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

Jerry Meece, BPharm, CDE, FACA, FAADE
Director of Clinical Services Plaza Pharmacy and Wellness Center Gainesville, Texas
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>
<tr>
<td>Humalog 70/30</td>
<td></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 hrs</td>
<td>4-10 hrs</td>
<td>14-18 hrs</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 hrs</td>
<td>Minimal</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-4 hrs</td>
<td>Minimal</td>
<td>Up to 24 hrs</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 hrs</td>
<td>None</td>
<td>Approx 42 hrs</td>
</tr>
<tr>
<td>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
NPH Resurgence

- 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\(^1\)

**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\(^2\)

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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>Drug</th>
<th>Efficacy</th>
<th>Hypoglycemia Risk</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low risk</td>
<td>Neutral/loss</td>
<td>G/Lactic acidosis</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- and disease-specific factors).

### Dual Therapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>Efficacy</th>
<th>Hypoglycemia Risk</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>High</td>
<td>Moderate risk</td>
<td>Gain</td>
<td>Hypoglycemia</td>
<td>Rare</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- and disease-specific factors).

### Triple Therapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>Efficacy</th>
<th>Hypoglycemia Risk</th>
<th>Weight</th>
<th>Side Effects</th>
<th>Costs</th>
</tr>
</thead>
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<td>Metformin +</td>
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<td>Moderate risk</td>
<td>Gain</td>
<td>Hypoglycemia</td>
<td>Rare</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 mealtime 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).

### Combination Injectable Therapy

(See Figure 3)

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**Johnson & Johnson INSTITUTE**
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**

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**

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.
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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