Type 2 Diabetes Management: Case 3: Initiation and Intensification of Insulin

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Case 3: Barbara

52-year-old woman with 6-year history of T2DM
- Also has hypertension and dyslipidemia, both controlled on medications; no history of CVD
- Takes metformin 1,500 mg QD and glimepiride 8 mg QD
- A1C was 8.2%, but has increased to 9.1%; patient reports compliance with antihyperglycemic medications, but has experienced several episodes of dizziness and fatigue over past month
- Weight = 186 lb, height = 5’7” (BMI = 29.1 kg/m²)

ADA/EASD Position Statement

When to Consider Insulin in a Person with Type 2 Diabetes
- Consider as initial therapy in T2DM if A1C >9% or symptomatic
- When a combination of non-insulin antihyperglycemic medications are unable to achieve A1C target
- Unacceptable side effects and/or contraindications to non-insulin medications
- Advanced hepatic or renal disease or other comorbidities precluding use of other agents
- Special considerations (steroids, infection, pregnancy)
- Hyperglycemia in a hospitalized patient
- “Severely” uncontrolled diabetes

* Random Glucose >300 mg/dL, A1C >10%, Ketonuria, Symptomatic polyuria/polydipsia, weight loss

ADA/EASD Position Statement

Initiation and Adjustment of Insulin Regimens: Basal Insulin (Analog or NPH)

Add 1 rapid insulin injection before largest meal
Change to premixed insulin twice daily

Insulin Preparations: Onset and Duration of Action

Analogue Biphasic / Premixed Insulin

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<thead>
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<th>Onset of action</th>
<th>Peak</th>
<th>Duration of action</th>
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<td>Degludec (U-100)</td>
<td>0-60 min</td>
<td>6-16 hr</td>
<td>&gt;18 hr</td>
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<tr>
<td>Degludec/aspart 70/30</td>
<td>Rapid</td>
<td>Minimal</td>
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Type 2 Diabetes Management:
Case 3: Initiation and Intensification of Insulin

**Time-Action Profiles of Human Insulins and Insulin Analogs**

**Insulin Glargine U-300**
- Once-daily long-acting basal insulin
- FDA approved 02/25/2015
- Trials comparing glargine U-300 with glargine U-100
- Similar rates of glucose control and HbA1C reduction
- Lower rates of nocturnal and severe hypoglycemia with U-300
- U-300 has longer duration of action compared with U-100
- U-300 has flatter pharmacokinetic profile compared with U-100

**Insulin Degludec**
- New-generation ultra-long-acting basal insulin analog
- FDA approved 09/25/2015
- Meta-analysis of treat-to-target trials (2,899 people randomized to insulin degludec and 1,431 randomized to insulin glargine)
  - Lower hypoglycemia* in T2DM RR = 0.83 [95% CI: 0.74; 0.94]
  - 86% reduction in insulin-naive patients
- Lower nocturnal hypoglycemia** in T2DM RR: 0.68 [95% CI: 0.57; 0.82]
- Lower hypoglycemia rate in elderly
- Improved treatment satisfaction and quality of life

**Ultra-long Basal Insulins: Place in Therapy**
- Patients needing less fluctuation of insulin levels
  - Includes those with:
    - Nocturnal hypoglycemia
    - Renal impairment, elderly
    - Variable schedules/lifestyle: shift workers, college students
    - Complaints of variability of fasting glucose levels
    - Adherence issues: can dose within 8 hours if dose was missed

**Insulin Glargine Follow-on (Biosimilar) Agent**
- FDA approved first follow-on insulin glargine agent in December 2015
- Also referred to as biosimilar
- Long-acting alternative form of currently available insulin glargine with the same protein sequence and similar glucose-lowering
  - Injected once daily, subcutaneously using a prefilled pen formulation
  - May be priced competitively
Case 3: Barbara – cont’d

- She has not met her A1C goal of <7% despite 56 units of glargine daily and metformin 1000 BID
- She has had several episodes of nocturnal hypoglycemia in the last month, so she started to reduce her glargine dose on her own

What are some reasons she hasn’t gotten to goal?

