Safe and Effective Use of New and Emerging Insulin Therapy

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Disclosures
Speaker’s Bureau (Honoraria):
Lilly, Sanofi, Novo-Nordisk, Merck, Takeda, AstraZeneca

Stocks, Advisory Committee, Review Panel, Royalty:
None

Learning Objectives

• Evaluate the role of insulin within the AACE and ADA guidelines for the treatment of T1 and T2DM.
• Differentiate the pharmacokinetic and pharmacodynamic actions of available and emerging basal insulins.
• Discuss strategies for overcoming common barriers to optimal glucose control with basal insulin therapy.
• Using patient specific information, make recommendations regarding insulin initiation, dose adjustments and monitoring.

Outline

Review Use of Insulin in Type 2 Diabetes
Why? When? Type of Insulin?

Barriers to Use of Insulin
Patients
Providers
Solutions

Why new insulins?
Discuss PK, PD,
New insulins
GlargineU300, Degludec,
Biosimilars
Role of U500 insulin
Emerging Bolus Insulins
Fast Acting Aspart

Physiologic Insulin Secretion: 24-Hour Profile

Changes in Insulin Secretion and Action:
Staying on the Curve

What is wrong with the β-cells in Type 2 diabetes?

- First-phase of glucose-induced insulin release is reduced or missing
- Second-phase of insulin secretion is reduced or inadequate (high or low)
- Changes of oscillatory secretion of insulin (brief, irregular pulses with small amplitudes)
- Reversible low response of glucose-induced insulin release due to gluco- and/or lipotoxicity
- Increase of proinsulin release

Progression of Type 2 diabetes relates to declining β-cell function rather than insulin resistance

- Patients with diet failure 2–4 years after diagnosis
- Patients with diet failure 5–7 years after diagnosis
- Patients with diet failure 8–10 years after diagnosis

Natural History of Type 2 Diabetes

- Impaired Glucose Tolerance
- Franks Diabetes
- Insulin Resistance
- Hepatic Glucose Production
- Endogenous Insulin
- Postprandial Blood Glucose
- Fasting Blood Glucose

Microvascular Complications

- Retinopathy
- Nephropathy
- Neuropathy

Typical Diagnosis of Diabetes

Addressing the Pathophysiologic Defects in T2DM

- Reduced food intake
- GLP-1 RA
- Reduced hepatic glucose production
- Biguanides, GLP-1 RA, TZD
- Reduced glucose reabsorption, increasing urinary glucose excretion
- SGLT2 inhibitors
- Reduced or delayed glucose absorption
- Biguanides, alpha-glucosidase inhibitors
- Slowed gastric emptying
- GLP-1 RA

CARL

67 yo retired chef, active lifestyle, an epicurean
15 yr Type 2 DM: BMI=35, BP 132/80
Hba1C=8.9, Cr=1.3 (eGFR=40), LDL=80, FBG=210
Hypertension, Hypercholesterolemia
Rx with metformin 500 mg BID, Glyburide 5 mg BID, atorvastatin 40 mg/d, lisinopril 10 mg QD
Recent complaints of fatigue, groin itching, urinary frequency, thirst

What is his next best treatment?
1) Gastric bypass
2) SGLT2i
3) Pioglitazone
4) Basal insulin
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ROCHESTER REGIONAL HEALTH

**TYPE 2 DIABETES … A PROGRESSIVE DISEASE**

*Over time, most patients will need insulin to control glucose*

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**MIMICKING NATURE WITH INSULIN THERAPY**

*Over time, most patients will need both basal and mealtime insulin to control glucose*

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**Barriers to Insulin Use: Patient Issues**

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of injections</td>
<td>Syringes, pens, and needles vastly improved</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>Low rate of severe hypoglycemia in type 2 diabetes</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>Glucose control is more important than mild-to-moderate weight gain</td>
</tr>
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Barriers to Insulin Use: Patients and Providers

<table>
<thead>
<tr>
<th>Concerns</th>
<th>Responses</th>
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<tbody>
<tr>
<td>Insulin equates to “worse diabetes” critical</td>
<td>Diabetes is a progressive disease: early intervention</td>
</tr>
<tr>
<td>Inconvenience</td>
<td>New delivery systems (pens, pumps) and insulins increase flexibility</td>
</tr>
<tr>
<td>Is insulin therapy atherogenic?</td>
<td>No evidence in clinical trials of exogenously administered insulin (UKPDS, DCCT, DIGAMI)</td>
</tr>
</tbody>
</table>

