Safety, Tolerability and Efficacy of Lanthanum Carbonate in Haemodialysis Patients: a 12-Month Study

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Introduction

- Hyperphosphataemia is associated with multiple adverse systemic effects that promote raised morbidity and mortality in end-stage renal disease (ESRD)[1]
- Elevated serum phosphorus and calcium × phosphorus product may increase the risk of cardiovascular calcification.[1,2] In addition, secondary hyperparathyroidism, which results from calcium–phosphorus imbalance, promotes renal osteodystrophy[3]
- Patients with ESRD invariably require treatment with phosphate binders to control serum phosphorus and reduce these effects. However, studies demonstrating a number of problems associated with conventional agents have highlighted an ongoing need for new, effective phosphate binders:
  - Calcium-based agents, prescribed in up to 60% of patients with ESRD in some regions, effectively control serum phosphorus but often produce hypercalcaemia due to a raised total calcium load. This may promote adynamic bone and cardiovascular calcification[2,4,5]
  - Although highly effective as a phosphate binder, aluminium can accumulate to toxic levels in renal patients[6,7]
- Non-aluminium, non-calcium phosphate binders offer the ability to reduce serum phosphorus without inducing hypercalcaemia and without toxic aluminium-like effects.[2] However, it has become clear that the effective achievement and long-term maintenance of target serum phosphorus levels is an important requirement for such agents[8]
- Lanthanum carbonate is a novel non-calcium, non-aluminium phosphate binder that has equivalent *in vivo* phosphate-binding potency to aluminium hydroxide in animal studies[9]
- During a randomized, 6-month clinical trial, lanthanum carbonate showed similar efficacy to calcium carbonate in controlling serum phosphorus, but was associated with a substantially reduced frequency of hypercalcaemia[10]
- Here, we present results from an open-label extension to that trial

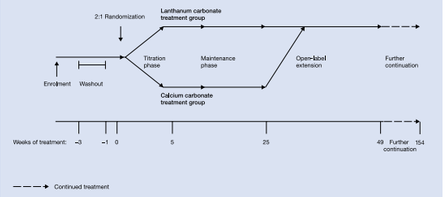
Methods

- Participants were male and female haemodialysis patients (aged ≥ 18 years) who had taken part in a previous 6-month, randomized, open-label trial[10] comparing lanthanum carbonate (lanthanum dose: 375–3000 mg/day) with calcium carbonate (calcium dose: 1500–9000 mg/day)
- Following initial randomized treatment, all patients were eligible to receive lanthanum carbonate (lanthanum dose: 375–3000 mg/day) during a 6-month extension period (Figure 1):
  - Those who had previously received calcium carbonate were switched to lanthanum carbonate, titrated over 5 weeks to maintain serum phosphorus at ≤ 1.80 mmol/L (≤ 5.6 mg/dL). Those already receiving lanthanum carbonate continued treatment at their established maintenance dose
- Patients completing the 6-month extension were allowed to continue treatment for 2 years. Initial results from this extension are presented here

Assessments

- Adverse events were monitored throughout treatment, along with routine biochemistry, haematology and vital signs; plasma lanthanum levels were also measured
- Maintained control of serum phosphorus and calcium × phosphorus product was evaluated

Figure 1. Study design summary



Results

Patients

- From a total of 767 patients in the initial ITT population (Table 1), similar proportions of lanthanum carbonate- and calcium carbonate-treated patients (44.3% *vs.* 46.1%, respectively) completed randomized therapy
- In total, 518 patients entered the open-label extension with lanthanum carbonate:
  - 185 patients had received randomized calcium carbonate treatment and were switched to lanthanum carbonate (CC/LC group)
  - 333 patients had received randomized lanthanum carbonate treatment and continued with lanthanum carbonate (LC/LC group)
- Overall, 375 patients (72.4%) completed the study (49 weeks of treatment); 262 (78.7%) in the LC/LC group and 113 (61.1%) from the CC/LC group
- Approximately half of patients in both the LC/LC and CC/LC groups (53.2% and 47.8%, respectively) received doses of lanthanum carbonate ≤ 2250 mg/day by the end of the initial extension treatment
- 161 patients participated in further extension treatment, with 46 patients having received lanthanum for ≥ 152 weeks

Table 1. Patient populations and baseline characteristics

	LC/LC*	CC/LC*
Numbers of patients		
ITT safety population	333	185
ITT efficacy population	332	181
Population characteristics		
Age, years		
Mean (SD)	57.0 (14.6)	58.6 (13.6)
Range	19–85	24–85
Sex (% male)	67.2	65.2
Renal disease characteristics		
Months on haemodialysis, mean (SD)	41.8 (36.9)	42.7 (45.1)
Patients with residual renal function, *n* (%)	210 (65.6)	113 (66.1)
Patients with previous kidney transplant, *n* (%)	36 (10.8)	20 (11.0)

