DIALYSIS update

Practical approaches to manage disorders in mineral and bone metabolism and anaemia in dialysis patients

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Contents

Preface

End-stage renal disease (ESRD) is accompanied by profound changes in mineral metabolism. The laboratory manifestations include hypocalcaemia, hypercalcaemia, hyperphosphataemia, Vit D deficiency, and hyperparathyroidism. Abnormal mineral metabolism leads to metabolic bone disease and contributes to other clinical problems, such as muscle and joint disease, anaemia, neuropathy, and impotence. Moreover, disorders of mineral and bone metabolism are major contributors to cardiovascular morbidity and mortality.

Several investigators have suggested a link between mineral metabolism and anaemia. Hyperparathyroidism is usually listed as a contributor to renal anaemia and as a possible reason for impaired erythropoietin (EPO) response in CKD (chronic kidney disease) patients. Possible pathogenic links are reduced erythropoiesis due to calcitriol deficiency, direct or indirect effects of iPTH on EPO release and shortened red blood cell survival.

This Dialysis Update deals with publications referring to mineral and bone disorders as well as with the issue of EPO response in CKD patients. Among them, results from the randomized, controlled, multicentre CALMAG study, demonstrate how the phosphate level in dialysis patients can be cost-effectively reduced with a calcium acetate/magnesium carbonate phosphate binder.

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1. Evaluation of calcium acetate/ magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability

Treatment of hyperphosphataemia is a key therapeutic goal in dialysis patients, thereby oral phosphate binders are required to control the serum phosphorus (P). A phosphate binder combining calcium and magnesium offers an interesting therapeutic option, because the intake of calcium is reduced compared with phosphate binders containing calcium salts only. In addition, increased serum magnesium levels in patients with end stage renal disease have been associated with beneficial effects such as reduced cardiovascular calcification, reduced hypertension and reduced mortality.

This prospective, controlled, randomized, investigator-masked non-inferiority study investigated the effect of calcium acetate/magnesium carbonate (CaMg, 110 mg elemental calcium, 60 mg elemental magnesium, OsvaRen®) on serum P levels compared with sevelamer hydrochloride (HCl, 800 mg, Renagel®) for 24 weeks (w) in 255 patients from 36 dialysis centres in five European countries. HD patients were on 4 – 6 hour HD or online-HDF 3x/w for at least three months. After a washout/run-in phase of 2 to 3 weeks, during which all phosphate binders had to be discontinued and all patients were switched to the study dialysis fluid composition (dialysate calcium of 1.5 or 1.25 mmol/L, dependent on prior prescription, and dialysate magnesium of 0.5 mmol/L) for at least 2 w, patients were randomized in a 1:1 ratio. Only those patients being treated with a dialysate calcium of 1.25 mmol/L during the study could be switched to 1.5 mmol/L in the event of hypocalcaemia. The main population for the confirmative analysis of the primary efficacy variable was the per-protocol (PP) set. 204 patients completed the study PP (CaMg group: n = 105; sevelamer-HCl group: n = 99).

There were no statistically significant differences in baseline demographics, screening laboratory parameters and baseline covariates between the two groups. The mean percentage compliance with study medication intake was close to 100% in both groups. Average daily study medication intake was slightly but significantly higher in the sevelamer-HCl group at w 25 (CaMg: 7.3 ± 3.03; sevelamer-HCl: 8.1 ± 2.87 tablets/day; p = 0.0420). **Figure 1** depicts that serum P levels decreased significantly with both drugs at week 25. Both predefined target levels - K/DOQI (Kidney Disease Outcome Quality Initiative) target ≤1.78 mmol/L and KDIGO (Kidney Disease Improving Global Outcomes) target ≤1.45 mmol/L - were significantly more often reached with CaMg in comparison with sevelamer-HCl. Also the time to reach these targets was significantly shorter in the CaMg group. Ionized serum calcium did not differ between groups (in the CaMg

