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RCT: Buse JB, Rodbard HW, Trescoli Serrano C, et al. "Basal Insulin Peglispro and Insulin Glargine in Patients With Type 2 Diabetes Previously Treated with Basal Insulin: IMAGINE 5". Diabetes Care. 2015 pii:dc151531.

Take-Home Message:
Basal insulin with Peglispro provides better glycemic control than glargine. Patients in the peglispro arm achieved statistically lower HbA1c% , experienced fewer nocturnal hypoglycemic despite higher insulin doses, and had less glucose variability. However, patient taking peglispro showed increases in aminotransferases, triglycerides, and liver fat content. Due to the concerns for hepatic effects, Eli Lilly announced in December 2015 that it is halting development of this new insulin to focus its efforts on other diabetes treatments.

Executive Summary:
This phase 3 open label, randomized controlled trial sought to evaluate the safety and efficacy of treating type 2 diabetics with basal insulin peglispro versus insulin glargine. Four hundred sixty-six adults with type 2 diabetes treated with basal insulin (glargine, detemir, or NPH) alone or with ≤3 oral antihyperglycemic medications with hemoglobin A1c ≤9% were enrolled and randomly assigned to basal insulin treatment with either peglispro or glargine and monitored for changes to baseline HbA1c at twenty-six and achievement of a target HbA1c of ≤7 after initiation of treatment. Patients assigned to the peglispro arm achieved statistically lower HbA1c% (reduction -0.82% vs -0.29%; least squares mean difference -0.52%, 95% CI -0.67 to -0.38; P<0.001). This superior reduction was maintained when followed to treatment week fifty-two. They also experienced fewer nocturnal hypoglycemic events (P<0.001), more patients achieved target HbA1c (P<0.001), glucose variability was lower (P<0.01), and total hypoglycemic rates were lower (P=0.03). Other noteworthy findings included statistically significant higher insulin doses in the peglispro arm, increased mean aminotransferases, increased triglycerides, and higher liver fat content as assessed in a subset of patients.

This is one of the first direct comparisons of two basal insulins which demonstrated superiority of one treatment over another. Improved glycemic control was achieved without an increase in nocturnal hypoglycemic events which is often the limiting side factor in titrating basal insulin to achieve glycemic targets. Peglispro has a longer duration of action (half-life of 2-3 days) and lower peak-to-trough ratio and reduced glucose variability in comparison to other basal insulins which likely accounts for the decreased nocturnal hypoglycemic events observed in this trial. Basal insulin peglispro has hepatopreferential action compared with insulin glargine with a liver-to-peripheral tissue activity distribution that is more consistent with the physiologic action of endogenous insulin secretion. Though an increased mean aminotransferases within or slightly above reference range was seen in the peglispro arm, no cases were associated with increases in bilirubin at or above two times the upper limit of normal.

Potential limitations of this phase 3 study include that is was an industry sponsored, open-label design which may increase risk of bias. Critics call for a longer, larger double blinded trial. Furthermore, patients had overall reasonably controlled diabetes at baseline HbA1c ≤9% and response to peglispro by patients with less well-controlled type 2 diabetes has not been studied. Lastly, the rise in aminotransferases, triglycerides, and liver fat content could have potentially significant long term implications on morbidity and mortality and thus critics are calling for a longer duration of follow up. Most notably, as of December 5,2015 Eli Lilly announced plans to cease development on peglispro due to “unresolved questions regarding changes in liver fat that developed during the late stages of drug testing.” (see more at: https://investor.lilly.com/releasedetail.cfm?releaseid=945541)

Guidelines

ADA Medical Care in DM on glucose-lowering medications in Type 2 Diabetes

-metformin is first-line drug of choice for type 2 diabetes (ADA Grade A)

-add second drug if glycemic goals not met on maximal tolerated dose of metformin monotherapy (ADA Grade A)

-add third drug if glycemic goals not met on 2-drug combination; options include

-other oral antidiabetic agent

-Injectable antidiabetic agent such as insulin, pramlintide, or glucagon-like peptide-1 receptor agonist

Practice changer? This drug has yet to be released to the market, and may never based on Eli Lilly ceasing development due to safety concerns. I agree with critics that longer observation is necessary to understand the long term effects on cardiovascular, hepatic and overall morbidity and mortality. However, I would be inclined to transition my type 2 diabetics on basal insulin to basal insulin with peglispro . The most attractive benefit is the decrease in nocturnal hypoglycemic events and decrease in HgA1c as compared to glargine. Eli Lilly was concerned about the additional recources it would take to prove safety in the setting of the concerns for liver effects, we will have wait to see if any one else will take this up.

