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REVIEW

A Review of Sevelamer Hydrochloride in End-Stage Renal Disease Patients on Dialysis

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Abstract: It is known that in the presence of even subtle kidney dysfunction an intensive prevention of cardiovascular risk is required. Apart from the conventional factors which contribute to cardiovascular disease (CVD), there are also some specific conditions of the chronic kidney disease (CKD) population such as oxidative stress of uremia and dialysis (D). However, hyperphosphatemia, hypercalcemia, and elevated calcium-phosphorus product remain as major contributors to the development of vascular calcification (VC) in this population, as part of the systemic complication known as mineral and bone disorders (MBD) in CKD patients. Importantly, the retention of phosphate remains as main culprit in the pathogenesis of CKD—MBD. Over the years, various treatment options for phosphate removal and controlling mineral metabolism, bone health, VC and CVD have failed, mainly through an over-suppression of PTH, development of ABD and promotion of VC and mortality.

Although KDOQI and KDIGO published CKD—MBD guidelines has clearly stated where calcium-based phosphate binders should not be used in D patients (hypercalcemia and low PTH) and where non calcium-containing phosphate binders are preferred (patients with severe vascular and/or other soft tissue calcifications), the greatest controversy and disagreements within the nephrological community still exists upon the cost-effectiveness of non calcium binder (sevelamer) use. Indeed, despite the evidence and recognised trend towards both a decrease in VC and CVD associated with sevelamer use, it is still an ongoing matter of debate. The magnitude of this controversy is increased when the issue of advanced medical and/or budgetary evaluation related to the implementation of clinical guidelines for CKD—MBD treatment is considered. Despite advocated use of sevelamer across a range of common clinical scenarios in CKD, its widespread utilization is challenged as exceeding what would usually be considered good value for money. If so, it is questionable whether the recommendations and suggestions from the guidelines should be followed, and further, do we need guidelines and innovative drugs for treatment of hyperphosphatemia? While awaiting the answer, as clinicians we should proceed with a treatment to "do no harm", trying to at least limit the calcium exposure of our dialysis patients.

Keywords: hyperphosphatemia, KDOQI guidelines, KDIGO guidelines, calcium based binders, non calcium based binders, sevelamer

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Introduction

Because there is an undeniable link between kidney dysfunction and cardiovascular risk, the presence of even subtle kidney dysfunction should be considered as one of the conditions necessitating intensive prevention of such risk.[1] Apart from the conventional factors such as hypertension, dyslipidemia, and hyperhomocysteinemia which contribute to cardiovascular disease (CVD), there are also some specific conditions of the chronic kidney disease (CKD) population such as oxidative stress of uremia and hemodialysis.[2] However, hyperphosphatemia, hypercalcemia, and elevated calcium-phosphorus product remain as major contributors to the development of vascular calcification (VC) in this population.[3,4] This issue should also be looked at from a perspective of the common clinically defined systemic complication known as mineral and bone disorders (MBD) in CKD patients.[5] MBD consists of a combination of mineral, hormonal and bone abnormalities, as well as vascular and soft tissue calcifications paralleling progressive kidney dysfunction. Of note, the retention of phosphate is considered as the main culprit in the pathogenesis of MBD in patients with advanced CKD.[6] In addition, the production of fibroblast growth factor 23 (FGF-23), a novel bone-derived phosphaturic hormone that inhibits both renal phosphate reabsorption and calcitriol production, should be regarded as an important player in CKD-MBD.[7] Here, the decreased production of calcitriol is a negative signal for FGF23 production basically stimulating parathyroid hormone (PTH) secretion, which in turn increases relative phosphate excretion despite the reduction in glomerular filtration rate (GFR). On the other hand, the reduced GFR stimulates production of FGF-23 levels which activates the bone-kidney axis coordinating systemic phosphate homeostasis and bone mineralization to protect the body from hyperphosphatemia. Although FGF23 could not differentiate between bone biopsy diagnosed low- or high-turnover bone disease,[8] the beneficial effects of lowering FGF23 levels are suggested by the correlation between FGF23, vascular calcification, CKD progression and mortality.[9,10] In summary FGF23 has uncovered new regulatory pathways and system biology governing mineralization, vitamin D metabolism, parathyroid gland function, and renal phosphate handling. Thus FGF23 assessment will become important in diagnosing of hypo- and hyperphosphatemic disorders, for which pharmacological regulation of FGF23 levels may provide novel treatments.[11]

