Rosiglitazone in Diabetes Control in Hemodialysis Patients With and Without Viral Hepatitis Infection

Effectiveness and side effects

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OBJECTIVE — Thiazolidinedione (TZD) may provide an additional benefit of cardiovascular protection in diabetic patients through targeting of insulin resistance. However, use of a TZD is hampered by possible effects of fluid retention and hepatotoxicity. In this study we aimed to determine whether the risk of TZD-induced fluid retention or hepatic injury is higher in hemodialysis patients with persistent viral hepatitis infection.

RESEARCH DESIGN AND METHODS — This was a prospective, cohort study on hemodialysis patients. Type 2 diabetic patients with A1C levels of >8% were followed for at least 12 months. Rosiglitazone was initiated at 2–4 mg/day. The primary outcome was the target A1C (<7%) achieved and dosages of rosiglitazone. Secondary outcomes included changes in lipid profile and inflammatory biomarkers. Safety evaluations were number of hypoglycemic episodes, changes in liver transaminase levels, cardiothoracic ratio (CTR), fluid status control during dialysis, and events of symptomatic heart failure.

RESULTS — A total of 78 patients, including 15.4% ($n = 12$) hepatitis B surface antigen–positive and 16.7% ($n = 13$) anti–hepatis C virus (HCV)-positive patients, were enrolled. The mean follow-up period was 15.4 ± 3.8 months. The diabetic response rate (A1C <7%) to rosiglitazone was 86.1%. The serum triglyceride level was reduced (194 ± 112.5 to 168 ± 88 mg/dl, $P = 0.037$) more significantly than the total cholesterol level (178 ± 42.1 to 174 ± 46.5 mg/dl, $P = 0.13$). High-dose rosiglitazone (8 mg/day) reduced the serum level of C-reactive protein and increased the serum adiponectin level significantly. After rosiglitazone, interdialysis weight gain (2.07 ± 1.6 to 3.2 ± 1.2 kg, $P < 0.01$) and mean CTR (48.2 ± 5.6 to 50.4 ± 6.2%, $P = 0.0213$) of individuals increased significantly. Nevertheless, liver aminotransferase (aspartate aminotransferase and alanine aminotransferase) levels did not show a tendency to increase in patients ($n = 25$) with viral hepatitis B or C infections.

CONCLUSIONS — Among regular hemodialysis patients with chronic viral hepatitis infections, rosiglitazone may be safely used for diabetes control. However, one must be aware that a possible effect of its use is a deterioration in cardiovascular reserve.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CTR, cardiothoracic ratio; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Taiwan has the highest incidence of end-stage renal disease (ESRD) in the world (1). Diabetes not only leads to ESRD but also predisposes patients to higher cardiovascular risk and chronic inflammatory conditions through multifactorial mechanisms including insulin resistance (2,3). Previously, we demonstrated that the prevalence of insulin resistance in patients receiving long-term dialysis is high (4,5). Thiazolidinediones (TZDs) enable effective targeting of insulin resistance, which may provide an additional cardiovascular benefit with control of diabetes in ESRD patients. Rosiglitazone, classified as a TZD, has been reported to possess cardiovascular protection with its anti-inflammatory (2,6) and lipid-lowering effects (7). However, because of concerns about fluid retention and hepatic injury associated with TZDs, their use is not recommended in patients with advanced heart failure (8,9) and/or liver insufficiency (10,11).

Hemodialysis patients, because of their nearly absent urine output, may have additional risks of water retention if they are given TZDs. In contrast, we believe that hemodialysis therapy may reduce the risk of fluid retention by regular fluid removal every 2–3 days. Whether TZDs are associated with a net advantage or disadvantage among hemodialysis patients remains undetermined.

Taiwan is an endemic area for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections (12,13). Although there are a few reports of TZD-induced acute hepatic injury (10,11), a systemic study of safety issues with regular use of TZDs in high-risk patients, such as those with chronic HBV or HCV infections, is lacking. Thus, in this study, we elucidate whether the risk of TZD-induced hepatic injury is higher in ESRD patients with HBV or HCV infections.

