

Effect of Thiazolidinediones on Glycemia

Yale JF, Valiquett TR, Ghazzi MN, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001;134(9 Pt 1):737-45.

Study Overview

Objective. To determine the effects of troglitazone on hemoglobin A_{1c} (HbA_{1c}) levels in diabetic patients with poor glycemic control. (This trial was completed before troglitazone was taken off of the U.S. market.)

Design. Randomized, double-blind placebo-controlled trial followed by an open-label extension.

Setting and participants. Patients aged 40 years and older with a diagnosis of type 2 diabetes mellitus were screened at 16 sites in Canada. Inadequate glycemic control, defined as HbA_{1c} levels of at least 0.085 despite stable treatment with maximum tolerated doses of metformin and sulfonylurea, was required for recruitment into the study. Patients were excluded for a variety of reasons, including previous long-term insulin treatment, current use of fenfluramine or glucocorticoids, elevated serum creatinine concentration or alanine aminotransferase (ALT) level, cardiac insufficiency, active cancer within 5 years of screening, or body mass index greater than 40 kg/m².

Intervention. After a 4-week placebo lead-in period, patients were randomized to receive either troglitazone 400 mg/day or placebo once daily for 24 weeks in addition to current treatment with metformin and sulfonylurea. This double-blind phase was followed by a 24-week open-label phase, during which all study patients either started or continued troglitazone 400 mg/day. Fasting glucose levels and biochemical measures of safety (ALT and aspartate aminotransferase levels, hematologic tests, urinalysis) were performed at 4-week intervals throughout the study. Levels of HbA_{1c}, total plasma insulin, and lipids were measured at randomization and at 4-week intervals beginning with week 12. Researchers also documented symptomatic hypoglycemic events, which were characterized by type of intervention required to alleviate the event and by severity. Physical examination and electrocardiography were performed as additional safety assessments before randomization and at the end of the double-blind and open-label studies. Patients were withdrawn at their own discretion or if a clinician

judged that their glucose levels were acutely deleterious, if patients did not adhere to the protocol (less than 80% adherent to the study drug regimen), or if patients had an intolerable adverse event.

Main outcome measures. Levels of HbA_{1c}, fasting plasma glucose, total insulin, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Main results. Out of 328 patients screened, 200 were randomized: 99 to the placebo group and 101 to the troglitazone group. Baseline patient characteristics were similar between groups. A small number of patients (13 receiving placebo and 9 receiving troglitazone) withdrew early, primarily because of lack of treatment efficacy. At the end of the double-blind phase, troglitazone significantly increased the proportion of patients achieving target HbA_{1c} levels compared with placebo (HbA_{1c} of 0.08 or less, 43% versus 6% [$P < 0.001$]; HbA_{1c} of 0.07 or less, 14% versus 1% [$P < 0.001$]). The proportion of patients achieving a fasting plasma glucose level of 140 mg/dL or less was also greater in the troglitazone group (17% versus 4%, $P = 0.004$). When switched to troglitazone in the open-label phase, placebo patients achieved target glucose control measures in similar proportions to troglitazone patients (HbA_{1c} of 0.08 or less, 50%; HbA_{1c} of 0.07 or less, 19%; fasting plasma glucose of 140 mg/dL or less, 23%). Treatment efficacy was maintained after 12 months among troglitazone patients who reached target glycemic levels in the double-blind phase (HbA_{1c} level of 0.08 or less, 45%; fasting plasma glucose level of 140 mg/dL or less, 14%); these numbers were significantly lower when lower target levels were assessed (HbA_{1c} of 0.07 or less, 15%; fasting plasma glucose of 126 mg/dL or less, 9%). During the double-blind study,

(continued on page 15)

"Outcomes Research in Review" is edited by Adam Jonas, MD, MPH, Medical Director for Health Services, Washington State Department of Corrections, Olympia, WA, and Benoit Tonneau, MD, Clinical Assistant Professor of Medicine, Department of Medicine, Albany Medical College, Albany, NY. Dr. Tonneau prepared review 1; Dr. Jonas prepared reviews 2-4.