Barriers to Insulin Therapy

Common Concerns

Insulin therapy might cause
- Worsening Insulin Resistance
- More Cardiovascular Risk
- Weight Gain
- Hypoglycemia
- Side Effects (Ads, friends, Internet)

Correlation Between Weight Gain and Treatment


Fear of Hypoglycemia: The Closer to Target, the Higher the Risk


BARRIERS TO INSULIN THERAPY

Reassurance About Common Concerns

Insulin Therapy in Type 2 DM
- Improves Insulin Sensitivity by Reducing Glucotoxicity
- Probably Reduces Cardiovascular Risk
- Causes Modest Weight Gain
- Rarely Causes Severe Hypoglycemia

Philosophy for earlier insulin treatment (1)

- The patient wants to have insulin therapy
- Greater flexibility in lifestyle
- Insulin replacement is more physiological
- The individual treatment goal has not been achieved with non-pharmacological intervention and other agents within 3–6 months
- Reduction of complicated and complex oral/injectable polypharmacy
- Relative/absolute contraindications for OAD/injectables
- Side effects with OAD/injectables
• The traditional insulinotropic agents, such as glibenclamide and glimepiride, result in delayed and sustained insulin release and are, therefore, effective mainly in controlling fasting and postabsorptive glycaemia, while being poorly adapted for controlling postprandial hyperglycaemia
• Meglitinides are more effective in controlling postprandial glycaemia
• Glp1 agonists, DPP4i, and SGLT2i useful but often insufficient to control hyperglycaemia, especially late in disease progression
• Short-acting insulins and rapid-acting insulin analogues can replace, at least in part, first-phase insulin release
• Long-acting insulins (Degludec, Glargine 300, Glargine, Detemir, NPH) are able to control postabsorptive and, especially, fasting hyperglycaemia

Philosophy for earlier insulin treatment (2)

MIMICKING NATURE WITH INSULIN THERAPY

The Basal/Bolus Insulin Concept

• Basal Insulin
  — Suppresses glucose production between meals and overnight
  — Nearly constant levels
  — 50% of daily needs
• Bolus Insulin (Mealtime or Prandial)
  — Limits hyperglycemia after meals
  — Immediate rise and sharp peak at 1 hour
  — 10% to 20% of total daily insulin requirement at each meal
• Ideally, for insulin replacement therapy, each component should come from a different insulin with a specific profile

Consistent Blood Glucose Response

Basal Insulins

Correlation Between Variability in Blood Glucose Response and Incidence of Hypoglycemia

Variability in Blood Glucose Is an Independent Risk Factor for Mortality
Optimal Starter Insulin Properties

- Once-daily dosing
- Low intra-patient variability/high consistency of time-action profile
- Low risk of hypoglycemia
- Little or no weight gain
- Easy to teach, easy to learn

Molly

33yo female with Type 2 DM for 8 years
Hyperlipidemia, Hypertension, Sedentary lifestyle
Wt 156 lbs (BMI=28) BP=120/76
RX: glargine 40 u at supper; pre meal lispro insulin 10-12 units; liraglutide 1.8 mg/d; metformin 750 mg BID
Most recent HbA1C=6.4 range of 5.9-6.4 in past 2 years; LDL=87; Cr=0.6
At office visit complains of nightmares, often awakes with damp night shirt
Pre bk glucoses range from 85-175; pre lunch, dinner, bedtime 96-166

Best option for change in her treatment regimen:
1) Reduce liraglutide to 1.2 mg/d
2) D/C glargine and replace with 40 units glargine 300 or degludec insulin
3) Stop metformin
4) Reduce pre meal insulin to 8 units
5) Add a SGLT2i

Pharmacodynamic Profile of Human NPH and Insulin Glargine

Duration of Action of Ultralong-Acting Insulins vs U-100 Insulin Glargine

Glargine 300

- Approved as a new drug and not therapeutically equivalent to insulin glargine 100 Units/mL
- 1/3 the injection volume of standard insulin (100 Units/mL)
- Has a different pharmacodynamic distribution profile than Lantus®
- Forms a precipitate from which small amounts of glargine are slowly released over 24 hours
  - Stable release of insulin from a compact depot over 24 hours
**PK/PD Profile with Insulin Glargine 300 Units/mL Compared to Insulin Glargine 100 Units/mL**

- Reduction of volume by 2/3
- Slower insulin release
- More constant PK/PD profile
- Baseline insulin sensitivity, 
- Insulin clearance

