Created by Austin Rich, PharmD

Article Review: Insulin Icodec for Type 2 Diabetes Mellitus

Journal Article

Citation

Rosenstock J, Bajaj HS, Janez A, et al. Once-weekly insulin for type 2 diabetes without previous insulin treatment. *N Engl J Med*. 2020;383:2107-16.

Background

Type two diabetes mellitus (T2DM) is a chronic condition that results from insulin resistance or impaired insulin production. The ADA recommends the initiation of basal insulin in patients presenting with an A1c > 10% or in patients that cannot achieve glycemic control despite lifestyle modifications and maximum tolerated anti-diabetic medications. The initiation of insulin can be a challenge for many patients for a variety of reasons including needle phobia. There is data suggesting that once weekly formulations of GLP-1 receptor agonists improved adherence and consequently glycemic control compared to daily injections. Weekly insulin icodec was developed to overcome the barrier of daily injections for insulin initiation, improve patient adherence, and improve glycemic control.

Methods

Study Design

- Phase 2, randomized, double blind, double dummy, active control, parallel-group, multinational trial
- 247 participants underwent 1:1 randomization (125 to weekly icodec, 122 to daily glargine)
- 2-week screening period followed by a 26-week treatment period and then a 5-week follow up
- Treatment exposure period (per-protocol): participants were only included in final analysis if they did not have ancillary treatment (increase in metformin or DPP4 or initiation of a non-trial drug) or discontinued the trial

Intervention

- Initiation: insulin icodec 70 units weekly vs. insulin glargine 10 units daily
- Insulin dose adjusted weekly to achieve fasting BG of 70-108 mg/dL through an algorithm
  - Dose increased by an equivalent of 2 units/day or 14 units/week if fasting BG 100-126 mg/dL and by 4 units/day or 28 units/week if > 126 mg/dL
  - Dose decreased by an equivalent of 2 units/day or 14 units/week if lowest BG 54-69 mg/dL and by 4 units/day or 28 units/week if < 54 mg/dL

Inclusion and Exclusion

Inclusion	Exclusion
- Age 18-75 year - Diagnosed with T2DM $\geq$ 180 days prior to screening - A1c 7.0-9.5% - Stable daily dose of metformin > 1500 mg/day $\pm$ DPP4 inhibitor $\geq$ half max dose for 90 days prior to screening - Insulin naïve (< 14 days of insulin therapy or gestational diabetes treatment allowed) - BMI $\leq$ 40.0 kg/m^2	- Pregnant, breast feeding, intend to become pregnant, or of childbearing age without adequate contraception - Received any investigational medication within 90 days prior to screening - eGFR < 60 mL/min/1.73m^3, AST $\geq$ 2.5x or bilirubin > 1.5x upper normal limit, blood pressure $\geq$ 180/110 mmHg, uncontrolled diabetic retinopathy or maculopathy, or other conditions investigators thought would affect safety or compliance not related to T2DM - DKA within 90 days prior to screening and between randomization - MI, stroke, hospitalization for unstable angina pectoris/ transient ischemic attack within 180 days of screening - Planned coronary, carotid, or peripheral arterial revascularization - Anticipated initiation or change in concomitant medications know to alter weight or glucose metabolism (orlistat, thyroid hormones, or corticosteroids)

Results

Outcomes

Primary outcome: mean change in A1c from baseline to week 26

- Mean A1c in the icodec group decreased from 8.09% to 6.69% (-1.33%) and decreased from 7.96% to 6.87% (-1.15%) in the glargine group; estimated mean treatment difference of -0.18 (95% CI, -0.38 to 0.02; P = 0.08)

Secondary and safety outcomes

Outcome	Icodec	Glargine	Difference or Ratio (95% CI)
Fasting plasma glucose from baseline to week 26 – mg/dL)	-57.74	-53.86	-3.9 (-11.9 to 4.2)†
Mean 9-point patient measured blood glucose from baseline to week 26 – mg/dL	-48.63	-40.77	-7.86 (-14.10 to -1.62)†
Time with glucose level in range of 70-140 mg/dL during last 2 weeks of treatment – % participants	66.11	60.71	5.39 (0.69 to 10.09)†
Average weekly insulin dose – units	229.06	284.05	0.81 (0.69 to 0.94)*
Hypoglycemia alert - <70 and > 54 mg/dL – % participants	53.6	37.7	2.42 (1.50 to 3.88)‡
Combined level 2 (< 54mg/dL) or level 3 hypoglycemia (cognitive dysfunction) – % participants	16	9.8	1.09 (0.45 to 2.65)‡

†estimated difference *estimated ratio (icodec:glargine) ‡rate ratio

Authors Conclusion

Once weekly insulin icodec provided glucose lowering effects and a safety profile similar to those of once daily glargine for initial insulin therapy in patients with T2DM who were inadequately controlled with metformin with or without a DPP-4 inhibitor. Additionally, insulin icodec provided better control in 9-point patient measure blood glucose and resulted in about 78 minutes more time per day within glycemic range of 70-140 mg/dL. These clinical benefits in combination with reducing the number of yearly injections from 365 to 52 would provide a favorable alternative to daily basal insulin injections.

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Discussion	
Strengths	- Patient population consisted of candidates for initial insulin therapy rather than patients established on insulin - Per-protocol analysis allowed for comparisons of true medication effect differences and controlled for adherence - Blinded, double dummy design provided robustness to efficacy and safety findings
Limitations	- Patients failing to meet glycemic goals on metformin ± DPP4 inhibitor were included in this study, however patients were excluded if they were taking GLP-1 receptor agonists or SGLT2 inhibitors which are in many cases preferred adjunct therapies - Like other studies investigating glycemic control in patients with T2DM patients with an A1c > 10% were excluded, however the ADA mentions that insulin initiation at an A1c > 10% is common practice - Aggressive glycemic goal of 70-108 mg/dL may have inflated results of glycemic control and hypoglycemia rates - Doses of insulin were adjusted weekly for blinding purposes which delayed increases of daily glargine that would be done in clinical practice
Application	- Data from this trial warrants further investigation of insulin icodec as initial insulin therapy, particularly in those with an A1c > 10% or with the concomitant use of other anti-diabetics that are considered standard of care - There is potential to reduce patient pushback of insulin initiation with weekly insulin therapy if benefits are seen in a larger phase 3 trial with more inclusive criteria representing candidates for insulin initiation - There is a need for further investigation of equipotency of insulin icodec compared to other insulins due to the results showing differences in total weekly dose of icodec vs glargine