Efficacy and Safety of Long-Term Treatment with Lanthanum Carbonate – A Novel Phosphate-Binding Agent

W Finn, M Joy

University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

Introduction

- Elevated levels of serum phosphorus, secondary hyperparathyroidism and renal osteodystrophy are well-known, inter-related conditions that occur in patients with end-stage renal disease (ESRD), and require treatment with phosphate binders in order to reduce patient morbidity
- The risk of increased patient mortality associated with cardiovascular calcification in patients with ESRD appears to be related to elevated calcium load and levels of calcium × phosphorus product, and has led to the search for better treatments for the management of hyperphosphatemia[1–3]
- Traditionally used phosphate binders are effective in reducing serum phosphorus, but they also have a number of limitations. For example, aluminum-based agents can promote severe bone pathology, central nervous system disorders and iron depletion, and calcium-based agents frequently cause hypercalcemia, which is believed to increase the risk of cardiovascular calcification[3–6]
- Non-aluminum-, non-calcium-based phosphate binders offer a means of reducing serum phosphorus while avoiding these problems. The first such agent was sevelamer hydrochloride – a synthetic, resin-based formulation that showed some efficacy during clinical trials
- There is a remaining need for more effective, non-hypercalcemic phosphate binders that can reduce serum phosphorus to within recommended clinical limits and can maintain this effect over the long term
- Lanthanum carbonate (Fosrenol™, Shire Pharmaceuticals) is a novel non-aluminum, non-calcium phosphate binder that has undergone extensive pre-clinical and clinical development for use in the treatment of hyperphosphatemia
  - Lanthanum carbonate consistently lowers serum phosphorus levels to within recommended clinical limits in around 60% of patients[7–11]
  - Reductions in serum phosphorus were maintained for the duration of randomized clinical studies[7–11]
  - Compared with calcium carbonate, lanthanum carbonate was associated with a significantly reduced incidence of hypercalcemia in a large-scale, multicenter trial (0.4% with lanthanum carbonate *versus* 20.2% with calcium carbonate)[8]
- We report on the long-term safety and efficacy of lanthanum carbonate in a 1-year, open-label study in patients on hemodialysis

Methods

Study design and patients

- Seventy-seven male and female patients with ESRD (aged ≥ 18 years) were assessed
- Patients who had participated in either of two previous trials on lanthanum carbonate (see below) were allowed to continue lanthanum carbonate therapy in a long-term (1-year), open-label extension
- The previous trials were as follows:
  - Study 1 – a dose-finding trial[9] incorporating a 1- to 3-week single-blind placebo run-in, a 6-week randomized double-blind period and a 2-week single-blind placebo run-out, followed by possible extension treatment up to 48 weeks
    - « During the double-blind treatment, patients received placebo or lanthanum carbonate at fixed doses containing 225, 675, 1350 or 2250 mg/day of elemental lanthanum
    - « Doses of lanthanum carbonate during the initial 48-week extension period contained 300–2250 mg/day of elemental lanthanum, and were titrated as necessary to maintain control of serum phosphorus
  - Study 2 – a trial comprising a 1- to 3-week screening and washout period, a 6-week open-label dose-titration period and a 4-week, randomized, double-blind, placebo-controlled period[10]
    - « During titration, all patients received lanthanum carbonate at doses of 750–3000 mg/day of elemental lanthanum. Patients were titrated weekly as necessary to control serum phosphorus
- Following Studies 1 and 2, all patients participating in the pooled extension study were given lanthanum carbonate at doses already established as optimal for the control of serum phosphorus

Assessments

- The primary efficacy measure during the extended maintenance treatment period was the effectiveness of lanthanum carbonate in maintaining pre-dialysis levels of serum phosphorus at less than 5.9 mg/dL (< 1.9 mmol/L)
- Effects on other parameters, including serum calcium, calcium × phosphorus product and parathyroid hormone (PTH) levels, were also evaluated
- Efficacy assessments were based on the intention-to-treat (ITT) population, who were defined as all patients enrolled into the study who had at least one serum phosphorus level assessment during the maintenance treatment period
- Safety and tolerability were assessed by adverse-event monitoring and full laboratory and vital signs measurements

Results

Patients

- In total, 77 patients (11 from Study 1 and 66 from Study 2) were enrolled into the extension study. The characteristics of the patients enrolled into the study are summarized in Table 1

Table 1. Patient characteristics at enrolment in the extension study

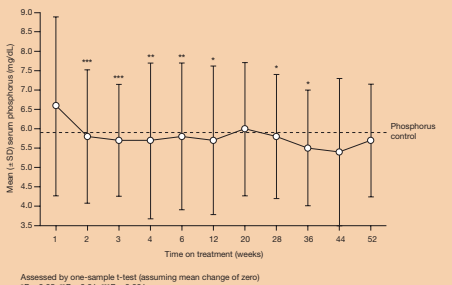
Characteristic	Value
Number of patients	77
Age, years (mean ± SD)	60.9 ± 12.5
Gender (% male)	64.9
Race (%)	
Caucasian	32.5
Black	53.2
Hispanic	7.8
Asian/Pacific	2.6
Native American	2.6
Other	1.3
Adverse events before extension treatment (%)	
Transient hypertension	50.6
Muscle cramps	49.6
Headache	28.6
Nausea	27.3

