PRACTICAL CLINICAL GUIDE: ADDING GLP-1 RAs TO INTENSIFY TYPE 2 DIABETES THERAPY

Patient selection guided by SEMDSA Guidelines and international approaches

Introduction

The availability of Glucagon-Like Protein-1 Receptor Agonists (GLP-1 RAs) presents new therapeutic options for clinicians and patients with type 2 diabetes. These agents, of which currently only exenatide and liraglutide are available to the South African clinician, offer glycaemic efficacy without the unwanted effects of hypoglycaemia and weight gain. Available since late 2005, increasing evidence of weight loss, blood pressure-lowering and cardiovascular benefits has resulted in careful evaluation of how to incorporate this relatively expensive, but effective therapy into daily clinical practice.

The Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) 2017 type 2 diabetes Guidelines have proposed particular categories of patients for whom GLP-1 RAs offer substantial advantages.1 Recent international reviews2,3 have also collated evidence from clinical trials and suggested patient groups that would benefit from GLP-1 RAs added to basal insulin, as well as their addition to oral therapies.

This report concentrates on the evidence for the use of GLP-1 RAs to intensify therapy in selected patients already on basal insulin therapy using BIT (BIT = basal insulin combined with GLP-1 RA); and contrasts this approach with basal insulin plus oral therapy and insulin aspart (referred to as ‘Basal and Oral Therapy plus’, BOTPlus),3 in the context of South African guidelines.

KEY MESSAGES

- GLP-1 RAs offer glycaemic efficacy without hypoglycaemia or weight gain
- Clinical consensus is emerging on practical usage of these anti-hyperglycaemic therapies and optimisation of their additional non-glycaemic benefits in selected patients.
Pathophysiological background

GLP-1 RAs are able to enhance or normalise the so-called ‘incretin effect’ in relation to a meal-induced glucose transfer from the intestine to the blood in type 2 diabetes. This is done by activating the GLP-1 receptor on β-cells. In addition, the GLP-1 RAs delay gastric emptying, enhance satiety related to gastric and cerebral signals, as well as suppress glucagon and its effects on gluconeogenesis.1

Liraglutide has a moderate effect on gastric emptying during the early phase of a breakfast meal, but most of its prandial glucose-lowering effect is related to enhanced insulin secretion.4 Its glucagon suppression does contribute to the post-prandial glucose lowering effect.5

In a randomised clinical trial comparing liraglutide with exenatide twice daily, liraglutide was superior with regard to number of patients reaching target HbA₁c (<7%) and its effect on fasting blood glucose, while exenatide was more effective after breakfast and dinner.6

A comparison of available GLP-1 RAs is provided in Table 11 (Extended release exenatide is not available in South Africa).

Table 1: Comparison of available GLP-receptor agonists*

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist:</th>
<th>Exenatide</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid sequence similarity to native GLP-1</td>
<td>53%</td>
<td>97%</td>
</tr>
<tr>
<td>Half-life (t½)</td>
<td>2.5 hrs</td>
<td>11-15 hrs</td>
</tr>
<tr>
<td>Starting dose</td>
<td>5μg BD for 4 weeks</td>
<td>0.6mg OD for 1 week</td>
</tr>
<tr>
<td>Usual dose</td>
<td>10μg BD</td>
<td>1.2mg OD Max dose 1.8mg OD</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Timing of dose</td>
<td>Within 60 min before morning and evening meal; not after a meal</td>
<td>Any time of the day</td>
</tr>
<tr>
<td>HbA₁c, reduction (%)</td>
<td>~ 0.8%</td>
<td>1.2mg: 0.8% 1.8mg: 1.1-1.3%</td>
</tr>
<tr>
<td>Weight reduction (kg)</td>
<td>1.1-2.9kg</td>
<td>2.1-2.6kg</td>
</tr>
<tr>
<td>Non-responders (no weight loss)</td>
<td>~ 25%</td>
<td>~ 25%</td>
</tr>
<tr>
<td>Renal dose</td>
<td>Do not use if eGFR &lt;30ml/min</td>
<td>No dose adjustment required**</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diarrhoea (%)</td>
<td>12.1</td>
<td>12.3</td>
</tr>
<tr>
<td>• Nausea (%)</td>
<td>28.0</td>
<td>25.5</td>
</tr>
<tr>
<td>• Vomiting (%)</td>
<td>9.9</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Extracted from JEMDSA 2017; 22(1): Appendix 9.5: Drug review – GLP-1 receptor agonists
**Post-marketing reports of acute kidney injury in patients with pre-existing kidney disease. Use with caution in patients with chronic kidney disease.
Practical approach to the use of GLP-1 RAs

A useful clinical diagram (Figure 1) aids the discussion of the use of GLP-1 RAs for particular type 2 diabetes patients. This diagram is discussed in the context of the SEMDSA recommendations in each category (Table 2).

