A comparison of the effects of calcium acetate and sevelamer on mortality and cardiovascular events in end stage renal disease: A prospective randomized placebo-controlled double-blinded trial

Ethan P. Marin

A. Study Purpose and Rationale

Patients with end stage renal disease on hemodialysis have extremely high rates of mortality, due in part to high rates of cardiovascular events (1). The rate of cardiovascular disease in this patient population has been found to be in excess of that attributed to traditional cardiovascular risk factors. Thus, investigators have sought additional risk factors unique to end stage renal patients.

One factor that has been identified is dysregulation of bone mineral metabolism, which often manifests as the development of the bone disease renal osteodystrophy. Derangements of serum calcium, phosphorus, calcium x phosphorus product, and PTH levels are very common in the end stage renal disease patient population (2). In particular, elevated serum phosphorus levels have been found in multiple observational studies to be associated with significantly higher levels of mortality and cardiovascular events (3;4). As a result, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) has recommended that nephrologists strive for tight control of indices of bone mineral metabolism (5).

Several modalities have emerged to control phosphorus level, including dietary modifications, dialysis techniques and phosphorus binding drugs. Of the latter category, two major classes are used today: calcium-based drugs, such as calcium acetate, and newer non-calcium based agents such as sevelamer. Earlier drugs, such as aluminum based agents, have fallen out of favor due to unacceptable toxicity risks.

Sevelamer, which was FDA approved in 1998, has been compared with the more established calcium-based agents in a number of studies using serum phosphorus, calcium, and PTH levels as the main primary outcomes. The bulk of the evidence, with some notable exceptions (6), suggest that sevelamer is at least as efficacious as calcium acetate, a commonly used preparation.

The recent Treat to Goal study (7) looked at the comparison of sevelamer with calcium acetate in a new light, with specific ramifications for the potential of either agent to affect rates of cardiovascular disease. The study found that while calcium acetate and sevelamer afforded similar rates of control of serum phosphorus and calcium, calcium acetate led to increasing levels of calcification of the aorta and coronary arteries, whereas sevelamer did not. Since calcification of the arterial system is linked to cardiovascular events, and is thought to be one of the mechanisms by which elevated phosphorus levels might increase mortality rates, this study revealed an important potential advantage of sevelamer.

Nonetheless, despite the accumulation of observational data, no prospective randomized trials have demonstrated that lowering serum phosphorus levels using any oral phosphorus binding agent leads to reduction in mortality or rate of cardiovascular events (5). In fact, some previously used phosphorus binding agents (e.g., aluminum based agents) were ultimately found to be deleterious. Data showing that calcium based binders allow progressive calcification of the coronary arteries might hint at a deleterious effect of these agents, as well (7).

In addition, no prospective randomized data are available regarding whether calcium based or non-calcium non-aluminum based binders are superior in terms of mortality or cardiovascular events, despite a number of studies comparing the two with respect to indices of bone mineral metabolism.

This proposal is for a randomized blinded placebo-controlled prospective trial of calcium acetate versus sevelamer versus placebo in a population of patients with end stage renal disease and

hyperphosphotemia newly starting hemodialysis therapy. The primary endpoints are all cause mortality and a combined endpoint of cardiovascular events and mortality. This study will address the lack of prospective randomized studies on the management hyperphosphatemia, which has been postulated to significantly increase mortality rates of patients with end stage renal disease.

B. Study Design and Statistical Analysis

a. Hypothesis

Patients maintained on sevelamer will have lower rates of death and cardiovascular events than those taking placebo or calcium acetate.

b. Study subjects:

Patients enrolled in the study will have the following characteristics:

1. Stage 5 renal disease, as defined by the K/DOQI (i.e., a GFR < 15 ml/ hr), without reasonable expectation of return of normal renal function
2. on maintenance hemodialysis therapy; first HD session within 90 days
3. Serum phosphorus levels > 5.5 as measured following a two week period during which any phosphorus-binding agents were withheld.

Exlusionary characteristics include:

1. hypercalcemia (an albumin-corrected calcium >11.0)
2. previous parathyroidectomy or PTH levels > 1000
3. bowel obstruction
4. conversion to transplant or other dialysis modality

Patients will be recruited from a network of dialysis centers across the United States.

c. Study arms

The study will consist of three arms, distinguished by the means of phosphorus control used:

1. Calcium acetate (PhosLo)
2. Sevelamer (Renagel)
3. Placebo

A placebo group is justified in this study despite the widespread use of phosphorus binders in ESRD patients since randomized prospective data have not conclusively shown that lowering phosphorus using available agents is beneficial with respect to mortality. Each of the agents to be tested in this protocol has significant potential drawbacks that warrant evaluation as compared to placebo. Calcium acetate may actually lead to higher levels of cardiovascular disease by promoting arterial calcification. Sevelamer is very expensive; one cost analysis suggests that it would cost nearly 1 billion more to prescribe it for each patient with an indication in the U.S. as compared to calcium acetate. Since the study is powered assuming very large rates of reduction in mortality resulting from use of phosphate binder, only relatively small numbers of patients need be enrolled in the placebo arm.

d. Primary Outcomes

1. Mortality
2. Combined end point of mortality and cardiovascular events, including acute myocardial infarction, cardiac arrest, CVA/TIA, CHF (as defined by the USRDS and adjudicated by a blinded committee of credentialed physicians)

e. Additional Outcomes

1. serum phosphorus
2. serum calcium
3. calcium phosphorus product
4. intact PTH levels
5. cholesterol levels

f. Number of patients enrolled and duration of study

The study will strive to enroll 1200 patients in each study drug arm and 150 patients in the placebo arm for an average observation period of two years. These parameters are based on the following estimates derived from published data.

Baseline event rates were estimated using published data from the U.S. Renal Data System, a registry of the end stage renal disease population in the U.S (1). For patients with ESRD on HD in the US, at two years after the initiation of end stage renal disease the mortality rate is roughly 40% and the combined rate of cardiovascular event and mortality is approximately 75%.

For the comparison of the treatment arms with placebo, the rate of reduction in mortality anticipated in this study was determined using published estimates for the relative risk of death as a function of phosphorus levels. In particular, patients with serum phosphorus levels of 6-7 mg/dL and 7-8 mg/dL have a 1.4 and 1.25 corrected relative risk of mortality as compared to patients with serum phosphorus of 4-5 (8). The anticipated serum phosphorus levels of patients in the placebo and treatment arms was estimated using studies with similar patient selection criteria and treatment schemes (6;7). Patients on placebo would be expected to have serum phosphorus levels of ~7-8, and those on treatment ~5-6. Thus, we estimate a 30% relative mortality rate reduction in the treatment as compared to the placebo arms. Given an absolute mortality rate after 2 years of 40% (as described above), an absolute rate of 27% is expected. Power calculations using the chi square test on proportions reveals that if each treatment arm has 1200 patients (see below), then the placebo arm need only 150 enrollees for 80% power testing at $p<0.05$.

Estimation of differences in outcomes anticipated between the two treatment arms is more difficult as fewer data are available. The magnitude of reduction in arterial calcification observed with sevelamer compared with calcium acetate has been reported (7). This change in arterial calcification can be converted into an estimate of reduction in cardiovascular events using observational data on the strength of the association between those two measurements (9). This analysis yields a rough estimate of a 5-6% reduction in cardiovascular events using sevelamer as compared to calcium acetate, which correlates to a clinically important effect.

The chi squared test on proportions predicts that 1200 patients in each of the treatment arms is required to see a absolute difference of 5-6% between the two treatment arms for both the outcomes of mortality (anticipated baseline rate of 40%) and cardiovascular event/mortality (anticipated baseline rate of 75%).

Approximately 80000 patients began hemodialysis in 2001 in the U.S. and 6000 in New York (10). Thus the target levels of enrollment should be attainable within several years with recruitment at multiple hemodialysis centers.

