Lanthanum carbonate (Fosrenol®): a novel agent for the treatment of hyperphosphataemia in renal failure and dialysis patients

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SUMMARY
Approximately 70% of patients with end-stage renal disease and dialysis have hyperphosphataemia, which is associated with renal osteodystrophy, metastatic calcification and increased mortality and morbidity. Despite dietary restriction and dialysis, most patients will require a phosphate-binding agent to treat this condition. However, phosphate control has not significantly improved over the last two decades, mainly because of the lack of an ideal phosphate-binding agent. Aluminium-based and calcium-based agents are associated with major side-effects despite their efficacy. Although sevelamer hydrochloride represents a step forward in the management of hyperphosphataemia, it has drawbacks and therefore is not the ideal phosphate binder. Lanthanum carbonate is a non-calcium, non-aluminium phosphate-binding agent. It has shown to be effective, well-tolerated and has a positive effect on bone histology.

Keywords: Lanthanum carbonate; phosphate; phosphate binders; hypercalcaemia; dialysis

INTRODUCTION
Elevated serum phosphate is a usual accompaniment of end-stage renal disease (ESRD) and dialysis, even in the presence of dietary phosphate restriction or oral phosphate binders. The pathological consequences of hyperphosphataemia include the development and progression of secondary hyperparathyroidism, soft tissue calcification and possibly cardiovascular calcification (1). Indeed, poor phosphate control correlates significantly with morbidity and mortality in dialysis patients. Increased hospitalisation, premature death, reduced quality of life and increased cost of care have been reported (2). However, Block et al. (3–5) surprised the renal community with the finding that not only is hyperphosphataemia associated with reduced survival but that most of the excess deaths were from cardiac causes. The magnitude of the risk is illustrated by the fact that hyperphosphataemic compared with normophosphataemic patients have a 52% higher risk of death from coronary artery disease, a 26% higher risk of sudden death, a 34% higher risk from other cardiac causes and a 39% higher risk of death from cerebrovascular accidents (6).

Despite this, phosphate control has not improved over the last two decades. Block et al. (3) found that 50% of haemodialysis patients have a serum phosphate level >6.0 mg/dl and 25% of patients have a level >7.4 mg/dl. These results were similar to those published by Lowrie and Lew for over 17,000 patients receiving haemodialysis in 1988. Indeed, their analysis also showed that 25% of patients had a phosphate level >7.2 mg/dl (7). Several factors could be responsible for this. Poor compliance with both diet and medication use is common among patients with ESRD but most importantly is the lack of an ideal phosphate binder.

Conventionally, hyperphosphataemia has been treated using aluminium- or calcium-based phosphate binding agents. Although these agents are effective, they are associated with serious side-effects. Aluminium-based agents cause bone and central nervous system toxicity. Calcium-based agents increase the risk of hypercalcaemia and cardiovascular calcification. Sevelamer hydrochloride can achieve effective phosphate lowering and is associated with less coronary and aortic calcification and lower cholesterol levels but has some drawbacks, such as the gastrointestinal adverse effects, large pill burden and high cost.

Lanthanum carbonate (Fosrenol®), Shire Pharmaceuticals, Basingstoke, Hampshire, UK is another non-calcium, non-aluminium phosphate binder now available commercially in the US, and awaiting final licensing in the EU. In this article, we will look at the experimental, clinical and safety issues associated with lanthanum carbonate.

LANTHANUM CARBONATE
Lanthanum (La) is a rare-earth element in transition Group IIIb of the periodic table. It is a ductile and malleable,
silvery-white metal, soft enough to be cut with a knife. The element was discovered first by Carl Gustaf Mosander in 1839. Its name is derived from the Greek lanthanein, meaning ‘to be concealed’, indicating that it is difficult to isolate (8). It is exclusively trivalent in its compounds, and its ionic radius is the largest of the rare-earth trivalent ions, and as a consequence, the white oxide La₂O₃ is the most alkaline rare-earth oxide (9). Its atomic number is 57, weight 138.91 and the valency is 3.

