

Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage

BACKGROUND:

- It has been shown that over time metformin monotherapy may be ineffective in maintaining glycemic control long-term.
- Because metformin has been associated with increasing adverse effects as the dose increases, it was hypothesized that adding saxagliptin would allow for better control of blood glucose without unnecessary adverse effects.
- Due to the multifactorial pathophysiology of diabetes, the use of medications with multiple mechanisms of action is logical.

OBJECTIVE

- The objective of the study was to determine if adding saxagliptin to extended-release metformin therapy was superior to up-titrating metformin daily dosage in the maintenance of type 2 diabetes.

METHODS

- **Design:** Phase IIIb, randomized, double-blind, multicenter, parallel, experimental trial; duration 18 weeks
- **Inclusion criteria:** Adults with type 2 diabetes mellitus taking stable daily doses of metformin (between 850-1500mg daily) for at least 8 weeks before screening with HbA1c between 7.5-11.0%, fasting C-peptide levels above 1ng/ml and a BMI less than 45 kg/m².
- **Exclusion criteria:** Patients with poorly controlled diabetes, those who had a weight loss >10% in the previous 3 months, pregnancy or lack of contraception in women of childbearing age, history of diabetic ketoacidosis or hyperosmolar nonketotic coma, insulin therapy within 1 year, significant cardiovascular history, renal disease, alcohol or drug abuse within 1 year, unstable psychiatric disorder, hemoglobinopathies, donation of plasma within 3 months, acute liver disease or abnormal liver function tests, anemia, significant abnormalities on lab screening tests or electrocardiograms, use of investigational drugs within 1 month, any anti-hyperglycemic therapy other than the qualifying dose of metformin within 8 weeks, treatment with potent CYP 3A4 inhibitors or inducers, contraindications to treatment with saxagliptin or previous intolerance to metformin 2000mg.
- **Primary outcome measure:** Change from baseline HbA1c at week 18
- **Secondary outcome measures:** Change from baseline in 120 minutes post-prandial glucose, fasting plasma glucose, and the proportion of patients with a HbA1c <7.0% at week 18
- **Treatments assigned:** Of the 393 patients that participated in the lead in phase, 282 patients were randomized into two treatment groups. 138 patients received 5mg saxagliptin plus metformin XR 1500mg, and 144 patients were assigned to receive the up-titrated metformin dosage of 500mg XR plus 1500mg XR daily.
- Data handling method was intent-to-treat.

RESULTS

- A total of 279 patients completed the study, with 137 in the saxagliptin plus metformin arm and 142 in the up-titrated metformin arm.
- **Primary outcome measure:**
 - Patients receiving saxagliptin plus metformin had a statistically significant reduction in HbA1c compared to those receiving up-titrated metformin. Adjusted mean change from baseline was -0.88% (SE 0.071%) for the saxagliptin group and -0.35% (SE 0.081%) for the uptitrated group. The between group difference was -0.53% (95% CI -0.73 to -0.31, $P < 0.0001$).

- **Secondary outcome measures:**
 - For the change from baseline in 120 minutes post-prandial glucose (measured by a mixed meal tolerance test), the saxagliptin group saw a mean change from baseline of -1.75 mmol/L (SE 0.277) and the uptitrated group saw a change of -0.46mmol/L (SE 0.282). The between group difference was -1.29mmol/L (95% CI -2.07 to -0.51, $P = 0.0013$).
 - The change in fasting plasma glucose was -1.11mmol/L (SE 0.17) for the saxagliptin group and -0.38mmol/L (SE 0.17) for the uptitrated group. The between group difference was -0.73 (95% CI -1.21 to 10.25, $P = 0.0030$).
 - The proportion of patients with a HbA1c <7.0% at week 18 was 51% (SE 37.2) in the saxagliptin group and 37% (SE 26.1) in the uptitrated group. The between group difference was 11.2 (95% CI 0.2-22.0, $P = 0.0459$).
- **Author's conclusion:** The addition of saxagliptin 5mg to metformin XR 1500mg provided significantly greater improvements in HbA1c, 120 minute post prandial glucose, fasting plasma glucose, and the proportion of patients achieving HbA1c < 7.0% in 18 weeks versus increasing the dose of metformin XR to 2000mg daily.

STRENGTHS

- Assessed the role of combination therapy in diabetes patients compared to current first-line treatments
- Minimized the risk of Type I error by using a fixed-sequence statistical analysis method

LIMITATIONS

- Bias of the authors is present, as evidenced by downplaying the adverse effects of saxagliptin plus metformin, outcome measures that would be affected by saxagliptin but not an increase in metformin dosage, and presenting outcome results using SE
- The lead-in period resulting in an unaccounted for increase in daily metformin dose for some patients could affect results of the study
- Overall short duration of study

CONCLUSION

- The study showed that treatment saxagliptin plus metformin produced better results than increasing the dose of metformin therapy.
 - However, bias is a huge concern for this study, due to the authors' affiliations and study support.
 - The true benefit of adding saxagliptin to metformin therapy versus uptitrating metformin dosage remains to be shown in a well-designed, credible study.
- Future research:
 - Well-designed, bias-free studies are needed in the same area of study to prove or disprove the results found in this article.
 - A study in patients recently diagnosed (and therefore using lower doses of metformin) would be helpful to better assess the glycemic outcomes.
 - Research involving other DPP-4 inhibitors would be beneficial to determine if these medications possess a class-effect of better glycemic control.

Reference: Foncseca V, Zhu T, Karyekar C, Hirshberg B. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. *Diabetes, Obesity, and Metabolism*. 2012;14:365-71.

Heather Hall, PharmD Candidate