Practical Considerations in Using Basal Insulin–GLP-1 RA Combination

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Practical Considerations in Using Basal Insulin–GLP-1 RA Combination Therapy

- Rationale for fixed-dose combination therapy
- Which patients are eligible for fixed-dose combination therapy?
- Administering IDegLira
- Summary

GLP-1 RA, glucagon-like peptide 1 receptor agonist; IDegLira; a fixed-ratio combination of basal insulin degludec and the GLP-1 RA liraglutide.
Rationale for Combining Basal Insulin With a GLP-1 RA

• Basal insulin helps control fasting glucose, but has limited effects on postprandial hyperglycaemia¹

• GLP-1 RAs have a complementary mechanism of action to basal insulin and decrease postprandial glucose excursions by:¹
  – inhibiting glucagon secretion
  – suppressing appetite
  – delaying gastric emptying

• Combining basal insulin and a GLP-1 RA may offer a safe and effective alternative to basal–bolus insulin²

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## Characteristics of Basal Insulin, GLP-1 RAs, and Combination Basal Insulin–GLP-1 RA

<table>
<thead>
<tr>
<th></th>
<th>Basal insulin</th>
<th>GLP-1 RA</th>
<th>Basal insulin–GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta cell</strong></td>
<td>Rests beta-cells, relieves glucotoxicity</td>
<td>Improves beta-cell function</td>
<td>Additive improvement in prandial insulin</td>
</tr>
<tr>
<td><strong>Alpha cell</strong></td>
<td>–</td>
<td>Reduced glucagon secretion</td>
<td>GLP-1 RA alternative to prandial insulin</td>
</tr>
<tr>
<td><strong>Glucose control</strong></td>
<td>Reduces FPG</td>
<td>Reduces PPG and FPG</td>
<td>Maximum HbA1c reduction</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Weight gain</td>
<td>Weight loss</td>
<td>Weight gain minimized or avoided</td>
</tr>
<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>High risk</td>
<td>Low risk</td>
<td>Decreased risk vs basal–bolus insulin</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; HbA1c, glycated haemoglobin A1c; PPG, postprandial glucose.

Fixed-Dose Combination of Basal Insulin–GLP-1 RA

• Clinical trials have confirmed the safety and efficacy of:
  – basal insulin plus short-acting GLP-1 RAs\textsuperscript{1,2}
  – basal insulin plus long-acting GLP-1 RAs\textsuperscript{3}

• Fixed-dose combinations provide basal insulin and a GLP-1 RA in a single injection:
  – IDeg + Lira (IDegLira)\textsuperscript{4}
  – IGlar + Lixi (LixiLan)\textsuperscript{5}

5. Rosenstock J, et al. ADA. 2014;A87:abstract 332-OR.

IDeg, insulin degludec; IGlar, insulin glargine; Lira, liraglutide; Lixi, lixisenatide.
Basal Insulin–GLP-1 RA Combination Therapies

IDegLira\(^1\)
- Fixed-ratio combination delivered once daily in 1 pen\(^1\)
- 1 dose step = 1 U IDeg and 0.036 mg Lira
- Maximum dose 50 U IDeg and 1.8 mg Lira
- Approved in Europe (UK, Germany, Switzerland)

_long-acting GLP-1 RA Lira_

LixiLan\(^2\)
- Fixed-ratio combination delivered once daily in 1 pen\(^2\)
- Maximum dose 60 U IGlar and 30 μg Lixi\(^2\)

Basal IGlar + Short-acting GLP-1 RA Lixi

2. Wilding JPH, Bain SC. Diabet Med. 2015 Dec 8 [Epub ahead of print].
## Basal Insulin–GLP-1 RA Combination Therapies

### Published clinical studies: trial designs

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL I(^1,2)</td>
<td>3</td>
<td>IDegLira vs IDeg vs Lira, all with Met ± Pio</td>
<td>26 + 26-week extension(^2) (total: 52 weeks)</td>
</tr>
<tr>
<td>DUAL II(^3)</td>
<td>3</td>
<td>IDegLira + Met vs IDeg + Met</td>
<td>26</td>
</tr>
<tr>
<td>DUAL V(^4)</td>
<td>3</td>
<td>IDegLira + Met vs IGlar + Met</td>
<td>26</td>
</tr>
<tr>
<td>LixiLan(^5)</td>
<td>2</td>
<td>Once-daily LixiLan vs IGlar</td>
<td>24</td>
</tr>
</tbody>
</table>

Met, metformin; Pio, pioglitazone.

