Update on New Basal Insulins and Combinations: Starting, Titrating and Adding to Therapy

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Discussion Points

• What new basal insulins and fixed-ratio combinations of basal insulin + GLP-1 receptor agonists (RA) are available?

• Why do we need them?

• How do we initiate, titrate and intensify them?

• What other drugs can we put with them to improve outcomes for type 2 diabetes?
Actions/Uses of Basal Insulin

Basal insulin (NPH, glargine [U-100 and U-300], detemir, degludec U-100, U-200)

- Controls fasting and preprandial glucose
- Titration is targeted at fasting plasma glucose (FPG)
- Released at nearly constant levels throughout the day

Common mistake: Using basal insulin to try and control postprandial glucose (PPG)

1. Insulin Therapy for Type 2 Diabetes: Making It Work. JFPONLINE.com Vol 59, Apr 2010
2. Insulin Regimens for Type 2 Diabetes Mellitus. JFPONLINE.com (December 2006-Supplement)
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novolin, Humulin</td>
<td>NPH</td>
</tr>
<tr>
<td>Levemir</td>
<td>Detemir</td>
</tr>
<tr>
<td>Lantus</td>
<td>Glargine 100 U/ml</td>
</tr>
<tr>
<td>Toujeo</td>
<td>Glargine 300 U/ml</td>
</tr>
<tr>
<td>Tresiba</td>
<td>Degludec</td>
</tr>
<tr>
<td>Novolog 70/30</td>
<td>70% insulin aspart protamine suspension and 30% insulin aspart</td>
</tr>
</tbody>
</table>
## Insulin Pharmacokinetics: Quick Summary

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
<td>14-18 hours</td>
</tr>
<tr>
<td><strong>Peakless Basal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine 100 U/ml</td>
<td>1-4 hours</td>
<td>Minimal</td>
<td>24 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-4 hours</td>
<td>Minimal</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td><strong>Increased Duration Basal Insulins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine 300 U/ml</td>
<td>Develops over 6 hrs</td>
<td>None</td>
<td>&gt; 30 hours (median)</td>
</tr>
<tr>
<td>Degludec 100 U/ml</td>
<td>1-4 hours</td>
<td>None</td>
<td>Approx 42 hrs</td>
</tr>
<tr>
<td>Degludec 200 U/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why the Need for Newer Insulins?

**NPH**

- The same dose by the same person in the same site at the same time of day under the same conditions can vary up to 50% in absorption!

- NPH peaks in 4-6 hours, possibly resulting in nocturnal hypoglycemia
More people having to switch from basal insulin analogs due to cost

Be prepared if switching from NPH insulin to go down in dose until glycemic control is established

Patient demonstrates how to use vial and syringe

Patient understands mixing (rolling technique)

Help patients be more aware of activity levels, meals/snacks and possibly greater night time hypoglycemia
Why the Need for Newer Insulins?

Glargine and Detemir
• Still slight peak
• Some variability
• Hypoglycemia
• In some cases twice daily injections
• More injections, less adherence
Polling Question

Basaglar (insulin glargine 100 U/ml) is a generic version of Lantus and can be substituted for the brand name.

A) True

B) False
Basaglar (Insulin glargine 100 U/ml)

- Not a generic of Lantus
- Has similar properties
- Considered a follow-on biologic
- Identical amino acid sequence
Why the Need for Newer Basal Insulins?

Smother, Flatter and More Constant Profiles

• Lower intra-patient variability
• Increased adherence
• Less hypoglycemia
• Less weight gain
Newer Insulin Starts

• Single insulin
• Easy education (insulin pen only)
• Clear and defined glucose target (FPG)
• Once daily injection
• Straightforward titration
• Low dose initiation
• Low incidence of hypoglycemia
Newest Insulins are “Forgiving” Leading to Greater Adherence

Glargine 300 U/ml
- Dose is given once daily but can be administered within a 3 hour window either way

Degludec 100 U/mL and 200 U/mL
- If dose is missed may be given the next day as long as there is 8 hours before next dose

Decreased Hypoglycemia

Both degludec and glargine 300 U/ml were associated with 25% less nocturnal hypoglycemia (vs NPH)

Fear of hypoglycemia

- Less adherence
- Suboptimal control

Accessed 3/24/2016

Reuter’s, Sat Jun 14, 2014 Sanofi Reports Positive Phase 3 Results for Toujeo
Other Considerations

Degludec
- Comes as 100 U/ml and 200 U/ml
- Pharmacodynamics are similar and flat
- U-200 pen delivers up to 160 units per injection

Glargine 300 U/ml
- When converting from glargine U-100 is unit for unit but studies show that dose may need to be titrated up by 10-18%
- Pen delivers 80 units max

Titrate both insulins in 3-4 day increments to FPG target
Initiation
Titration
Intensification
Various Basal Insulin Starts For Glargine 100 U/ml

Treat to Target Trial “2-4-6-8” algorithm
• Add 2, 4, 6, or 8 units of glargine weekly until mean FPG=100 mg/dl (5.6 mmol/L)

ATLANTUS Study “3-2-1” algorithm
• Add 2 units glargine every 3 days until mean FPG=100 mg/dl (5.6 mmol/L)

No compromise in safety

Straightforward and standardized approach
Example: Once-Daily Dosing for Glargine

