REVIEW ARTICLE

Phosphate binders: Sevelamer in the prevention and treatment of hyperphosphataemia in chronic renal failure

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Abstract

In chronic kidney disease patients, bone and mineral abnormalities have a major impact on morbidity and mortality. Hyperphosphatemia has been associated with increased mortality and with the development of cardiovascular calcification, an independent predictor of mortality. Sevelamer, or more precisely 'sevelamer hydrochloride', is a weakly basic anion-exchange resin in the chloride form that was introduced in 1997 for the treatment of the hyperphosphataemia of patients with end-stage renal failure. Sevelamer sequesters phosphate within the gastrointestinal tract, so prevents its absorption and enhances its faecal excretion. Over the succeeding years, large numbers of patients have been treated with sevelamer, and it has fulfilled expectations in helping to control the hyperphosphataemia of end-stage renal failure. Additionally treatment with sevelamer was accompanied with lower incidence of hypercalcemia, decreased incidence of low PTH levels, a 15-31% decrease of LDL-cholesterol both in dialysis and predialysis patients, decreased C-reactive protein, amelioration of hyperuricemia and low fetuin A, decrease of uremic toxins, suggesting an overall anti-inflammatory effect. In incident dialysis patients, treatment with sevelamer has been associated with better survival, while in prevalent patients a clear benefit could only be demonstrated in older patients and in patients treated for more than 2 years. In dialysis patients, the treatment of hyperphospathemia with calcium based compounds, when compared with sevelamer, is associated with more frequent episodes of hypercalcemia, suppression of intact PTH and with progression of coronary calcifications. In the presence of adynamic bone disease, calcium load has a significantly higher impact on aortic calcifications and stiffening. Sevelamer treatment resulted in no statistically significant changes in bone turnover or mineralization compared with calcium carbonate, but bone formation rate increased and trabecular architecture improved only with sevelamer. In conclusion, the treatment of hyperphosphatemia with sevelamer hydrochloride, a noncalcium and non-metal containing phosphate binder, is associated with a beneficial effect on vascular calcification progression, bone disease and most likely with a survival benefit in some hemodialysis patients populations.

Sevelamer carbonate is an improved, buffered form of sevelamer hydrochloride developed for the treatment of hyperphosphataemia in CKD patients. Sevelamer carbonate formulated as a powder for oral suspension presents a novel, patient-friendly alternative to tablet phosphate binders. Safety and efficacy of sevelamer carbonate powder compared with sevelamer hydrochloride tablets in CKD patients are equivalent, with Sevelamer carbonate having fewer side effects from gastrointestinal tract. Hippokratia 2011; 15 (Suppl 1): 22-26

Key words: sevelamer hydrochloride, sevelamer carbonate, hyperphosphatemia, vascular calcification

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According to KDIGO, derangement of metal metabolism in patients with kidney disease represents a systematic disease which is not comprised only of disordered metabolism of Ca, P and their product, PTH and bone metabolism but also of vascular calcification and its clinical consequences. This disorder has a critical impact on patients' mortality. Hyperphosphatemia indicates ''A silent killer of patients with renal failure''. Half of patients with levels of P at the upper limit don't survive after 4 years. In chronic kidney disease patients, bone and mineral abnormalities have a major impact on morbidity and mortality[1]. Hyperphosphatemia has been associated with increased mortality and with the development of cardiovascular calcification, an independent predictor of mortality. The pathophysiology of CKD is complex. Events of underlying disorders of bone and mineral metabolism have an origin early in kidney disease. Mechanisms of calcification are triggered very early with derangement of Na/P transport at the level of vascular smooth muscle cell and sequential calcified vessel[2].

Primary care physicians typically play a key role in the early treatment and management of patients with CKD. The most common point of referral to the nephrologist is usually at stage 4 or even 5, point where most of the above have already been established and evolved from latent to apparent symptoms[3].

Extra osseous calcifications very early have been associated with age, time on dialysis, hypecalcemia and calcium load. Patients receiving > 1, 5 gr elemental Ca/day, as $CaCO_3$ binder, had a calcification score of 2 in a scale from 0 to 4[4]. Several published studies show that the process of vascular calcification begins rather early in CKD and is particularly severe among elderly and type 2 diabetic patients. Furthermore, among both diabetics and

non-diabetics, vascular calcification was seen in patients who were new to dialysis, in patients with CKD, and in patients with established disease on dialysis.

