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A multicenter study on the effects of lanthanum carbonate (Fosrenol™) and calcium carbonate on renal bone disease in dialysis patients

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A multicenter study on the affects of lanthanum carbonate (Fosrenol™) and calcium carbonate on renal bone disease in dialysis patients.

Background. Lanthanum carbonate (LC) (Fosrenol™) is a novel new treatment for hyperphosphatemia. In this phase III, open-label study, we compared the effects of LC and calcium carbonate (CC) on the evolution of renal osteodystrophy (ROD) in dialysis patients.

Methods. Ninety-eight patients were randomized to LC ($N = 49$) or CC ($N = 49$). Bone biopsies were taken at baseline and after one year of treatment. Acceptable paired biopsies were available for static and dynamic histomorphometry studies in 33 LC and 30 CC patients. Blood samples were taken at regular intervals for biochemical analysis and adverse events were monitored.

Results. LC was well tolerated and serum phosphate levels were well controlled in both treatment groups. The incidence of hypercalcemia was lower in the LC group (6% vs. 49% for CC). At baseline, subtypes of ROD were similarly distributed in both groups, with mixed ROD being most common. At one-year follow-up in the LC group, 5 of 7 patients with baseline low bone turnover (either adynamic bone or osteomalacia), and 4 of 5 patients with baseline hyperparathyroidism, had evolved toward a normalization of their bone turnover. Only one lanthanum-treated patient evolved toward adynamic bone compared with 6 patients in the CC group. In the LC group, the number of patients having either adynamic bone, osteomalacia, or hyperpara decreased overall from 12 (36%) at baseline to 6 (18%), while in the calcium group, the number of patients with these types of ROD increased from 13 (43%) to 16 (53%).

Conclusion. LC is a poorly absorbed, well-tolerated, and efficient phosphate binder. LC-treated dialysis patients show almost no evolution toward low bone turnover over one year (unlike CC-treated patients), nor do they experience any aluminum-like effects on bone.

Key words: phosphate binder, osteodystrophy, bone histomorphometry, chronic renal failure, open-label study.

Hyperphosphatemia continues to be a challenge for the clinical nephrologist, as it may lead to extraosseous calcification of both vascular and nonvascular tissues, secondary hyperparathyroidism, and osteitis fibrosa, particular types of renal osteodystrophy (ROD) responsible for significant morbidity [1, 2]. To prevent hyperphosphatemia, most patients with end-stage renal failure require an exogenous phosphate binder.

Aluminium-containing phosphate binders have been widely used in the past. The systemic absorption of aluminium hydroxide over time, however, can lead to the development of the so-called aluminium-related bone diseases (either osteomalacia or adynamic bone), dementia, and more subtle disorders at the level of the parathyroid gland, hematopoiesis, and myopathy [3, 4].

The use of calcium salts for phosphate binding is complicated by the development of hypercalcemia and an increased risk of metastatic calcifications in a substantial fraction of patients, particularly those taking vitamin D analogs and those with adynamic bone disease [5–7].

Alternative phosphate binders have been developed in recent years with the aim of avoiding side effects during phosphate control. Polyallylamine-hydrochloride (sevelamer, RenaGel®) is a nonabsorbed cationic polymer that binds phosphate anions through ion exchange and hydrogen binding. This class of compounds was originally developed to lower plasma lipids; this effect is still seen with sevelamer [8]. Compared to calcium-based phosphate binders, evidence has shown that with sevelamer, fewer coronary and aortic calcifications are seen [9]. However, the efficacy of this polymer in lowering phosphate levels is still a matter of debate, as the target serum phosphate level of 5.5 mg/dL cannot be reached in the majority of patients, especially when the compound is used as monotherapy [10]. Moreover, as a lipid-binding compound, sevelamer has the ability to sequester fat-soluble vitamins and nutrient compounds [11]. Although no problems in this respect have emerged so far, more information on long-term safety is required.

Because the solubility product of trivalent iron and phosphate is extremely low, polynuclear iron preparations constitute another group of alternative phosphate binders. The use of trivalent iron has recently generated substantial interest; it is effective and well tolerated, but is still in the early stages of clinical development [12].