* LC/LC – patients receiving lanthanum carbonate during both randomized and open-label extension treatment; CC/LC – patients receiving calcium carbonate during randomized therapy, then switching to lanthanum carbonate for extension treatment

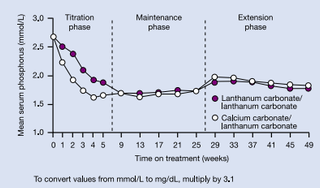
Tolerability and safety

- The tolerability profile of lanthanum carbonate during extension treatment up to 1 year remained similar to that seen during the initial 6-month randomized period:
  - During the previously reported randomized treatment period, hypercalcaemia was more frequent with calcium carbonate *versus* lanthanum carbonate (20.2% *vs.* 0.4%, respectively)
  - Hypercalcaemia was experienced by 0.3% of patients in the LC/LC group and 2.7% in the CC/LC group in the extension study
  - The most frequent adverse events reported by ≥ 5% of patients were gastrointestinal in nature (Table 2)
  - The incidence of serious adverse events was similar in the two groups (37.5% in the LC/LC group and 39.5% in the CC/LC group); none were considered by investigators to be related to lanthanum carbonate
  - Plasma lanthanum levels appeared to reach steady state at an early stage of treatment (Week 6 in the randomized lanthanum carbonate group) and were generally very low up to Week 49
    - « Mean (± SD) values in the lanthanum carbonate and calcium carbonate groups at screening were 0.01 ± 0.06 ng/mL and 0.01 ± 0.04 ng/mL, respectively. This demonstrates that lanthanum is present in the treatment-naive patients
    - « Mean (± SD) levels across the lanthanum carbonate dose range were between 0.37 ± 0.31 and 0.58 ± 0.50 ng/mL at Week 6 and 0.23 ± 0.17 and 0.67 ± 0.65 ng/mL at the end (Week 25) of randomized treatment, and between 0.0 ± 0.0 and 0.65 ± 0.45 ng/mL at Week 49 (end of open-label extension treatment)
    - « Plasma lanthanum levels showed a weak dose response, but were not dose-proportional

Table 2. Treatment-emergent adverse events occurring in > 5% of patients during extension treatment

	LC/LC *n* = 333	CC/LC *n* = 185
Patients reporting ≥ 1 adverse event, *n* (%)	297 (89.2)	169 (91.4)
Patients reporting ≥ 1 serious adverse event, *n* (%)	125 (37.5)	73 (39.5)
Individual adverse events, *n* (%)		
Nausea	50 (15.0)	30 (16.2)
Vomiting	45 (13.5)	31 (16.8)
Diarrhoea	39 (11.7)	25 (13.5)
Hypotension	37 (11.1)	21 (11.4)
Cramps	36 (10.8)	19 (10.3)
Bronchitis	29 (8.7)	9 (4.9)
Rhinitis	28 (8.4)	17 (9.2)
Headache	23 (6.9)	14 (7.6)
Dialysis graft occlusion	22 (6.6)	16 (8.6)
Abdominal pain	15 (4.5)	10 (5.4)
Hypocalcaemia	4 (1.2)	10 (5.4)

Figure 2. Mean serum phosphorus levels with up to 49 weeks of lanthanum carbonate treatment



To convert values from mmol/L to mg/dL, multiply by 3.1

Efficacy

- Lanthanum carbonate showed similar efficacy to calcium carbonate during the initial randomized treatment period (Figure 2):[9]
  - Responses to the two treatments were initially different during randomized dose titration due to protocol-specified dosing regimens; lanthanum carbonate was initiated at a sub-optimal dose (375 mg/day), whereas calcium carbonate was initiated at 1500 mg/day
- Throughout 24 weeks of extension treatment, mean serum phosphorus levels were maintained at approximately 1.8 mmol/L (5.58 mg/dL) in the LC/LC and CC/LC groups (Figure 2)

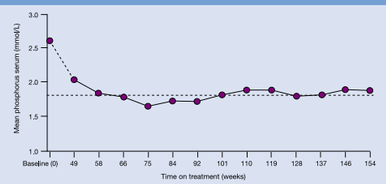
Table 3. Mean calcium × phosphorus product during extension treatment

Time	Mean value, mmol²/L² (mg²/dL²)	
	LC/LC group *n* = 332	CC/LC group *n* = 181
Baseline* (Week 0)	6.04 (74.9)	6.02 (74.6)
End of 6-month maintenance (Week 25 of treatment)	4.01 (49.7)	4.19 (51.9)
Extension period (all patients on treatment)		
Week 30	4.30 (53.3)	4.52 (56.0)
Week 49	4.20 (52.1)	4.30 (53.3)

* Baseline prior to initial open-label randomized treatment (number of patients = 510 and 257 in lanthanum carbonate and calcium carbonate groups, respectively); to convert values from mmol²/L² to mg²/dL², multiply by 12.4

