ICCR Protocol, October 31, 2006

A Randomized, Controlled Trial of Pioglitazone in Addition to Irbesartan for Decreasing Microalbuminuria (PAIDM)

Pietro Canetta

A. Study Purpose

Microalbuminuria is the earliest clinical sign of diabetic nephropathy, and one of the strongest known predictors of cardiovascular disease in diabetics and non-diabetics alike. Defined as persistent albumin excretion of between 30 and 300 mg/day (20 to 200 μg/min), it has a prevalence of roughly 25-30% in middle-aged patients with type 2 diabetes mellitus (DM2), and is often present at diagnosis [1,6,7,10]. Progression to macroalbuminuria occurs in 20-40% of type-2 diabetics with microalbuminuria over 10 yrs, and powerfully predicts end-stage renal disease (ESRD). Several studies have firmly established that microalbuminuria independently predicts future cardiovascular events and deaths. For example, data from the Heart Outcomes Prevention Evaluation (HOPE) trial showed that presence of microalbuminuria in diabetics conferred nearly double the risk of MI, stroke, or cardiovascular death (adjusted risk 1.97, 95% confidence interval 1.68-2.30) and more than double the risk of death from any cause (AR 2.15, 95%CI 1.78-2.60) [7]. Moreover, this study and others seem to indicate that the risk of cardiovascular outcomes or of developing overt diabetic nephropathy appears to be linearly related to albumin excretion, even within the microalbuminuric range.

Hypertension is a critical factor in the development and progression of microalbuminuria, and diabetic patients with microalbuminuria can be effectively treated with blockers of the renin-angiotensin system, specifically angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs). These drugs have been shown to decrease the incidence of cardiovascular events, delay the progression to overt proteinuria, and delay the progression to nephropathy [1,7,10]. While much of this effect is due to blood pressure control, ACEIs and ARBs confer additional protection compared to other antihypertensives at similar levels of blood pressure control. Furthermore, improvements in clinical endpoints are mirrored by a reduction in microalbuminuria. Current K/DOQI and ADA guidelines give class “A” recommendations for the institution of an ACEI or ARB in any diabetic patient with either hypertension, microalbuminuria, or both [1, 10].

The thiazolidenediones (TZDs) are a relatively new class of antidiabetic drugs that are potent agonists of peroxisome proliferator-activated receptor-gamma (PPAR-γ). Their main use is as insulin-sensitizers, increasing insulin-dependent glucose disposal and decreasing hepatic glucose output by decreasing insulin resistance in the periphery and in the liver. However, they have been found to have pleiotropic beneficial effects on various markers of cardiovascular risk. These include a small reduction in blood pressure, improvement in the diabetic dyslipidemic profile, decreased levels of vascular inflammation and improvements in vascular endothelial function [4,8,13-17,19,20]. Furthermore, these agents have been shown to decrease microalbuminuria.

Several human studies have been carried out establishing a definite reduction in microalbuminuria by the TZDs, in the range of 20-70% decrease [2,3,9,11-16,18]. However, in many of these studies use of ACEIs or ARBs was prohibited or present among a minority of the population, in contrast with current treatment guidelines. No study has specifically examined the question of whether TZDs confer an additional benefit in microalbuminuria reduction to patients

who are already on maximally dosed ACEI or ARB. The current study proposes to answer this very question. The hypothesis tested will be:

H: In type-2 diabetics with microalbuminuria, the TZD pioglitazone lowers urine albumin excretion beyond the level achieved by the ARB irbesartan alone.

If this hypothesis were found to be true, this would increase the evidence for potential beneficial effects of TZDs on renal and cardiovascular outcomes in patients who are already receiving standard-of-care therapy according to the clinical guidelines. It would further provide rationale for designing large, long-term studies of such outcomes and their correlation with reduction in microalbuminuria.

B. Study Design and Statistical Analysis

Design:

This is a randomized, double-blind, placebo-controlled crossover study of pioglitazone intended to evaluate its incremental effectiveness in reducing microalbuminuria when added to irbesartan. The study population will consist of patients with type 2 diabetes mellitus (DM2) and microalbuminuria who have never received treatment with TZD. All patients will receive irbesartan. They will then be randomized to placebo or pioglitazone for a 20 week treatment period. In accordance with the crossover design, treatment assignment will then be reversed and the subjects followed for a second 20 week treatment period.

Outcomes:

The primary outcome will be the difference in albumin to creatinine ratio (ACR) following 20 weeks of pioglitazone compared to 20 weeks of placebo. This is a well-validated measure of microalbuminuria, and more clinically relevant and convenient than the 24-hr urine collection [1]. Secondary outcomes will include fasting plasma glucose, glycosylated hemoglobin, blood pressure, weight and BMI, serum creatinine, and lipid profile.

Power Calculation:

Using conservative estimates extrapolated from the literature [2,3,9,11-16,18], we assume a 30% (STD 70%) additional decrease in microalbuminuria afforded by pioglitazone when added to irbesartan. To detect this difference with a power of 0.80 and alpha of 0.05, 45 patients must complete the study. Assuming an attrition rate of 25%, we will seek to enroll a total of 60 patients.