A third alternative is lanthanum carbonate. Lanthanum, discovered in 1839 by Mosander, is a rare earth element (molecular weight: 139 kD). As this trivalent hard acid cation has a high affinity for phosphate (phosphate binding capacity in vitro >97%), is minimally absorbed gastrointestinally, is not excreted by the kidneys, and is well tolerated, the investigation of lanthanum as a phosphate binder is warranted [13]. The excretion of absorbed lanthanum by the biliary system contrasts with aluminium, which is excreted almost entirely (>95%) in the urine and, consequently, is associated with an increased risk of toxicity in patients with renal disease [14]. Plasma lanthanum concentrations have rarely exceeded one part per billion. There has been no evidence of lanthanum toxicity in any of the clinical studies hitherto performed.

In light of the past tragic experience with aluminium in dialysis patients, information on the effects of lanthanum carbonate on bone is necessary. The present bone biopsy-based study aimed to: investigate the effect of phosphate management by the administration of lanthanum carbonate compared with calcium carbonate on renal bone disease; check the lanthanum accumulation in bone; and evaluate long-term safety and tolerability of lanthanum in dialysis patients after one year of treatment.

METHODS

Patients

Key inclusion criteria were male or female patients aged >18 years who had started dialysis treatment (hemodialysis or CAPD) within the 12 weeks prior to study entry, or had been diagnosed with chronic renal failure and were scheduled to begin dialysis prior to randomization. No preset limit was applied to serum PTH on entry to the study and there was no restriction of concomitant vitamin D therapy. Patients with significant hypocalcemia or concurrent illness were excluded.

A total of 98 patients ('intent to treat' patients) were randomized to the study medication and received at least one dose of lanthanum carbonate ($N = 49$) or calcium carbonate ($N = 49$). In this group all aspects of efficacy, safety, and tolerability were monitored. Safety was assessed at each study visit by recording adverse events and vital signs. Full blood biochemical and hematologic parameters were monitored and the plasma levels of lanthanum were measured at visits throughout the study.

Patients were recruited from 18 centers in 12 countries. The mean ± SD age was 55 ± 14.3 years; 59 (60%) patients were males. There was no relevant difference between treatment groups with respect to underlying nephrologic diagnosis: diabetes (26%); glomerulonephritis (9%); other known disease (12%); unknown cause (14%); cystic kidney disease (14%); hypertension (14%); and urologic disease (10%).

A total of 68 patients ($N = 34$ in each group) completed the study (i.e., underwent a bone biopsy at baseline and follow-up. Patients discontinued the study because of the investigator's decision ($N = 1$); protocol violation ($N = 1$); kidney transplantation ($N = 10$); death ($N = 11$); serious adverse events ($N = 2$); and others ($N = 5$). Of the patients randomized, 63 pairs of bone biopsies were suitable for histomorphometric measurements, 33 of which belonged to the lanthanum group and 30 to the calcium group.

Written informed consent was obtained from all patients and the study was conducted in compliance with the declaration of Helsinki and approved by Local Ethical Committees at each of the participating centers.

Study set up

The study was conducted over a one-year period. Following screening, all phosphate binders were stopped and double tetracycline labeling administered, with an interval of 8 to 12 days. A baseline bone biopsy was taken 2 to 6 days following the second label. Patients were then randomized in a 1:1 ratio to receive lanthanum or calcium carbonate. All patients were titrated to a lanthanum dose (up to 3750 mg/day) or calcium (up to 9000 mg/day) that achieved optimal reduction of serum phosphate levels, and were maintained at this dose, or titrated further when necessary. The second biopsy was obtained following double tetracycline labeling and one year of treatment, or at time of discontinuation if >6 months treatment received. A follow-up period was included, during which patients were examined and all

adverse events reviewed 28 days after discontinuation of the study medication (or early withdrawal from the study).

Laboratory methods

Blood and bone biochemistry. Blood samples were taken at study visits throughout the study period for the determination of a series of routine biochemistry and hematology screening tests. In addition, a panel of serum parameters relevant to bone [i.e., phosphorous, calcium, bone specific and total alkaline phosphatase, iPTH, 25-(OH)-, vitamin D, and 1,25-$(OH)_2$ vitamin D] were measured using the appropriate kits and methodologies.