Addition of GLP-1 RAs vs Prandial Insulin to Basal Insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LIRA OD vs ASP QD</th>
<th>EXN BD vs LIS TID</th>
<th>ALBI QW vs LIS TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔΔA1C (%)</td>
<td>-0.2%</td>
<td>-0.4%</td>
<td>-0.3%</td>
</tr>
<tr>
<td>Δ Weight (kg)</td>
<td>-2.0%</td>
<td>0.9%</td>
<td>-2.0%</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>1.0%</td>
<td>0.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hypo (EPF)†</td>
<td>1.0%</td>
<td>0.2%</td>
<td>0.5%</td>
</tr>
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</table>

DULA is approved only with prandial insulin; EXN QW is not approved with any insulin.

GLP-1 RA Fixed-Ratio Co-formulations: Emerging Basal Insulin

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<tr>
<th>Outcome</th>
<th>ΔA1C (%)</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDegLir1.2,†</td>
<td>-1.9%</td>
<td>-0.5%</td>
</tr>
<tr>
<td>DEG + GLP</td>
<td>-1.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>LIRA + GLP</td>
<td>-1.3%</td>
<td>-3.0%</td>
</tr>
<tr>
<td>iGlarLixi + GLP</td>
<td>-1.3%</td>
<td>-1.0%</td>
</tr>
<tr>
<td>GLAR + GLP</td>
<td>-1.5%</td>
<td>0.5%</td>
</tr>
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</table>

Current GLP-1 RAs should not be mixed with or injected adjacent to insulin.

GLP-1 RA + Prandial Insulin vs Basal Insulin + Prandial Insulin

- With GLP-RA vs basal insulin:
  - Lower rate of nocturnal hypoglycemia
  - Less weight gain

Concentrated Insulins: Guidance on How to Change to and from Formulations

- Dose differences in general:
  - U-300 glargine > U-100 glargine > U-100/U-200 degludec

<table>
<thead>
<tr>
<th>Current Insulin</th>
<th>Change to U-300 glargine</th>
<th>Change to U-100 glargine</th>
<th>Change to U-100/U-200 degludec</th>
<th>Change to U-100 Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-300 Glargine</td>
<td>Consider decreasing dose by 10%</td>
<td>No dose change at initial change will probably need to updose</td>
<td>Decrease by 20%</td>
<td>Decrease by 20%</td>
</tr>
<tr>
<td>U&lt;0.5/0.25 Degludec</td>
<td>No dose change at initial change will probably need to updose</td>
<td>---</td>
<td>---</td>
<td>---</td>
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3. SE et al. Drugs@FDA 2015;38:140.
4. ALBI QW vs LIS; n = 177); DEG is not approved by the US FDA.
6. 30% of insulin is usually prandial in patients on DULA regimen.
Case 3: Barbara – cont’d

- Her glargine was changed to degludec at 50 units. She continued her metformin at 500 BID and was started on 0.75 mg dulaglutide weekly.
- Diet and exercise options were again reviewed with the patient. She promised to walk several times a week with a friend.
- Follow-up 3 months later: she did not report any hypoglycemic episodes. Patient had lost 14 lb. Her A1C was 7.4%; her dulaglutide dose was increased to 1.5 mg/weekly.

What does the endocrinologist expect of the PCP regarding the ongoing management this patient?

Summary of Intensification of Treatments

- Hypoglycemia often limits intensification of insulin regimen.
- Consider metformin, TZDs, ultra-long acting insulins, SGLT-2 inhibitors, and incretin agents.
- Per ADA guidelines, if basal insulin dose becomes excessive, consideration should be given to use GLP-1 RA or bolus insulin with 1-3 meals daily.