Effectiveness of Lanthanum Carbonate Treatment Used in Combination with Other Phosphate Binders in Peritoneal Dialysis Patients

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Abstract

Objective Phosphate binders are used in the treatment of hyperphosphatemia in peritoneal dialysis (PD) patients. An ideal phosphate binder for long-term use must be effective with little or no side effects. We evaluated the long-term efficacy and side effects of lanthanum carbonate (LaC) used in combination with other phosphate binders in PD patients.

Patients The subjects of this retrospective study were 30 PD patients who received LaC at Kyushu University. The effect of LaC on various biochemical parameters (serum phosphate, calcium and parathyroid hormone), daily dose of other phosphate binders, gastrointestinal side effects, and nutritional status were determined during the 24-week treatment. We also evaluated the rate of achievement of the Japanese Society of Dialysis Treatment guidelines for secondary hyperparathyroidism and used multivariate analysis to determine the factors associated with the efficacy of LaC.

Results LaC (960±412 mg/day) reduced serum phosphate from 6.2 to 5.3 mg/dL. The rate of achievement of the guideline target improved after 24 weeks of LaC treatment. The dose of other phosphate binders and dialysis volume remained unchanged during the treatment. Although 53% of patients experienced at least one gastrointestinal side effect, LaC treatment did not affect the nutritional status, and none of the patients discontinued LaC. Multivariate analysis identified low stature, old age and high baseline total creatinine clearance as significant factors that determine the effectiveness of LaC in PD patients.

Conclusion Low dose LaC treatment used in combination with other phosphate binders improved serum phosphate control with tolerable gastrointestinal symptoms in PD patients.

Key words: hyperphosphatemia, lanthanum carbonate, nutrition, peritoneal dialysis, phosphate binder

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Introduction

Hyperphosphatemia, which is highly prevalent in both hemodialysis and PD patients, is a serious complication that can lead to secondary hyperparathyroidism (SHPT), renal osteodystrophy and vascular calcification (1-3). The control of serum phosphate (Pi) level within the recommended range is an important therapeutic goal for better prognosis of patients on dialysis (4-6). Among the treatment modalities

available for hyperphosphatemia, administration of Pi binders is the preferred therapy (7). Although several types of Pi binders are currently used clinically in PD patients, they are known to have serious side effects. For example, aluminum salts can cause bone and neurological disorders, calcium (Ca) carbonate can result in Ca overload and has gastrointestinal side effects, and sevelamer hydrochloride has several gastrointestinal side effects, pH lowering effect and high pill burden (8). Therefore, new types of Pi binders that can on one hand lower serum Pi and on the other have little

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or no side effects are desirable.

Lanthanum carbonate (LaC), an aluminum-free and Ca-free, pH independent, less absorbable P binder, has been available in Japan since 2009 (9). LaC is less hypercalcemic and comparably tolerable compared to the conventional Pi binders albeit a certain percentage of hemodialysis patients develop gastrointestinal symptoms (10). To date, two clinical studies have demonstrated that LaC effectively reduces serum Pi and is devoid of serious side effects in PD patients (11, 12). However, the treatment duration in these two clinical studies was relatively short (8 weeks), and they only tested the efficacy of LaC monotherapy, not combination therapy with other conventional Pi binders as is the case in the clinical setting. In other words, there is no information on the efficiency and tolerability of long-term LaC therapy used alone or in combination with conventional Pi binders in PD patients.

The purpose of the present study was to determine the additive effect of LaC in PD patients already treated with other Pi binders. For this purpose, we retrospectively evaluated the efficacy and tolerability of 24-week treatment with LaC in PD patients. We also assessed the factors that influence the Pi-lowering effect of LaC.

