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ORIGINAL ARTICLE

Rosiglitazone is a safe and effective treatment option of new-onset diabetes mellitus after renal transplantation

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Summary

The purpose of this study was to assess the safety and efficacy of the insulin sensitizer rosiglitazone in patients with new-onset diabetes mellitus (NODM) after renal transplantation. Twenty-two patients with NODM after renal transplantation were selected to receive rosiglitazone therapy. All patients received prednisone, 15 patients were treated with tacrolimus and seven patients received cyclosporine A. For 16 of the 22 patients treatment with rosiglitazone therapy was successful and mean fasting blood glucose decreased from 182 ± 17 to 127 ± 7 mg/dl. Six patients were not treated successfully with rosiglitazone alone, one patient needed a second oral antidiabetic agent and four patients insulin therapy. In one patient rosiglitazone was stopped because of edema after 5 days. There were no changes either in serum creatinine concentrations, or cyclosporine and tacrolimus blood levels respectively. Treatment with rosiglitazone appears to be safe and effective in patients with NODM after renal transplantation.

Introduction

New-onset diabetes mellitus (NODM) in renal transplant recipients is a serious complication associated with a higher long-term morbidity and mortality [1–3]. The use of immunosuppressive drugs, such as corticosteroids, cyclosporine and tacrolimus has been recognized as a risk factor for the development of NODM with an incidence ranging from 2% to 53% among renal transplant recipients [4,5]. The risk for the development of NODM is highest during the first months after transplantation or during the course of antirejection treatment. Insulin resistance and a defect in insulin secretion have been identified as the key mechanisms of immunosuppression-associated diabetes mellitus [6,7].

The thiazolidinediones are a new class of oral antidiabetic agents that act as insulin sensitizers leading to improved glycemic control with reduced insulin requirements in diabetes mellitus. Both rosiglitazone and pioglitazone are approved for the use as monotherapy and in combination with metformin or sulfonylurea. Monotherapy with rosiglitazone or pioglitazone results in significant improvements in fasting plasma glucose by 60–80 mg/dl and in glycosylated hemoglobin ($HbA1_c$) by 1.4–2.6% compared with placebo [8]. As most patients with NODM after renal transplantation are insulin resistant, insulin sensitizers have been proposed as a promising therapy for this group of patients [9,10]. The use of rosiglitazone after solid organ transplantation has recently been documented in 18 diabetic patients who were pretreated with insulin or oral antidiabetic agents. Two of these patients had NODM following renal transplantation [11]. The purpose of this study was to assess the safety and efficacy of rosiglitazone in patients with NODM after renal transplantation.

Patients and methods

Study population

Twenty-two patients with NODM after renal transplantation were selected to receive rosiglitazone therapy and data were collected from our transplantation database (11 male, 11 female, age: 55 ± 3 years, median time of

diagnosis after transplantation 3 months, body weight 73 ± 3 kg, BMI 25 ± 1 kg/m^2). The diagnostic criteria for diabetes mellitus as recommended by the 2003 international consensus guidelines for new-onset diabetes after transplantation were used [12]. These criteria were: symptoms of diabetes plus casual plasma glucose concentrations >200 mg/dl or fasting plasma glucose >126 mg/dl or 2-h plasma glucose >200 during an oral glucose tolerance test [12]. These criteria had to be confirmed on another day to result in the diagnosis of NODM.

Sixteen of the 22 patients had developed diabetes mellitus within the first year following transplantation. None of the patients had diabetes mellitus diagnosed prior to renal transplantation. Successful rosiglitazone treatment was defined as a significant improvement of blood glucose concentrations and HbA1c with the absence of glucosuria without the need for the addition of further antidiabetic agents. Treatment failure was defined as the need for insulin therapy or for the addition of other oral antidiabetics or insulin because of persistence of hyperglycemia and glucosuria.

The underlying disorder for terminal renal failure was chronic glomerulonephritis in nine patients, cystic kidney disease in seven patients, nephrosclerosis in three patients, chronic pyelonephritis in two patients and dysplastic kidney disease in one patient. Five patients had chronic hepatitis C and one patient chronic hepatitis B as a concomitant disorder.

Immmunosuppression

Fifteen patients were treated with tacrolimus (mean trough level 10 ± 1 ng/ml), seven patients received cyclosporine A (mean trough level 151 ± 33 ng/ml $n = 5$, C2-level 1350 ± 350 ng/ml $n = 2$). All patients received prednisone (10 ± 1 mg/day), seven mycophenolate mofetil and three sirolimus.

Statistical analysis

All data are expressed as mean ± SEM. Mean values were compared using the Student *t*-test or with a nonparametric test when the variable was not normally distributed. $P < 0.05$ was considered to be significant.