Lanthanum was measured in plasma and bone by means of inductively-coupled plasma mass spectrometry (ICP-MS) using methodologies developed and optimized at the Centre for Analytical Sciences (CAS) at the University of Sheffield, United Kingdom.

Bone histomorphometry. In each patient, a single transiliac bone biopsy (± 1 cm length; 5 or 7 mm diameter) was taken after double tetracycline labeling. The biopsy was divided into two parts. One part (mainly cortical bone) was used to measure the bulk lanthanum content. The remaining part was fixed in absolute ethanol and then embedded in a methylmethacrylate-based resin for histology and histomorphometric analysis. Undecalcified 7-μm thick sections were stained with Toluidine blue [15]. Seven-μm sections were mounted unstained in immersion oil for visualization of tetracycline labels.

Criteria for classification of the various types of ROD were:

Adynamic bone disease: Bone formation rate (BFR) <5% of age- and sex-corrected mean and osteoclast surface (OcS) <20% of age- and sex-corrected mean.
Hyperparathyroidism: BFR >2x age- and sex-corrected mean and OcS >100x age- and sex-corrected mean.
Normal: BFR and OcS within 2SD of the age- and sex-corrected mean.
Osteomalacia: Mineralization lag time (MLT) >100 days and osteoid volume >5x age- and sex-corrected mean.
Mixed ROD: All bone biopsies that do not fulfill the criteria listed above.

RESULTS

Lanthanum carbonate taken with meals was well tolerated throughout the study period. The type and incidence of adverse events were well balanced between the two treatment groups, with 96% of patients in both groups reporting at least one treatment-emergent adverse effect. Gastrointestinal effects were the most common events and were typically mild (lanthanum: 53% vs. calcium: 49%). Withdrawal rates due to adverse events were comparable between lanthanum (24%) and calcium (22%). There was, however, a higher incidence of hypercalcemia (serum calcium above upper limit of normal) (i.e., >2.65 mmol/L or >10.6 mg/dL) in the patients treated with calcium carbonate (49%) compared to those receiving lanthanum carbonate during the study period (6%).

There were no significant differences in hematologic or biochemical safety parameters over time. A more detailed description of clinical safety results will be presented elsewhere.

There were no significant differences in the concentration of the various biochemical bone-related parameters between the two groups; these parameters also did not significantly change during the study period (Fig. 1). Both treatment groups showed well controlled phosphorus levels throughout the trial, using doses up to 3750 mg/day for lanthanum (median dose 1250 mg/day), and 9000 mg/day (median dose 2000 mg/day) for calcium carbonate. With respect to vitamin D usage, no differences were noticed between treatment groups (lanthanum: 63% vs. calcium: 53%).

Patients of the lanthanum group had plasma lanthanum levels that were slightly increased for all doses administered, compared with baseline levels of patients receiving 1500 to 2250 mg lanthanum per day, with mean plasma lanthanum levels ranging from 0.51 to 1.08 μg/L. Lanthanum levels did not depend on the dose administered and reached a plateau after 12 weeks of treatment. The patients treated with lanthanum carbonate for up to one year had a median bone concentration of 1.8 μg/g, the highest value in any patient being 5.5 μg/g. In the calcium carbonate group, bone lanthanum levels at the end of the study also showed a slight increase, with the highest value in any patient being 1.0 μg/g.

The histomorphometric data are shown in Figure 2. Five out of 7 patients (71%) of the lanthanum group with either adynamic bone or osteomalacia at baseline (Fig. 2, upper panels), and 4 out of 5 patients (80%) with baseline hyperparathyroidism (Fig. 2, lower panels) evolved toward a normalization of their bone turnover as compared to only 3 out of 7 (42%) and 3 out of 6 (50%) of the calcium group.