Materials and Methods

Patients and study protocol

The present retrospective observational study included PD patients who were treated for 24 weeks with LaC at Kyushu University Hospital between April 2006 and March 2011. In March 2011, 49 patients were receiving PD therapy at our hospital. Among them, 33 patients whose serum Pi control was not optimal had been treated with LaC. We excluded patients who, within 24 weeks after the start of LaC underwent kidney transplantation ($n=1$), or started cinacalcet hydrochloride therapy ($n=1$). We also excluded patients who received the combination of hemodialysis and PD ($n=1$). The remaining 30 patients were the subjects of the study. The starting dose of LaC ranged from 500 to 1,000 mg/day. The dose was increased by the attending physician based on the serum Pi level measured at each regular follow-up as far as permitted by the gastrointestinal side effects. When serum Pi level decreased to less than the lower limit, the doses of Pi binders other than LaC were reduced. The target range was set as recommended by the Japanese Society of Dialysis Treatment (JSDT). Some of these 33 patients received LaC because they could not start or increase the dose of other Pi binders for the following reasons; some patients did not use Ca-based Pi binders for hypercalcemia, and others could not use or increase the dose of sevelamer hydrochloride due to the associated gastrointestinal side effects.

Serum Pi, Ca, and albumin were measured every 4 weeks. Whole parathyroid hormone (PTH) level was measured every 12 weeks. We determined the basal serum Pi level as calculated according to the average of serum Pi level re-

corded in the last three months at the start of LaC treatment. The ΔPi was defined by the following equation: $\Delta\text{Pi} = \text{serum Pi (each week)} - \text{serum Pi (baseline average)}$. Serum Ca refers to albumin-adjusted Ca concentration when serum albumin was below 4.0 g/dL. The present study was approved by the Ethics Committee at Kyushu University, and written-informed consent was obtained from each patient.

Rate of achievement of target rate recommended by JSDT guidelines for SHPT

We also evaluated the rate of achievement of the target range recommended by JSDT guidelines for SHPT with regard to serum Pi ($3.5 \text{ mg/dL} \leq \text{Pi} \leq 6.0 \text{ mg/dL}$), and Ca ($8.4 \text{ mg/dL} \leq \text{Ca} \leq 10.0 \text{ mg/dL}$), and whole PTH ($35 \text{ pg/mL} \leq \text{whole PTH} \leq 106 \text{ pg/mL}$) (13).

Assessment of LaC-related side effects

To determine the prevalence of gastrointestinal side effects associated with LaC, the medical records were checked for the following gastrointestinal symptoms: reflux, abdominal pain, indigestion, diarrhea and constipation.

Assessment of nutritional status and adequacy of dialysis

Nutritional status was assessed by various biochemical parameters (blood urea nitrogen, serum creatinine, total protein, albumin, total cholesterol, triglyceride, and normalized protein catabolic ratio), as well as by body weight. We also assessed the adequacy of dialysis, by dialysis volume, Kt/V urea and weekly creatinine clearance. These parameters were recorded at baseline and at week 24.

Comparison of effects of LaC in patients with different serum Ca and serum P control at baseline

To determine the effect of LaC in patients with different Pi control, patients were divided into two groups based on the baseline Pi level; patients with serum Pi $\geq 6 \text{ mg/dL}$ and those with serum Pi $< 6 \text{ mg/dL}$. Similarly, to determine the effect of LaC on patients with different Ca control at baseline, patients were divided into two groups based on the baseline serum Ca level: $\geq 10.0 \text{ mg/dL}$ and $< 10.0 \text{ mg/dL}$.

Factors associated with the effectiveness of LaC treatment

To assess the effectiveness of LaC treatment, we divided the 30 patients into two groups based on the mean ΔPi value calculated during the entire 24 weeks of treatment. The cutoff value for separating the patients into two groups was the mean ΔPi , calculated by the following equation; $\text{mean } \Delta\text{Pi} = (\Delta\text{Pi}_{\text{week-4}} + \Delta\text{Pi}_{\text{week-8}} + \Delta\text{Pi}_{\text{week-12}} + \Delta\text{Pi}_{\text{week-16}} + \Delta\text{Pi}_{\text{week-24}}) \text{ divided by } 5$. Twelve patients with ΔPi higher than the cutoff value were considered the “responders”, while the remaining 18 patients with ΔPi values lower than the cutoff value were defined as “non-responders”. Multiple logistic regression analysis was used to determine the factors associated with serum Pi reduction

Table 1. Clinical and Biochemical Parameters at Baseline (n=30)