**Table 2: SEMDSA recommendations**

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Dual therapy</td>
<td>In established cardiovascular disease as an alternative option (not as routine use)</td>
</tr>
<tr>
<td>3</td>
<td>Triple therapy</td>
<td>In selected (obese and hypoglycaemia-prone) patients, as a third glucose lowering drug</td>
</tr>
<tr>
<td></td>
<td>Complex therapy</td>
<td>As a preferred option with either basal insulin or oral agents</td>
</tr>
</tbody>
</table>

Figure 1: BOTPlus (Basal, Oral Therapy + Aspart) vs. BIT (Basal + Incretin Therapy) – A clinical decision guide

Amended from: Scholz GH and Fleischmann H. Basal insulin combined incretin mimetic therapy with glucagon-like protein 1 receptor agonists: a practical guide to decision making. Ther Adv Endocrinol Metab 2014; 5(5) 95-123.
Patient groups

In obesity or intended weight loss

GLP-1 RAs are particularly useful in type 2 diabetes-related obesity with visceral fat accumulation and non-alcoholic fatty liver disease (NAFLD) because of this phenotype’s association with insulin resistance, accelerated gluconeogenesis, hypertension, inflammation and risk for cardiovascular events.\(^7\)

In a recent review of 21 trials using GLP-1 RAs,\(^8\) GLP-1 RAs were associated with greater weight loss than control groups (weighted mean difference -2.9kg, 95% confidence interval -3.6 to -2.2kg).

A study of insulin-naïve, obese type 2 diabetes patients uncontrolled on metformin ± sulphonylurea, treated with liraglutide 1.8mg for 12 weeks and then randomised to add-on insulin detemir to achieve a year’s treatment and compared to the non-insulin detemir control group, is important for obese type 2 diabetes patients.\(^9\) The 3.5kg mean weight loss achieved with 12 weeks of GLP-1 RA added to therapy was maintained at 52 weeks of added insulin detemir therapy. Hypoglycaemic events were very low (0.23 minor events/patient year, no major events). Glycaemic control was improved from 8.3% to 7.6% in the GLP-1 RA added group.

Patients at high risk of hypoglycaemia

Many patients have conditions that increase the risk of hypoglycaemia, including renal failure, autonomic neuropathy, adrenocortical insufficiency and mental disorders such as depression, anxiety, dementia or affective disorders.

Hypoglycaemia, including silent hypoglycaemic episodes, is associated with increased cardiovascular morbidity and mortality. Severe hypoglycaemia is a strong predictor of cardiovascular morbidity and mortality and should be avoided – this is particularly pertinent in those with pre-existing cardiovascular disease.\(^10\)

According to their mode of action, GLP-1 RAs do not enhance the risk of hypoglycaemia and are particularly useful in these patients.

The question of whether to use intensification with a short-acting insulin as BOTPlus therapy or using BIT therapy was addressed by a recent study of 177 type 2 diabetes patients requiring intensification of basal insulin therapy (Liraglutide add-on study)\(^11\) (Figure 2).

The rate of hypoglycaemia was 8.15 episodes per patient year of exposure on BOTPlus and 1.0 episodes on BIT therapy respectively. Hypoglycaemia was significantly lower by 87% in the insulin degludec plus liraglutide group with an estimated risk ratio of 0.13 (95%CI 0.08-0.21), as compared to insulin degludec plus a single daily dose of insulin aspart. Also, nocturnal hypoglycaemia was 86% lower with the addition of a GLP-1 RA as compared to the addition of insulin aspart.

There was significantly greater weight loss (-2.8kg) in the BIT group versus a gain of 0.9kg in the BOTPlus therapy group. The HbA1c reduction was also significantly better with the BIT (-0.74%) as compared to the insulin aspart group (minus 0.39%).

This efficacy favours the use of liraglutide in patients who are obese with a certain higher risk of hypoglycaemia, or in patients who have to avoid hypoglycaemic episodes because of pre-existing cardiovascular disease or professional circumstances.
Aged patients

The age-related risk of increased hypoglycaemia with added-insulin therapy must be considered, especially in patients older than 80 years, as visits to the emergency department frequently lead to hospitalisation in the older patient (>64 years of age). There are however no data on the benefit of BIT therapy in the age group older than 80 years, but clinical usage studies have shown a preference for this approach in the ‘young old’ (65-79 year group).

Because of the higher associated risk with the use of short-acting insulin added to basal insulin, the older age group should enjoy the benefit of the GLP-1 RAs, but special attention must be paid to gastrointestinal side-effects, renal effects and comorbidity-related unintended weight loss.

Patients with micro- and macrovascular disease

Vascular disease such as acute coronary syndromes (ACSs) frequently predicates diabetes diagnosis. The presence of established cardiovascular disease influences the choice of anti-hyperglycaemia strategies because of safety and the need for further protection.

Accumulating evidence of GLP-1 RAs’ cardiovascular benefits favours their use in those patients with micro- and macrovascular disease.

Figure 2: Comparison of the addition of a GLP-1 RA compared to insulin aspart
Caution in renal and hepatic failure

Renal failure must be taken into account because of the reduced degradation of insulin and the associated risk of hypoglycaemia, which is dependent on renal function. Insulin is, however, indicated in renal failure when other antidiabetic medications fail or are contra-indicated.

In the case of renal or hepatic failure, BOTPlus is the preferred option, rather than the use of liraglutide. It should be noted that liraglutide should not be used at creatinine clearance (CrCl) of <60ml/min.

Caution in pancreatic and gastrointestinal dysfunction

There is no restriction in the use of insulin and BOTPlus in patients with pancreatic or gastrointestinal dysfunction. Nevertheless, in the former, a reduced glucagon response and changes in digestion have to be considered; and in the latter, an unpredictable resorption of nutrients.

Although safety concerns are now largely diminished, GLP-1 RAs alone or in BIT are not recommended for use in patients with previous or current dysfunctions of the pancreas, stomach and gut.

References: