New Therapies for Diabetes Management: Hope or Headache?

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Disclosures

• None
Objectives

• Discussion of 3rd line agents
• New insulin options, and what to consider when cost is a barrier
• Tools to help make diabetes easier…
• *Keeping it practical and clinically oriented*…

Case #1

• 62 yo woman, type 2 DM x 9 years, history of MI, dx with CHF last month- controlled
• Currently on metformin 500mg QD, glipizide 10mg bid, pioglitazone 45mg QD
• A1c 9.2%, BMI 42
• Normal renal & liver function
• Complains of fatigue
Considerations:

• Would you continue her on her current regimen?

• What would you consider adding?

• What would you target for A1c?

Metformin Review

• Considerations:
  – Lowers A1c 1-1.5% (when you start higher)
  – Weight neutral, less hypoglycemia risk, ↓ CVD (UKPDS)
  – XR tends to be easier to tolerate (GI)
  – Check eGFR
    • Contraindicated if <30mL/min/1.73m2
    • Don’t start if between 30-45mL/min/1.73m2
    • If eGFR < 45mL/min/1.73m2, consider ↓ dose
  – Follow renal function annually, or more often if at risk
Pioglitazone- Review

- Considerations:
  - A1c lowering: 1-1.5%, lower cost
  - No hypoglycemia, durable effect
  - Issues with fluid retention, weight gain—generally seen with higher doses and worse when used with insulin
  - Shown to prevent fibrosis in those with NASH, reduce inflammation in those with fatty liver [Bril F et al, Diabetes Care 2017;40:419]
  - Reduces recurrent stroke and vascular events in those with ischemic stroke + DM [Lee M, Stroke 2017;48:388]

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2I)
SGLT2-Inhibitors- Review

• Considerations:
  – A1c lowering: .5-1%, $400-500/month
  – Oral, less hypoglycemia risk
  – Pros:
    • Weight loss (1-3kg), BP ↓ (3-4mmHg)
    • CV benefit- empagliflozin (Jardiance®) + canagliflozin
      (Invokana®)- Canvias, NEJM 2017; EMPA-REG, NEJM 2015
    • Reduction in proteinuria, GFR benefit
  – Cons:
    • Genital infections, DKA, bone loss/fracture risk, volume
      loss, Fournier’s gangrene
    • Amputation risk with canagliflozin

GLP-1 Receptor Antagonist (RA) Review

• Considerations:
  – A1c lowering: 1-1.5%, $630-870/month
  – Weekly are useful for reluctant injectors
  – Some differences:
    • Semaglutide (Ozempic®) better weight loss, A1c lowering c/w
      glargine (Lantus®), dulaglutide(Trulicity®) exenatide XR
      (Bydureon®) — Sustain trials, 3,4,6,7
  – Needle-phobic: Dulaglutide
  – CV benefit: Liraglutide (Victoza®) and semaglutide
  – Need for re-suspension and nodules with Exenatide XR
  – Remember ALL GLP-1’s provide more weight loss c/w
    insulin
GLP-1 RA: safety concerns

- Thyroid Cancer
  - Medullary only
  - Based on rodent models, increased levels of calcitonin
  - Not seen in humans
  Take home: would not recommend using in patients with family/personal history of medullary thyroid cancer

- Pancreatitis, pancreatic cancer
  - Cancer – no causal relationship determined
  - Pancreatitis in clinical trials – occurrence rate low
    • Patients with DM have ↑ risk of pancreatitis
  Take home: avoid in those with history of pancreatitis or risk factors (ie alcoholism, hypertriglyceridemia)

Third-Agent Considerations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| DPP-4      | - Less hypoglycemia  
- Good for elderly, renal impairment (linagliptin)  
- Few side effects (pancreatitis) | - Cost $$  
- Potency  
- Pancreatitis, CHF |
| TZD        | - Beneficial with fatty liver, stroke  
- Less hypoglycemia  
- Cost | - Edema, weight gain  
- Durability |
| SGLT-2     | - ↓ wt, BP  
- Rare hypoglycemia  
- ↓ CV events/mortality  
- Renal protection | - Cost $$  
- GU infections, Fournier’s  
- Polyuria/vol loss, bones  
- DKA |
| GLP-1 RA   | - Wt loss  
- Less hypoglycemia  
- CV benefit | - Cost $$  
- Injectable  
- Pancreatitis  
- GI side effects |
Considerations for case:

- Would you continue her on her current regimen? ↑Metformin (change to XR) + glipizide, follow renal function, consider d/c of SU if hypoglycemia an issue
- Anything you would change? Stop Pioglitazone with CHF
- What would you consider adding? GLP-1, (Semaglutide, Liraglutide) or Empagliflozin
- Target be for A1c? <7-7.5%

ACP Guidance Statements:

1. Goals should be personalized
   - Benefits/harms of meds, preferences, general health/life expectancy, treatment burden and costs
2. Clinicians should aim for A1c between 7-8%
3. Consider de-intensifying treatment in those with A1c < 6.5% + type 2 dm
4. Those with life expectancy < 10 years, complex medical issues, etc, treatment should target minimizing symptoms of hyperglycemia not A1c.