Age, year	50.9 ± 10.0
Sex, male (%)	20 (67)
Weight, kg	62.6 ± 11.6
Height, m	1.65 ± 0.10
BMI, kg/m ²	23.0 ± 3.1
Underlying kidney disease	
DM, n (%)	10 (33)
Non-DM, n (%)	20 (67)
Time on dialysis, days	575 ± 312
Phosphate, mg/dL	6.2 ± 0.7
Calcium, mg/dL	9.8 ± 0.6
Calcium phosphate product, mg ² /dL ²	56.9 ± 9.1
ALP, U/L	247 (173-423)
Whole PTH, pg/mL	85.4 (48.3-167.8)
Blood urea nitrogen, mg/dL	61.8 ± 12.7
Serum creatinine, mg/dL	12.1 ± 2.9
Total protein, g/dL	6.3 ± 0.6
Albumin, g/dL	3.5 ± 0.5
Total cholesterol, mg/dL	144 ± 109
Triglyceride, mg/dL	185 ± 48
Dialysis modality	
APD (%)	20 (67)
CAPD (%)	5 (17)
Icodextrin use, %	23 (77)
Phosphate binder use	
Calcium carbonate, n (%)	22 (73)
Sevelamer hydrochloride, n (%)	8 (27)
Both, n (%)	5 (17)
Cinacalcet hydrochloride use, n (%)	1 (3)

Data are mean ± SD, median (1st quartile, 3rd quartile), or number (percentage).

BMI: body mass index, DM: diabetes mellitus, ALP: alkaline phosphatase, PTH: parathyroid hormone, APD: automated peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis

Table 2. Categorization of Serum Levels of Ca and Pi at Baseline Based on the Japanese Society of Dialysis Treatment Guidelines (n=30)

	Ca < 8.4 mg/dL	8.4 ≤ Ca ≤ 10.0 mg/dL	Ca > 10.0 mg/dL
Pi < 3.5 mg/dL	0 (0%)	0 (0%)	0 (0%)
3.5 ≤ Pi ≤ 6.0 mg/dL	5 (17%)	5 (17%)	3 (10%)
Pi > 6.0 mg/dL	1 (3%)	11 (36%)	5 (17%)

Data are number (percentage) of patients.

Ca: calcium, Pi: phosphate

after LaC treatment in PD patients, with “responders” set as the dependent variable.

Statistical analysis

Data were expressed as mean ± SD, median (1st quartile, 3rd quartile), or number (percentage) unless otherwise specified. The chi-square test or unpaired *t*-test was used to compare differences between the two groups. Dunnett test was used to compare the serial changes in serum Pi and Ca after LaC treatment with the baseline values. Kruskal-Wallis analysis of variance was used to compare the serial changes

in whole PTH. Multivariate logistic regression analysis was conducted to provide adjusted odds ratio for “responders”. Variables that achieved statistical significance in univariate analysis were included in the multivariate analysis. A two-tailed *p* value less than 0.05 was considered statistically significant. All statistical analyses were conducted using JMP 8.0 (SAS Institute, Tokyo, Japan).

Results

Clinical characteristics

Table 1 shows the demographic and laboratory characteristics recorded at baseline. Twenty patients were males, and 10 patients had diabetes mellitus. The time on dialysis ranged from 130 to 1,071 days, and 22 patients used automated PD systems. Serum levels of Pi, Ca, and whole PTH ranged from 6.2±0.6 mg/dL, 9.8±0.6 mg/dL, and 48.3-167.8 pg/mL, respectively. The results of categorization of serum Ca and Pi levels at baseline are shown in Table 2. At baseline, 14% of the patients achieved the target range of serum Ca and Pi. Seventy-three percent of the patients used Ca carbonate alone, while 27% used sevelamer hydrochloride. In the single patient who used cinacalcet hydrochloride at baseline, the dose did not change during the 24-week period. None of the patients discontinued LaC during the 24-week period.

Serial changes in biochemical parameters

Figure 1 shows the serial changes in serum Pi, and ΔPi, Ca, and whole PTH. Compared to the baseline, serum Pi and ΔPi significantly decreased at 8 weeks after LaC treatment. In contrast, serum levels of Ca and whole PTH did not change during the study period.

Rate of achievement of JSDT guidelines for each biochemical parameter

Table 3 also lists the serial changes in the rate of achievement of JSDT guidelines for SHPT in each biochemical parameter. The rate of achievement of serum Pi following the use of LaC was higher at the end of the study period (93%) than at baseline (43%), while that for Ca and whole PTH did not change during the 24 weeks.