**EDITION 1: Study Design**

**Inclusion criteria**
- Males and females
- Aged 18 years
- T2DM as defined by the WHO
- A1C 7.0–10.0%

**Treatment**
- Once-daily dosing on top of mealtime insulin ± metformin
- Injections given in evening from before dinner to bedtime
- Dose titrated to predose FPG 80–100 mg/dL
- Titration of mealtime insulin at investigator’s discretion after basal insulin was optimized

**Participants**
- n=807
- Randomized 1:1

**Primary efficacy endpoint:** A1C change from baseline to Month 6 or last visit on treatment

**EDITION 1: Objectives and Endpoints**

- **Primary efficacy endpoint:**
  - A1C change from baseline to Month 6 or last visit on treatment

- **Secondary efficacy endpoints:**
  - Incidence (% of participants with at least one confirmed (275 mg/dL) or severe nocturnal (400–499 mg/dL) hypoglycemic event from Week 0 to Month 6
  - Change in and variability of pre-injection self-monitoring plasma glucose (SMPG)
  - Change in fasting plasma glucose (FPG) from baseline to Month 6
  - Change and variability of the mean 24-hour plasma glucose values based on SMPG
  - Proportion (% of participants with A1C <7% and ≤8.5%, and FPG <120 mg/dL)
  - Change in basal insulin dose and total insulin dose
  - Change in body weight

**Hypoglycemic events**
- Hypoglycemia according to definitions (confirmed or severe; documented symptomatic or asymptomatic, together with severe events)
- Hypoglycemia according to the time (nocturnal, at any time, daytime)

**Safety and tolerability**

**EDITION 1: Rates of Severe and/or Confirmed Hypoglycemia Events per Patient**

**Hypoglycemia at any time of the day (24 hours)**

**Nocturnal hypoglycemia (00:00–05:59 hours)**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Confirmed (≤70 mg/dL)</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**EDITION 1: Nocturnal Hypoglycemic Events** by ADA Definitions

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Threshold</th>
<th>Relative Risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed (≤70 mg/dL)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Documented symptomatic</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Legend**
- RR: Relative Risk
- CI: Confidence Interval

*Percent calculated as percentage with 95% CI*
Insulin Degludec: Pharmacodynamics

- Degludec is almost identical to human insulin
  - Last amino acid deleted from B-chain
  - Addition of glutamyl link from LysB29 to a hexadecandioic fatty acid
- Prolonged duration of action and flat plasma profile
  - Terminal half-life of > 25 hours and activity > 40 hours
  - Reduced variability in plasma concentration and activity
  - Flat steady-state plasma profile with once-daily injection
- Albumin binding
  - Degludec forms multihexamer insulin chains in SC depots
  - Accumulation slows release of insulin monomers, which are retained longer in circulation by attachment to albumin

SC = subcutaneous.
Recent Trial Highlights – BEGIN

Type 2

Type 2 DM

insulin degludec vs. glargine

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design &amp; Treatment arms</th>
<th>Trial population</th>
<th>Results</th>
</tr>
</thead>
</table>
| BEGIN Basal–Bolus Type 2.1 | • 52 weeks, randomized, controlled, open-label, treat-to-target, multinational, non-inferiority trial | • 1006 patients with type 2 DM                                                                                           | • HbA1c fall at year 1
• Diabetes duration for > 6 months, any insulin use for at least 3 months, BMI of 40.0 kg/m² or less, with or without oral antidiabetic drugs
• 744 patients to degludec
• 262 patients to glargine
• Excluded: glp-1 agonist or rosiglitazone use within previous 3 months | • 1.1% degludec
• 1.2% glargine
• Treatment difference: 0.08% [95% CI -0.05 to 0.21], confirming non-inferiority |

Effect of BEGIN® BB T2D Basal–bolus in T2D: confirmed hypoglycaemia

1.2% lower rate with Degl, p<0.009

Effect of BEGIN® BB T2D Basal–bolus in T2D: confirmed nocturnal hypoglycaemia

35% lower rate with Degl, p=0.0399
Hypoglycemia: Summary of Data Comparing IDEG With IGLAR

- Three phase 2 studies have similar hypoglycemia rates\(^1\)\(^-\)\(^3\)
  - Exception is post hoc analysis of Zinman et al.\(^2\)
- Inconsistent results for Phase 3 studies in Type I and Type II DM\(^4\)\(^-\)\(^6\)
- Meta-analysis demonstrates significantly lower rates of both overall and nocturnal hypoglycemia than IGLAR at similar levels of A1C\(^6\)
- Severe hypoglycemic events very low in all studies of IDEG vs IGLAR

IDEG, insulin degludec; IGLAR, insulin glargine.