Over the years various treatment options for phosphate removal or reduction were adopted in routine clinical practice.[12] Unfortunately, some treatment modalities to control mineral metabolism, bone health, VC and CVD have failed.[13] Thus, the great expectations for calcium based phosphate binders were dissolved in the last decade when enhanced risk for over-suppression of parathyroid hormone (PTH) and development of adynamic bone disease (ABD), especially when used in combination with vitamin D, promoting VC and mortality became apparent.[14–16] Indeed, hyperphosphatemia has been considered as one of the most "expensive" complications in treatment of CKD population. The aim of this review is to provide better insight in the newer treatment of hyperphosphatemia based on the evidence and surrounding controversy for its cost-efficiency.

Guidelines for Treatment of Hypersphosphatemia

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) has published the first Bone Metabolism and Disease Treatment Guidelines in 2003, in line with the growing body of evidence linking various treatment strategies and related clinical outcomes, following their goal of improving the quality of care and outcomes of patients with kidney disease.[17] In the guidelines 5.6 (evidence) and 5.7 (opinion based) it is clearly stated where calcium-based phosphate binders should not be used in dialysis patients (hypercalcemia and low PTH levels below 150 pg/mL on 2 consecutive measurements)[18,19] and where noncalcium-containing phosphate binders are preferred (patients with severe vascular and/or other soft tissue calcifications).[20]

Although the authors of these guidelines acknowledged that additional hard evidence is needed to complete future revisions to these guidelines, the low evidence 'judgements' presented in the guidelines was generally perceived as much as absolute truth by the medical community as it is in the high evidence 'guidelines'.[21] Considering the bias of the existing evidence especially in the field of newer therapeutics and related clinical outcomes KDIGO initiative has recently launched the new guidelines on CKD-MBD.[22] In the presence of not conclusive evidence of non- vs.

calcium-based binders, KDIGO recommended and suggested in guidelines 4.1.5 (1B) and (2C) limited calcium intake in the form of phosphate binders as more beneficial than harmful until further research is available. Repeatedly the restriction was proposed in the presence of arterial calcification, ABD and/or persistently low serum PTH levels and hypercalcemia in addition to stopped therapy with vitamin D. So both KDOQI and recent KDIGO guidelines were not different with respect to the limited treatment with calcium based binders. In addition, KDIGO guidelines pointed to at least some evidence in humans showing beneficial effects of sevelamer-HCl compared with calcium-based binders mainly on progression of arterial calcification and partially on mortality risk reduction. It should also be noted that there was no consensus for this guideline production from all the KDIGO members, considering its potential impact as too large in the presence of the scarce evidence to support it.

Sevelamer Hydrochloride in Treatment of CKD Patients—What is the Evidence?

The management of hyperphosphatemia and other components of MBD may be evaluated through various surrogate clinical endpoints (vascular calcification and bone disease), or hard clinical outcomes (cardiovascular events). Although a number of newer therapeutics are already available: Renagel® and Renvela® (Genzyme Corporation, Cambridge, MA); Fosrenol® (Shire Pharmaceuticals, Hampshire, UK); Sensipar® and Mimpara® (Amgen, Inc., Thousand Oaks, CA) to facilitate the achievement of consistent control of multiple MBD parameters, the majority of beneficial outcome data were reported only for sevelamer use.[12] At the same time, the greatest controversy and disagreements within the nephrological community continue on the cost-effectiveness of sevelamer use, especially during the global economic and medicare crisis, in both developed and developing countries.

What is the real evidence?

Considering the limitations of data generated from existing meta-analysis,[23] the two systematic reviews comparing sevelamer to other therapies could not find convincing evidence that sevelamer improves clinically relevant outcomes in ESRD patients,[24] pronouncing it as economically unattractive treatment strategy.[25] Later data on mortality benefits with sevelamer treatment emerged from randomised clinical trials. Namely, Block et al demonstrated significant survival benefit (as a secondary endpoint) in incident dialysis patients receiving sevelamer vs. calcium-based binders in a relatively small trial of 127 subjects (11 vs. 23 deaths, respectively).[26] On the other hand, the expectations in the largest outcome study ever conducted in the prevalent dialysis population (Dialysis Clinical Outcomes Revisited—DCOR) were not confirmed for all-cause mortality in the overall population.[27] Nevertheless, in a specified subgroup analysis of older population (age >65 years) and in patients treated with sevelamer for more than 2 years, sevelamer treatment was associated with a lower all-cause mortality. A possible difference in the reports from these two studies may be related to the various study designs (age, diabetes, dialysis duration, type of the study population, incident vs. prevalent) and the shorter follow up in the DCOR trial. Of note, in a secondary analysis of the DCOR study, there was evidence that sevelamer treated patients were less frequently (11%) hospitalized and spent less time (12%) in hospital.[28] In addition, beneficial effects of sevelamer treatment with increased bone formation and improved trabecular architecture although without statistically significant changes in bone turnover or mineralization compared with calcium carbonate were recently reported in a single 1-year bone biopsy based study.[29]

