Innovations in Insulin: New Opportunities to Individualize Therapy

CLINICAL INSIGHT

Dear Colleague:

Do you want to ensure the best management for your patients with type 2 diabetes mellitus? If so, remember these key points from our CME-certified activity, *Innovations in Insulin: New Opportunities to Individualize Therapy*:

Approximately half of patients do not attain their target glycated hemoglobin (HbA1c) level (generally <7.0%) after titrating a basal insulin analog

- Both fasting and postprandial glucose contribute to the HbA1c level
- As HbA1c drops below 8.0% or so, the postprandial glucose has a larger influence on the HbA1c level than fasting plasma glucose
- Basal insulin has negligible effect on postprandial glucose; thus adding a medication that targets postprandial glucose is often needed to lower HbA1c to 7% or less.

Degludec and glargine U-300 have a duration of action longer than 24 hours and a time-action profile that is flatter than detemir and glargine U-100

- The longer duration of action with degludec and glargine U-300 provides for once-daily dosing
- The flatter time-action profile contributes to a lower incidence of hypoglycemia, particularly nocturnal hypoglycemia

The cardiovascular safety of glargine U-300 and degludec are noninferior to glargine U-100

- Cardiovascular outcomes with glargine U-100 were shown to be noninferior to standard care over a median follow-up of 6.2 years in the ORIGIN trial (N=12,537)
    - Composite of myocardial infarction, stroke, cardiovascular death (hazard ratio 1.02; 95% confidence interval 0.94-1.11)
    - Composite of revascularization or heart failure hospitalization (hazard ratio 1.04; 95% confidence interval 0.97-1.11)
- Review of the new drug application for glargine U-300 led the US Food and Drug Administration (FDA) to conclude that glargine U-300 posed no cardiovascular safety concerns compared with glargine U-100+
- Cardiovascular outcomes with degludec were shown to be noninferior to glargine U-100 over a median follow-up of 2 years in the DEVOTE trial (N=7637)
    - Composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (hazard ratio 0.91; 95% confidence interval 0.78-1.06)
    - Composite of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, and unstable angina leading to hospitalization (hazard ratio 0.92; 95% confidence interval 0.80-1.05)

Aggressive titration of the basal insulin dose may increase the rate of severe hypoglycemia without improving HbA1c

- Results of a 24-week randomized trial (N=4823) resulted in HbA1c of 7.6% with a total basal insulin dose of 59.4 units/day compared with a HbA1c of 7.3% with a total basal insulin dose of 78.2 units/day (32% higher)
- The rates of severe hypoglycemia were 0.02 episodes/year vs 0.13 episodes/year in the 59.4 units/day and 78.2 units/day groups, respectively.

Consideration should be given to stop titrating the dose of basal insulin and initiating treatment aimed at lowering postprandial glucose if:

- HbA1c still not at goal with daily basal dose ≥0.5 units/kg
- HbA1c still not at goal despite normal fasting plasma glucose
- Fasting plasma glucose is normal, but the postprandial glucose is persistently above goal
- Further increases in the total daily dose of basal insulin result in hypoglycemia

Prandial (bolus) insulin is often initiated once daily before the largest meal of the day, ie, 'basal-plus'

- Aspart, glulisine, or lispro are preferred over regular human insulin because of their faster onset and shorter duration of action
- Dose can be initiated with 4-5 units or 0.1 unit/kg and then titrated upwards to achieve a:
    - 2-hour postprandial glucose <140 mg/dL
    - next meal or bedtime glucose <110mg/dL
- Self-monitoring of blood glucose (SMBG) is generally done 2 hours after the meal
    - Alternatively, SMBG can be done prior to the next meal or at bedtime (if prandial insulin is given with dinner)
- Sulfonylureas or meglitinides should be discontinued
    - Can continue metformin, thiazolidinedione, alpha-glucosidase inhibitor, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitor

Prandial insulins continue to evolve to offer a faster onset and shorter duration of action than regular human insulin or in a more concentrated formulation

- Inhaled Technosphere insulin has a faster onset and shorter duration of action than regular human insulin
    - Note: Faster-acting insulin aspart was approved by the US FDA in September 2017 as a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
- Lispro U-200 is more concentrated than U-100 bolus insulins, offering the advantage of a smaller injection volume for patients with high prandial insulin requirements.

Yours sincerely,

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