Results

Rosiglitazone therapy was started 56 ± 23 days (median 15 days) after diagnosis of NODM in a daily dose of 4 mg in 19 patients and of 8 mg in three patients. In seven of the 19 patients started on 4 mg rosiglitazone, the dosage was increased to 8 mg during follow up. One patient had been on sulfonylurea treatment that was stopped because of side effects (diarrhea, abdominal pain) before rosiglitazone was instituted. Three patients were treated with sulfonylureas at the beginning of the rosiglitazone medication, two patients with fasting blood glucose levels >200 mg/dl were treated with either insulin or a combination of insulin and sulfonylurea, before rosiglitazone was started.

Rosiglitazone therapy in 22 patients for a total time of 220 months was analyzed (mean follow-up 10 ± 2 months). During treatment with rosiglitazone 16 of the 22 patients had sufficient glycemic control, five patients had a treatment failure with persistence of hyperglycemia during follow-up.

Four patients without sufficient glycemic control after 2, 4, 10 and 12 weeks of rosiglitazone medication were switched to insulin therapy. One patient received a second oral antidiabetic agent (repaglinide) in a low dose after 14 months of rosiglitazone medication in order to control hyperglycemia (see Table 1). One patient had to stop rosiglitazone because of a weight gain of 4 kg with development of edema within 5 days and was excluded from further analysis.

At the time of the first complete follow-up (after a mean of 44 days of rosiglitazone treatment) the mean fasting plasma glucose level had decreased from the initial 188 ± 15 to 145 ± 11 mg/dl ($P < 0.05$). In some patients, on rosiglitazone monotherapy fasting blood glucose was determined after 7–10, 14–20 or 20–35 days. Blood glucose was nearly unchanged after 7–10 days of rosiglitazone treatment (177 ± 25 to 171 ± 27 mg/dl, $n = 6$) while it decreased after 14–20 and 20–35 days, respectively (14–20 days: 179 ± 18 to 157 ± 19 mg/dl, $n = 9$; 20–35 days: 179 ± 17 to 154 ± 10 mg/dl, $n = 7$).

In the 16 patients considered to have successful treatment, mean fasting glucose decreased from 182 ± 17 mg/dl before rosiglitazone treatment to 127 ± 7 mg/dl

Table 1. Efficacy of rosiglitazone treatment after the first complete follow-up at 44 ± 9 days. Treatment failure was defined as the need for the addition of an oral antidiabetic agent (one patient) or for insulin therapy (four patients). Data from the 16 patients with successful treatment and from the five patients with treatment failure were included in the analysis.

Parameter	Baseline	Follow-up
Fasting blood glucose (successful treatment, $n = 16$)	182 ± 17 mg/dl	127 ± 7 mg/dl
Fasting blood glucose (treatment failure, $n = 5$)	216 ± 20 mg/dl	202 ± 22 mg/dl
HbA1c (successful treatment, $n = 16$)	7.2 ± 0.4%	6.2 ± 0.2%
HbA1c (treatment failure, $n = 5$)	7.0 ± 0.7%	8.5 ± 0.5%

($P < 0.01$). Mean HbA1c decreased from 7.2 ± 0.3% to 6.6 ± 0.3% in all patients and from 7.2 ± 0.4% to 6.2 ± 0.2% in the patients without persistence of hyperglycemia ($P < 0.05$) but increased from 7.0 ± 0.7% to 8.5 ± 0.5% in the five patients with persistence of hyperglycemia. During further follow-up after 180 ± 40 days fasting blood glucose was 123 ± 10 mg/dl and HbA1c 6.0 ± 0.2% in the patients who were successfully treated with rosiglitazone. The five patients who were pretreated with either insulin or sulfonylureas when rosiglitazone therapy was started were all successfully treated with a strong decrease in fasting blood glucose (212 ± 52 to 109 ± 7 mg/dl) and normalization of HbA1c levels (7.8 ± 0.8% to 6.0 ± 0.2%). All three patients treated with sulfonylureas and one patient treated with sulfonylureas and insulin were able to stop these medications because of improvements in glycemic control after rosiglitazone therapy was started.

In three patients immunosuppression was switched from tacrolimus to cyclosporine in order to improve the management of diabetes mellitus. This attempt was successful in one patient, the other two patients had to continue rosiglitazone treatment.

In four patients rosiglitazone medication was stopped after 2, 2, 3 and 6 months as hyperglycemia had improved and medical treatment was no longer necessary. All of these four patients had their immunosuppressive medication reduced after the diagnosis of diabetes mellitus.