(continued from page 11)

triglyceride levels increased in the placebo group (+17%) and decreased in the troglitazone group (-5%); neither result was significant. Troglitazone patients showed a significant increase in HDL and LDL cholesterol levels ($P = 0.012$ and 0.002 , respectively, compared with controls) but not in total cholesterol ($P > 0.2$). In addition, mean body weight increased significantly in the troglitazone group from baseline to week 24 (2.4 ± 0.4 kg, $P < 0.001$). Adverse events occurred at similar rates in both groups.

Conclusion. The thiazolidinedione troglitazone, at 400 mg/day, is effective in combination with metformin and sulfonylurea. Thiazolidinediones may therefore offer an alternative to insulin therapy for patients taking metformin and sulfonylurea who do not achieve adequate glycemic control.

Commentary

This study is the first to examine thiazolidinedione use in combination with sulfonylurea and metformin. Some research has focused on therapy with a thiazolidinedione and either sulfonylurea or metformin but not both. A study by Einhorn et al [1] demonstrated that combined pioglitazone and metformin was more effective than metformin alone at reducing HbA_{1c}; another study showed similar results using rosiglitazone [2]. The strengths of Yale and colleagues' study lie in its design (randomized controlled trial) and acceptable drop-out rate. Several weaknesses are also apparent. For example, the number of subjects enrolled in the study was relatively small, which probably explains why no cases of liver toxicity were found in the treatment group. (Troglitazone's association with liver toxicity resulted in the agent's removal from the U.S. market.) The authors did not measure the occurrence of fluid retention with occasional edema, an important side effect of thiazolidinediones. Further, the question of whether study patients received nonpharmacologic interventions (eg, diet or exercise counseling, diabetes education) in conjunction with drug therapy remains unclear. Use of such interventions would affect the study's applicability to a general office where intensive nonpharmacologic treatment may not be available.

Some of Yale and colleagues' findings confirm other study results, particularly from the UKPDS, suggesting the difficulty of achieving HbA_{1c} levels of 0.07 in type 2 diabetes. Only 43% of Yale et al's patients had an HbA_{1c} level of less than 0.08 at 6 months. Compared with the most recent guidelines from the American Diabetes Association (ADA)

[3], the authors' findings seem even less favorable. The ADA now recommends that target HbA_{1c} levels in patients with type 2 diabetes should be 0.07 or less; in this study, only 14% of troglitazone patients achieved that goal. Thus, although it shows some effectiveness, the tri-drug study therapy is not effective enough to achieve HbA_{1c} goals in the majority of patients. Larger questions about this treatment must be addressed in future research. Because the study was limited to 48 weeks, the therapy's long-term effectiveness is not known. Also, given that troglitazone is not available as a treatment option, the applicability of study findings to newer thiazolidinediones should be determined. Further studies are needed to examine the effects of tri-drug therapy (combined thiazolidinediones, metformin, and sulfonylurea) on microvascular and macrovascular complications as well as the long-term significance of the slight rise in HDL and LDL cholesterol levels seen in the lipid profile.

Applications for Clinical Practice

Although this study demonstrated the effectiveness of troglitazone combined with sulfonylurea and metformin, troglitazone is no longer available in the United States. Safety profiles of the new thiazolidinediones seem better; however, a few cases of liver toxicity have been documented [4], and liver function should be monitored in patients receiving these agents. Notably, the majority of patients receiving tri-drug therapy will likely not reach the goal HbA_{1c} level of less than 0.07. Because of these findings, thiazolidinediones should not be used as first-line agents until more is known about their long-term efficacy and safety.

References

1. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. *Clin Ther* 2000;22:1395-409.
2. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000;283:1695-702.
3. American Diabetes Association: clinical practice recommendations 2001. *Diabetes Care* 2001;24:S1-126.]
4. Al-Salman J, Arjomand H, Kemp DG, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone. A case report [published erratum appears in *Ann Intern Med* 2000;133:237]. *Ann Intern Med* 2000;132:121-4.

Copyright 2001 by Turner White Communications Inc., Wayne, PA. All rights reserved.