Twenty-six (26) patients (79%) of the lanthanum group and 23 (77%) of the calcium group had a normal or increased bone turnover (hyperpara, mixed, normal) at baseline. Both groups showed markedly different responses. While 6 out of 23 patients (26%) of the calcium group developed adynamic bone disease, this was seen in only 1 out of 26 patients (4%) of the lanthanum group (Fig. 2, upper panels). This particular lanthanum-treated patient had been taking oral calcitriol throughout the study at varying doses (0.5 to 1.5 μg TDS), despite having a PTH (baseline, 4.56 pmol/L to follow-up, 5.53 pmol/L) below the optimum level for an end-stage renal failure patient, and having a good control of serum phosphate

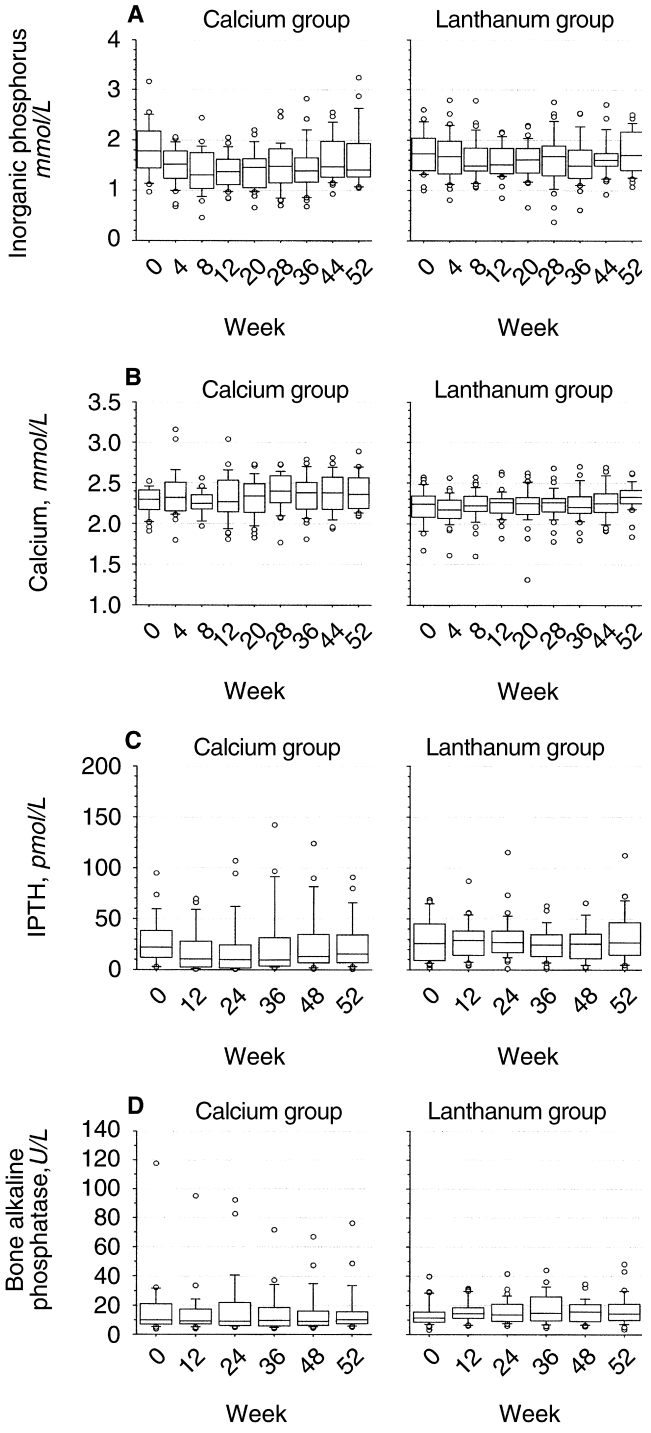

Fig. 1. Comparison and temporal evolution of some relevant bone-related parameters in both study groups.

(mean, 1.53 mmol/L) and serum calcium (mean, 2.38 mmol/L) throughout the study period.

Five patients (1 with osteomalacia and 4 with mixed bone disease at baseline) of the calcium group (17%) developed hyperpara compared to only 2 patients (mixed bone disease at baseline) of the lanthanum group (7.5%) (Fig. 2, lower panels).

The distribution of the various types of ROD assessed at baseline using the proposed criteria for classification was similar in both treatment groups (Fig. 2, lower panels).