We had four aims in this study: *1*) to evaluate the effectiveness of rosiglitazone in diabetic patients receiving regular hemodialysis; *2*) to evaluate the impact of rosiglitazone on fluid control and cardio-

Table 1—*Baseline demographic data and characteristics of type 2 diabetic patients undergoing hemodialysis who received rosiglitazone and were included for effectiveness* (n = 72) *and safety* (n = 78) *evaluation*

Age (years)	56.8 ± 7.2
Sex (male:female)	36:42
Duration on hemodialysis (months)	28.2 ± 8.4
Kt/V	1.62 ± 0.26
Existing hypoglycemic agent (%)	28
Existing insulin (%)	42
Physical measurements	
Systolic blood pressure (mmHg)	134 ± 16
Diastolic blood pressure (mmHg)	86 ± 14
Weight (kg)*	57.4 ± 10.6
BMI (kg/m^2)	24.2–33.6
CTR (%)†	48.2 ± 5.6
Biochemical parameters	
Fasting glucose level (mg/dl)	142 ± 21
A1C (%)	8.6 ± 0.6
Albumin (g/dl)	3.8 ± 0.3
Blood urea nitrogen (mg/dl)	78 ± 16
Creatinine (mg/dl)	8.6 ± 1.6
AST (IU/l)	19.2 ± 5.4
ALT (IU/l)	13.4 ± 4.8
Alkaline phosphatase (IU/l)	75 ± 8.6
Total cholesterol (mg/dl)	178 ± 42.1
Triglyceride (mg/dl)	194 ± 112.5
HDL cholesterol (mg/dl)	36 ± 16
LDL cholesterol (mg/dl)	110 ± 23
Comorbidities	
Hypertension (%)‡	46
Coronary artery disease (%)	26
HBV (%)§	15.4
HCV (%)§	16.7
Smoking (%)	9.1

Data are means ± SD or range unless otherwise indicated. *Weight, expressed as midweek predialysis weight (dry weight). †The CTR is the maximum transverse diameter of the heart divided by the greatest internal diameter of the thoracic cage (from inside of rib to inside of rib). ‡Hypertension was defined by midweek predialysis levels of blood pressure, measured at the hemodialysis unit, according to criteria of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) or receipt of antihypertensive agents. §HBV is defined as patients with hepatitis B surface antigen-positive carrier status, and HCV is defined as patients with anti-HCV antibody.

vascular function in this hemodialysis population; 3) to evaluate variations in liver enzyme levels during TZD therapy in hemodialysis patients with or without chronic viral hepatitis infections; and 4) to compare inflammatory parameters and lipid profiles before and during TZD therapy. Our observations may provide the clinical basis for the pharmacological effectiveness and safety of rosiglitazone in ESRD patients.

RESEARCH DESIGN AND METHODS

— At the time of this study, there were >400 ESRD patients receiving regular renal replacement therapy in our unit. We prospectively established annual mortality and hospitalization indexes as well as collecting patients' demographic and laboratory data since 2002 as mentioned elsewhere (14,15). Among this population, patients with type 2 diabetes were included if their A1C was >8% at enrollment, despite management with diet alone or with medications (oral hypoglycemic agents or insulin). None of the patients used any form of TZD or hydroxymethylglutaryl-CoA reductase inhibitor (statin) at enrollment. All patients studied underwent hemodialysis two to three times weekly for 4 h/session with a bicarbonate-based dialysate.

The exclusion criteria were renal transplantation, symptomatic heart failure (New York Heart Association class III or above), poor compliance with water control (history of acute lung edema in the past 3 months before enrollment or ultrafiltration volume >4 kg at most hemodialysis sessions), and elevated baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels (>2.5 times the upper limit of normal). All of the data were obtained by routine biochemical, hematological, and other studies. The institutional review board approved the study.

Blood pressure was measured before hemodialysis with patients in the recumbent position. Blood samples were drawn immediately before hemodialysis was started, collected in Vacutainer tubes containing EDTA, centrifuged, and aliquoted, and then kept frozen at −80°C until assay.

