

Treatment of hyperphosphataemia with sevelamer hydrochloride in dialysis patients: is there a survival advantage? A close look into a meta-analysis

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The last few years have seen major developments in the management of bone and mineral disorders. The knowledge that these bone and mineral abnormalities have a major impact on morbidity and mortality has made nephrologists pay more attention to control of these alterations. In addition, new compounds have been developed for the control of hyperphosphataemia and for the treatment of secondary hyperparathyroidism, raising many questions towards the use of non-calcium containing phosphate binders.

Until recently, the only phosphate binders available were aluminium or calcium based compounds. These compounds were efficacious but also associated with significant side effects. The use of aluminium-containing phosphate binders is associated with bone disease and haematologic and central nervous system toxicity while the use of calcium-containing phosphate binders is associated with increased risk of hypercalcaemia and cardiovascular calcification¹⁻⁴. It is now known that serum calcium levels are not accurate in predicting calcium balance and burden. The excessive amount of calcium ingested from diet and calcium-containing binders has been associated with cardiovascular calcifications, even in the presence of normal calcium serum levels¹⁻⁴. The non-calcium, non-metal containing and non-absorbed phosphate binder, sevelamer hydrochloride, has provided an effective way to bind phosphorus in the gut without the risks of hypercalcaemia, soft tissue or vascular calcifications, or heavy metal accumulation.

The promise of a survival benefit with the use of sevelamer hydrochloride has been evaluated in two randomised, prospective, controlled studies with interesting results that generate some controversy and certainly have not completely solved the issue.

The first was the “Dialysis Clinical Outcomes Revisited (DCOR)” study⁵. This three-year trial involving more than 2,100 patients compared the difference in mortality and morbidity outcomes for patients receiving sevelamer hydrochloride and those receiving calcium-containing phosphate binders⁵. This was the largest outcomes study ever conducted in the haemodialysis population. This study showed that the patients treated with sevelamer hydrochloride experienced a reduction of 7% in the risk of death from all causes when compared to the patients treated with calcium-based phosphate binders, statistically not significant ($p=0.3$). The patients aged 65 years old or over (a predefined analysis) were 23% less likely to die when treated with sevelamer hydrochloride, compared to treatment with calcium-based binders. Also, patients treated with sevelamer hydrochloride for more than two years had a 34% reduction of the mortality risk for all causes compared to those treated with calcium-containing binders.

The second study was the “Renagel in New to Dialysis Patients (RIND)”⁶. This was a randomised, controlled, prospective, open label study with 127

patients incident to dialysis, assigned to 18 months treatment with sevelamer hydrochloride or calcium-containing phosphate binders to assess coronary artery calcification progression. Mortality was a pre-determined secondary endpoint⁶. Twenty three deaths in the calcium-containing phosphate binders group and 11 deaths in the sevelamer hydrochloride assigned patients occurred during the median 44 months of follow-up time after randomisation, a significant lower mortality for patients treated with sevelamer hydrochloride. The survival benefit observed with sevelamer hydrochloride treatment persisted after full multivariate adjustment.

It is very important to analyse the reasons for the differences observed in the outcomes of these two trials. The review article published by Teresa Adragão in this current issue of the Portuguese Journal of Nephrology and Hypertension proposes some important explanations for such different results. The DCOR trial evaluated prevalent patients probably with a more important burden of calcification, while RIND trial was performed in patients new to dialysis. It is probably very difficult to reverse already existing vascular calcifications. The DCOR trial has been criticised for the short follow-up time of less than two years. The median follow-up was shorter in DCOR trial compared to the RIND, 19 *versus* 44 months, respectively. The short follow-up time in the DCOR did not allow the differences in mortality to appear. In fact, for the patients followed more than two years, the difference in mortality became significant. In the DCOR trial, the number of pre-viewed cardiovascular events necessary to demonstrate a difference between the two treatment groups was not reached. Annual mortality rate in DCOR trial was inferior to the annual mortality rate reported in USRDS⁷.

The results of these two studies strongly suggest that the use of sevelamer as a phosphate binder decreases mortality in incident and in elderly haemodialysis patients and reinforce the importance of earlier initiation of treatment with sevelamer hydrochloride in haemodialysis patients.

My final comment is on the systematic review of the clinical efficacy and safety of sevelamer hydrochloride in dialysis patients published by Tonelli M, *et al.*⁸. The authors included in the mortality analysis 5 studies (Table I). Only in one study was mortality the primary endpoint⁵. Other 3 studies included (Table I) in the mortality analysis involved a small number of patients, had a short follow-up and mortality was not an endpoint. These studies^{4,9,10} were

not powered in terms of time, number of patients, and endpoints to evaluate mortality. For example, in my view it is impossible to draw any mortality information in studies with 42 patients and a 5 month follow-up or a cross-over study with 20 patients and a total follow-up of 18 weeks. The Chertow study's⁴ primary endpoint was vascular calcification, mortality was not even an endpoint and received a 24% weight in the analysis. Regarding the RIND study, with a long follow-up for the secondary endpoint mortality and evidence of survival benefit in the sevelamer treated group, the weight attributed was only 4.26%.

Table I

Summary of the studies used for the mortality analysis

Author	Number of patients	Follow-up	Primary Endpoints
Block ⁶	127	18 months for the primary endpoint (calcifications) and 44 months for the secondary endpoint (mortality).	Progression of calcifications
Chertow ⁴	200	52 weeks	Progression of calcifications
Sadek ⁹	42	5 months	Biochemical parameters
Shaheen ¹⁰	20	Cross-over 8 – 2 – 8 weeks	Biochemical parameters
Suki ⁵	2103	22 months	Mortality

In my opinion the available data on mortality benefit with sevelamer hydrochloride treatment from two randomised, prospective controlled trials is a very positive fact and certainly innovative in the nephrology field. I am not aware of any other pharmacological intervention in the dialysis patient with such ground in terms of hard outcomes data. With that in mind it seems to me that the use of meta-analysis for the evaluation of the same question already studied with randomised controlled trials needs to be critically studied and with a great deal of caution.

In a recent editorial¹¹ the authors state that “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 generate hypothesis and certainly should be carefully interpreted. One should always keep in mind that well designed randomised controlled trials are the strong basis for evidence-based medicine.

There is mounting evidence from basic science¹², observational studies¹³ and randomised trials with surrogate endpoints such as cardiovascular calcification^{4,14} and mortality⁶ that calcium can be toxic for dialysis patients.

As recently mentioned¹⁵ rather than questioning if sevelamer's outcomes data can make us change our standard of care, we should be asking what level of scientific proof is needed to convince us to discontinue a potentially harmful therapy.

Conflict of interest statement. João M. Frazão is a consultant and advisory board member for Amgen and Genzyme and served as an advisory board member for Abbott.

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