Qaseem A et al, Annals IM 2018;168:569
My perspective:

• Personalization is critical—reviewing gains in outcomes, treatment burden, and cost all need to be considered.
  – The patient needs to participate
• A1c targets need individualization.
  – Lower likely better for more recently diagnosed, younger, uncomplicated
• Considering other co-morbidities and risk as people age (hypoglycemia, falls)

Case # 2

• 53 year-old woman with type 2 diabetes for 12 years, BMI 42, limited income
• Currently on metformin, glimepiride
  – Tried on other medications but couldn’t afford
• Limited monitoring, but most readings > 200mg/dl, A1c 10.3%
• Also symptomatic with polyuria, significant fatigue, recurrent yeast infections
**Key**

- **Analog**: Modified human insulin to act faster or slower
- **Short-acting**:  
  - Lispro: Admelog®, Humalog®  
  - Aspart: Novolog®  
  - Glulisine: Apidra®  
  - Regular - Novolin®, Humulin®, Relion®  
  - Afrezza®
- **Longer-acting**:  
  - NPH: Novolin®, Humulin®, Relion®  
  - Glargine: Lantus®  
    - Basaglar  
    - U300: Toujeo®  
  - Detemir: Levemir®  
  - Degludec: Tresiba®  
    - U100 and U200

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**Options for insulin**

<table>
<thead>
<tr>
<th>Basal- Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>1-2 hrs</td>
<td>4-8 hrs</td>
<td>14-18 hrs</td>
<td>$25-300</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-4 hrs</td>
<td>4-6 hrs</td>
<td>12-20 hrs</td>
<td>$300-450</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-6 hrs</td>
<td>Flat/3 hrs</td>
<td>22-24 hrs/24-36 hrs (U300)</td>
<td>$190-250</td>
</tr>
<tr>
<td>Degludec</td>
<td>1-9 hrs</td>
<td>10-12 hrs</td>
<td>42 hours</td>
<td>$450-550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bolus- Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>30-60 min</td>
<td>2-4 hrs</td>
<td>4-8 hrs</td>
<td>$25-140</td>
</tr>
<tr>
<td>Aspart, lispro, glulisine</td>
<td>5-15 min</td>
<td>1-2 hrs</td>
<td>3-5 hrs</td>
<td>$180-500</td>
</tr>
<tr>
<td>Inhaled</td>
<td>~ 15 min</td>
<td>~ 50 min</td>
<td>3 hours</td>
<td>$300</td>
</tr>
</tbody>
</table>
New Insulins:

- Afrezza® (inhaled insulin)
- Ademlog® (insulin lispro): biosimilar, no difference in efficacy/safety, cannot be substituted in pharmacies
- Fiasp® (insulin aspart): new ultra-rapid insulin, peak 1.5-2.2 hrs, approved to be dosed up to 20 min after eating
- Basaglar® (insulin glargine): biosimilar, no difference in outcomes, only in pens, no substitutions

My opinion on New Basal Insulins

<table>
<thead>
<tr>
<th>Pros/considerations</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Degludec (Tresiba®, U100 and U200) | - Shift workers  
- Missed doses  
- BID long-acting  
- Variable BG  
- Big doses (up to 160u) | - Only available in pens  
- Cost |
| U300 Glargine (Toujeo®) | - Missed doses  
- BID long-acting  
- Variable BG | - May require ↑ dose amount (up to 20%)  
- Cost |
Case for using Degludec:

- 23 year-old male with type 1 diabetes
- Very unstable household, food insecurity
- No monitoring, inconsistent insulin dosing
- At PPMC monthly with DKA
- Started on degludec (Tresiba®)
- Outcome: Assists with unpredictable schedule, dosing, not admitted for 6 months

Case # 2

- 53 year-old woman with type 2 diabetes 12 years, BMI 42, limited income
- Currently on metformin, glimepiride
  - Tried on other medications but couldn’t afford
- Limited monitoring, but most readings > 200mg/dl, A1c 10.3%
- Also symptomatic with polyuria, significant fatigue, recurrent yeast infections
Adding Basal Insulin
ADA Algorithm- 2018

• Start 10U/day, or .1-.2units/kg/day
  – Bedtime or AM, depending on pattern/adherence
  – Usually with metformin +/- other agent
• Adjust 10-15% or 2-4U once/twice weekly to reach FPG target
  – Generally fasting goals of 80-130mg/dl
    • Maybe higher in certain populations
• For hypoglycemia: determine cause
  – ↓ dose by 4U or 10-20%

Comparing Insulins

• In terms of A1c:
  – Degludec = glargine = detemir = NPH
• Small differences in weight
  – Less with detemir and Glargine-U300
• Less nocturnal hypoglycemia
  – Degludec, Glargine-U300
  – No difference in severe hypoglycemia
What is this?