Efficacy

Serum phosphorus

- Mean pre-dialysis levels of serum phosphorus throughout 1 year of extension treatment are shown in Figure 1:
  - At the start of the extension treatment, the mean pre-dialysis level of serum phosphorus was 6.6 ± 2.0 mg/dL (2.1 mmol/L), which was above the pre-defined target level of ≤ 5.9 mg/dL (≤ 1.9 mmol/L). This is likely to be due to the inclusion of patients in the extension study who had been receiving placebo in Study 2
  - Mean levels of serum phosphorus decreased by approximately 1 mg/dL to 5.7 ± 2.0 mg/dL (1.8 mmol/L) by Week 4 of treatment, representing a statistically significant reduction *versus* the target level ($P = 0.002$)
  - Serum phosphorus remained below 5.9 mg/dL for the rest of the maintenance treatment period (up to Week 52), except at Week 20 when it was 6.0 ± 1.7 mg/dL

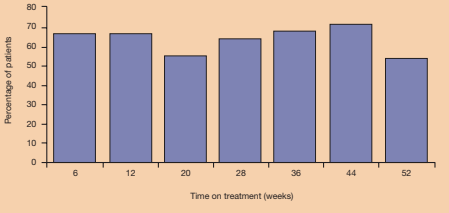
Figure 1. Mean (± SD) serum phosphorus levels (ITT population)



Assessed by one-sample t-test (assuming mean change of zero)
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

- A high proportion of patients were 'phosphorus controlled' (serum phosphorus ≤ 5.9 mg/dL) throughout the 1 year of extension treatment (Figure 2):
  - Up to 66% of patients were controlled by Week 6; 71% of patients were controlled at Week 44

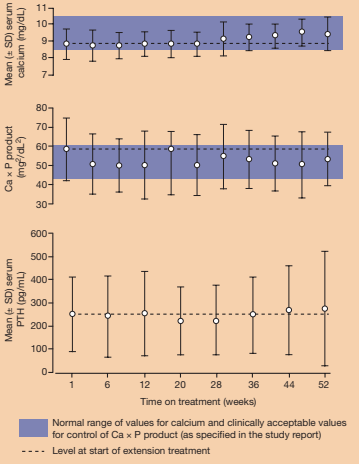
Figure 2. Proportions of patients with controlled serum phosphorus (< 5.9 mg/dL [< 1.9 mmol/L]) during extension treatment (ITT population)



Other serum parameters

- Other serum parameters measured are summarized in Figure 3
- Mean levels of calcium × phosphorus product were closely related to serum phosphorus levels
  - Throughout the entire extension treatment period, calcium × phosphorus product values remained within protocol-defined clinically acceptable levels (43–60 mg^2/dL^2 [3.2–4.8 $mmol^2/L^2$])
- Lanthanum carbonate had no clinically significant effect on serum levels of calcium
  - Serum calcium concentrations remained within the protocol-specified normal range of values (8.4–10.4 mg/dL [2.15–2.67 mmol/L]) throughout extension treatment
- Levels of PTH did not change substantially throughout the treatment period

Figure 3. Mean (± SD) levels of calcium, calcium × phosphorus (Ca × P) product and PTH (ITT population)



Safety

- Prior to extension treatment in the present study, the most frequently observed adverse events were transient hypertension, muscle cramps, headache and nausea. The majority of these events were of mild or moderate intensity
- The most frequently reported adverse events during 1 year of extension treatment were nausea (26.0%), peripheral edema (23.4%) and myalgia (20.8%)
- The only adverse events considered by the investigators to be related to study treatment and occurring in more than one patient were dyspepsia ($n = 3$; 3.9%) and constipation ($n = 2$; 2.6%)
- Six patients (7.8%) withdrew from the study because of adverse events, two of which (constipation [$n = 1$] and tongue irritation [$n = 1$]) were considered to be related to study treatment
- No treatment-related serious adverse events occurred throughout 1 year of treatment
- Three patients (3.9%) died during the study, all from causes reported as 'definitely not' related to study treatment
- No pattern of clinically or statistically significant abnormal laboratory events was observed
  - Abnormal laboratory results reflected ESRD in the study population and were not considered to be associated with study treatment
  - Of note, there were no significant changes in serum levels of bicarbonate or bone alkaline phosphatase

Conclusions

- **Lanthanum carbonate, at doses providing 250–3000 mg/day of elemental lanthanum, effectively reduced and maintained levels of serum phosphorus and calcium × phosphorus product to within prospectively defined, clinically acceptable limits in the majority of patients with ESRD over the 1-year study period**
- **Lanthanum carbonate was well tolerated throughout this study, and showed a good safety profile over 1 year. The only adverse events considered to be related to study medication were gastrointestinal and non-serious in nature, and occurred at low frequencies**
- **These results support findings from the initial short-term, randomized, placebo-controlled studies (Study 1 and Study 2), which showed the effective reduction of serum levels of phosphorus to target levels[9,10] and a low incidence of hypercalcemia[8] with lanthanum carbonate**
- **The final results from other studies that assessed the long-term (up to 3 years) safety and tolerability profile of lanthanum carbonate are awaited with interest[11]**

References

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Poster presented at the National Kidney Foundation Clinical Meeting, Dallas, Texas, USA, 2–6 April, 2003.