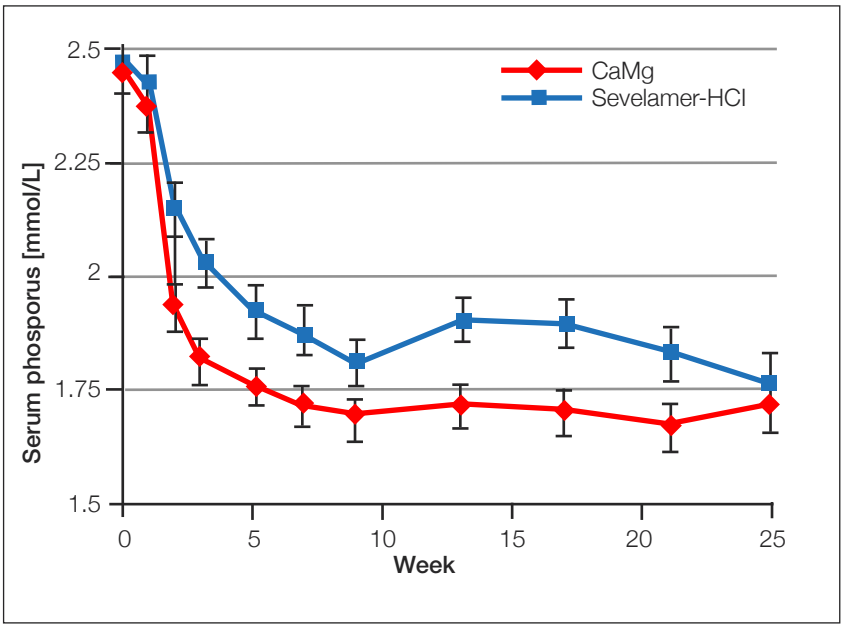

Fig. 1: *Time course of serum phosphorus over 24 weeks for the CaMg PP group (n=105) and the sevelamer-HCl PP group (n=99).*

group 1.071 ± 0.1608 mmol/L at baseline, 1.104± 0.1210 mmol/L at w 25; in the sevelamer group 1.076 ± 0.1306 and 1.113 ± 0.1063 mmol/L, resp.). While no changes were observed in the sevelamer-HCl group for total serum calcium, it increased statistically significantly in the CaMg group (treatment difference 0.0477 mmol/L), but this was not associated with a higher risk of hypercalcaemia. An asymptomatic but statistically significant increase in serum magnesium occurred in CaMg-treated patients, at w 25 serum magnesium was 1.297 ± 0.2547 mmol/L in the CaMg group and 1.039 ± 0.1851 mmol/L in the sevelamer-HCl group, $p < 0.0001$.

There was no difference regarding occurrence of any adverse events between the groups.

In conclusion, the phosphate binder combining calcium and magnesium salts was not inferior to a non-calcium-containing phosphate binder at controlling serum phosphorus levels after 25 weeks and it showed a good tolerability profile. Thus, calcium acetate/magnesium carbonate may offer an effective and cost-efficient treatment of hyperphosphataemia in HD patients. *CL*

de Francisco ALM, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, Scholz C, Ponce P, Passlick-Deetjen J: Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability; Nephrol Dial Transplant, advance access publishsed June 7, 2010

2. Serum iPTH, calcium, phosphate, and the risk of mortality in a European haemodialysis population

Most epidemiological clinical studies investigating the relationship between markers of mineral and bone disorder (MBD) and mortality in patients with chronic kidney disease (CKD) have been performed in USA. Generally it has been found that higher levels of intact parathyroid hormone (iPTH), calcium and/or phosphate were associated with an increased risk of mortality. **Floege J et al.** aimed to assess this issue in the European population.

The association between the markers of MBD [phosphate, iPTH, calcium] and clinical outcomes was examined in 7970 haemodialysis patients treated in European Fresenius Medical Care facilities over a median of 21 months. Baseline and time-dependent Cox regression were performed using Kidney Disease Outcomes Quality Initiative (KDOQI) target ranges as reference categories. The analysis was adjusted for demographics, medical history, dialysis parameters, inflammation, medications and laboratory parameters.

