Ultra-Rapid-Acting and Basal Insulins: What’s New ...

Linda A. DiMeglio MD MPH
2018 ATDC CONFERENCE: CONFLICT OF INTEREST

I have the Following Disclosures to Report:

✧ Grants/Research to my Institution
  ▪ Sanofi, Xeris, Locemia, Janssen
  ▪ Dexcom, Medtronic

✧ Consultant: Lilly

I will be speaking on off-label topics.
Outline: Next 20 Min

• Why we need new therapies
• Promising new/emerging insulins
• Perspective/considerations
Incremental Advances...
Therapy Advances Have NOT Prevented HbA1c Rise

Foster et al ADA 2018
Barriers to Using Insulin to Achieve Glycemic Goals

- Non-physiologic pharmacokinetic profiles
- Non-adherence
- Erratic drug absorption
- Complex regimens/human error calculating doses
- Inability to adjust basal once given
- Weight gain with therapy
- Cost
Outline

• Why we need new therapies
• Promising new insulins
  • Faster-acting Rapid
  • Better Basal
• Novel directions/considerations
Note: “Recent” FDA approvals

- Feb 2015: U300 insulin glargine approved (adults only)
- Sept 2015: Insulin degludec (Tresiba®) approved
- Dec 2015: Basaglar® approved*
- Dec 2016: Tresiba® approved for pediatrics*
- Sept 2017: Fiasp® approved (adults only)
- Dec 2017: Admelog® approved*

- Also: Biosimilar glargine LUSDUNA Nexvue has “tentative” approval

*Relabeling or generic of already-available insulin.
Hexamers

Dimers

Monomers

Cengiz Exper Rev Med Dev 2016
Faster insulin aspart (Fiasp®)

• Insulin aspart + Generally Regarded as Safe (GRAS) excipients
Faster aspart is insulin aspart in a new formulation

Nicotinamide: absorption modifier

Vitamin B3

L-Arginine: added for stability

Naturally occurring amino acid

Faster aspart, faster-acting insulin aspart; FDA, US Food and Drug Administration
• Time profile left-shifted
• Circulation appearance 5-7 min earlier than Novolog®
• Time profile left-shifted
• Circulation appearance 5-7 min earlier than Novolog®
• Time to 50% of maximum concentration 6-11 min faster
Fast-Acting Insulin: On the Horizon

- BioChaperone® Lispro (Adocia)
  - Excipient: modified dextran molecule
Other approaches

• Add hyaluronidase to rapid acting insulin
  – Improves tissue permeability (Halozyme)

• Add EDTA to insulin
  — Linjeta® (Albireo)
Faster-acting Insulin: Exubera

- FDA-approved Jan 2006
- “Dumped” by Pfizer Oct 2007
Enter Afrezza

• FDA-approved June 2014
• Initially marketed by Sanofi (available Feb 2015), dropped Jan 2016 due to poor sales
• Now marketed directly by MannKind
A breath of fresh insulin?

Pharmacokinetics

Fastest insulin action vs. other insulins!

www.afrezza.com
Afrezza Improves Postmeal Glucose Control in Type 1 Diabetes

Mean Postprandial Glucose Levels:
Meal Challenge Results Week 16 (MKC-TI-171)
Downsides

- Requires spirometry (FEV-1) before starting therapy
- Expense:

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Dosage form/product</th>
<th>Median AWP (min, max) Per 1000 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lispro</td>
<td>U-100 vial;</td>
<td>$330</td>
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<tr>
<td></td>
<td>U-100 3 mL cartridges;</td>
<td>$408</td>
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<td></td>
<td>U-100 prefilled pen; U-200 prefilled pen</td>
<td>$424</td>
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<tr>
<td>• Aspart</td>
<td>U-100 vial;</td>
<td>$331</td>
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<td></td>
<td>U-100 3 mL cartridges;</td>
<td>$410</td>
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<td></td>
<td>U-100 prefilled pen</td>
<td>$426</td>
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<tr>
<td>• Glulisine</td>
<td>U-100 vial;</td>
<td>$306</td>
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<tr>
<td></td>
<td>U-100 prefilled pen</td>
<td>$394</td>
</tr>
<tr>
<td>• Inhaled insulin</td>
<td>Inhalation cartridges</td>
<td>$725 ($544, $911)</td>
</tr>
</tbody>
</table>

ADA 2018 Standards of Care
123 doctors! 27 states!
Afrezza Script Tracking Since MannKind Re-Launch

Total Prescriptions

New Prescriptions

Refills

June 2016

May 2018
• Insulin disappearance from the subcutaneous skin tissue increased by 110% and reduced post-prandial blood glucose excursion when subjects are kept in the sauna for a total of 50 min.
Other Ways to Warm

- Insuline Medical (InsuPad®)

http://www.insuline-medical.com/product
The Meal Tolerance Test Study - Results

Same insulin aspart dose when using InsuPad

Glucose Excursion [mg/dl]

Time [min.]