Lanthanum Metabolism

Lanthanum carbonate binds phosphate optimally at pH 3–5, while retaining binding activity at pH 1–7 (10). It is therefore able to bind phosphate efficiently at the low pH of the stomach as well as the higher values in the duodenum and jejunum. Lanthanum carbonate also has no effect on the absorption of fat-soluble vitamins. However, lanthanum phosphate is highly insoluble (Table 1) (1) and therefore not reabsorbed further along the gastrointestinal tract.

Lanthanum carbonate has minimal potential for accumulation compared with aluminium, with only 0.00005% of an oral dose being absorbed in the canine gastrointestinal tract (Shire Pharmaceuticals Group, data on file) vs. 0.05–0.1% for aluminium (11). La is eliminated primarily by the liver and not the kidneys, with approximately 80% of the absorbed La being eliminated in the bile and 13% directly across the gut wall. In rats, the majority of an oral dose is excreted in the faeces (99.3%), while urinary excretion accounts for only 0.004%. In man, urinary excretion in healthy individuals represents only 0.000031% of the administered dose (12), because the vast majority of an oral dose passes straight through the gastrointestinal tract. Furthermore, in contrast to aluminium, La does not appear to cross the blood–brain barrier (13), and hence, the potential for neurological adverse effects is extremely low.

Lanthanum carbonate has been extensively studied. More than 1754 patients have been exposed to lanthanum carbonate for variable periods up to 5 years. There have been 11 phase I studies, 10 phase II and III studies, with two long-term safety studies still ongoing.

Effects on Phosphate Levels

The results of the preclinical studies have shown that lanthanum carbonate has the characteristics of an effective phosphate binder. A statistically significant decrease in serum phosphate levels was observed in patients receiving lanthanum carbonate at doses of 500–3000 mg/day, in two double-blind, placebo-controlled phase II studies (14,15). The maximal decreases in serum phosphorus levels occurred after 3 weeks of treatment and were maintained over the 4–6 weeks of treatment.

Two phase III studies were performed to evaluate the efficacy and safety of lanthanum carbonate. The first of these trials (study 302) was a 13-week, randomised, double-blind, placebo-controlled, parallel group study. The primary efficacy parameter was the ability to maintain control of the serum phosphorus level to ≤1.9 mmol/l (≤5.9 mg/dl). A highly significant difference in mean serum phosphorus levels between the lanthanum carbonate and placebo groups was seen. Serum phosphorus levels were controlled at ≤1.9 mmol/l in 59% of the patients receiving lanthanum carbonate compared with that in 23% of the placebo group. Furthermore, of those patients whose serum phosphorus levels were controlled at the time of entering the maintenance phase, 66% of the lanthanum carbonate-treated patients and 31% of the placebo-treated patients maintained control at study endpoint (16).

Study 301 (17) was a much larger prospective, randomised, multicentre, open-label, comparator study. The primary efficacy parameter was reduction of serum phosphorus levels to ≤1.8 mmol/l (≤5.6 mg/dl). The secondary parameter was the maintenance of control at ≤1.8 mmol/l for 6 months or longer. In total, nearly 800 haemodialysis patients received treatment in the 6-month comparator phase. After 9 weeks of treatment, both the groups had serum phosphorus levels of 1.69 mmol/l (Figure 1). In the lanthanum carbonate group, 67.9% of patients showed controlled serum phosphorus levels compared with 65.8% of patients of the calcium carbonate-treated patients. At the end of 6-month maintenance period,

| Agent        | Relative solubility | Absorption |
|--------------|---------------------|------------|
| Lanthanum    | 1                   | 0.02       |
| Aluminium    | 9900                | 0.1        |
| Calcium      | 29,000,000          | 30.0       |

Table 1 Comparative solubility and absorption of phosphate binders
there was no significant difference in the proportions of patients with controlled phosphorus levels (65.8 vs. 63.9% in the lanthanum carbonate and calcium carbonate groups, respectively). Importantly, however, lanthanum carbonate resulted in fewer episodes of hypercalcaemia than calcium carbonate (12).

Similar results were noted in a phase III, open-label study (303), to investigate the effect of lanthanum carbonate, compared to calcium carbonate, on bone metabolism in chronic renal failure patients receiving dialysis. Although the study was not designed to compare the phosphate-binding efficacy of the two treatment groups on average both the treatment groups showed well-controlled phosphate levels during the study. There was a slight increase at visit 20, but this was following a period when phosphate-binder treatment has been interrupted to allow tetracycline labelling prior to bone biopsy (Figure 2) (18).

