SAFETY AND EFFICACY OF EXENATIDE OVER 16 WEEKS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS USING A THIAZOLIDINEDIONE WITH OR WITHOUT METFORMIN

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Exenatide, an incretin mimetic for the treatment of type 2 diabetes mellitus (T2DM), mimics several glucose-lowering actions of GLP-1 including glucose-mediated insulin secretion. Adjunctive therapy of exenatide and a TZD with or without metformin may reduce glucose levels by targeting the central defects of T2DM: beta cell dysfunction and insulin resistance.

This study was a randomised, placebo-controlled, parallel, double-blind trial in 233 patients with elevated HbA_{1c} (range: 7.1-10.0%) in spite of therapy with a TZD alone (20%) or a TZD with metformin (80%). Patients (129M, 56±10y, BMI 34±5kg/m^2, HbA_{1c} 7.9±0.9% [mean±SD]) received subcutaneous injections of placebo or exenatide BID for 16 weeks. Patients that received exenatide received 5 μg BID for 4 weeks followed by 10 μg BID for 12 weeks. Endpoint measures included HbA_{1c}, fasting serum glucose (FSG), body weight, 7-point self-monitored blood glucose (SMBG), safety, and tolerability.

For exenatide, 71% of patients completed the study versus 86% for placebo. Exenatide decreased mean HbA_{1c} by -0.8±0.9% from baseline (treatment effect, -0.9%, p<0.0001). With exenatide, 62% of patients achieved HbA_{1c} ≤7% versus 16% with placebo (p<0.0001); 29% achieved HbA_{1c}≤6.5% with exenatide versus 8% with placebo (p=0.0002). Mean FSG for patients who received exenatide was -1.5mmol/L lower than placebo (p<0.0001). Exenatide reduced mean body weight from baseline versus placebo (-1.5±3.1 kg vs. -0.2±2.5 kg, respectively, p<0.001). Mean daily 2-h SMBG postprandial excursions for exenatide were lower than baseline (-1.4±1.4mmol/L, p<0.0001) with greatest differences after breakfast (-1.9±2.9mmol/L, p<0.0001) and dinner (-1.9±2.5 mmol/L, p<0.0001). Placebo-treated patients showed no significant reductions in postprandial glucose excursions from baseline at any meal but demonstrated a reduction in the daily mean glucose concentration (p=0.0408). Exenatide reduced the proinsulin/insulin ratio over placebo (p=0.0337) and increased HOMA-B versus placebo (p=0.0032). No statistically significant difference in HOMA-S existed between groups. The most frequent adverse event was nausea (40% exenatide vs. 15% placebo); there was no significant difference in incidence of hypoglycaemia.

These findings support the potential use of exenatide as adjunctive therapy for patients with T2DM who inadequately control glucose levels with a TZD alone or in combination with metformin.