Of the 7970 patients selected for analysis, 1477 (19%) died, 399 (5%) underwent a successful renal transplant, 884 (11%) were lost to follow-up and 5210 (65%) completed the study.

Hazard ratio (HR) estimates from baseline analysis for the 3 investigated parameters were U-shaped. Adjusted baseline Cox analysis showed that patients with high iPTH levels (> 600 pg/mL) experienced a 2-fold increase in risk of death (HR: 2.10, 95% CI: 1.62 – 2.73, $p < 0.001$) whereas those in the lowest iPTH category (< 75 pg/mL) had almost a 50% greater risk of death (HR: 1.46, 95% CI: 1.17 – 1.83, $p = 0.001$) compared to the KDOQI range (150 – 300 pg/mL).

In the adjusted baseline Cox analysis, patients with low serum phosphate as well as those with high serum phosphate had an increased risk of death compared to

those who were within target range (1.13 – 1.78 mmol/mL) (HR: 1.18, 95% CI: 1.01 – 1.37, p = 0.033 and HR: 1.32, 95% CI: 1.13 – 1.55, p = 0.001, respectively), see **figure 2**.
The test for interaction between history of diabetes, mortality and serum phosphate was marginally significant in the baseline analysis (p = 0.044), but not in the time-dependent analysis (p = 0.831).

With regard to the adjusted baseline analysis for total serum calcium, patients with high serum calcium levels (> 2.75 mmol/L) had a higher risk of death than those who were within target range (2.10 – 2.37 mmol/L) (HR: 1.70, 95% CI: 1.19 – 2.42, p = 0.003).

In conclusion, the overall findings of this study for the three MBD markers (Ca, P and iPTH) show that the lowest risk of mortality was among patients whose MBD markers were within the KDOQI target range. These data are consistent with the more recent Kidney Disease: Improving Global Outcomes (KDIGO) recommendations on CKD-MBD target parameters, although some patients could be at increased risk of mortality compared to those treated within KDOQI target range. *KB*

J Floege, J Kim, E Ireland, C Chazot, T Drueke, A de Francisco, F Kronenberg, D Marcelli, J Passlick-Deetjen, G Schernthaner, B Fouqueray, DC Wheeler and on behalf of the ARO Investigators: Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population; Nephrol Dial Transplant, advance access published April 25, 2010

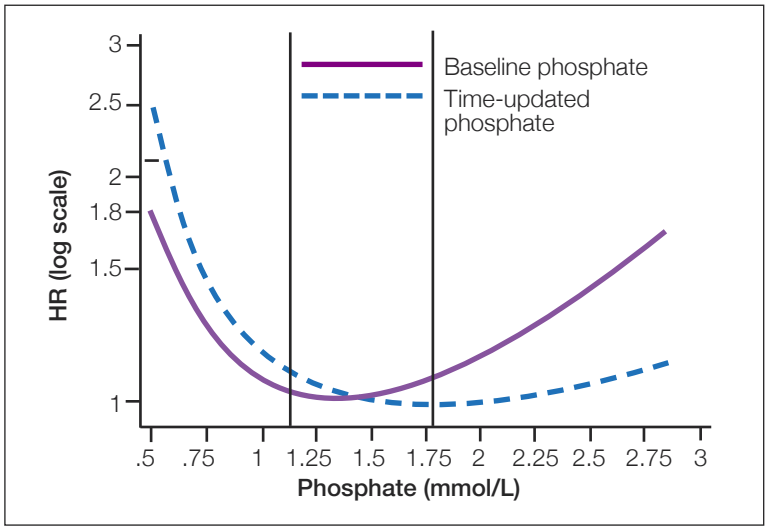

Fig. 2: *Relative risk of all-cause mortality for serum phosphate comparing baseline versus timedependent Cox regression.*

3. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response

Haemoglobin (Hb) variability in anaemia of chronic kidney disease is often described as a risk factor for increased mortality. **Gaweda AE et al.** tested in their study the effects of different factors, which influence the Hb sensitivity to erythropoiesis stimulating agents like iron stores, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism.