What Are Biosimilars?

- **Biosimilars**
  - Are biological products that are highly similar to a reference product, notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences in safety, efficacy, and purity.
  - Are not generics; they are similar but not the same.
  - Provide valuable options that create choice for prescribers and patients.
- **Biosimilar manufacturing quality matters**
  - Manufacturing processes that may influence quality and/or immunogenicity of biological products include protein production, purification, formulation, and storage and handling.

### Demonstrating Biosimilarity: How Similar Is Similar?

- **When compared to the reference product, a biosimilar medicine must comply with regulatory guidelines and demonstrate:1,2**
  - In vitro & in vivo nonclinical characteristics similar to the reference product
  - Similar PK and PD within predefined regulatory acceptance limits
  - Similarity demonstrated in clinical trials designed to assess PK and PD against standard acceptance limits3-5
  - Identical amino acid sequence as IGlar
  - Same pharmaceutical form and strength (concentration of active ingredient) as IGlar
  - No clinically meaningful difference in efficacy (eg, based on noninferiority studies)
  - No clinically meaningful differences in safety profile, including drug-related AEs and immunogenicity
  - Currently, a number of biosimilar products are available in the EU; in the US, the first biosimilar, filgrastim-sndz was approved in March 2015.

### Insulin Glargine: Introduction

**Insulin glargine**1,2
- Long-acting human insulin analog
- An important treatment option for patients requiring a basal insulin as part of their diabetes treatment plan
- In 2000, Lantus® insulin glargine (IGlar) gained FDA and EMA approval for once-daily subcutaneous administration for treatment of type 1 and type 2 diabetes mellitus (T1DM and T2DM).1,2
- In patients with T1DM or T2DM, IGlar, when compared to neutral protamine Hagedorn (NPH), was shown to:
  - Provide similar glycemic control
  - Have lower or similar rates of hypoglycemia

### Has LY IGlar Met Biosimilarity Criteria?

- **Similarity demonstrated in preclinical in vitro and in vivo PD and toxicology studies.3-5**
- **Similarity demonstrated in clinical trials designed to assess PK and PD against standard acceptance limits.3-5**
- **No clinically meaningful differences in immunogenicity.6,7**
- **Head-to-head clinical trials to detect relevant differences in efficacy or drug-related safety.6,7**

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1. Blevins TC et al. Diabetes Obes Metab 2015;17:726-33
5. Biotechnology and Bioengineering 2011;108:42-52
7. Diabetes Obes Metab 2015;17:734-41
Safety and Tolerability

- No notable differences were observed in AE profiles of LY IGlar and IGlar in healthy subjects, and no safety concerns were noted in the clinical laboratory evaluations, vital signs, or ECG data, in any of the 3 studies.

Linnebjerg H et al. Diabetes Care 2015;38:2226-33

Comparison of Pharmacokinetics of U-500 and U-100 Human Regular Insulin

U-500 Human Regular Insulin: Clinical Pharmacology

- Clinical experience has shown that U-500 human regular insulin frequently has time action characteristics reflecting both prandial and basal activity.
- U-500 human regular insulin has an onset within 30 minutes and has a relatively long duration of action (up to 24 hours following a single dose) compared with other regular insulins; this effect has been attributed to the high concentration of the preparation.
- U-500 human regular insulin is not modified by any agent that might prolong its action.

Comparison of Pharmacodynamics of U-500 and U-100 Human Regular Insulin

Potential Candidates for U-500 Human Regular Insulin Therapy

- Patients with the following medical conditions may be considered for U-500 human regular insulin therapy:
  - Type 2 diabetes with obesity and/or severe insulin resistance
  - Type 2 diabetes with insulin requirements >200 units per day
    - Postoperative or post-transplant state
    - High-dose glucocorticoid therapy
    - Severe systemic infection
  - Gestational diabetes mellitus with severe insulin resistance
  - Genetic defects of insulin action
    - Type A insulin resistance syndromes
    - Lipodystrophic diabetes
  - Rare forms of immune-mediated diabetes such as anti-insulin receptor antibodies (type B insulin resistance syndrome)

U-500 = 500 units/mL, U-100 = 100 units/mL
Nonsyndromic Severe Insulin Resistance