Statistical analysis:

All measurements of ACR will be log-transformed and the statistical significance will be tested using a paired Student's t-test. Results will be back-transformed and expressed as percentage difference (using the placebo arm as reference). All other outcomes are continuous variables and will be compared using Student's t-test for paired samples. Regression analysis will be performed to assess the relative contribution to the primary outcome caused by changes in blood pressure or glycemic control. Level of significance will be considered at 0.05.

C. Study Procedure

The study is designed to last a total of 48 weeks. At the start of the study, all patients will receive dietary and lifestyle recommendations according to national guidelines for diabetic patients with microalbuminuria [1]. In an initial 4-week run-in period, all patients will be started on irbesartan, 150 mg daily (any patients currently taking an ACEI or ARB will have it discontinued and replaced by the equivalent dose of irbesartan, 150 or 300 mg daily). Over the

course of the run-in period, all patients will have irbesartan up-titrated as tolerated to a dose of 300 mg daily. All other necessary medications will be continued for the duration of the study.

Following run-in, patients will be randomized to placebo or pioglitazone (initial dose 30 mg, up-titrated after 2 weeks to 45 mg) for 20 weeks. At the completion of 20 weeks, patients will enter a 4-week washout period during which the study drug is discontinued. Following washout, patients will be crossed over in their treatment assignment and will complete another 20-week treatment period.

Patients will be followed with outpatient visits every 2 weeks during the run in period, then at 4, 12, and 20 weeks during the treatment period. At each visit, history and physical examination will be performed to assess for compliance and adverse events. All patients will have baseline blood and urine collections at the start of the study (prior to run-in) and at the completion of each 20-week treatment period. Visits will take place in the morning; patients will have been instructed to fast for 8 hours prior to the visit and to avoid exercise for 24 hours prior. ACR will be obtained from a morning urine specimen (collected 8:00 - 10:00 am). All measurements will be performed by Columbia University Medical Center core laboratory.

D. Study Drugs

Irbesartan is an angiotensin II receptor blocker that has been FDA approved for use in hypertension and diabetic nephropathy. Usual dosing is 150 or 300 mg orally once daily, with a 75 mg dose reserved for the elderly, patients in renal failure, or patients who are volume depleted. Irbesartan is contraindicated in pregnancy. It is generally well-tolerated, with adverse effects that include diarrhea and headache. It is associated with an increase in the levels of serum creatinine and potassium.

Pioglitazone is a thiazolidinedione that has been FDA approved for use in type 2 diabetes mellitus. Dosing begins at 15 to 30 mg orally once daily, with maximum dose of 45 mg once daily. It is generally safe and well-tolerated, common adverse effects include edema (5%), weight gain, anemia (1%), myalgia (3%), and headache (7%). Serious side effects are rare, and include hepatotoxicity and macular retinal edema. In a recent large randomized trial of pioglitazone, there was a slightly increased incidence of congestive heart failure noted in the treatment group (0.5%, vs 0.1% in placebo) [5].

E. Medical Device

N/A.

F. Study Questionnaires

N/A

G. Study Subjects

Subjects will be patients >18 years of age with type 2 diabetes mellitus as defined by the World Health Organization [1] and microalbuminuria defined as a urinary albumin to creatinine ratio (ACR) of 30-300 mg/g or 24-hr urinary albumin excretion (UAE) of 30-300 mg/day, measured at least twice over a 6 month period. Patients cannot have been receiving treated with TZD within 6 months of the study. Patients may have been receiving treatment with either an ACEI or ARB, but not both. Female patients have to be postmenopausal, sterilized, or using satisfactory contraception.

Exclusion criteria will include history of diabetic ketoacidosis, BP > 159/99 mmHg despite therapy, pregnancy or plans to become pregnant, congestive heart failure, liver disease

[including levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin, >2 times the upper limit of normal], hematuria or casturia, or known nondiabetic renal disease.

H. Recruitment of Subjects

Patients will be recruited at New York Presbyterian Hospital - Columbia University Medical Center. Letters describing the study and seeking referrals will be distributed to residents, fellows, and attending physicians working in outpatient clinics for general medicine, endocrinology, and diabetes care, as well as those working on inpatient general medical services. Such letters will briefly detail the inclusion and exclusion criteria, however final screening and informed consent for the study will be obtained by the investigators.

I. Confidentiality of Study Data

Patient information will be kept confidential in accordance to HIPAA guidelines. All data will be coded without the use of any personal identifiers, and kept in a password-protected database on a computer in the locked office of the principal investigator.

J. Potential Conflict of Interest

The author asserts no conflicts of interest, nor proprietary interest in the drugs under study.

K. Location of the Study

The study will be carried out at New York-Presbyterian Hospital, Columbia University Medical Center and its associated outpatient clinics.