They performed a retrospective, observational cohort study of all 209 patients receiving in-center haemodialysis at the Kidney Disease Program, University of Louisville, between January 1996 and December 2001. All patients were dialyzed three times weekly and received EPOetin alfa (EPO) intravenously. Predialysis Hb, transferrin saturation, serum albumin, and dialysis adequacy (Kt/V) were observed monthly, whereas predialysis serum ferritin (Ferr) and intact parathyroid hormone (iPTH) were analyzed quarterly over a period of 13 to 69 months. The study analyzed the dynamic relationship between Hb and EPO, considering nonlinear effect modification by Ferr, transferrin saturation, Kt/V, albumin, and iPTH individually.

The maximum EPO response was associated with…

- Ferr between 350 and 500 ng/mL, see **figure 3**. Ferr below 350 ng/mL was associated with a drastic decrease of EPO response, whereas Ferr above 500 ng/mL was associated with a gradually decreasing EPO response
- a transferrin saturation greater than 30%. Transferritin levels of 20% and 10% were associated with erythropoietic response decreases by approximately 8% and 75%, respectively

- a Kt/V of 1.4 or greater. Kt/V values of 1.2 and 1.0 were associated with about 10% and 85% decrease in EPO response, respectively
- an albumin value greater than 3.8 g/dL. Albumin levels of 3.4 and 3.0 g/dL were associated with a decrease of EPO response by about 10% and 70%, respectively
- iPTH level between 0 and 100 pg/ml. iPTH levels of 300, 600, and 900 pg/ml were associated with about 90%, 79%, and 67% of the maximum EPO response, respectively.

The authors note that this study was retrospective and that some factors of interest were not collected or even not measured.

The study results show that serum ferritin, transferrin saturation, Kt/V, serum albumin, and intact parathyroid hormone are markers of nonlinear effect modification of the erythropoietic response in HD patients. KB

AE Gaweda, LJ Goldsmith, ME Brier, GR Aronoff: Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response; Clin J Am Soc Nephrol 5, 576 – 581, 2010

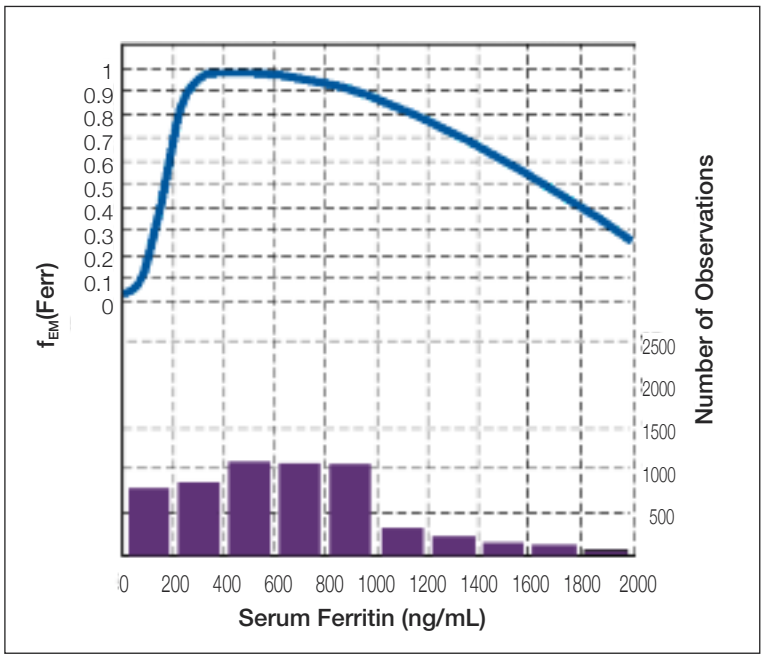

Fig. 3: *Plot of the mean effect modification by serum ferritin (top, left y-axis) and the histogram of data distribution (bottom, right y-axis). Maximum Hb response between 350 and 500 ng/mL.*

4. Impact of haemoglobin and erythropoietin dose changes on mortality: a secondary analysis of results from a randomized anaemia management trial

Several studies have been published in the last years pointing to the adverse associations between variability in haemoglobin (Hb) levels and important clinical outcomes including mortality. Potential factors that contribute to Hb variability are drug related factors, factors related to patient demographics and clinical status, practice pattern related factors including the abrupt non-physiologic increases of circulating erythropoiesis-stimulating agents (ESA) levels with ESA therapy, and finally reimbursement related factors. **Lau JH et al.** examined the association of Hb variability, ESA dosing parameters and the use of intravenous (IV) iron supplementation with mortality in HD patients.