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Basal Insulin–GLP-1 RA Combination Therapies

Published clinical studies: patient populations

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Eligible patients were...</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL I</td>
<td>1,663 (1,311 for extension)</td>
<td>Insulin-naive, not adequately controlled with Met ± Pio</td>
</tr>
<tr>
<td>DUAL II</td>
<td>413</td>
<td>Not adequately controlled with basal insulin (20–40 U) and Met ± SU/glinides</td>
</tr>
<tr>
<td>DUAL V</td>
<td>557</td>
<td>Not adequately controlled with IGlar (20–50 U) and Met</td>
</tr>
<tr>
<td>LixiLan</td>
<td>323</td>
<td>Insulin-naive, not adequately controlled with Met</td>
</tr>
</tbody>
</table>

SU, sulfonylurea.

Basal Insulin and GLP-1 RA Combination Therapy: Reduction in HbA1c and Target Achievement

Patients achieving HbA1c < 7.0% (%)

DUAL I\(^1,2\)  
- HbA1c change from baseline (%)
  - IDegLira: -1.8
  - IDeg: -1.4
  - Lira: -1.2

DUAL II\(^3\)
- HbA1c change from baseline (%)
  - IDegLira: -1.9
  - IDeg: -0.9
  - Lira: -1.2

DUAL V\(^4\)
- HbA1c change from baseline (%)
  - IDegLira: -1.8
  - IDeg: -1.1
  - Lira: -1.8

LixiLan\(^5\)
- HbA1c change from baseline (%)
  - IDegLira: -1.6
  - IDeg: -1.8

References:
### Basal Insulin–GLP-1 RA Combination Therapy: Insulin Dose, Hypoglycaemia, and Weight Gain

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>End-of-trial basal insulin dose, U</th>
<th>Reduction in the risk of hypoglycaemia</th>
<th>Change in body weight from baseline, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL I(^1,^2)</td>
<td>IDegLira</td>
<td>39</td>
<td>37% vs IDeg*</td>
<td>– 0.5</td>
</tr>
<tr>
<td></td>
<td>IDeg</td>
<td>62</td>
<td>–</td>
<td>+ 1.6</td>
</tr>
<tr>
<td></td>
<td>Lira</td>
<td>–</td>
<td>–</td>
<td>– 3.0</td>
</tr>
<tr>
<td>DUAL II(^3)</td>
<td>IDegLira</td>
<td>45</td>
<td>34% vs IDeg</td>
<td>– 2.7</td>
</tr>
<tr>
<td></td>
<td>IDeg</td>
<td>45</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>DUAL V(^4)</td>
<td>IDegLira</td>
<td>41</td>
<td>57% vs IGlar*</td>
<td>– 1.4</td>
</tr>
<tr>
<td></td>
<td>IGlar</td>
<td>66</td>
<td>–</td>
<td>+ 1.8</td>
</tr>
<tr>
<td>LixiLan(^5)</td>
<td>LixiLan</td>
<td>NR</td>
<td>Similar to IGlar (22% vs 23%)</td>
<td>– 1.0</td>
</tr>
<tr>
<td></td>
<td>IGlar</td>
<td>NR</td>
<td>–</td>
<td>+ 0.5</td>
</tr>
</tbody>
</table>

\(^*\)p < 0.01
NR, not reported.