In another study, Hutchison et al. (19) demonstrated that lanthanum carbonate is effective in reducing serum phosphate to ≤1.8 mmol/l regardless whether patients were receiving continuous ambulatory peritoneal dialysis or haemodialysis.

**Effects on Calcium Phosphate Product (Ca × P product)**

Given that lanthanum carbonate has been shown to be an effective phosphate binder and that it does not contain calcium, it would be expected to have a beneficial effect on Ca × P product. This is borne out by a number of clinical studies.

In phase II studies, the Ca × P product was unsurprisingly significantly higher in the placebo group because of uncontrolled serum phosphorus levels (14,15). Likewise, in study 302, Ca × P product was significantly lower in lanthanum carbonate-treated patients than with placebo (52.37 ± 14.89 vs. 66.59 ± 18.30 mg²/dl², p < 0.0001) (16). In study 301, the reductions in Ca × P product were generally greater with lanthanum carbonate maintenance treatment than with calcium carbonate (−1.59 vs. −1.26 mmol²/l²) (18), which was statistically significant.

In a study of bone histomorphometry, which was not designed to compare the phosphate-binding efficacy but investigated the effects of lanthanum carbonate compared with calcium carbonate on bone metabolism in chronic renal failure patients receiving dialysis, the mean Ca × P values were generally similar for both the lanthanum- and calcium-treated groups and showed no particular trend as a result of treatment. The ranges of calcium phosphate levels were also similar between treatment groups. This reflects the efficient control of serum calcium in the calcium carbonate-treated patients and the absence of a strict target for serum phosphate control in this study (Figure 3) (18).

**Effects on Serum Parathyroid Hormone (PTH)**

No studies of lanthanum carbonate have been designed with the effect on serum PTH as a primary end-point. Indeed, it is very difficult to do this in a clinical setting, because PTH is...
influenced by many factors including serum calcium, phosphate, vitamin D status and modality of dialysis. Understanding of PTH metabolism is still evolving, but it is now appreciated that while severe hyperparathyroidism should be controlled quickly, over-suppression of PTH is associated with the adynamic bone lesion, an increased Ca×P product, and vascular calcification. Therefore, control of serum PTH requires individual tailoring depending on the patient’s circumstances and starting point.

In general, reduction of oral calcium load is likely to be associated with an increase in serum PTH, which would be beneficial for patients with suppressed levels but detrimental to those with severe hyperparathyroidism. However, this effect may be ameliorated by better phosphate control.

In study 302, serum PTH levels were significantly lower after lanthanum carbonate treatment compared with placebo, presumably reflecting better phosphate control (mean ± SD: 209.41 ± 152.65 vs. 291.80 ± 194.82 pg/ml; p < 0.01) (16). Similarly, in study 301, the median serum PTH levels decreased by around 5% during 5 months of maintenance treatment with lanthanum carbonate and increased by around 15% with calcium carbonate (20). However, in study 303, the mean and median PTH levels for the La group showed stability throughout treatment, and the extent of the data ranges did not show substantial change. In the calcium carbonate group, however, there was general reduction in both the mean and median PTH levels during the middle period of the study and larger variations in the data range (Figure 4) (18).

Effects on Bone

The effects of aluminium on bone histology initially gave rise to concern that La might have similar effects, and therefore, study 303 was designed to look specifically at this possibility. In one of the largest paired, open-label bone histomorphometry studies ever undertaken, the long-term effects of lanthanum carbonate and calcium carbonate on the development and progression of renal osteodystrophy (ROD) were evaluated in patients undergoing dialysis. At baseline, 98% (48/49) of patients in each group had ROD. Indeed, ROD subtypes were similarly distributed in both groups, with mixed ROD being the most common. After 1 year of treatment, a greater proportion of patients with low bone turnover lesions (adynamic bone or osteomalacia) at baseline approached normalisation on lanthanum carbonate compared with those in the calcium carbonate group (71 vs. 42%, respectively). Only one lanthanum carbonate-treated patient (4%) evolved towards adynamic bone compared with six (26%) patients in the calcium carbonate-treated group (21). Furthermore, no correlations between bone La content, PTH levels or bone histology were found (18).