Between January 2002 and July 2005, we conducted this prospective, observational cohort study through a nonrandomized intervention. We monitored patients who were treated with rosiglitazone in addition to their existing therapy, including other oral hypoglycemic agents or insulin. Rosiglitazone was initiated at 2–4 mg/day and could be titrated to a maximum of 8 mg/day as judged by the investigators to achieve a glycemic target of A1C <7%. For study subjects, A1C was monitored once every 2–3 months or when adverse effects occurred. During the observational period, doses of preexisting antidiabetic agents and other required medications could be administered or altered with detailed recording. Patient characteristics at enrollment are listed in Table 1.

Study evaluations

Outcome assessments. The primary outcomes were levels of A1C achieved and the doses of rosiglitazone prescribed. Secondary outcomes included changes in lipid profiles and inflammatory biomarkers during the study period. The intended observation period for each patient was at least 12 months after initiation of rosiglitazone. Subjects followed for <3 months but >1 month were excluded from the efficacy analysis and were included in the final analysis of safety.

Safety assessments. Safety evaluations were number of hypoglycemic episodes during the study, changes in profiles of liver transaminase enzymes, cardiothoracic ratio (CTR) (routinely performed on a regular basis of 3–6 months in our hemodialysis unit), changes in body weight and ultrafiltration volume during each hemodialysis session, and events of symptomatic heart failure.

Blood sample assays. Biochemical data were determined through standard laboratory techniques and by using a Hitachi

Table 2—*Effectiveness and safety profiles during rosiglitazone therapy

Category and variables	At baseline	At end	*P* value
Effectiveness profiles			
Diabetic parameters			
Fasting glucose level (mg/dl)	142 ± 21	102.8 ± 24	<0.01
A1C (%)	8.6 ± 0.6	7.1 ± 0.5	<0.01
Lipid profiles			
Total cholesterol (mg/dl)	178 ± 42.1	174 ± 46.5	0.589
Triglyceride (mg/dl)	194 ± 112.5	168 ± 88	0.037
HDL cholesterol (mg/dl)	36 ± 16	38.6 ± 7.8	0.217
LDL cholesterol (mg/dl)	110 ± 23	118.2 ± 14	0.141
Inflammatory biomarkers: human serum CRP (mg/l)	4.22 ± 1.2	3.24 ± 0.9	0.092
Safety parameters			
Kt/V	1.62 ± 0.26	1.58 ± 0.31	0.403
Systolic blood pressure (mmHg)	134 ± 16	128 ± 21	0.061
Diastolic blood pressure (mmHg)	86 ± 14	88 ± 16	0.407
Weight (kg)†	57.4 ± 10.6	60.2 ± 11.8	0.121
Ultrafiltration (kg/per hemodialysis session)	2.07 ± 1.6	3.2 ± 1.2	<0.01
CTR (%)‡	48.2 ± 5.6	50.4 ± 6.2	0.0213
Albumin (g/dl)	3.8 ± 0.3	3.9 ± 0.4	0.081
Blood urea nitrogen (mg/dl)	78 ± 16	76 ± 12	0.381
Creatinine (mg/dl)	8.6 ± 1.6	8.8 ± 1.4	0.395
AST (IU/l)	19.2 ± 5.4	18.6 ± 4.3	0.443
ALT (IU/l)	13.4 ± 4.8	11.2 ± 5.7	0.097
Alkaline phosphatase (IU/l)	75 ± 8.6	79 ± 9.4	0.115

Data are means ± SD. *Effectiveness profiles (n = 72) include effects on diabetes control and changes in lipid profiles and inflammatory biomarkers during rosiglitazone therapy. Safety parameters (n = 78) indicate the safety profile recorded during rosiglitazone therapy. †Weight, expressed as midweek predialysis weight (dry weight). ‡The CTR is the maximum transverse diameter of the heart divided by the greatest internal diameter of the thoracic cage (from inside of rib to inside of rib).

747 autoanalyzer for blood urea nitrogen, ALT, AST, and alkaline phosphatase. C-reactive protein (CRP) was assayed on an Immage autoanalyzer with the nephelometric method (Beckman Coulter) (5). Plasma adiponectin and interleukin-6 levels were assayed using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) (5). Serum HBV antigen, anti–hepatitis B surface antibody, and anti-HCV antibody were measured with third-generation enzyme-linked immunosorbent assay kits (Abbott, Abbott Park, IL) (14).