Thus, calcification in early CKD is an important predictor of subsequent progression of CKD. Vascular calcifications have been associated with low bone turnover, low bone volume and lower activation frequency. In dialysis patients, the treatment of hyperphospathemia with calcium based compounds is associated with more frequent episodes of hypercalcemia, suppression of intact parathyroid hormone and with progression of coronary calcifications. In the presence of adynamic bone disease, calcium load has a significantly higher impact on aortic calcifications and stiffening. Prevalence of CAC is predominantly higher in diabetics than in non-diabetics[5-10].

It is of pivotal importance to maintain very narrow limits of P, Ca and PXCa product according to more recent suggestions[11].

Ideal phosphate binder should not only bind phosphate adequately but also protect renal patients from accumulation of various metals like aluminum or calcium. In spite our conception that hypocalcaemia accompanies deterioration of renal function, true hypocalcaemia is present in less than 5% of patients in stage 3 and in less than 20% of patients in stage 4[12].

Sevelamer

In 1997 sevelamer hydrochloride (Renagel®) and in 2007 the newer sevelamer carbonate (Renvela) were presented as nonabsorbable agents that contain neither calcium nor aluminum. These drugs are cationic polymers that bind phosphate through ion exchange, in the gastrointestinal tract. As noted with other phosphate binding agents, a significant number of trials have found that sevelamer is effective in lowering serum phosphate levels[13-18] (Figure 1). The important issues with respect to the choice of sevelamer versus other agents are their relative effects on mortality, vascular calcification, bone disease, and biochemical effects, particularly hypercalcemia. The following sections will address some of the evidence evaluating the relative effects of sevelamer on mortality, vascular calcification, and biochemical indices.

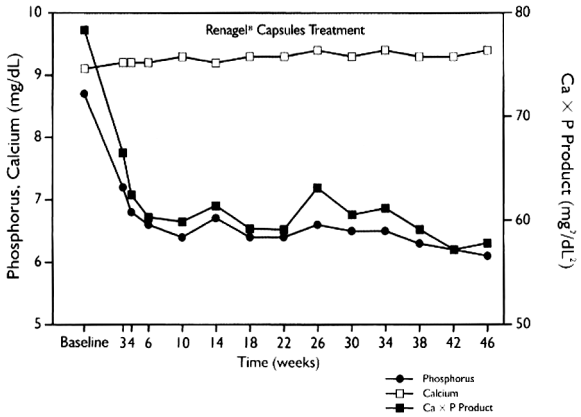

Figure 1: Calcium, Phosphorus and CaXP product through one year of sevelamer treatment. (Adapted from Chertow GM. Nephrol Dial Transplant 1999).

Mortality

A small number of randomized trials and a meta-analysis have evaluated mortality with sevelamer versus calcium-based phosphate binders[18,19,20-26]. The following is a brief review of the largest studies:

The three-year Dialysis Clinical Outcomes Revisited (DCOR) trial evaluated mortality and morbidity outcomes among 2103 prevalent hemodialysis patients randomly assigned to either sevelamer or calcium-based phosphate binders[22]. A secondary analysis reported no differences in mortality, but there were benefits with sevelamer on all cause hospitalizations and hospital days[25]. DCOR is the largest prospective outcomes study ever conducted in dialysis population. This 3-year trial enrolled more than 2100 patients (50% of patients were diabetic) and compared the difference in outcomes for patients receiving sevelamer hydrochloride with those receiving calcium-based phosphate binders in 75 sites in the United States. Patients were randomly assigned to either sevelamer hydrochloride (Renagel®) or calcium-based binders (PhosLo® [calcium acetate] or TUMS® calcium carbonate). The median age of patients in the study was 62 years old. Up to 45 months, there was no significant difference in all-cause mortality (RR 0.93, 95% CI 0.79-1.11) and cardiovascular mortality (RR 0.93, 95% CI 0.74-1.17) though a 7% reduction in mortality in favor of sevelamer was noticed p=0.40). However, a clinically meaningful benefit was associated with sevelamer use for older patients. In a pre-specified secondary analysis, those 65 years or older achieved a 23% reduction in all-cause mortality compared with those 65 or older using calcium-based phosphate binders, a result that was statistically significant in favor of the sevelamer-treated patients (p=0.02). The mean number of hospitalizations per patient per year was lower in the sevelamer-treated arm (p=0.07), with the biggest difference seen in patients > 65 years. Additionally, for patients remaining on study for at least two years (43% of the study population) a difference in mortality emerged favoring the sevelamer patients (p=0.02).