The following will be included as a linked attachment in the weekly announcements:

Design

- Study design: phase 3, open-label, multicenter, multinational, randomized, controlled parallel-design trial.
- Patients: N=466
  - Intervention: Peglispro (n=307)
  - Control: Glargine (n=159)
- Setting: 65 centers in eight countries (Czech Republic, Germany, Greece, Israel, Romania, Russia, Spain, US)
- Enrollment: May 2012-December 2013
- Analysis: treat to target
- Mean follow-up: defined 52 week study

Population

- **Inclusion Criteria**
  - Adults ≥ 18yrs with Type 2 diabetes mellitus
  - Diabetes duration ≥1 year
  - Hemoglobin A1c ≤9%
  - Treatment with basal insulin (insulin glargine, insulin detemir, or NPH insulin) alone or with three or fewer oral antihyperglycemic medications for ≥90 days
  - BMI ≤ 45
- **Exclusion Criteria**
  - Use of a routine regimen of insulin glargine twice daily in the past 90 days or routine use of prandial insulin (rapid-acting) therapy anytime in the past 6 months, use of rosiglitazone, pramlintide, glucagon-like peptide-1 receptor agonist or weight loss medications within 90 days prior to screening
  - Use of niacin within 90 days
  - Use of lipid-lowering medication at a dose that was not stable within 90 days

- Any episodes of severe hypoglycemia, DKA, or hyperglycemic hyperosmolar nonketotic coma within 6 months
- NYHA class III or IV cardiac disease
- History of renal transplantation
- Current HD
- Serum Cr ≥2mg/dL
- Obvious clinical signs of liver disease (excluding NAFLD)
- Acute or chronic hepatitis
- Non-alcoholic steatohepatitis
- Elevated liver enzyme measurements (T bili ≥2x ULN, ALT and/or AST>2.5x ULN)
- Fasting triglycerides >400mg/dL
- Active or untreated malignancy
- In remission from clinically significant malignancy for <5 yrs
- Increased risk for new or recurrent cancer in the opinion of the investigator
- Blood transfusion or severe blood loss within 3 months
- Hgb abnormality known to interfere with measurement of HbA1c
- A known hypersensitivity or allergy to study insulins

- **Baseline Characteristics**
  - Mean age: 60 (Glargine arm) and 62 (peglispro arm)
  - Mean BMI: 32 (both arms)
  - Mean HbA1c ≤8%: 79% of patients (both arms)
  - Duration of diabetes: 12 years (both arms)
  - Baseline insulin use:
    - Glargine arm: 75% glargine, 16% detemir, 9% NPH
    - Peglispro arm: 71% glargine, 21% detemir, 8% NPH
  - Oral antihyperglycemic medications at or prior to randomization
    - Glargine arm: 88% metformin, 47% sulfonylureas or meglitinides, 21% dpp4 inhibitors, 4% thiazolidinediones
    - Peglispro arm: 86% metformin, 47% sulfonylureas or meglitinides, 26% dpp4 inhibitors, 6% thiazolidinediones
  - Oral antihyperglycemic medication use during treatment
    - Glargine arm: 5% none, 36% one, 52% two, 7% three
    - Peglispro arm: 5% none, 35% one, 46% two, 13% three

Interventions

- Randomized to basal insulin therapy with peglispro or glargine, oral antihyperglycemic medication doses were to remain stable except in emergency situations
- Bedtime dosing of study basal insulin was initiated and adjusted according to a treat-to-target algorithm defined in Supplementary Figure B. Algorithm adherence was mandatory up to week 26.
- Self-monitored blood glucose was performed each morning fasting, with two 6-point additional testing profiles (fasting prior to mid-day/evening meals, bedtime, 0300h and next day fasting) and whenever hypoglycemia was suspected.

- Hypoglycemia was defined as signs/symptoms of hypoglycemia or measured blood glucose ≤70mg/dL. Nocturnal hypoglycemia was an event occurring between bedtime and waking.

Outcomes Comparisons are peglispro therapy vs. glargine therapy

- **Primary Outcomes**
  - Change from baseline HbA1c to 26 weeks
    - -0.82% vs. -0.29%, least squares mean difference -0.52% (CI -0.67 to -0.38 P<0.001)
- **Secondary Outcomes:** To demonstrate superiority of peglispro versus glargine at/during 26 weeks of treatment for:
  - nocturnal hypoglycemia rate
  - percent patients with HbA1c<7% without experiencing nocturnal hypoglycemia
  - change in HbA1c
  - percent patients with HbA1c<7%
  - total hypoglycemia rate
  - laboratory fasting serum glucose
- **Adverse Events**
  - More injection site reactions with peglispro (n=6 versus n=0 with glargine). Serious adverse events were similar between groups (nonfatal MI, nonfatal stroke, CV death).
  - At 26 weeks, statistically significant higher values in the peglispro group in several parameters were noted: aminotransferases (AST 23.3 vs 28.7; p<0.001) (ALT 26.6 vs 35.9; p<0.001), triglycerides (143 vs 169; p <0.001) and liver fat content % based in MRI evaluation (9.1 vs 15.1; p<0.001)
- **Subgroup Analysis**

A subgroup analysis to assess liver fat content and abdominal visceral-to-subcutaneous fat ratio using MRI was performed. Patients receiving peglispro had higher visceral-to-subcutaneous fat ratios (0.72 versus 0.69 P=0.001). This contrasts with the phase 2 study findings in insulin-naïve patients with type 2 diabetes, where peglispro-treated patients and glargine patients demonstrated similar ratios.

Criticisms

- industry sponsored, open-label design which may increase risk of bias
- eligible patients had to have reasonably controlled diabetes at baseline (HbA1c ≤9%) which does not reflect the greater population of diabetics at large
- rise in aminotransferases, triglycerides, and liver fat content could have potentially significant long term implications on morbidity and mortality and thus there is a need for longer duration of follow up.

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