Serial changes in daily doses of Pi binders

The mean daily doses of Ca carbonate and sevelamer hydrochloride remained the same during the study period (Ca carbonate, baseline: 2,140±250, 24 weeks: 1,840±250 mg/day), sevelamer hydrochloride, baseline: 1,260±464, 24 weeks: 1,380±466 mg/day). The mean dose of LaC also remained unchanged during the study period [baseline: 930±497 (range, 750-1,500), 24 weeks: 960±412 (range, 750-2,250) mg/day] (Fig. 2).

LaC-induced gastrointestinal symptoms

Table 4 lists the percentage of patients who developed

Figure 1. Serial changes in various biochemical parameters after commencement of lanthanum carbonate therapy. Serum phosphate (Pi) (A), serum Δ Pi (B), serum corrected calcium (C), and serum whole parathyroid hormone (PTH) (D) are shown. Serum Δ Pi is defined as follows; serum Δ Pi = serum Pi (each week) - serum Pi (week 0). Serum levels of Pi and calcium at each week are compared to baseline value by Dunnett test. Serum whole PTH at each time point is compared to baseline value by Kruskal-Wallis analysis of variance. Data in (A), (B), and (C) are mean $\pm$ SEM. Data in (D) are box-and-whisker plots. In these plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. * $p < 0.05$ versus serum Pi at 0 week.

Table 3. Serial Changes in the Rate of Achievement of the Japanese Society of Dialysis Treatment Guidelines in 30 Patients who Received 24-week Lanthanum Carbonate Treatment

	week 0	week 4	week 8	week 12	week 16	week 20	week 24
$8.4 \leq \text{Ca} \leq 10.0 \text{ mg/dL}$	73%	67%	73%	80%	83%	73%	67%
$3.5 \leq \text{Pi} \leq 6.0 \text{ mg/dL}$	43%	73%	73%	77%	70%	80%	93%
$35 \leq \text{whole PTH} \leq 106 \text{ pg/mL}$	73%	no data	no data	73%	no data	no data	70%

Data are percentages of the patients who achieved the target range of each biochemical parameter.

Ca: calcium, Pi: phosphate, PTH: parathyroid hormone

gastrointestinal symptoms after commencement of LaC treatment based on analysis of the medical records. Of the 30 patients treated with LaC, 53% developed at least one gastrointestinal symptom after starting LaC treatment. Four patients required laxatives for constipation and one patient was treated with a proton pump inhibitor for epigastralgia during the study period. Although the LaC dose was reduced in two patients due to gastrointestinal side effects, none of the 30 patients discontinued LaC treatment during the study period.

Effects of LaC treatment on nutritional status and adequacy of dialysis

LaC treatment did not influence the nutritional status, as

assessed by serum levels of urea nitrogen, serum creatinine, total cholesterol, triglyceride, albumin, and total protein. Furthermore, LaC treatment had no effect on the adequacy of dialysis, as assessed by total Kt/V urea and total creatinine clearance (Table 5).

Effects of LaC on serum Pi in patients with different serum Ca and serum Pi levels at baseline

Serum Pi levels were approximately comparable between the high serum Pi group and low Pi group in the last of 24 weeks of treatment although the mean dose of LaC was higher in patients with higher serum Pi level at baseline (Fig. 3A, B). Similarly, serum Pi levels were approximately comparable between the high Ca group and low Ca group at

Figure 2. Serial changes in the daily dose of Pi binders. Daily doses of calcium carbonate (A), sevelamer hydrochloride (B), and lanthanum carbonate (C) are shown. Data shown in (A), (B), and (C) are mean $\pm$ SEM. Data at each time point are compared with the baseline value (week 0) by Dunnett test. * $p < 0.05$ versus serum phosphate (Pi) at 0 week.

Table 4. Gastrointestinal Symptoms after Starting Lanthanum Carbonate (n=30)

	Number (%) of patients
Reflux, n (%)	11 (37)
Abdominal pain, n (%)	10 (33)
Indigestion, n (%)	7 (23)
Diarrhea, n (%)	4 (13)
Constipation, n (%)	6 (20)
Any symptom, n (%)	16 (53)

Data are number (percentage) of patients.

almost the same dose of LaC (Fig. 3C, D).