- The proportions of patients with serum phosphorus levels ≤ 1.8 mmol/L (≤ 5.58 mg/dL) at the end of extension therapy were 63.3% and 58.4% in the LC/LC and CC/LC groups, respectively
- Calcium × phosphorus product levels remained constant throughout extension with lanthanum carbonate treatment (Table 3)

Figure 3. Mean serum phosphorus levels during 3 years' lanthanum carbonate treatment



- Encouraging findings have also been obtained during a further 24-month continuation period following on from the initial 6-month extension period (total treatment duration, 3 years):
  - The proportion of long-term exposure subgroup patients with controlled serum phosphorus was high throughout extension treatment; 71.7% at Week 58 (start of 24-month extension) and 68.9% at Week 154 (endpoint); in the overall 3-year extension group (*n* = 161), up to 72.7% of patients showed controlled serum phosphorus
  - Mean serum phosphorus levels are shown in Figure 3
  - Throughout the long-term extension period, plasma lanthanum levels remained similar to those seen during previous randomized and extension therapy
  - There were no overt differences in the incidence or types of adverse events seen in patients between the 3 individual years of the study in long-term exposure patients

Conclusions

- Lanthanum carbonate is well tolerated in haemodialysis patients at doses providing 375–3000 mg/day elemental lanthanum, and plasma lanthanum levels remained low and stable for up to 3 years of treatment
- The effective control of serum phosphorus with lanthanum carbonate, shown in the initial (6-month) randomized study to be similar to that of calcium carbonate,[10] was maintained throughout extension treatment
- A low incidence of hypercalcaemia was also maintained with lanthanum carbonate. Moreover, patients previously exhibiting high rates of hypercalcaemia with calcium carbonate during randomized treatment showed reduced rates after switching to lanthanum carbonate
- The safety and efficacy findings shown here support findings from other studies of treatment with lanthanum carbonate over both the short term[11] and the long term (up to 2 years)[12]
- Initial 3-year extension results suggest that lanthanum carbonate is effective in maintaining serum phosphorus within target (controlled) levels over the long term
- The low level of hypercalcaemia seen with lanthanum carbonate, coupled with relatively low dose requirements and the avoidance of any rise in calcium × phosphorus product, indicate significant advantages over calcium-based phosphate binders for the treatment of hyperphosphataemia

References

1. Block GA. Prevalence and clinical consequences of elevated Ca × P product in hemodialysis patients. *Clin Nephrol* 2000;54:318–24.
2. Malluche HH, Monier-Faugere MC. Hyperphosphatemia: pharmacologic intervention yesterday, today and tomorrow. *Clin Nephrol* 2000;54:309–17.
3. Drueke TB. Renal osteodystrophy: management of hyperphosphataemia. *Nephrol Dial Transplant* 2000;15(Suppl 5):32–3.
4. Hsu CH. Are we mismanaging calcium and phosphate metabolism in renal failure? *Am J Kidney Dis* 1997;29:641–9.
5. Moe SM. Current issues in the management of secondary hyperparathyroidism and bone disease. *Peritoneal Dial Int* 2001;21(3):S241–6.
6. Bushinsky DA. Bone disease in moderate renal failure: cause, nature and prevention. *Annu Rev Med* 1997;48:167–76.
7. Cannata-Andia JB, Fernandez-Martin JL. The clinical impact of aluminium overload in renal failure. *Nephrol Dial Transplant* 2002;17(Suppl 2):9–12.
8. Fournier A. Greater PTH suppression in dialysis patients taking sevelamer hydrochloride (Renagel). *Clin Nephrol* 2000;54:81–2.
9. Locatelli F, D'Amico M, Pontoricro G. Lanthanum carbonate. *Curr Opin Invest Drugs* 2003; in press.
10. Hutchison A. The novel, non-aluminium, non-calcium phosphate binder, lanthanum carbonate (Fosrenol™), is an effective treatment for hyperphosphataemia and has a good safety profile. Poster presented at the 35th American Society of Nephrology Meeting, Philadelphia, PA, USA, 2002.
11. Stewart J, Frazer N. Administration of a novel phosphate binder, Fosrenol™, with food is associated with good tolerability and low systemic absorption. Poster presented at the 35th American Society of Nephrology Meeting, Philadelphia, PA, USA, 2002.
12. Finn WF, Joy MS. Fosrenol™, a novel, non-aluminum, non-calcium phosphate binder, has a good safety and efficacy profile in the long-term treatment of hyperphosphatemia in hemodialysis patients. Poster presented at the 35th American Society of Nephrology Meeting, Philadelphia, PA, USA, 2002.

Poster presented at the 40th ERA–EDTA World Congress of Nephrology, Berlin, Germany, 8–12 June, 2003.