During rosiglitazone treatment, body weight did not change significantly (before rosiglitazone: 73 ± 3 vs. 72 ± 3 kg after a mean of 44 ± 9 days of rosiglitazone therapy). Serum triglycerides and total serum cholesterol also did not change significantly during follow-up (see Table 2). There was no case of increase in serum creatinine associated with the rosiglitazone medication. The prednisone dosage at baseline and at the follow-up after 44 ± 9 days was not significantly different (10.1 ± 1.1 mg/day vs. 8.6 ± 0.6 mg/day, $P = 0.15$). Cyclosporine A and tacrolimus blood levels did not change significantly and relevant dose adjustments were not necessary (see Table 2). We did not observe a clinical or biochemical evidence of liver disease in patients without previous liver disease or a worsening of liver disease in the six patients with chronic hepatitis.

Table 2. Biochemical and clinical parameters before and after rosiglitazone treatment of 44 ± 9 days in 21 patients. There were no significant differences between baseline and follow-up parameters ($P > 0.1$).

Parameter	Baseline	Follow-up
Body weight (kg)	73 ± 3	72 ± 3
Serum creatinine (mg/dl)	1.6 ± 0.1	1.6 ± 0.1
Tacrolimus trough levels (ng/ml)	10.1 ± 1.1	9.5 ± 1.0
Cyclosporine trough levels (ng/ml)	151 ± 33	145 ± 29
Prednisone dosage (mg/day)	10.1 ± 1.1	8.6 ± 0.6
Total cholesterol (mg/dl)	211 ± 11	228 ± 12
Triglycerides (mg/dl)	304 ± 40	279 ± 34

Discussion

The data from our observational study indicate that rosiglitazone treatment is a safe and effective new treatment option in patients with NODM after renal transplantation. Deleterious effects on the transplant or interactions with immunosuppressive medication were not observed. Our findings are supported by a report from Baldwin & Duffin [11] who successfully used rosiglitazone in 18 patients with diabetes mellitus after solid organ transplantation. In contrast to our patients, however, only two of these patients had NODM after renal transplantation and all patients were pretreated with either insulin or oral antidiabetic agents with rosiglitazone being added. Baldwin & Duffin [11] observed a decrease of mean HbA1c levels of 1.2%, whereas the decrease was only 0.6% in our patient cohort, most likely resulting from a different patient selection. Baldwin & Duffin had investigated pretreated diabetic patients whereas the majority of our patients presented with NODM developed shortly after transplantation. Some of the patients in our study had HbA1c levels within the normal range as rosiglitazone was begun with a median time of 15 days after diabetes mellitus was diagnosed. As HbA1c represents a marker for glycemic control within the last three months a relevant increase in the fraction of glycosylated HbA1c cannot be expected in those patients with a short history of diabetes mellitus.

Our data further indicate that the need for rosiglitazone therapy may only be temporarily in a fraction of patients possibly bridging time periods of insulin resistance because of exposure to higher doses of corticosteroids or calcineurin inhibitors. This can be deduced from the fact that four of 22 patients were able to discontinue rosiglitazone therapy after immunosuppression had been reduced in the further course after transplantation. However, the improvement in glycemic control seen after rosiglitazone treatment can clearly be segregated from the effect of dose reduction of immunosuppressants as at the time of the complete follow-up prednisone dosage and tacrolimus and cyclosporine blood levels were not different from baseline.

Insulin sensitizers may be the ideal oral agents for the early period after transplantation as sulfonylureas (agents stimulating insulin secretion) may further promote insulin resistance and metformin is contraindicated in cases

of renal dysfunction. This is supported by the fact that all five patients who were pretreated with either insulin or sulfonylureas were effectively treated after the addition of rosiglitazone and four of these five patients were able to terminate insulin and sulfonylureas completely. However, therapy with insulin sensitizers is not effective in all patients indicating that reduced insulin secretion may have contributed to the development of diabetes mellitus in this fraction of patients. Furthermore, our data indicate that rosiglitazone does not affect glycemic control immediately but the full therapeutic effect is reached after a period of several weeks as also shown in other studies [13,14].

In accordance with Baldwin & Duffin we did not observe increases of serum creatinine or liver function parameters. Furthermore, we did not observe problems with liver function tests in patients with infectious chronic hepatitis. Relevant changes in cyclosporine A or tacrolimus blood levels did not occur. Rosiglitazone was used for our patients as it is predominantly metabolized by the P450 isoenzyme 2C8, with CYP2C9 serving as a minor pathway [8]. In contrast, pioglitazone, the other insulin sensitizer that is available is extensively metabolized by CYP3A4 thereby potentially interacting with cyclosporine A and tacrolimus metabolism. Furthermore, rosiglitazone has been shown to be safe in patients with renal failure and no dose adjustments are necessary [15,16].

In conclusion, our data show that treatment with rosiglitazone appears to be a safe and effective treatment option in patients with NODM after renal transplantation.

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