In the prospective randomized Renagel in New Dialysis Patients (RIND) trial, there was relatively less progression of coronary artery calcification in 127 incident hemodialysis patients randomly assigned to sevelamer versus calcium-based phosphate binders[20]. In a post-hoc analysis of this study, mortality at a median follow-up of 44 months was (borderline) significantly lower with sevelamer (5.3/100 patient-years versus 10.6/100 patient-years)[21]. With multivariate analysis, there was a greater risk for death with calcium-based phosphate binders (hazard ratio 3.1, CI: 1.23 to 7.61). In addition, the baseline coronary artery calcium level was a significant predictor of mortality. Subjects with no evidence of CAC (CAC=0) had a significantly lower mortality rate (3.3/100 patient years, CI: 0.4-6.1) compared to subjects

with a CAC score 1-400 (7.0/100 patient years, CI: 2.7-11.4) and those with a CAC score >400 (14.7/100 patient years, CI:8.1-21.4) (p=0.002). After multivariable adjustment, the presence of a baseline CAC score >400 remained significantly associated with increased mortality (HR=4.5, p=0.016, CI: 1.33-15.14).

In 1377 new to dialysis patients concerning veterans, use of sevelamer was associated with 33% advantage in mortality rate compared to the use of calcium containing phosphate binders (p< 0,001)[26]. It seems that sevelamer hydrochloride is associated with with a survival benefit in some hemodialysis patients populations.

A meta-analysis of five trials consisting of 2429 patients (2103 from the DCOR study) reported a similar risk difference for all-cause mortality between sevelamer and calcium-based phosphate binders (-2 percent, 95% CI: -6 to +2 percent). Tonelli et al state that there was no evidence that sevelamer reduced all-cause mortality, cardiovascular mortality, the frequency of symptomatic bone disease or health-related quality of life[23]. In respond Frazao and Adragao[27] in a systematic review argue that three of the studies included in the mortality analysis of Tonelli et al involved a small number of patients (20 to 42 patients), had a short follow-up (18 weeks to 5 months), and mortality was not an end point to most of them. These studies[18,19,24] were not powered in terms of follow-up time, number of patients, and end points to evaluate mortality. It is impossible to withdraw any mortality information in studies with 42 patients and a 5-month follow-up, or a crossover study with 20 patients and a total follow-up of 18 weeks. The Chertow study's primary end point was vascular calcification; mortality was not even an end point and received 24% weight in the analysis. Regarding the RIND study[21], with a long follow-up for the secondary end point mortality and evidence of survival benefit in the sevelamer-treated group, the weight attributed was only 4.26%.

It is critical to cultivate a balanced approach to understanding results generated by meta-analysis of data from small trials.It is important to accept the limitations implicit in this method.' Meta-analysis only generates hypotheses and certainly should be carefully interpreted. One should always keep in mind that well designed; randomized controlled trials are the strong bases for evidence-based medicine[28].

Effect on calcification

There appears to be relatively less progression of vascular calcification with sevelamer versus calcium-containing phosphate binders among patients with CKD. The prospective and randomized "Treat-to-Goal" and RIND trials both reported relatively less progression of coronary artery calcification with sevelamer versus calcium-containing phosphate binders[18,19-21,29]. By comparison, the Calcium Acetate Renagel Evaluation (CARE)-2 trial found similar progression of coronary artery calcification with sevelamer and calcium acetate after intensive lipid control[30]. The differences observed between the "Treat-to-Goal", RIND, and the CARE-2 trial may be due, in part, to study limitations of CARE-2. Treatment assignment was not blinded in CARE-2, the 1.8 a priori margin for drug equivalence in favor of calcium acetate was large, CAC is only a surrogate outcome, duration of treatment was short(1-year), and dropout rate was high.

