Efficacy and Safety of Initial Combination Therapy with Linagliptin and Pioglitazone in Patients with Inadequately Controlled Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study

BACKGROUND

- Type 2 diabetes is characterized by a progressive decline in beta cell function as well as insulin resistance. Many patients eventually require combination therapy for additive or synergistic improvement in glycemic control while aiming to minimize side effects.
- Linagliptin is a novel DPP-4 inhibitor that is excreted mainly via the enterohepatic system. Concomitant treatment with a DPP-4 inhibitor and a thiazolidinedione, such as pioglitazone, can be seen as rational without exacerbating adverse events.

OBJECTIVE

- To compare the efficacy, safety and tolerability of linagliptin 5mg and placebo when administered once daily for 24 weeks in combination with pioglitazone 30 mg once daily in patients with type 2 diabetes and insufficient glycemic control, as defined by HbA1c between 7.5-11.0%.

METHODS

- **Design:** 43 sites in seven countries, double-blinded, placebo-controlled, randomized parallel trial; Duration: 24 months
- **Inclusion criteria:** Patients with type 2 diabetes, age 18-80, inadequate glycemic control as evidenced by HbA1c between 7.5-11.0%, BMI less than or equal to 40 kg/m^2.
- **Exclusion criteria:** Myocardial infarction, stroke, transient ischemic attack or diabetic ketoacidosis within 6 months of enrollment; impaired hepatic function; known hypersensitivity or allergy to the study drugs or their excipients; treatment with GLP-1 analogues or agonists, insulin or anti-obesity drugs during the three months before enrollment; pre-menopausal women who were nursing, pregnant or of childbearing potential and not practicing birth control and patients with fasting blood glucose > 240 mg/dl at screening.
- **Primary outcome measure:** Change from baseline in HbA1c after 24 weeks of treatment.
- **Secondary outcome measures:** Percentage of patients achieving an HbA1c < 7.0%, the proportion that showed a reduction in HbA1c of at least 0.5% after 24 weeks and over time, change from baseline in fasting plasma glucose after 24 weeks and over time, changes in markers of beta cell function.
- 389 patients received either:
    - Pioglitazone 30 mg + linagliptin 5 mg once daily (N=259)
    - Pioglitazone 30 mg + placebo once daily (N=130)
- Power 97% to detect a 0.7% difference in HbA1c change from baseline.
- Data handling method was intent-to-treat.

RESULTS

- 111 patients in the placebo group and 244 patients in the linagliptin group completed the study.
- **Primary outcome measure:** Mean % change in HbA1c between the linagliptin and placebo arms was -0.51% [95% confidence interval (CI) -0.71, -0.30; $p < 0.0001$]

- **Secondary outcome measures:** Secondary outcome measures that were found to be statistically significant include results for patients achieving HbA1c < 7.0%, patients who achieved an HbA1c reduction of HbA1c ≥ 0.5%, percentage of patients with a reduction in non-adjusted HbA1c over time, mean change in FPG after 24 weeks of treatment, mean change from baseline in FPG between groups, ratio of relative change in adjusted geometric mean HOMA-IR. Non-statistically significant findings included the adjusted mean change from baseline for HOMA-IR, adjusted mean change from baseline in HOMA-β, adjusted geometric mean for the ratio of relative change at week 24 for HOMA-β, and adjusted mean change from baseline for DI. The safety analysis showed that the percentage of patients that experienced at least one adverse event was similar in both groups and that most adverse events were of mild or moderate intensity.
- **Author's conclusion:** Linagliptin 5 mg combined with pioglitazone 30 mg was effective and well tolerated.

STRENGTHS

- Random assignment adjusted for HbA1c and previous use of an oral anti-diabetic medication
- Study design was the gold standard for clinical trials

LIMITATIONS

- Pioglitazone was not an optimal anti-diabetic agent for use in this study as it is not one of the more widely used agents in type 2 diabetes and it does possess an unfavorable safety profile
- Diet, exercise, lifestyle factors, non-study concomitant medications and concomitant disease states were not addressed
- No power reported for subgroup analyses
- Not able to assess patients with hepatic or severe renal impairment

CONCLUSION

- Linagliptin may have advantages in that its main route of excretion is not renal or hepatic, but it is probably not going to be a widely used initial agent for type 2 diabetes due to cost and efficacy.
- Linagliptin does appear to produce an additional lowering of HbA1c of ~0.5% compared to pioglitazone alone. Clinical relevance may be limited due to the poor study design of this trial.
- Further research:
    - It would be important to conduct research in patients with hepatic and severe renal impairment, patients of varying race, obese patients, elderly patients, and patients younger than 18 to determine safety and efficacy in these populations.
    - It would also be useful to conduct research studying linagliptin monotherapy and/or in combination with metformin.

Reference: Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and Safety of Initial Combination Therapy with Linagliptin and Pioglitazone in Patients with Inadequately Controlled Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study. Diabetes Obes Metab. 2011 Jul;13(7): 653-61.

Prepared by: Megan Bodge, Doctor of Pharmacy Candidate