The Efficacy and Safety of Sitagliptin in Patients with Type 2 Diabetes and ESRD Receiving Dialysis: A 54-week Randomized Trial

BACKGROUND

- Diabetes is a leading cause of end-stage renal disease
- Treatment options for patients with diabetes and ESRD are limited due to safety and tolerability issues as they are often excluded from clinical studies

OBJECTIVE

- To determine the efficacy and safety of sitagliptin and glipizide monotherapy in patients with type 2 diabetes mellitus (T2DM) and ESRD on dialysis therapy

METHODS

- **Design:** Multinational, randomized, double-blind, parallel-group trial
- **Duration:** 54 weeks
- **Inclusion criteria:**
    - Age 30 or older at the screening visit with type 2 diabetes and ESRD
    - Hemodialysis or peritoneal dialysis therapy for at least 6 months
    - Patients on monotherapy or low-dose combination therapy with oral antihyperglycemic agents if their treatment could be discontinued during the run-in period
- **Exclusion criteria:**
    - Insulin therapy within 12 weeks of the screening visit
    - Type 1 diabetes
    - History of ketoacidosis
    - Acute kidney disease
    - History of kidney transplantation
    - Liver disease
    - A recent (within 6 months) cardiovascular event
    - Hepatic transaminase level 2 or more time the upper limit of normal
    - Repeated FPG level > 240 mg/dL
    - Triglyceride level > 600 mg/dL
- **Patients enrolled:** 129 patients total (64 in sitagliptin; 65 in glipizide)
- **Drug regimen:** Patients were randomly assigned to receive either sitagliptin 25 mg or glipizide initially started at 2.5 mg with the ability to titrate the dose as needed
- **Primary outcome:** To determine the safety and efficacy of sitagliptin by evaluating the A1c level from baseline
- **Secondary outcomes:** Comparison of sitagliptin versus glipizide on the incidence of symptomatic hypoglycemia and the change in A1c level from baseline; FPG, fasting serum insulin and proinsulin, and plasma lipid profiles; Homeostasis model assessment (HOMA) of beta-cell function, HOMA of insulin resistance (HOMA-IR), and proinsulin-to-insulin ratio were calculated from fasting values of FPG, insulin, and/or proinsulin
- **Power:** Assuming 10% of patients discontinued without a postrandomization measure, the study had 76% power to detect a true difference of 0.40 in the within-group mean decrease in A1c level from baseline, using a standard deviation of 1.1%
- **Data handling method:** intent-to-treat

RESULTS

- 92 patients completed the study (47 – sitagliptin; 45 – glipizide)
- **Primary outcome measure**: Sitagliptin led to a significant ($P < 0.001$) reduction in A1c level from baseline at week 54 and was well tolerated over the 54 weeks
- **Secondary outcome measures**: The difference in least squares mean (LSM) change for sitagliptin vs glipizide was 0.15% (95% CI, -0.18% to 0.49%). The plot of change in A1c level from baseline shows generally sustained

treatment effects from week 18 to week 54 for both treatment groups. The proportion of patients with an A1c level < 7% at week 54 was higher with glipizide (55.9%) compared with sitagliptin (43.5%) whereas the proportion of patients with an A1c level < 6.5% was not different between the glipizide (30.5%) and sitagliptin (29%);no p-values were reported. Both treatments led to reductions in FPG level from baseline at week 54. The between-group difference in LSM FPG level change at week 54 was 4.6 (95% CI, -11.5-20.7) mg/dL. No other outcomes were found to be statistically significant.

- **Author's conclusion:** Treatment with dose-adjusted sitagliptin provided clinically meaningful reductions from baseline A1c and FPG levels similar to those observed with glipizide over 54 weeks in patients with type 2 diabetes and ESRD on dialysis therapy. Sitagliptin was generally well tolerated in subjects.

STRENGTHS

- Counseling on diet and exercise based on ADA guidelines and ESRD recommendations
- The use of least squares means was appropriate
- Study design was multinational, randomized, double-blind, parallel-group trial
- The washout period was of appropriate length

LIMITATIONS

- Power was < 80%; increased chance of type II error limits the between-treatment efficacy comparison
- There is potential bias in the study based on support and financial disclosure indicated by the inclusion of slanted statements emphasizing non-statistically significant differences
- Patients' blood levels were assessed periodically but did not indicate how often
- Patients were informed ahead of time when adherence was going to be assessed
- Differences in clinical practices could exist between study sites
- Although the study was double-blind, the investigators could change the dose of the glipizide at will
- A1c and FPG were expressed as the mean +/- standard error rather than standard deviation
- The placebo run-in period was single-blind

CONCLUSION

- The present results showed that a once-daily sitagliptin dose of 25 mg for patients with ESRD produced a similar change in A1c level from baseline as glipizide
- A small sample size and weaknesses in the study design and analyses makes full comparisons between sitagliptin and glipizide difficult
- **Future research:** Further research should be done using a larger study sample with adequate power to better determine the role of sitagliptin for patients with diabetes and ESRD.

Reference: Arjona Ferreria JC, Corry D, Mongensen CE, Sloan L, Xu L, Golm GT, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis 2013;61(4):579-587

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