controlled on sitagliptin and metformin in combination with other oral antidiabetic drugs (OADs).

Adult type 2 diabetes patients were eligible for inclusion if they had been diagnosed more than six months prior to the study, their HbA1c was between 7-10%, BMI was ≤40 kg/m² and they were insulin-naïve. All OADs, except for metformin (at least a dosage of 1000mg daily), were discontinued after randomisation. Patients were included in the study if they had been on sitagliptin (100 mg daily) prior to the study and were stratified accordingly. Patients who had used thiazolidinediones or GLP-1 agonists in the previous three months were excluded. The presence of cardiac disease, severe hypertension (>180/>100mmHg) and/or...
impaired hepatic and renal function (<60 ml/min) also resulted in exclusion from the study.

Five hundred and eighty-two patients were included in the randomised, open-label, three-arm parallel study of BIAsp 30 BID + sitagliptin (100 mg/day), BIAsp 30 QD (once daily) + sitagliptin and BIAsp BID. Patients included were willing to administer subcutaneous injections and were in the routine of at least two main meals per day and were able to perform self-measured plasma glucose (SMPG) readings seven times daily over the period.

Patients participating in the study had a mean age in the mid-50s, BMI was 30 kg/m² and numbers of men and women were equal, except for the BIAsp BID arm which had slightly more men. The baseline mean HbA1c level was 8.4%. Seventy percent of patients were receiving OADs before the study; 3-6% of patients at baseline experienced nephropathy; 10-13% neuropathy; 7-9% retinopathy and 1.5-6% macro-angiopathy. At baseline, the starting dose of the BIAsp 30 was 6 U pre-breakfast and 6 U pre-dinner in the BID arm, and 12 U pre-dinner in the QD group. Dosages were up-titrated based on SMPG and according to the study guidelines.

The primary endpoint was change in HbA1c from baseline after 24 weeks of treatment. Secondary efficacy endpoints included the percentage of patients achieving target HbA1c ≤7% and the proportion reaching target without hypoglycaemia (symptoms at plasma glucose levels of ≤3.9mmol/l or any single plasma glucose value <3.1mmol/l in the last three months of treatment). Safety endpoints were assessed and included change in body weight, hypoglycaemia, haematology and biochemistry measurements.

Results

All three intensification regimens (for patients poorly controlled on sitagliptin and metformin in combination with other OADs) were efficacious and well tolerated. The attributes of the three regimens are summarised in Table 1.

Efficacy

The major outcomes in terms of efficacy are:

• The HbA1c reduction (primary endpoint) was statistically superior with BIAsp BID + sitagliptin (Figure 1).
• The fasting plasma glucose reduction was comparable across all treatment arms.
• The odds of reaching an HbA1c <7% were significantly higher with BIAsp BID + sitagliptin as compared to the BIAsp BID regimen, but the BIAsp QD + sitagliptin was not statistically different from the two BIAsp BID regimens.
• The odds of reaching target without hypoglycaemia were significantly higher with BIAsp BID + sitagliptin versus BIAsp BID, but were not significantly different versus BIAsp QD + sitagliptin.

<table>
<thead>
<tr>
<th>Table 1. Profiles of three regimens in terms of benefits and risks</th>
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<tr>
<td>Factor</td>
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<tr>
<td>HbA1c reduction</td>
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<tr>
<td>HbA1c ≤7%</td>
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<tr>
<td>% reaching HbA1c target without hypoglycaemia</td>
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<tr>
<td>Rate of Minor Hypoglycaemia*</td>
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<tr>
<td>Weight gain (kg)</td>
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<td>Costs</td>
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<td>Adverse events</td>
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Footnote:
*Too few severe events to evaluate.
+, ++, +++ – the use of positive signs is illustrative.
**Odds favour BIAsp QD + sitagliptin to reach a target of HbA1c <7% when compared to two BIAsp BID regimens.
PREMIX INSULIN AND DPP-4 INHIBITORS

Safety outcomes

Hypoglycaemia

Overall, hypoglycaemic episodes were 1.17, 1.50 and 2.24 episodes/patient year in the BIAsp QD + sitagliptin, BIAsp BID + sitagliptin and BIAsp BID groups, respectively.

Similar studies in insulin-naïve patients with type 2 diabetes using a basal insulin (either insulin glargine or insulin detemir) in combination with sitagliptin are available. The patients’ experience of hypoglycaemia is summarised in Table 2.

Changes in body weight, insulin dose and treatment satisfaction

Weight gain occurred with the BIAsp BID regimens but not in the BIAsp QD + sitagliptin arm.

Final total daily dose was 0.66 U/kg, 0.72 U/kg and 0.39 U/kg in the BIAsp BID + sitagliptin, BIAsp BID and BIAsp QD + sitagliptin arms, respectively.

There were no differences in satisfaction scores among the treatment groups.

Discussion and conclusion

Type 2 diabetes mellitus is a progressive disease with continuous decline in β-cell insulin secretory capacity. Ultimately all type 2 diabetes patients will require insulin therapy, as oral treatment will fail at some point in the treatment continuum - this was clearly demonstrated in the UKPDS studies and recently in the ADOPT study.

In the modern era of treatment individualisation this trial provides evidence that, intensification with BIAsp 30 in patients with type 2 diabetes inadequately controlled with sitagliptin and metformin was shown to be efficacious and well tolerated using three distinct intensification regimens, clearly demonstrating the benefits of combining BIAsp 30 BID + sitagliptin with low risk of hypoglycaemic episodes.

Clinicians need to balance risks, costs and benefits of different treatment...
approaches when choosing a suitable treatment plan for patients with diabetes. Moreover, to optimise outcomes when choosing an antihyperglycaemic strategy, individual circumstances should be considered, i.e. age, comorbidities, baseline HbA1c, and ability to adhere to complex regimens. This study will help clinicians in a simple practical way to initiate insulin in those poorly controlled on sitagliptin and metformin without compromising their patients’ quality of care.

References