Overall, in the lanthanum group the total number of patients having either adynamic bone, osteomalacia, or hyperpara decreased from 12 (36%) at baseline, to 6 (18%) at one-year follow-up, while in the calcium group, the number of patients with these types of ROD increased from 13 (43%) to 16 (53%) (Fig. 2, lower panels).

DISCUSSION

Treatment of uremic hyperphosphatemia remains a major challenge to the nephrologist because phosphate retention is associated with a variety of clinical problems, including secondary hyperparathyroidism and soft tissue mineralization.

Until now, aluminium-containing and calcium-based phosphate binders have been most frequently used in the treatment of hyperphosphatemia. Although highly efficacious, the chronic therapeutic use of these compounds goes along with serious side effects [3–5, 16]. Lanthanum carbonate has recently been proposed as a nontoxic and efficacious alternative.

In this phase III, open-label study, we compared the effects of a one-year treatment with either lanthanum carbonate or calcium carbonate on the evolution of renal bone disease in dialysis patients.

The serious adverse events for both treatment groups observed during the study period were balanced and were typical for a population with chronic renal failure receiving hemodialysis or peritoneal dialysis. Thus, data of the present study confirms the safe profile of lanthanum previously observed in phase II studies [17]. The incidence and types of adverse effects were similar in the two treatment groups. An exception to this was hypercalcemia, which was appreciably lower in the lanthanum-treated group compared to the calcium carbonate group (6% and 49%, respectively).

Despite the additional calcium intake in the calcium carbonate group, mean serum calcium levels did not differ significantly between the groups, which must be ascribed to careful monitoring of calcemia throughout the study and immediate adjustment of the dialysate calcium concentration or vitamin D intake. Nevertheless, the number of hypercalcemic episodes was substantially greater in the calcium carbonate group. This reduced propensity for hypercalcemic episodes on lanthanum carbonate must be considered a major benefit.

The serum phosphate levels were well controlled in both treatment groups throughout the study. There was little change in iPTH or bone alkaline phosphatase concentration in either treatment group during the study period.