C. Study Procedure

a. Baseline Data

For all study participants, data will be collected on baseline characteristics including age, race, sex, diabetes, hypertension, smoker, primary cause of end stage renal disease, incidence of known cardiovascular disease, type of phosphate binder use prior to study entry, type and quantity of vitamin D supplementation. In addition, baseline levels of calcium, phosphorus, intact PTH, and lipids (total cholesterol, HDL, LDL, triglycerides) will be determined.

b. Treatment Interventions:

Treatment phase will last two years. The study will be double blinded. The medications used will be packaged so as to be indistinguishable, as previously described (6). The preparations will consist of sevelamer, 403 mg capsules and calcium acetate (PhosLo), 667mg capsules. Both are FDA approved medications, and will be given by the usual route in doses consistent with typical clinical practice.

Following a two week wash out period during which no phosphorus binders will be used, participants will initially receive a number of capsules based on the level of serum phosphorus: for 6 –

7.5 mg/dL 2 caps TID; for 7.5 to 9.0 mg/dL, 3 caps TID; and for >9.0 mg/dL, 4 caps TID. On a biweekly basis, doses will be adjusted to achieve a goal serum phosphorus of 3.5 - 5.5 mg/dL. For serum calcium > 11.0, the dose of study drug will be reduced by 1 capsule per day. Other interventions likely to affect phosphorus and calcium levels, such as diet, dialysis frequency, dialysate calcium concentration, levels and type of vitamin D supplementation should be held constant at pre-study doses during the initial twelve weeks of the study. Thereafter, dialysis conditions and vitamin D supplementation, as well as doses of study drugs may be adjusted monthly as needed to maintain goal serum phosphorus concentrations of 3.5 – 5.5 mg/dL, as well as goals delineated by K/DOQI for albumin-corrected serum calcium (8.5-10.2) and intact PTH (150-300 pmol/L).

Laboratory data including calcium, phosphorus, iPTH will be collected weekly for the first 12 weeks then monthly thereafter. Data on other medications used, dialysis conditions and frequency will also be collected.

c. Analysis

All data will be analyzed on an intention to treat basis. Rates of the primary outcomes will be compared in successive groups using the chi-squared test. Differences for the laboratory based outcomes will be compared using the t-test of group means. Differences in the rates of outcomes in different study arms will be considered statistically significant when the $p<0.05$.

D. Confidentiality of study data

All study data will be kept confidential.

E. Potential conflict of interest

None of which I am currently aware.

F. Reference List

1. U.S.Renal Data System (2004) USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.

2. Young, E. W., Akiba, T., Albert, J. M., McCarthy, J. T., Kerr, P. G., Mendelssohn, D. C., and Jadoul, M. (2004) *Am. J. Kidney Dis.* **44,** 34-38

3. Block, G. and Port, F. K. (2003) *Semin. Dial.* **16,** 140-147

4. Block, G. A., Hulbert-Shearon, T. E., Levin, N. W., and Port, F. K. (1998) *Am. J. Kidney Dis.* **31,** 607-617

5. National Kidney Foundation (2003) K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.

6. Qunibi, W. Y., Hootkins, R. E., McDowell, L. L., Meyer, M. S., Simon, M., Garza, R. O., Pelham, R. W., Cleveland, M. V., Muenz, L. R., He, D. Y., and Nolan, C. R. (2004) *Kidney Int.* **65,** 1914-1926

7. Chertow, G. M., Burke, S. K., and Raggi, P. (2002) *Kidney Int.* **62,** 245-252

8. Block, G. A., Klassen, P. S., Lazarus, J. M., Ofsthun, N., Lowrie, E. G., and Chertow, G. M. (2004) *J. Am. Soc. Nephrol.* **15,** 2208-2218

9. Raggi, P., Boulay, A., Chasan-Taber, S., Amin, N., Dillon, M., Burke, S. K., and Chertow, G. M. (2002) *J. Am. Coll. Cardiol.* **39,** 695-701

10. Chertow, G. M., Raggi, P., McCarthy, J. T., Schulman, G., Silberzweig, J., Kuhlik, A., Goodman, W. G., Boulay, A., Burke, S. K., and Toto, R. D. (2003) *Am. J. Nephrol.* **23,** 307-314