Univariate and multivariate analyses

Univariate analysis showed that old age, high total creatinine clearance and short stature were significantly associated with response to LaC treatment (Table 6). On the other hand, sex, underlying kidney disease, PD vintage, body weight, body mass index, urine volume, total Kt/V urea, dialysis fluid volume, albumin, corrected Ca, Pi, alkaline phosphatase, whole PTH, and the daily dose of Pi binders (Ca carbonate, sevelamer hydrochloride) did not significantly influence the response to LaC treatment. The above three independent variables were subsequently entered into multivariate logistic regression analysis. The results also showed that age, height and total creatinine clearance were independent and significant determinants of the response to LaC treatment.

Discussion

The present study demonstrated that low-dose LaC treatment for 24 weeks effectively reduced the serum Pi level in Japanese PD patients who were already treated with conventional Pi binders, and hence the same treatment increased the rate of achievement of JSDT guidelines for serum Pi. Previous studies have demonstrated the effectiveness of LaC in PD patients (11, 12). However, these studies only examined the short-term efficacy of LaC on serum Pi in PD patients. To our knowledge, there are no studies that have examined the effects of long-term treatment or the additive effects of LaC in PD patients who had already been treated with other Pi binders. Thus, the present study contributes to the management of hyperphosphatemia in PD patients in that it is the first to have examined the effectiveness and tolerability of low-dose LaC used in combination with other Pi binders for 24 weeks.

The effects of LaC on mineral metabolism other than serum Pi should be elucidated. In the present study, serum levels of Ca, and PTH remained unchanged during the 24-week LaC treatment, indicating that LaC treatment prevented the progression of SHPT. With regard to the effect of LaC treatment in dialysis patients, previous studies showed that 2-year LaC treatment improved bone metabolism and increased bone mineral density (14). In addition, experimental studies have demonstrated that long-term LaC treatment inhibited SHPT, renal osteodystrophy and vascular calcification (15, 16). These results indicate that LaC can potentially

Table 5. Clinical and Biochemical Parameters Related to Nutritional Status and Dialysis Adequacy before and after Lanthanum Carbonate Treatment in 30 Patients

	Pre-treatment (week 0)	Post-treatment (week 24)	p value*
Blood urea nitrogen, mg/dL	61.8 ± 12.7	64.5 ± 11.6	0.458
Serum creatinine, mg/dL	12.1 ± 2.9	12.3 ± 2.7	0.769
Total protein, g/dL	6.3 ± 0.6	6.2 ± 0.7	0.873
Albumin, g/dL	3.5 ± 0.5	3.4 ± 0.4	0.895
Total cholesterol, mg/dL	144 ± 109	189 ± 44	0.074
Triglyceride, mg/dL	185 ± 48	155 ± 75	0.102
Body weight, kg	62.7 ± 11.3	62.8 ± 11.7	0.659
nPCR, g/kg/day	0.96 ± 0.22	0.92 ± 0.17	0.890
Dialysis volume, L/day	8.00 ± 2.17	8.09 ± 2.26	0.602
Total Kt/V urea	1.81 ± 0.57	1.71 ± 0.37	0.366
Total CCr, L/week	59.1 ± 20.1	53.6 ± 15.7	0.222

Data are mean ± SD.

*by paired *t*-test, nPCR: normalized protein catabolic rate, Kt/V urea: urea clearance, CCr: creatinine clearance**Table 6. Univariate and Multivariate Adjusted Odds Ratios for Response to Lanthanum Carbonate Therapy (n=30)**

Variable	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Height, per 0.01 meter	0.869 (0.807-0.932)	0.025	0.818 (0.632-0.969)	0.018
Age, per 1 year	1.174 (1.107-1.237)	0.017	1.189 (1.023-1.529)	0.020
Total CCr, per 1 L/week	1.072 (1.039-1.105)	0.012	1.131 (1.024-1.324)	0.010

Odds ratio is for "responders".

A p value less than 0.05 is considered statistically significant.

CCr: creatinine clearance, OR: odds ratio, CI: confidence interval

prevent the progression of mineral and bone disorders through inhibition of Pi overload. Because Pi overload is located upstream of all disorders of bone and mineral metabolism in patients with renal failure (17), its control by Pi binder is probably the most important treatment strategy.