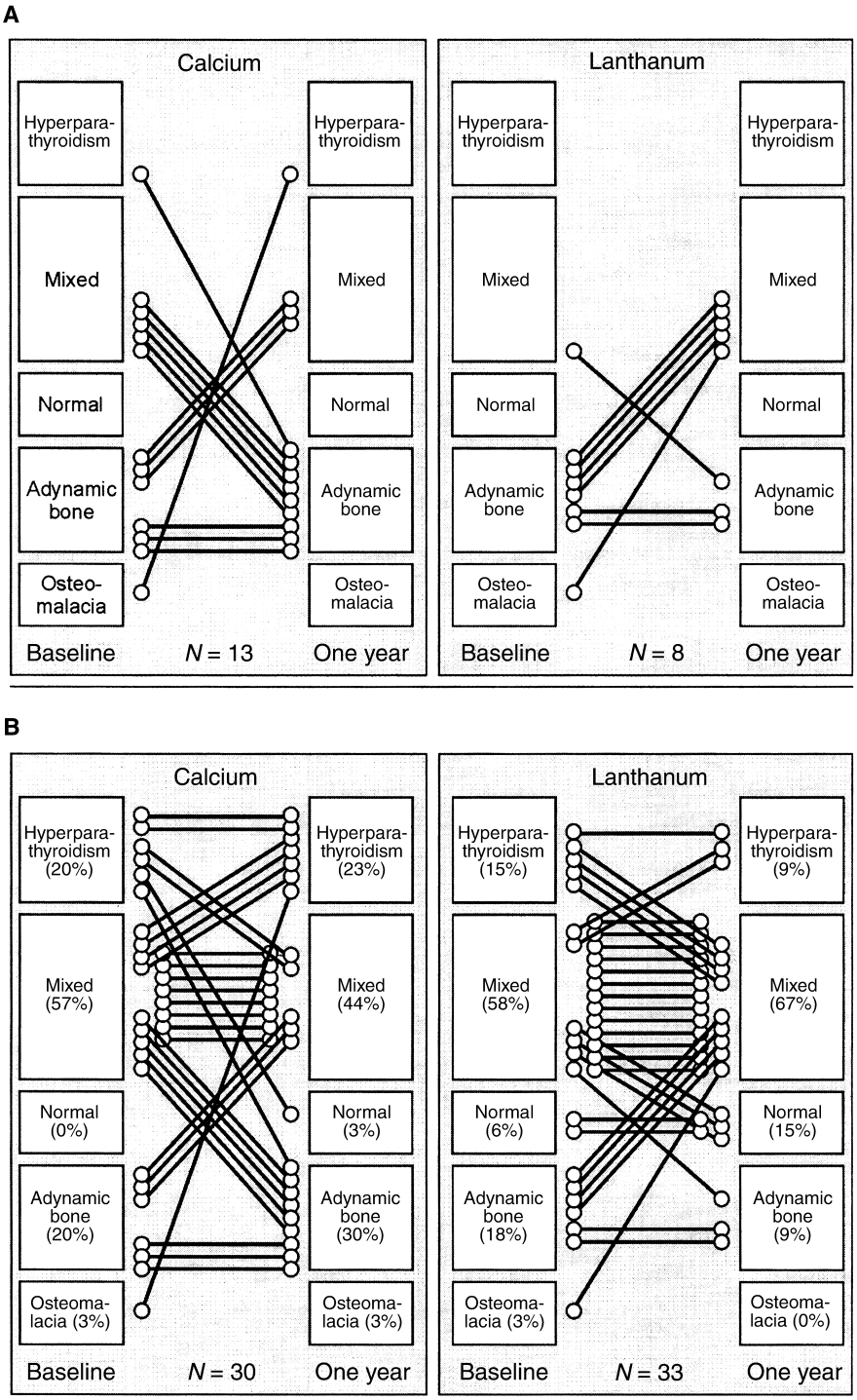

Fig. 2. Patients with either low bone turnover at baseline and those evolving toward low bone turnover at follow-up in both study groups are shown in the upper panels. Lower panels show temporal evolution of renal bone disease of all patients after one year of treatment with either lanthanum or calcium carbonate. Values between brackets indicate the prevalence of the various types of ROD.

Weighing any toxic effects of lanthanum against those experienced in the past with aluminium, the highly limited gastrointestinal absorption of lanthanum (0.00003% for lanthanum vs. 0.02% for aluminum), and the nonrenal routes of excretion for the absorbed fraction of the dose of lanthanum should be considered [18]. This is reflected by the very low concentrations of lanthanum found in bone and plasma after a one-year treatment, being 10- to 50-fold lower than those expected for aluminium [4]. Data furthermore has indicated that plasma lanthanum reached steady state early (i.e., after 12 weeks) in the study.

To the best of our knowledge, this is the first bone biopsy-based multicenter study to investigate and com-

pare the temporal effect of a phosphate binder on bone in dialysis patients. The extended group of study patients recruited from various centers in several countries can be considered a reliable reproduction of the current dialysis population.

Establishing that lanthanum did not induce aluminium-like toxic effects on bone was an important consideration when setting up the present study [4, 19, 20]. Bone histomorphometry clearly indicated that, in contrast to what has been reported for aluminium, lanthanum treatment for one year does not lead to the development of osteomalacia or adynamic bone. Patients in the calcium carbonate group were at a higher risk for the development of low bone turnover, as six patients of this group evolved toward adynamic bone disease, compared to only one subject from the lanthanum group. The majority of the patients (5 out of 7) of the lanthanum group having either osteomalacia or adynamic bone disease at baseline evolved toward a normalization of their bone turnover at follow-up.

At the group level, 12 patients of the lanthanum carbonate group (36%) had adynamic bone, osteomalacia, or hyperparathyroidism at baseline; this number fell to 6 (18%) at completion of the study. This was compared with 13 patients at baseline in the calcium carbonate group (43%), which increased to 16 (53%) at completion. Overall, lanthanum treatment led to a considerably better outcome than treatment with calcium.

CONCLUSION

Lanthanum carbonate was shown to be a safe, well-tolerated, and efficient phosphate binder. By comparison with calcium carbonate, treatment with lanthanum resulted in a normalization of the bone histomorphometric parameters during the study and there was almost no evolution toward low bone turnover at one-year follow-up. In addition, there was no suggestion of the adverse bone effects previously reported for aluminium hydroxide.

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