Basal Insulin–GLP-1 RA Combination Therapy

• Overall AEs were similar for IDegLira and comparators:
  – in DUAL I\(^1\) and II,\(^2\) the incidence of GI AEs was much lower with IDegLira vs Lira alone
  – in DUAL V,\(^3\) the incidence of non-serious GI AEs was higher with IDegLira vs IGlar
• LixiLan showed a low incidence of GI events\(^4\)

AE, adverse event; GI, gastrointestinal.

Practical Considerations in Using Basal Insulin–GLP-1 RA Combination Therapy

• Rationale for fixed-dose combination therapy
• Which patients are eligible for fixed-dose combination therapy?
• Administering IDegLira
• Summary
Recommendations for Insulin Intensification in Patients With Type 2 Diabetes

Healthy eating, weight control, increased physical activity, and diabetes education

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Met + SU</th>
<th>Met + T2D</th>
<th>Met + DPP-4 inhibitor</th>
<th>Met + SGLT2 inhibitor</th>
<th>Met + GLP-1 RA</th>
<th>Met + insulin (basal)</th>
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</thead>
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<tr>
<td>Efficacy</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
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<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>low</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td>Weight</td>
<td>neutral</td>
<td>neutral</td>
<td>neutral</td>
<td>loss</td>
<td>low</td>
<td>loss</td>
</tr>
<tr>
<td>Side-effects</td>
<td>GI/lactic acidosis</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>high</td>
<td>variable</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>low</td>
<td>GI</td>
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<td>insulin</td>
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</table>

If HbA1c target not achieved after approx. 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors):

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<thead>
<tr>
<th>Dual therapy</th>
<th>Met + SU</th>
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If HbA1c target not achieved after approx. 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Triple therapy</th>
<th>Met + SU</th>
<th>Met + T2D</th>
<th>Met + DPP-4 inhibitor</th>
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<th>Met + GLP-1 RA</th>
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</table>

If HbA1c target not achieved after approx. 3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2i:

<table>
<thead>
<tr>
<th>Combination injectable therapy</th>
<th>Met + SU</th>
<th>Met + T2D</th>
<th>Met + DPP-4 inhibitor</th>
<th>Met + SGLT2 inhibitor</th>
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DPP-4i, dipeptidyl peptidase 4 inhibitor; fxs, fractures; GU, genitourinary; Hypo, hypoglycaemia; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, thiazolidinedione.

When Should We Consider Basal Insulin–GLP-1 RA Combination Therapy?

- For patients with T2D that are not adequately controlled with:
  - OADs, and considering switch to injection therapy
  - Basal insulin
  - GLP-1 RAs

OAD, oral antidiabetes drug; T2D, type 2 diabetes.

## Basal Insulin Therapy: Scenarios of Inadequate Control

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Potential role of fixed-dose combination basal insulin–GLP-1 RA therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Insufficient basal insulin dose</td>
<td>• Combination therapy may improve glycaemic control</td>
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• Single injection does not add complexity to regimen                     |
| 2. Hypoglycaemic events prevent patient from reaching glycaemic target   | • Combination therapy associated with relatively low risk of hypoglycaemia |
| 3. Target FPG achieved, but patient continues to experience postprandial hyperglycaemia | • Addition of GLP-1 RA may help control postprandial hyperglycaemia  
• Single injection of fixed-dose combination therapy is less complex than basal–bolus approach (multiple daily injections) |
Practical Considerations in Using Basal Insulin–GLP-1 RA Combination Therapy

• Rationale for fixed-dose combination therapy
• Which patients are eligible for fixed-dose combination therapy?
• Administering IDegLira
• Summary
**IDegLira Dosing**

- Subcutaneous injection
- 3 mL prefilled pen
- Fixed ratio of IDeg (100 U/mL) and Lira (3.6 mg/mL)

<table>
<thead>
<tr>
<th>Dose step</th>
<th>IDeg dose (U)</th>
<th>Lira dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.036</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0.36</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>0.58</td>
</tr>
<tr>
<td>50 (max.)</td>
<td>50</td>
<td>1.8</td>
</tr>
</tbody>
</table>