In incident dialysis patients, treatment with sevelamer has been associated with better survival, while in prevalent patients a clear benefit could only be demonstrated in older patients and in patients treated for more than 2 years. In conclusion, the treatment of hyperphosphatemia with sevelamer hydrochloride, a noncalcium and nonmetal containing phosphate binder, is associated with a beneficial effect on vascular calcification progression, bone disease and most likely with a survival benefit in some hemodialysis patients populations[27].

Given these findings, the risk of long-term calcium exposure remains a concern. Limiting calcium-containing phosphate binder use and the early use of sevelamer in patients with persistent hyperphosphatemia, even in combination with calcium-containing binders, may be most appropriate.

Bone histology

There appears to be no major difference between sevelamer and calcium-based phosphate binders in terms of bone histology. A few randomized prospective studies have been performed that found varying outcomes in different patients, with a consistent finding of improved bone volume with calcium therapy[31,32,33]. A small randomized, prospective, open label study, evaluated patients with bone biopsies at the beginning and after 1 year treatment period with sevelamer hydrochloride or calcium carbonate. Sevelamer treatment resulted in no statistically significant changes in bone turnover or mineralization compared with calcium carbonate, but bone formation rate increased and trabecular architecture improved only with sevelamer[31].

Although the evidence is somewhat inconsistent, there appears to be a correlation between increased calcium intake and an increased incidence of both adynamic bone disease and vascular calcification[31,34,35]. The increased calcium intake was most commonly the result of the use of calcium-containing phosphate binders compared with either sevelamer or lanthanum.

Effects on biochemical parameters

A number of randomized prospective studies have found that sevelamer compared with calcium-based phosphate binders is associated with lower serum calcium levels and higher phosphate and PTH levels[18,20,21,27,28,36]. In the prospective "Treat-to-Goal" trial, 200 patients undergoing maintenance hemodialysis were randomly assigned to sevelamer or calcium-based phosphate binders[16]. At one year, although serum phosphate control was similar with both agents, sevelamer was associated with the following:

Lower incidence of hypercalcemia (5 versus 16 percent)

A minimal decrease in the serum calcium concentration (9.5 versus 9.7 mg/dL [2.35 and 2.43 mmol/L])

Decreased incidence of low PTH levels (30 versus 57 percent)

Sevelamer causes 15-31% decrease of LDL-cholesterol both in dialysis and predialysis patients[37].

C-reactive protein levels decreased significantly after 52 weeks in sevelamer receiving patients while remained unchanged in calcium binder arm, suggesting an antiatheromatous, anti-inflammatory action of the drug[38].

Additionally use of sevelamer has been associated with amelioration of hyperuricemia, low fetuin A, decrease of uremic toxins, suggesting an anti-inflammatory action[39]. Although conventional dosing of sevelamer is effective, compliance with the requirement for thrice daily dosing with any phosphate binder can be problematic. A small crossover study found that thrice daily and once daily dosing were equally effective[40]. Although further study is required, once daily dosing may simplify the dosing regimen, thereby resulting in increased compliance and overall efficacy.

One problem associated with sevelamer hydrochloride is the possible induction of metabolic acidosis. As a result, a buffered form of sevelamer, sevelamer carbonate (Renvela®), has been developed. It is associated with higher serum bicarbonate levels than sevelamer hydrochloride (Renagel®), but these agents appear to be equivalent in their ability to control phosphate levels. This was shown in a double-blind randomized trial of 79 hemodialysis patients in which patients were administered eight weeks of sevelamer carbonate or sevelamer hydrochloride and then crossed-over to the other agent for eight weeks[41]. Both agents similarly controlled mean serum phosphate levels, while bicarbonate levels were significantly higher with sevelamer carbonate (+1.3 mEq/L). Additional advantages of sevelamer carbonate (Renvela®) over sevelamer hydrochloride would be multiple dose forms of sevelamer carbonate, not only in tablet, but also in a powder that will be able to be mixed with a liquid and then have taken as an emulsion, that is, alternative dose forms. Also, the ability to lessen or eliminate acidosis with the carbonate moiety of Renvela® compared with the hydrochloride in Renagel® is a big benefit. (Figure 2) Overall adverse reactions among those treated with sevelamer hydrochloride occurring in > 5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%) and constipation (8%). If the clinical trial and cross-over design is held out in larger use, then it looks like the GI side effects won't even be an issue at all with sevelamer carbonate.