Among the several factors that enhance patient adherence to Pi binder therapy, gastrointestinal side effects and the dosage of Pi binders are the most important (18). Clinical data indicate that serum Pi can be reduced by all Pi binders irrespective of their types, provided they are administered in large doses. However, the incidence and severity of gastrointestinal symptoms are known to increase with the use of higher dosage (19). Thus, Pi binders that can reduce serum Pi with the smallest dose are desirable and preferred. Adherence to Pi binder therapy was recently reported to be the best with Ca carbonate, followed by LaC and sevelamer hydrochloride (20). In that study, patient preference was mostly related to gastrointestinal side effects and the drug dosage. In the present study, the gastrointestinal side effects were acceptable and none of the patients discontinued LaC therapy. One reason for the high LaC tolerability might be the relatively low dose of LaC used in the treatment (960 mg/day). In fact, one study reported that LaC can effectively reduce serum Pi when used at low dose compared with other Pi binders, leading to low incidence of gastrointestinal side effects per serum Pi reduction (21). From the point of LaC dosage and related side effects, the present study con-

firmed the potential tolerability of low dose LaC treatment, leading to better clinical outcome in PD patients.

Maintenance of a good nutritional status is also important in the management of PD patients since recent clinical data have shown that malnutrition is closely associated with high mortality in PD patients (22, 23). On the other hand, the use of Pi binders is often accompanied by gastrointestinal symptoms, occasionally leading to appetite loss and possible malnutrition. In the present study, LaC treatment did not influence the nutritional status, as assessed by various biochemical parameters, although more than half of the patients experienced at least one type of LaC-related gastrointestinal side effect. These results indicate that LaC treatment within the dose used in the present study is efficacious in controlling serum Pi level without affecting the nutritional status of PD patients.

Little is known about the factors that influence serum Pi reduction with the use of Pi binders. In the present study, low dose of LaC added on other Pi binders effectively reduced serum Pi level independent of the baseline serum Pi and Ca level. However, multivariate analysis revealed that a greater reduction in serum Pi level was associated with older age, low stature and high total creatinine clearance at baseline. These results can be better understood when we consider the following in-out balance model regarding Pi. In PD patients, serum Pi level is determined by: 1) Pi intake by meal, 2) distribution volume of Pi in the body, 3) Pi ex-

Figure 3. Effects of LaC on serum Pi reduction in patients with different serum Ca and Pi control levels at baseline. Serial changes in serum phosphate (Pi) in the two groups divided by the basal level of serum Pi and calcium (Ca), respectively (A, C) are shown. Serial changes in the dose of LaC in both groups (B, D). Data shown in (A) and (C) are mean $\pm$ SEM. Data between two groups at each time point were compared by un-paired t-test. * $p < 0.05$ versus serum Pi at baseline < 6 mg/dL. LaC: lanthanum carbonate

change between bone and blood and 4) renal excretion of Pi and removal through PD dialysate (24). Thus, smaller Pi intake, large distribution volume and higher Pi clearance through the kidney and PD dialysate should lower the serum Pi level. With regard to the factors identified in the present study, elderly patients take less Pi, and low stature is related to small distribution volume of Pi, and high total creatinine clearance is thought to be closely related to greater Pi excretion.

The present study has several limitations. First, the present study was a retrospective study with a small sample size and without controls. Second, we did not determine whether independent factors related to Pi reduction identified by multivariate analysis might be also true in the different Pi-binders such as Ca carbonate or sevelamer hydrochloride. Third, some patients in the present study started to receive LaC because they could not use other Pi binders for hypercalcemia or gastrointestinal side effects; the present study could have some inclusion bias. Accordingly, the effects of LaC could be different if used in another PD population. Thus, further large scale studies with controls are necessary to determine the additive effects of low-dose LaC in PD patients.

In conclusion, the combination therapy of low-dose LaC with other Pi binders effectively reduced serum Pi level in Japanese PD patients and improved the rate of achievement of Pi target recommended by the JSDT guidelines with tolerable gastrointestinal side effects. The addition of low-dose LaC could be a useful therapeutic option in PD patients with persistent hyperphosphatemia already treated with other Pi binders.

The authors state that they have no Conflict of Interest (COI).

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