In spite of all the above mentioned evidence and a recognised trend towards both a decrease in cardiovascular mortality and all measures of coronary artery calcification, in a two recent meta-analyses the decrease in mortality associated with sevelamer was still questioned as controversial matter.[30,31] In fact, the authors could not conclude whether the beneficial effects came from an associated decrease in cholesterol, a decrease in coronary artery calcification, other pleiotropic effects of sevelamer or contrarily, an increase in mortality associated with calcium-based phosphate binders (CBPB).[31]

Benefits of Treatment with Sevelamer Compared to Calcium Based Binders

There is a plenty of new evidence with significantly lower coronary artery calcification scores in prevalent dialysis patients treated with sevelamer as compared to CBPB.[32] Most probably besides the reduced calcium loading, there is an additional effect of sevelamer

increasing the calcification inhibitor levels of fetuin-A.[33] Other pleiotropic effects which may play a key role in the vascular protective activities of sevelamer as shown in a recent meta-analysis are lowering of the C-reactive protein levels, and a higher alkaline phosphatase and intact parathyroid hormone levels found among sevelamer-treated patients.[34] Thus, although calcium-based binders and sevelamer are almost equally effective for treatment of hyperphosphatemia, it is obvious that both phosphate binders have different mechanisms of action. The main adverse effect of CBPBs is the calcium excess accumulated through the use of binders, supplements, and dialysate which can lead to hypercalcemia, contribute to VC, and potentially affect bone histology and mortality. In contrast, sevelamer treatment (once or three times daily) results only in mild gastrointestinal adverse effect.[35]

Recently, a new combined phosphate binder calcium acetate/magnesium carbonate (CaMg) has been offered as a therapeutic option, non-inferior in comparison with sevelamer at controlling serum phosphorus levels.[36] However, this report was challenged assuming that one (phosphate) CKD-MBD variable was well controlled in the CaMg group vs. total of four in the sevelamer group (calcium, PTH, magnesium). Additionally, the control of LDL cholesterol and potassium levels which was superior under sevelamer-treatment should have been taken into account as an important factor in survival outcomes.[37]

Despite all existing data, there is still uncertainty in the nephrological community that the most cost-effective way to treat hyperphosphatemia in patients with end-stage renal disease is to be determined.[38] The magnitude of controversy is increased when the issue of advanced medical and/or budgetary evaluation related to the implementation of clinical guidelines for CKD—MBD treatment is considered. On top of it, the growing number of patients requiring dialysis and especially the high cost of CKD-MBD treatment itself are pressing clinicians to pharmaco-economically justify the management of hyperphosphatemia with new drugs available on the market and related outcomes. Thus, despite of the advocated use of sevelamer across a range of common clinical scenarios in CKD[22] and demonstrated evidence of reduced morbidity and mortality,[27,28] its widespread utilization was challenged as exceeding what would usually be considered good value for the money.[39,40]

In conclusion, the controversy with regard to the sevelamer treatment seems to be against compelling adoption of the K/DOQI recommendations today and those of KDIGO's in the future. The extrapolated conclusion which should be drawn here is about the assessment of the worthwhile medical values which should be implemented for the improved well being of our patients. Medical professionals need an answer to the question whether they should follow recommendations and suggestions from the guidelines or if economic constraints should take precedence? Finally, one could ask, do we need guidelines and innovative drugs for treatment of hyperphosphatemia, if there is no possibility that they can be implemented in everyday clinical practice? Unfortunately, while awaiting answers, the only clinical perspective for treatment is to "do no harm", trying to at least limit the calcium exposure of dialysis patients.

Disclosure

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