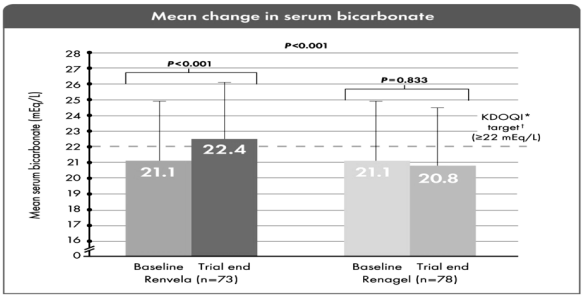

Figure 3: Treatment with sevelamer carbonate powder improves serum bicarbonate in chronic kidney disease patients on haemodialysis. (Adapted from Delmez J. Clin Nephrol. 2007; 68: 386-391).

Another potential weakness of sevelamer is that it may have an effect on concomitant vitamin D treatment. Pre-clinical studies suggest that high doses of sevelamer may reduce absorption of fat-soluble vitamins, including vitamin D. Sevelamer carbonate has been studied in human drug to drug interaction studies with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug to drug interaction studies with ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50%. No interaction was noticed with digoxin, warfarin, enalapril, metoprolol and iron.

Though there is a large difference in cost between sevelamer and calcium based phosphate binders, with sevelamer being much more expensive, we must have also in mind that there is mounting evidence from basic science, observational studies, and randomized trials with surrogate end points such as cardiovascular calcification and mortality that calcium can be toxic for dialysis patients. So, with this level of information, the nephrology community should be asking what level of scientific evidence is needed to convince us to discontinue, or at least to be extremely cautious with the use of calcium-containing phosphate binders, a potentially harmful therapy.

Table 1: Sevelamer presents a benefit in survival in certain patient groups.

	Number of patients	Patient Population	Reduction in mortality risk compared to Ca Binders	P value
Block et al. (RIND Outcomes)	127 Patient	New dialysis patients	28% NNT=4*	0.016
Suki et al.	2103 Patients (1068 completed the study)	Patients >65 Patients treated >2yrs	23% 34%**	0.02 0.02
Borzecki et al.	1377 patients	New Dialysis Patients	33%	<0.001