Statistical analysis

Data are expressed as means ± SD except where stated otherwise. Differences in the patient characteristics before and after rosiglitazone were assessed with a χ^2 test for categorical variables and by ANOVA. Bonferroni tests were used for continuous variables. All of the statistical calculations were performed with SPSS 10.0 for Windows.

RESULTS — By the end of July 2005, 78 patients were enrolled (Table 1). Of these, 72 (92.3%) were eligible for analysis, and 6 (7.7%) who received rosiglitazone therapy for <3 months were included in the safety evaluation only. The main reason for stopping rosiglitazone was the patient's wish. The mean follow-up period was 15.4 ± 3.8 months (range 10–21 months). The mean age was 56.8 years. The mean duration of regular hemodialysis was 28.2 ± 8.4 months (16–62 months). A total of 5.4% (n = 12) of patients were carriers of HBV infection, defined as serum hepatitis B surface antigen–positive, whereas 16.7% (n = 13) had chronic HCV infection. Serum AST and ALT levels (means ± SD) at enrollment were 19.2 ± 5.4 and 13.4 ± 4.8 IU/l, respectively.

Effectiveness study

A total of 72 patients were enrolled for analysis of effectiveness. We show in Table 2 and Fig. 1 the effects of rosiglitazone on diabetes control and changes in lipid profiles and inflammatory biomarkers. As shown, the mean levels of A1C and fasting blood glucose were reduced after addition of rosiglitazone in 86.1% of patients (n = 62), who maintained the same preexisting dosage of antidiabetic agents (Fig. 1). With an increased dose of rosiglitazone, the proportion of patients achieving the target A1C (7%) increased and a reduction in absolute levels of A1C were observed. At the end of the observation period, lipid levels were likewise reduced, especially the serum triglyceride level (Table 2). Serum total cholesterol and triglyceride levels were reduced from 178 ± 42.1 to 174 ± 46.5 mg/dl (P = 0.13) and from 194 ± 112.5 to 168 ± 88 mg/dl (P = 0.037), respectively.

Inflammatory parameters

There was no significant change in inflammatory parameters, such as the CRP level after rosiglitazone (Table 2). To elucidate whether high-dose rosiglitazone (8 mg/day) makes any difference in the inflammatory status of patients (n = 37), we conducted a retrospective assay of cytokine levels within individually collected, well-preserved serum during the observation period (Fig. 2). Serum levels of CRP were reduced significantly, whereas the

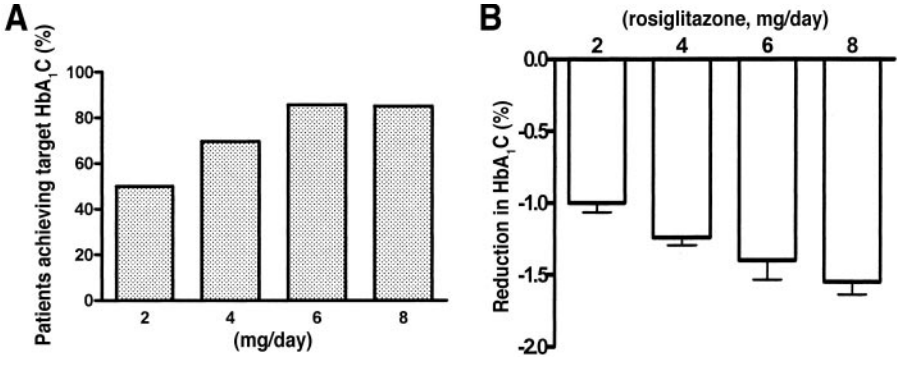

Figure 1—*The effectiveness of rosiglitazone for diabetes control in hemodialysis patients. Treatment results at the end of the observation period for each subject are shown.* A*: Proportions of patients achieving target A1C (7%) treated with different doses of rosiglitazone.* B*: Reduction in absolute value of A1C after rosiglitazone.*