This trial was based on a previously published randomized controlled trial evaluating the helpfulness of an anaemia management protocol to achieve Hb targets (110–125 g/L). Those patients who had completed at least 20 weeks of the original study and were alive on HD at the end of the study (154 patients) were followed up in the present analysis using data collected during or at the end of the original study as baseline data. Thus, patients were followed up from completion of the original anaemia management study (July 2002) until June 2008.

The mean age of the 154 HD patients was 65.7 ± 14.3 years, 59.1% were males, and mean dialysis vintage was 2.51 ± 2.52 years. ESA dose was 11 357 ± 9305 units weekly and the median dose change was 4000 (interquartile range: 2000 – 7525). Intravenous iron was prescribed to 72.9 % of patients, thereby the average dose was 37.5 ± 21.8 mg/wk. The average mean Hb of last six values was 117 ± 8.6 g/L.

More rapid rises in Hb and ESA dose increases (see **figure 4**) were independently associated with mortality in multivariate analysis. For every 1000-unit increase in ESA dose, the adjusted HR was 1.12 (1.01 - 1.24), p = 0.027. The authors discuss that large increases in ESA dose may have harmful effects, either through sudden increases in Hb leading to thrombosis or through other pleiotropic effects of erythropoietin including its effects on the vessels via nitric oxide inhibition, increased oxidative stress and improved platelet function. Factors associated with rapid Hb rises were frequency of ESA dose changes, magnitude of ESA dose increase, baseline Hb, patient weight and presence of an HD catheter. In contrast, more rapid Hb declines and ESA dose decreases were not associated with mortality.

One important limitation of the study was that data were collected retrospectively. Although variables likely to affect outcome were included other potential confouders may have not been capatured in the study.

In conclusion, the present study demonstrates that the rate of Hb rise and magnitude of ESA dose increase were independently associated with mortality in HD patients. Some of the factors influencing these anaemia management variables are modifiable, e.g. more ESA-responsive patients may need to be treated with smaller dose increments. *CL*

Lau JH, Gangji AS, Rabbat CG, Brimble KS: Impact of haemoglobin and erythropoietin dose changes on mortality: a secondary analysis of results from a randomized anaemia management trial; Nephrol Dial Transplant, advance access published June 8, 2010