References

1. Amann K, Gross ML, London GM & Ritz E. Hyperphosphatemia: A silent killer of patients with renal failure. Nephrol Dial Transplant 1999; 14: 2085–2087.
2. Moe S, Chen N.Mechanisms of Vascular Calcification in Chronic Kidney Disease J Am Nephrol 2008: 19: 213-216.
3. National Kidney Foundation (NKF). K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42: S1-S201.
4. Guurin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplantation. 2000; 15: 1014-1021.
5. Mehrotra R, Budoff M, Christenson P, Ipp E, Takasu J, Gupta A, et al: Determinants of coronary artery calcification in diabetics with and without nephropathy. Kidney Int 2004; 66: 2022-2031.
6. Russo D, Palmiero G, De Blasio AP, et al. Coronary artery calcification in patients with CRF not undergoing dialysis. Am J Kidney Dis 2004; 44: 1024-1030.
7. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between Chronic Kidney Disease and Coronary Artery Calcification: The Dallas Heart Study J Am Soc Nephrol. 2005; 16: 507-513.
8. Qunibi WY, Abouzahr F, Mohammad R, et al. Cardiovascular calcification in Hispanic Americans with chronic kidney disease due to type 2 diabetes. Kidney Int 2005; 68:271-277.
9. Spiegel DM, Raggi P, Metha R et al. Coronary and aortic calcification in patients new to dialysis. Hemodialysis Int 2004; 8: 265-272.
10. Mehrotra R. Disordered mineral metabolism and vascular calcification in nondialyzed chronic kidney disease patients. J Renal Nutr 2006; 16: 100-118.
11. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol 2006; 17: 2275-84.
12. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007; 71: 31-38.
13. Chertow GM, Burke SK, Lazarus JM, et al. Poly[allylamine hydrochloride] (RenaGel): A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. Am J Kidney Dis 1997; 29: 66-71.
14. Goldberg DI, Dillon MA, Slatopolsky EA, et al. Effect of RenaGel, a non-absorbed, calcium- and aluminum-free phosphate binder, on serum phosphorus, calcium, and intact parathyroid hormone in end-stage renal disease patients. Nephrol Dial Transplant 1998; 13: 2303-2310.
15. Slatopolsky EA, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. RenaGel study group. Kidney Int 1999; 55: 299-307.
16. Chertow GM, Dillon M, Burke SK, et al. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium - Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Clin Nephrol 1999; 51: 18-26.
17. Bleyer AJ, Burke SK, Dillon M, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis 1999; 33: 694-701.
18. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62: 245-252.
19. Sadek T, Mazouz H, Bahloul H, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. Nephrol Dial Transplant 2003; 18: 582-589.
20. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005; 68: 1815-1824.
21. Block GA, Raggi P, Bellasi A, et al. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007; 71: 438-441.
22. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int 2007; 72: 1130-1137.
23. Tonelli M, Wiebe N, Culleton B, et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant 2007; 22: 2856-2866.
24. Shaheen FA, Akeel NM, Badawi LS, Souqiyyeh, MZ. Efficacy and safety of sevelamer. Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients. Saudi Med J 2004; 25:785-791.
25. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. Am J Kidney Dis 2008; 51: 445-454.
26. Borzecki AM, Lee A, Wang SW, et al. Survival in end stage renal disease: calcium carbonate vs. sevelamer. J Clin Pharmacy & Ther 2007; 32: 617-624.
27. Joao M. Frazao and Teresa Adragao: Treatment of hyperphosphatemia with sevelamer hydrochloride in dialysis patients: effects on vascular calcification, bone and a close look into the survival data. Kidney Int 2008; 74 (Suppl 111), S38–S43.
28. Farkouh ME, Fuster V. Meta-analysis of small trials: proceed with caution.Nat Clin Pract nephrol 2008; 4: 115.
29. Chertow GM, Raggi P, Chasan-Taber S, et al. Determinants of progressive vascular calcification in haemodialysis patients. Nephrol Dial Transplant 2004; 19: 1489-1496.
30. Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: The Calcium Acetate Renagel Evaluation-2 (CARE-2) Study. Am J Kidney Dis 2008; 51: 952-965.
31. Ferreira A, Frazao JM, Monier-Faugere MC, et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. J Am Soc Nephrol 2008; 19: 405-412.
32. Barreto DV, Barreto FC, de Carvalho AB, et al. Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study. Nephron Clin Pract 2008; 110: c273-283.
33. Salusky IB, Goodman WG, Sahney S, et al. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. J Am Soc Nephrol 2005; 16: 2501-2508.
34. Malluche HH, Siami GA, Swanepoel C, et al. Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clin Nephrol 2008; 70: 284-295.
35. Barreto DV, Barreto FC, Carvalho AB, et al. Coronary calcification in hemodialysis patients: the contribution of traditional and uremia-related risk factors. Kidney Int 2005; 67: 1576-1582.
36. Kestenbaum B. Calcification in CKD: No closer to the Cure. Am J Kidney Dis 2008; 51: 877-879.
37. Ketteler M, Rix M, Fan S et al. Efficacy and Tolerability of Sevelamer Carbonate in Hyperphosphatemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis. Clin J Am Soc Nephrol. 2008; 3: 1125-1130.
38. Ferramosca E, Bruke S, Chasan-Taber S, et al. Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. Am Heart J 2005; 149: 820-825.
39. Evenepoel P. Control of hyperphosphatemia beyond phosphate. Kidney intern 2007: 71: 376-379.
40. Fischer D, Cline K, Plone MA, Dillon M, Burke SK, Blair AT Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. Am J Kidney Dis. 2006 Sep; 48: 437-444.
41. Delmez J, Block G, Robertson J, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. Clin Nephrol 2007; 68: 386-391.