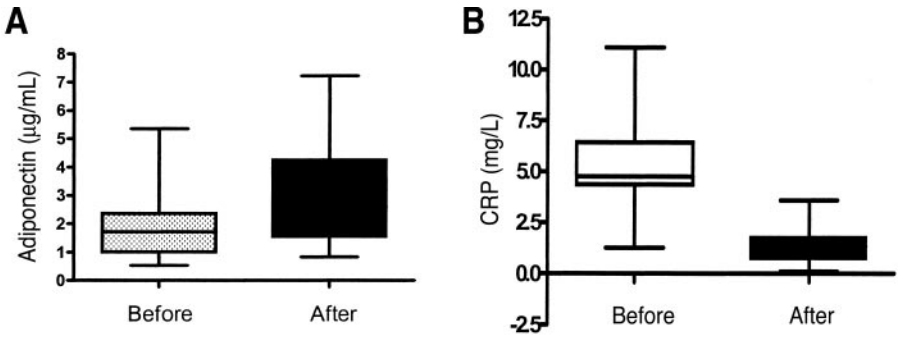

Figure 2—*CRP levels during the observation period (n = 37). Serum levels of CRP were reduced significantly (*P *< 0.01), whereas serum levels of adiponectin increased with borderline significance (*P *= 0.052). Values with the most profound difference from the baseline are shown.*

serum adiponectin level increased with borderline significance.

Safety evaluation

During the run-in phase and observation period, no symptomatic hypoglycemia was reported after addition of rosiglitazone. As shown in Table 2, the mean CTR gradually increased with statistical significance after rosiglitazone (48.2 ± 5.6 to 50.4 ± 6.2%, $P = 0.0213$). The dry weight of individual patients also was elevated significantly during treatment with rosiglitazone. Moreover, the interdialysis body weight gain increased significantly from 2.07 ± 1.6 to 3.2 ± 1.2 kg ($P < 0.01$). There was no significant change in blood pressure during the study period.

To evaluate the safety of rosiglitazone on liver status, levels of AST and ALT were evaluated and did not show a significant change after rosiglitazone (NS). In patients with chronic HBV ($n = 12$) or HCV ($n = 13$) infection, neither AST nor ALT levels showed a tendency to elevate further than in those ($n = 53$) without viral hepatitis infections (Fig. 3).

CONCLUSIONS — The purpose of this study was to evaluate the effectiveness and safety of rosiglitazone in hemodialysis patients with viral hepatitis infections. We found that addition of rosiglitazone therapy, although providing better diabetes control, causes an increase in body weight and possibly may deteriorate cardiovascular reserve (Table 2). For patients with chronic viral hepatitis infection, a medium duration (mean 15 months) of rosiglitazone therapy could be well tolerated without significant changes in hepatic parameters (Fig. 3). Moreover, high-dose (8 mg/day) rosiglitazone seemed to have a positive immunomodulatory effect with a demonstrated reduction in the proinflammatory index (CRP level) and a concomitant increment in adiponectin (Fig. 2).

However, several limitations of this observational study need to be addressed. The present study is limited by the lack of a control group. Because the beneficial effects of a TZD have been demonstrated in other trials, it was logically difficult to enroll appropriate control subjects during a long-term follow-up study. Instead, we compensated for this weakness by a relatively longer follow-up period. During the study period, we retained a prospective pattern and actively checked all of the medical records on a regular weekly basis. Through this check, we assured that the patients enrolled adhered to their medication prescription, which is also reflected in the effectiveness of the reduction in A1C. The mean A1C values in our patients decreased by 1 and 1.4%, respectively, which is consistent with decreases observed in the general population (16,17) and dialysis population (2,18).