• Some patients with type 2 diabetes, by virtue of their weight and/or severe insulin resistance, may require insulin doses exceeding 200 units/day.1-3
  - Many patients with type 2 diabetes who have severe insulin resistance (>2 units/kg/day insulin requirement) will require “high-dose insulin” (>200 units/day).
  - Some patients with type 2 diabetes will require high-dose insulin solely on the basis of their high body weight (eg, the 140 kg patient requiring exogenous insulin at 1.5 units/kg/day = 210 units/day).
• Occasionally, patients with type 1 diabetes may require >200 units/day.1,2

U-500 Regular Insulin: Dosage and Administration

• U-500 regular insulin takes effect within 30 minutes, therefore, it should be followed by a meal within 30 minutes of administration.1,3
• U-500 regular insulin should only be administered SC.1,3

Some patients with type 2 diabetes, by virtue of their weight and/or severe insulin resistance, may require insulin doses exceeding 200 units/day.1-3

Algorithm for U-500 Regular Insulin Dosing1,a (1 of 2)

<table>
<thead>
<tr>
<th>TDI Dose (units/day)</th>
<th>Injection Frequency/Delivery Method</th>
<th>Dosage Distribution (% of TDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 – 300</td>
<td>2 injections/day (before breakfast and evening meal)</td>
<td>60/40 or 50/50</td>
</tr>
<tr>
<td>300 – 600</td>
<td>3 injections/day (before meals)</td>
<td>40/30/30 or 33:33:33:33</td>
</tr>
<tr>
<td>&gt;600</td>
<td>3 meals/meal before meals (50% TDD with basal rate 30/30/30/10)</td>
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U-SID = 500 units/mL, U-100 = 100 units/mL, TDD = total daily dose, TDI = total daily insulin dose, A1C = glycated hemoglobin.

Algorithm for U-500 Regular Insulin Dosing1,a (2 of 2)

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U-500R TID Versus BID RCT: Key Inclusion Criteria

• Type 2 diabetes mellitus
• 18-75 years of age
• Body mass index ≥25 kg/m²
• HbA1c ≥7.5% and ≤12.0%
• Current high-dose U-100 users (201-600 units/day) for ≥3 months
• Comorbid medications: metformin, DPP-4 inhibitors approved for use with insulin, pioglitazone, and/or sulfonylureas/glinides for ≥3 months
  - Sulfonylureas/glinides were discontinued just after entry
Fast Acting Insulin Aspart

**U-500R TID Versus BID RCT: Study Design**

- 24-week, open-label, parallel, 2-arm, randomized clinical trial
- Randomization stratified by investigator site, baseline HbA1c (≤8.0 or >8.0%), TID (≥300 or >300 units), and lifestyle use

**U-500R TID Versus BID RCT: HbA1c Change Baseline Over 24 Weeks (Primary Outcome)**

- Significant HbA1c reduction after 24 weeks (-1.12% [TID] and -1.22% [BID], p=0.01 for both)
- Treatments clinically equivalent (LS mean difference (TID - BID) in HbA1c change from baseline was -0.10% [95% CI -0.33 to 0.12%], which was within the predefined non-inferiority margin of 0.4%)

**Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart**

- Faster-acting insulin aspart: towards an understanding of the mechanism(s) of action of noninsulins
1. Glargine 300 insulin as compared to glargine insulin...
   1. Reduces post meal glucoses
   2. Has a shorter duration of action
   3. Has 3x the amount of insulin in a given volume of insulin
   4. Increases nocturnal hypoglycemia

2. Degludec insulin benefits include...
   1. 12 hrs duration
   2. Availability in vials and pens
   3. Ability to reduce post meal glucose
   4. 25 hr half life-twice that of glargine insulin

3. The most significant reason for the progression (higher glucoses) of Type 2 DM is:
   1. Increase in insulin resistance
   2. Decline in Beta cell function
   3. Increase alpha cell secretion of glucagon
   4. Increase in catecholamine secretion from nerves/adrenal gland

4. Biosimilar insulins are:
   1. Generic insulins
   2. May have meaningful differences in purity, safety and efficacy from reference insulin
   3. Similar to a reference product with minor differences in clinically inactive components
   4. Different PK and PD from reference product

5. U500 regular human insulin’s principle role is:
   1. Patients developing rash/hives using aspart, lispro or regular human insulin
   2. Patients with a BMI > 40
   3. Patients requiring over 200 units daily to control hyperglycemia
   4. Patients moving away from basal/bolus insulin to pump delivered insulin