How to Initiate IDegLira Therapy (1)

As add-on to OADs: start at 10 dose steps

• 10 dose steps = 10 U IDeg + 0.36 mg Lira
• When adding IDegLira to SU therapy, consider reducing the dose of SU

Xultophy, SmPC. Available at:
How to Initiate IDegLira Therapy (2)

When transferring from basal insulin: start at **16 dose steps**

- 16 dose steps = 16 U IDeg + 0.6 mg Lira
- Do not exceed the starting dose of 16 dose steps
- Discontinue basal insulin therapy before initiating IDegLira
- Monitor glucose closely during the transfer and in the following weeks

How to Initiate IDegLira Therapy (3)

When transferring from GLP-1 RA: start at 16 dose steps

- 16 dose steps = 16 U IDeg + 0.6 mg Lira
- Do not exceed the starting dose of 16 dose steps
- If transferring from a long-acting GLP-1 RA (e.g. once-weekly dosing), consider the prolonged action
  - initiate treatment with IDegLira at the moment the next dose of the long-acting GLP-1 RA would have been taken
- Discontinue GLP-1 RA therapy before initiating IDegLira
- Monitor glucose closely during the transfer and in the following weeks

Algorithm for Dose Adjustment of IDegLira in DUAL I\textsuperscript{1,2} and DUAL II\textsuperscript{3} Trials

<table>
<thead>
<tr>
<th>Mean fasting blood glucose, mmol/L\textsuperscript{a}</th>
<th>Change in dose steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.0</td>
<td>− 2</td>
</tr>
<tr>
<td>4.0–5.0</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>+ 2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Mean of 3 FPG values obtained on 3 consecutive days prior to dosing adjustment days, which occurred twice weekly throughout the trial.

Talking to Patients About IDegLira (1)

• Patients should learn proper use of IDegLira:
  – IDegLira is used once daily, preferably at the same time every day
  – if it is not possible to use IDegLira at the same time every day, it can be used at a different time of day – provided that there is a minimum of 8 hours between doses
  – IDegLira can be taken with or without food
  – follow recommended dose and dose adjustments
  – patients should consult with a doctor, pharmacist, or nurse before changing their usual diet; a change in diet may alter the need for IDegLira

Xultophy, SmPC. Available at:
Talking to Patients About IDegLira (2)

• Patients should be made aware of the risk of GI AEs:
  – lower appetite, nausea and vomiting, diarrhoea, constipation, dyspepsia, gastritis, stomach ache, heartburn or bloating
  – persistent, severe stomach ache could be a sign of acute pancreatitis
  – patients with diarrhoea, nausea, or vomiting should be encouraged to drink plenty of liquids to avoid dehydration

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- Which patients are eligible for fixed-dose combination therapy?
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- Summary
Summary (1)

• The complementary effects of basal insulin and GLP-1 RAs provide a rationale for combining these therapies\textsuperscript{1,2}

• Basal insulin–GLP-1 RA combination therapy provides maximum glycaemic control with the additional benefits of:\textsuperscript{2–5}
  – lower doses of insulin needed to achieve target HbA1c
  – relatively low risk of hypoglycaemia
  – no weight gain (weight loss or maintenance of body weight)

5. Rosenstock J, et al. ADA. 2014;A87:abstract 332-OR.
Summary (2)

• The complementary effects of basal insulin–GLP-1 RA fixed-dose combination therapies like IDegLira and LixiLan offer the convenience of basal insulin and a GLP-1 RA in a single dose\textsuperscript{1,2}
• Dosing strategies for initiating IDegLira and modifying the dose based on FPG have been established\textsuperscript{2,3}
• Basal insulin–GLP-1 RA combination therapy may be an option for patients with type 2 diabetes inadequately controlled with other treatments

\textsuperscript{1} Rosenstock J, et al. ADA. 2014;A87:abstract 332-OR.  