Start with 10 units once daily and adjust weekly

<table>
<thead>
<tr>
<th>Self-monitored FPG from preceding 7 days with no episodes of severe hypo or prandial glucose ≤ 72 mg/dL (4.0 mmol/L)</th>
<th>Titration: Increase in insulin dose (units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100–120 mg/dL (5.6-6.7 mmol/L)</td>
<td>2</td>
</tr>
<tr>
<td>120–140 mg/dL (6.7-7.8 mmol/L)</td>
<td>4</td>
</tr>
<tr>
<td>140–180 mg/dL (7.8-10 mmol/L)</td>
<td>6</td>
</tr>
<tr>
<td>≥ 180 mg/dL (10 mmol/L)</td>
<td>8</td>
</tr>
</tbody>
</table>

### Monotherapy

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>G/lactic acidosis</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Dual Therapy

<table>
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<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
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<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>moderate risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 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- & disease-specific factors):

### Triple Therapy

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<th>Lifestyle Management</th>
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<tbody>
<tr>
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<td>WEIGHT</td>
<td>high</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>high</td>
</tr>
<tr>
<td>COSTS*</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin or (3) on optimally titrated basal insulin, add GLP-1 RA or bedtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e. adding a fourth antihyperglycemic agent).

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**American Diabetes Association Standards of Medical Care in Diabetes 2017.** Diabetes Care 2017;40(Suppl. 1):S54.
Degludec Start and Titration (Type 2)

Insulin naïve
- Start 10 units daily

If converting from long-acting or intermediate acting insulin is 1:1

Titration
- Every 3-4 days according to BG and glycemic control
Polling Question

The suggested starting dose for a person with type 2 diabetes for insulin glargine 300 units/ml is:

A) 0.5 units per kilogram

B) 0.2 units per kilogram

C) 10 units for all patients

D) Either 10 units or 0.2 units per kilogram is correct
Insulin Glargine 300 U/ml: Start and Titration (Type 2)

0.2 units/kg
- If converting from long-acting or intermediate acting insulin once daily is 1:1

For twice daily NPH start at 80% of TDD

Titration
- No more often than every 3-4 days according to BG and glycemic control
Insulin Intensification

• Basal plus one (prandial insulin after largest meal)
• Basal/bolus (2-3 prandial doses)
• Switch to insulin pre-mix twice daily (70/30, 50/50)
• Add GLP-1 RA once daily
Polling Question

The main side effect of GLP-1 RA and insulin combinations is listed as:

A) Gastrointestinal upset

B) Hypoglycemia

C) Cough

D) Jimmy legs
Why Combine GLP-1 RA with Basal Insulin?

- Improved A1C (comparable to adding prandial insulin)
- Added lowering of FPG
- Beneficial effects on PPG
- Lowers risk of hypoglycemia compared to increased basal insulin alone or adding prandial insulin
- Less weight gain
GLP-1 RA Plus Basal and Vice Versa

If adding GLP-1 RA to basal insulin, a downward titration of basal insulin is suggested

- Reduction of basal insulin dose reduces risk of hypo and weight gain

Adding basal insulin to GLP-1 RA obviates need for downward titration of basal

Both provide safer and easier way to achieving control

Riddle M, Metformin+exenatide+basal insulin vs metformin+placebo+basal insulin: reaching A1c <6.5% without weight-gain or serious hypoglycemia
Diabetes 2010;57(Suppl. 1)

US Indications for iGlarLixi and IDegLira

**INDICATION AND USAGE:**

**SOLIQUA** 100/33 is a combination of a long-acting human insulin analog with a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

**INDICATION AND USAGE:**

**XULTOPHY®** 100/3.6 is a combination insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).
EU Indications for iGlarLixi and IDegLira

**SULIQUA** is indicated in combination with metformin for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin.

**Xultophy** is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA), Suliqua Summary of Opinion 2016, Xultophy Summary of Opinion 2016
Fixed-Ratio Combinations of GLP-1 RAs and Basal Insulin

IdegLira (Xultophy 100/3.6) (administered once daily via pen)
- Liraglutide-Lira (GLP-1 RA)
- Degludec (insulin U-100)

Fixed-Ratio Combination
- 1 mL of IDegLira contains 100 units degludec and 3.6 mg Lira
- Max dose 50 units
  - 50 units degludec
  - 1.8mg liraglutide
- Slow titration=greater tolerability
IDegLira 100/3.6 Titration

Starting dose:
• Previously treated with GLP-1 RA or insulin:
  • 16 units
    • 16 units delgludec
    • 0.6 mg liraglutide
• Titrate by 2 units every 3-4 days
Fixed-Ratio Combinations of GLP-1 RAs and Basal Insulin

iGlarLixi

- Lixisenatide (GLP-1 RA)
- Glargine U-100 insulin

Fixed Ratio

- Dose range 15-60 units
- Maximum dose: 60 units of insulin glargine and 20 mcg lixisenatide
Soliqua 100/33 Titration

Starting dose:

• TDD of insulin < 30 units/day
  • Start at 15 units

• If TDD of insulin ≥30 units/day
  • Start at 30 units

• Titrate 2-4 units weekly until target FPG is reached
Overall Results of Fixed Combo GLP-1 RA/Basal

- Robust lowering of A1c
- Well tolerated
- Less weight gain versus basal insulin alone
- Possible lower (only one) co-pay
- Single injection daily
- Less burdensome to patients
- Consider using with patient above goal requiring basal insulin in place of insulin alone
- No increased risk of hypo versus basal insulin alone
Conclusions

• The new basal insulin formulations have considerable advantages over earlier insulins such as decreased hypoglycemia and increased adherence rates

• Earlier insulin initiation along with proper titration and intensification is essential to help patients get to goal and remain there

• Fixed ratio GLP-1 RA and insulin combinations offer greater flexibility and tolerability as well as decreased hypoglycemic events and weight gain
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