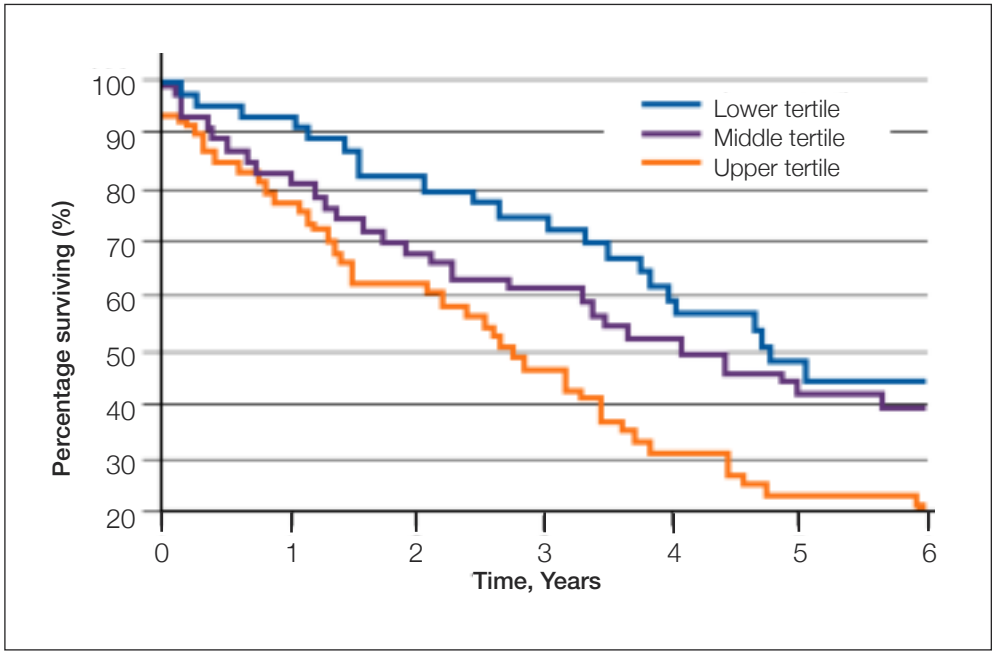

Fig. 4: *Kaplan-Meier survival curves based on tertiles of average ESA dose increase. (Log-rank statistic for linear trend: Chi square 9.73, p = 0.0018).*

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Reference: *1. De Francisco ALM, et al. A controlled randomized comparison of calcium acetate/magnesium carbonate (OsvaRen®) to Sevelamer Hydrochloride (Renagel®) in Haemodialysis Patients: The CALMAG Study, Poster no. TH-P0615, Poster presentation, Renal Week, 42nd Annual Meeting of American Society of Nephrology, San Diego, CA, 29.10.2009.*

OsvaRen® 435 mg / 235 mg film-coated tablets. Composition: Each film-coated tablet contains: Calcium acetate, 435.00 equivalent to 110 mg calcium and magnesium carbonate, heavy 235.00 mg equivalent to 60 mg magnesium. **Excipients:** Tablet core: Starch, pregelatinised, from maize, maize starch, sucrose, gelatine, croscarmellose sodium, magnesium stearate. Film coating: Castor oil, refined, hypromellose. **Indications:** Treatment of hyperphosphataemia associated with chronic renal insufficiency in patients undergoing dialysis (haemodialysis, peritoneal dialysis). **Contraindications:** OsvaRen® is contraindicated in patients with Hypophosphataemia, Hypercalcaemia with or without clinical symptoms, e.g. as a result of an overdose of vitamin D, a paraneoplastic syndrome (bronchial carcinoma, breast cancer, renal cell carcinoma, plasmacytoma), bone metastases, sarcoidosis or immobilisation osteoporosis; Elevated serum magnesium levels of more than 2 mmol/l, and/or symptoms of hypermagnesaemia; AV-block III°; Myasthenia gravis; Hypersensitivity to the active substances or to any of the excipients. **Side effects:** Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Gastrointestinal disorders: Common: Soft stools, gastrointestinal irritation like nausea, anorexia, sensation of fullness, belching and constipation, diarrhoea. Metabolism and nutrition disorders: Common: Hypercalcaemia either asymptomatic or symptomatic, asymptomatic hypermagnesaemia. Uncommon: Moderate to severe symptomatic hypercalcaemia, symptomatic hypermagnesaemia. Very rare: Hyperkalaemia, magnesium-induced osteal mineralisation disturbances. **Special warning:** Contains sodium (not more than 5.6 mg per each film coated tablet) and sucrose. Read the package leaflet before use. **Supply classification:** Prescription only medicine. **Fresenius Medical Care Nephrologica Deutschland GmbH**, 61346 Bad Homburg v. d. H., Germany. **Date:** February 2010 **The names of this medicinal product in the Member States of the EEA are as follows:** B: Renagho, Other countries: OsvaRen®. OsvaRen® has received marketing authorisations in: A, B, CY, CZ, D, DK, E, EST, F, FIN, GB, GR, H, IRL, IS, L, LT, LV, M, N, NL, P, PL, S, SK, SLO, SRB (status: February 2010). The registration procedure for other countries is currently in progress.