Control
Test

Raz et al JDST 2015
Accelerating Insulin Action

- Novel delivery methods
  - Microneedles
  - Intraperitoneal delivery
Intradermal microneedles

1.5 mm 34 G steel

6 mm 24-29 G Teflon catheters
Insulin levels after ID & SC dosing of insulin lispro
Intraperitoneal Insulin Delivery: DiaPort
Ideal basal insulin characteristics

- Longer duration of action
  - Control fasting blood glucose with minimal injections
  - ALLOW FLEXIBILITY/ Improve Compliance

- Flat time-action profile
  - Decrease risk of hypoglycemia

- Less day-to-day variability
  - Lower risk of hypoglycemia
  - Permits titration to lower fasting glucose
Basal Insulins: Degludec

Insulin Degludec*

Multihexamers contribute to a half-life of 25.4 hours.*
Basal Insulins: U300

Toujeo® Provides More Constant Absorption of Glargine after Subcutaneous Injection

Reduction of volume by 2/3

1x 3x

Same amount of units

GLA-100 GLA-300

Slower and more constant rate of absorption
Basal Insulins: U300

Pharmacokinetic Profile
Serum Insulin Glargine Concentration

Pharmacodynamic Profile
Glucose Infusion Rate

SANOFI

Dahmen R et al, AOA 2013. abstract no. 113-CR. Euglycemic clamp study in T1D in steady state.

SCHOOL OF MEDICINE
INDIANA UNIVERSITY
Non-inferiority, T2D: U300 glargine vs degludec

Anytime (24 h) hypoglycemia

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Incidence, %</th>
<th>OR (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Gla-300</td>
<td>IDeg-100</td>
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</tr>
<tr>
<td>Full study period (0–24 weeks)</td>
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<td></td>
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<tr>
<td>Confirmed (≤70 mg/dL [≤3.9 mmol/L])</td>
<td>66.5</td>
<td>69.0</td>
<td>0.88 (0.66 to 1.17)</td>
</tr>
<tr>
<td>Confirmed (&lt;54 mg/dL [&lt;3.0 mmol/L])</td>
<td>14.7</td>
<td>18.4</td>
<td>0.76 (0.53 to 1.08)</td>
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<tr>
<td>Titration period (0–12 weeks)</td>
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<tr>
<td>Confirmed (≤70 mg/dL [≤3.9 mmol/L])</td>
<td>47.4</td>
<td>54.3</td>
<td>0.74 (0.57 to 0.97)</td>
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<tr>
<td>Confirmed (&lt;54 mg/dL [&lt;3.0 mmol/L])</td>
<td>7.8</td>
<td>11.7</td>
<td>0.63 (0.40 to 0.99)</td>
</tr>
<tr>
<td>Maintenance period (13–24 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed (≤70 mg/dL [≤3.9 mmol/L])</td>
<td>54.1</td>
<td>55.8</td>
<td>0.93 (0.72 to 1.22)</td>
</tr>
<tr>
<td>Confirmed (&lt;54 mg/dL [&lt;3.0 mmol/L])</td>
<td>9.8</td>
<td>11.2</td>
<td>0.86 (0.56 to 1.33)</td>
</tr>
</tbody>
</table>

Cheng, BRIGHT TRIAL, ADA 2018
Basal Insulin: Nanoparticles

• Designed to extend basal action to over days/week
  – Some may permit oral delivery
• Different systems, including:
  – Aquasomes (controlled release)
  – Biodegradable nanoparticles (matrix/depots)
  – Injectable microgels/microspheres
Open source insulin
As a part of do-it-yourself movement, there is an initiative to create an open-source protocol for insulin.

the Open Insulin project team is made up of roughly 50 self-described “hackers and tinkerers” who proudly point out they are all “bio-curious” — with a mix of genetic engineering, software, biochemistry and biotech experience. [..] “People across the world are going without insulin because it’s so expensive, and we need to do something about that,” Anthony says. “Maybe someday, what we’re doing here could lead to a do-it-yourself insulin factory.”

— Biohackers Creating Open-Source Insulin
Outline

• Why we need new therapies
• Promising new drugs
• Recent device advances
• Perspective/considerations
Perspective

• Insulin is cornerstone of diabetes therapy
• Advances in therapy significant
• Yet, inherent narrow therapeutic index
  – Need to control hyperglycemia
  – Risk of hypoglycemia
INSULIN IS NOT A CURE FOR DIABETES. IT JUST KEEPS PEOPLE ALIVE UNTIL WE FIND ONE.

Support the Research of the American Diabetes Association
INSULIN PEARLS

✧ Despite advances in care, therapy not optimized/barriers to insulin use remain
  ✧ Fiasp: newest novel fast-acting insulin available
    ✧ Afrezza continues to be studied
  ✧ New approaches to insulin delivery possible
✧ With narrow therapeutic index, insulin alone will not provide a “near cure” for diabetes
Questions?