Starting insulin

- Rotating injection sites, using fresh needles, needle length (4mm vs 8mm)
- Needle disposal
- Hypoglycemia education- rule of 10-15
- Monitoring frequency and glucose targets
- Pens vs vials
- Diabetes education
What about other agents when adding insulin?

- GLP1, DPP-4 SGLT-2, Metformin:
  - May reduce wt gain/dose needed
  - May worsen hypoglycemia risk
- Sulfonylurea (SU):
  - Better post-prandial BG, but ↑ hypoglycemia
  - Consider d/c when prandial insulin started
- TZDs:
  - Increased risk for edema with insulin

Wallia A, Molitch M. JAMA 2014;311:2315; Diab Care Supp 2017

Case # 2

- 53 year-old woman with type 2 diabetes 12 years, BMI 42, limited income
- Currently on metformin, glimepiride
- Limited monitoring, but most readings > 200mg/dl, A1c 10.3%
- Also symptomatic with polyuria, significant fatigue, recurrent yeast infections
- Would start on 15-20 units of NPH in the evening, and ask for morning BG
A little advocacy

Options for Advocacy:
www.t1international.com/usainsulin4allaction
https://makeinsulinaffordable.org
https://www.endocrine.org/advocacy/advocacy-in-action

Case #3

- 68yo with long-standing type 2 dm
  -> 18 years, using insulin for 12 years
- Monitoring BG 3-5x per day
- Frustrated by variability in BG readings, and hypoglycemia
- Wondering about new tools that might be helpful?
## Continuous Glucose Monitoring (CGM) in Type 2 Diabetes

- Benefits noted with type 2 DM
  - Reduction in hypoglycemia
  - Benefits increase with more frequent use
- Commercial coverage: pharmacy benefit in many cases
- Medicare Coverage
  - Diabetes + monitoring 4x per day + on MDI of insulin + needs adjustment + f/u every 6 months

Danne T et al, Diab Care 2017;

### Current CGM’s

- **Freestyle Libre®**
  - Worn for 14 days
  - No need for fingersticks/calibration
  - No alarms, 1 hour warm up
- **Dexcom G6®**
  - Worn for 10 days, no calibrations
  - Programmed to alarm for high and low readings
- **Medtronic Guardian®**
  - 7 day wear, linked with Apple phone, 2 calibrations per day
  - Combined with SugarIQ app
What they look like…

Comparison of Data

OR
Recent case…

• 72 yo with long-standing type 2 dm
  – Started on insulin after renal transplant, supposed to be taking lantus bid + premeal insulin
  – Referred to me to “fix diabetes”
• Reports monitoring BG 3-5x per day
  – But no meter, very worried about lows
• A1c 12%
• Refusing to adjust insulin

Results from Libre Pro

<table>
<thead>
<tr>
<th>CGM Device: FreeStyle Libre Pro</th>
<th>N/A % Compliant w/Calibration*</th>
<th>100% Time Worn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>408 mg/dL</td>
<td>88-116*</td>
<td></td>
</tr>
<tr>
<td>Time In Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Target Range 70-180 mg/dL</td>
<td>0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Above 180 mg/dL</td>
<td>100 %</td>
<td>19.1 %</td>
</tr>
<tr>
<td>Below 70 mg/dL</td>
<td>0 %</td>
<td>78.1 mg/dL</td>
</tr>
<tr>
<td>Coefficient of Variation (CV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.1 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-25*</td>
<td></td>
<td>10-26*</td>
</tr>
</tbody>
</table>

*Reference ranges calculated from population without diabetes.
Objectives

- Discussion of 3rd line agents
- New insulin options, and what to consider when cost is a barrier
- Tools to help make diabetes easier…
- *Keeping it practical and clinically oriented…*
When to add bolus?

- Basal should be 50% of total daily dose (TDD)
  - Estimate based on TDD 1-2u/kg/day
  - Consider if using > 60-70 units per day basal, or considering splitting glargine
  - A1c above goal
  - Start with largest meal

**START:** 4U, .1U/kg or 10% of basal; if A1c < 8% consider ↓ basal by same

**ADJUST:** ↑ dose by 1-2U or 10-15% 1-2x weekly until bg goal reached

**For hypo:** ↓ dose by 2-4U or 10-20%
Switching to NPH insulin

- Either Novolin, Humulin and Relion
  - Is available in a pen
- With BID Glargine/levemir, can transition 1:1 to NPH
  - NPH best given at bedtime c/w dinner
  - Remember midday peak (so may need less meal insulin with lunch)
- Once daily glargine to NPH
  - NPH needs to be BID
  - 2/3 in the AM, 1/3 in the PM, OR
  - ½ in the AM, ½ in the PM

Mealtime insulin- Regular

- When switching to Regular insulin:
  - Same branding as NPH- Novolin, Humulin, Relion
  - Same dose as analog insulin, given with meals (or 30 minutes prior to eating)
    - Remember longer to kick in, and longer duration of effect
    - Beware sliding scales
      - Takes motivation, education to determine doses
- Consider referral to teach how to mix insulin (reduce injection frequency)