L. Potential Risks

The medical risks involved in this study are few, and limited to the known risks of treatment with irbesartan and pioglitazone as described above. Chief among these for irbesartan are angioedema and rhabdomyolysis (both rare), and for pioglitazone these include edema, weight gain, headache, and hepatotoxicity (rare).

M. Potential Benefits

Potential benefits, as described above, include decreased risk of cardiovascular outcomes and decreased risk of progression to macroalbuminuria. Patients randomized to the TZD group may see improvement in lipid profile, blood pressure, and glycemic control.

N. Alternative Therapies

All patients will be treated with the current class A recommended therapy for microalbuminuria (i.e., ACEI or ARB) [1,10]. There is limited data suggesting that improvement in microalbuminuria can be achieved with combined ACEI/ARB use, however this has not become standard accepted clinical practice, and outcome data have not conclusively shown combined therapy to be superior to monotherapy. Patients enrolled will not be offered treatment with combined ACEI/ARB therapy for the duration of the study.

O. Compensation to Subjects

None, however the subjects will not need to pay for the study drugs.

P. Costs to Subjects

None. Study drugs will be provided by the investigators.

Q. Minors as Research Subjects

This study includes only adults over 18 years of age.

R. Radiation or Radioactive Substances

N/A

S. References

1. American Diabetes Association, Standards of Medical Care in Diabetes–2006, Diabetes Care. 2006 Jan;29 Suppl 1:S4-42.

2. Bakris GL, Ruilope LM, McMorn SO, Weston WM, Heise MA, Freed MI, Porter LE. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006 Oct;24(10):2047-2055.

3. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens. 2003 Jan;17(1):7-12.

4. Buckingham RE. Thiazolidinediones: Pleiotropic drugs with potent anti-inflammatory properties for tissue protection. Hepatol Res. 2005 Oct;33(2):167-70.

5. The DREAM Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet, 2006 Sep 23; 368:1096-1104

6. Erdmann E. Microalbuminuria as a marker of cardiovascular risk in patients with type 2 diabetes. Int J Cardiol. 2006 Feb 15;107(2):147-53.

7. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001 Jul 25;286(4):421-6.

8. Gruden G, Setti G, Hayward A, Sugden D, Duggan S, Burt D, Buckingham RE, Gnudi L, Viberti G. Mechanical stretch induces monocyte chemoattractant activity via an NF-kappaB-dependent monocyte chemoattractant protein-1-mediated pathway in human mesangial cells: inhibition by rosiglitazone. J Am Soc Nephrol. 2005 Mar;16(3):688-96.

9. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR and Charbonnel BH, One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with Type 2 diabetes, Diabetes Care 27 (2004), pp. 141–147.

10. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004 May;43(5 Suppl 1):S1-290.

11. Imano E, Kanda T, Nakatani Y, Nishida T, Arai K, Motomura M, Kajimoto Y, Yamasaki Y, Hori M. Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy. Diabetes Care. 1998 Dec;21(12):2135-9.

12. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. Diabetes Metab Res Rev. 2005 Mar-Apr;21(2):167-74.

13. Nakamura T, Ushiyama C, Osada S, Hara M, Shimada N, Koide H. Pioglitazone reduces urinary podocyte excretion in type 2 diabetes patients with microalbuminuria. Metabolism. 2001 Oct;50(10):1193-6.

14. Nakamura T, Ushiyama C, Shimada N, Hayashi K, Ebihara I, Koide H. Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications. 2000 Sep-Oct;14(5):250-4.

15. Nakamura T, Ushiyama C, Suzuki S, Shimada N, Sekizuka K, Ebihara L, Koide H. Effect of troglitazone on urinary albumin excretion and serum type IV collagen concentrations in Type 2 diabetic patients with microalbuminuria or macroalbuminuria. Diabet Med. 2001 Apr;18(4):308-13.

16. Pistrosch F, Herbrig K, Kindel B, Passauer J, Fischer S, Gross P. Rosiglitazone improves glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in patients. Diabetes. 2005 Jul;54(7):2206-11.

17. Roberts AW, Thomas A, Rees A, Evans M. Peroxisome proliferator-activated receptor-gamma agonists in atherosclerosis: current evidence and future directions. Curr Opin Lipidol. 2003 Dec;14(6):567-73.

18. Schernthaner G, Matthews D, Charbonnel B, Hanefeld M and Brunetti P, Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial, J Clin Endocrinol Metab 89 (2004), pp. 6068–6076.

19. Tanimoto M, Fan Q, Gohda T, Shike T, Makita Y, Tomino Y. Effect of pioglitazone on the early stage of type 2 diabetic nephropathy in KK/Ta mice. Metabolism. 2004 Nov;53(11):1473-9.

20. Tsuchiya T, Shimizu H, Shimomura K, Mori M. Troglitazone inhibits isolated cell proliferation, and induces apoptosis in isolated rat mesangial cells. Am J Nephrol. 2003 Jul-Aug;23(4):222-8.

21. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI: Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001;86:280 –288.