It had been reported that TZDs may reverse insulin resistance through the peroxisome proliferator–activated receptor-γ effect. In this cohort, we observed that TZD administration is associated with a reduction in triglyceride levels, better diabetes control, and a significant increment in adiponectin, which may result from insulin sensitization through the TZD. We (4) have reported a high prevalence rate of insulin resistance in dialysis patients presenting with hypertriglyceridemia. However, as the homeostasis

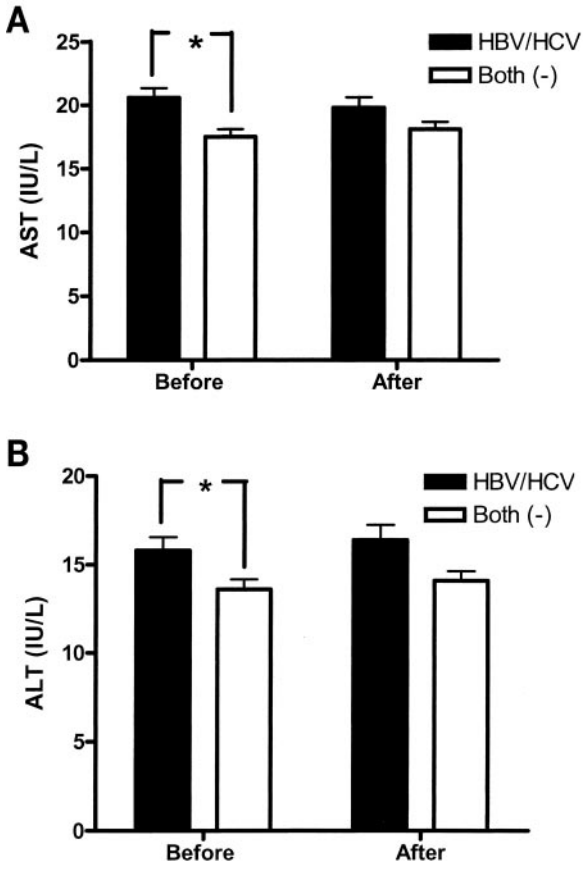

Figure 3—*Plasma values of AST* (A) *and ALT* (B) *at baseline and following add-on rosiglitazone treatment. HBV and HCV patients* (■) *are compared with patients without viral hepatitis infection* (□). *Values are expressed as means ± SD.*

model assessment values of individuals were lacking, we could not provide direct evidence for this association. In addition, the possible synergistic effect of the statin and TZD also could not be identified in this small-scale study, because we did not include data obtained while patients were receiving statin therapy. Further prospective studies may address these important issues.

Although a TZD may provide a protective effect on cardiovascular status, this beneficial result in dialysis patients may be hampered by weight increases. Although there is no concomitant increment in blood pressure, patients in this cohort showed increased body weight and CTR after rosiglitazone, which indicates a possible decompensation in cardiovascular status. This observation is somewhat different from those reported recently in another high-risk population (19). Nevertheless, our observations should be interpreted with caution, because there is an absence of patients with severe congestive heart failure in this cohort. Could the increased body weight in patients receiving rosiglitazone be attributed to improved nutritional status? The likelihood is low, as nutrition-related parameters were comparable, before and after rosiglitazone therapy (Table 2). Furthermore, whether the increased body weight resulted from fluid retention or fat redistribution could not be accurately determined at present. Studies examining body composition would be helpful with this issue.

Another main theme of this work was to determine the safety of rosiglitazone in patients with HBV and HCV infections. AST and ALT levels did not change significantly in hemodialysis patients with HBV or HCV infections compared with patients without these infections (Fig. 3). As we (20) reported elsewhere, baseline levels of AST and ALT are lower in the dialysis population. Even if we applied revised and much stricter criteria, say AST of 14 IU/l and ALT of 11 IU/l (20), in checking changes of AST or ALT levels in our patients, there were only 19 (1.7% of 1,164 data collected) episodes for which AST/ALT levels were >3 times this revised criteria. All episodes developed asymptomatically in different individuals who were anti-HCV$^+$. Therefore, rosiglitazone therapy seemed well tolerated in patients with viral hepatitis, which is consistent with the results observed in patients without uremia (10).

In summary, through this medium-scale, nearly 2-year observation study, we provide clinical clues that rosiglitazone may be safely used in diabetic patients receiving regular dialysis even if there was a concern about chronic viral hepatitis infection. Its long-term impact on the cardiovascular reserve deserves further study.

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