Safety

Preclinical animal studies of La have shown no adverse effects at doses up to 2000 mg/kg body weight, suggesting a large safety margin for this compound. In human studies, serum La levels were very low but increased slightly from baseline levels after 1-year treatment with lanthanum carbonate. Mean serum La levels in the highest dose groups ranged between 0.51 and 1.08 μg/l. The levels did not appear to be dose dependent and reached a plateau after 12 weeks of treatment. Furthermore, bone La levels did not exceed 6 μg/g wet weight (median 1.8 μg/g) after a full 1 year of treatment. Even in the calcium carbonate-treated group, bone La levels showed a slight increase over the course of the study reaching a maximum value of 1.0 μg/g (22). This probably reflects the fact that some areas of Europe have relatively high La levels in tap water and local vegetables.

![Figure 4] Mean serum parathyroid hormone (PTH) levels over time for lanthanum carbonate and calcium carbonate groups (303 study)
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In 303 study, 6% of patients in the La group and 48% of patients in the calcium carbonate group had at least one hypercalcaemic episode (serum calcium >2.65 mmol/l). The substantially greater incidence in the calcium carbonate group was predictable and was probably the result of greater calcium burden in these patients. The number of hypercalcaemic episodes for the La group was low and similar to that observed during La treatment in a previous study (LAM-IV-301 Clinical Study Report).

Long-term experience with lanthanum carbonate in patients continues to increase, such that over 1800 patients have been exposed in total – 996 for more than 6 months, 604 for more than 12 months, 299 for more than 18 months, 205 for more than 24 months and around 40 for more than 36 months, with some subjects now reaching 5 years on continuous treatment.

We recently reported (in abstract form) results from the first long-term (3 years) study assessing the safety, tolerability and efficacy of lanthanum carbonate for the control of hyperphosphatemia in haemodialysis patients. Following an initial 6-month randomised trial \( (n = 767) \), in which patients received either lanthanum carbonate or calcium carbonate, lanthanum carbonate-treated patients continued therapy while calcium carbonate-treated patients were switched to lanthanum carbonate (titrated over 5 weeks), during a 6-month extension study. After this extension, patients were invited to continue lanthanum carbonate \( (1500–3000 \text{ mg/day}) \) for a further 24 months (total treatment duration, 3 years). Safety, tolerability and maintenance of serum phosphorus control \( \leq 5.6 \text{ mg/dl} \ (1.8 \text{ mmol/l}) \) were assessed.

In total, 518 patients received 6 months of open-label extension treatment with lanthanum carbonate; 161 of these participated in the 24-month lanthanum carbonate extension, 46 (almost 30%) of whom underwent \( \geq 152 \) weeks of cumulative lanthanum carbonate therapy (long-term exposure subgroup). There was little change in plasma La levels during long-term therapy. There were no differences in the incidence or types of adverse events in the 3 individual years of the study. The proportion of long-term exposure patients with controlled serum phosphorus \( (1.8 \text{ mmol/l}) \) was high throughout; 71.7% at week 58 (start of 24-month extension), 76.1% at mid-point (week 75) and 68.9% at endpoint (week 154). These long-term results suggest that the good safety, tolerability and efficacy of lanthanum carbonate in dialysis patients are maintained over 3 years of treatment (23).

In all studies, patients have been very closely followed with accurate recording of adverse events of all types, and only a small number of these have been felt by the local investigator to be related to La treatment. Comparison of all types of adverse events in La-treated and calcium-treated groups has shown no significant difference, with the exception of hypercalcaemia (6% vs. 35% of patients, respectively). No pattern of particular adverse events has emerged with time on treatment, and no significant changes in vital signs have been seen (20).

CONCLUSION

Lanthanum carbonate received regulatory approval in Europe during 2004 and is likely to appear on the market during 2006. It would appear that lanthanum carbonate is an effective and safe oral phosphate binder in patients receiving dialysis therapy. It is well tolerated when taken during or after meals, with a profile of gastrointestinal side-effects that is similar to those reported with calcium carbonate. Detailed and long-term data on its metabolism continues to accumulate with no evidence of detrimental effects after three years, and in a small number of patients, almost 5 years of treatment.

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Paper received October 2004, accepted April 2005