Nephrol Dial Transplant (2013) 28: 1874–1888
doi: 10.1093/ndt/gft064
Advance Access publication 21 April 2013

Evaluation of colestilan in chronic kidney disease dialysis patients with hyperphosphataemia and dyslipidaemia: a randomized, placebo-controlled, multiple fixed-dose trial

Francesco Locatelli[1], Nada Dimkovic[2] and Goce Spasovski[3]

Correspondence and offprint requests to: Francesco Locatelli; E-mail: f.locatelli@ospedale.lecco.it

[1]Department of Nephrology Dialysis and Renal Transplantation, A Manzoni Hospital, Lecco, Italy,
[2]Medical Faculty University of Belgrade, Zvezdara University Medical Center, Belgrade, Serbia and
[3]Department of Nephrology, Clinical Centre Skopje, Macedonia

Keywords: colestilan, chronic kidney disease, dyslipidaemia, hyperphosphataemia, MCI-196

ORIGINAL ARTICLE

ABSTRACT

Background. Colestilan is a non-absorbed, non-calcium-based, phosphate binder. It also binds bile acids and reduces serum levels of low-density lipoprotein cholesterol (LDL-C). This study evaluated the efficacy of a range of fixed doses of colestilan compared with placebo for the control of serum phosphorus and LDL-C levels in patients with CKD stage 5 on dialysis.

Methods. This was a multicentre, randomized, double-blind, placebo-controlled, multiple fixed-dose trial in which 642 patients with CKD stage 5 on dialysis who had both hyperphosphataemia and dyslipidaemia, were randomized to treatment with colestilan 3, 6, 9, 12 or 15 g/day or placebo for 12 weeks. The co-primary endpoints were the mean changes in serum phosphorus and the mean per cent change in LDL-C from baseline to Week 12.

Results. A significantly greater mean reduction in serum phosphorus level from baseline to Week 12 than seen with placebo was seen with 9 g (−0.28 mmol/L) and pooled colestilan 12/15 g (−0.34 mmol/L). The per cent reduction in LDL-C level was significantly greater with colestilan 3, 6 and 9 g and pooled colestilan 12/15 g than with placebo (reduction ranged from 15.9 to 27.6% dependent on dose). Colestilan also reduced total cholesterol, oxidized LDL-C, HbA1c and uric acid levels, and did not increase serum calcium levels. Colestilan was generally well tolerated; the most common adverse events affected the gastrointestinal system.

Conclusions. Colestilan is an effective treatment for hyperphosphataemia, and provides beneficial effects on other metabolic parameters associated with cardiovascular risk, notably LDL-C.

INTRODUCTION

Cardiovascular disease is a leading cause of death in patients with chronic kidney disease (CKD) [1, 2], and the rate of cardiovascular morbidity and mortality among dialysis patients is up to 40-fold higher than in the general population [3]. A number of factors are thought to be involved in the development of cardiovascular disease in patients with CKD, including hyperphosphataemia and dyslipidaemia [4].

Elevated serum phosphorus levels are known to be common in patients with CKD, particularly in those at stage 5, and there is an association between hyperphosphataemia and increased cardiovascular morbidity and mortality [4–7]. More recent data suggest that the use of phosphate binders is associated with a reduction in mortality in this group of patients [8]. The management of hyperphosphataemia in these patients includes a low phosphate diet and treatment with phosphate binders, in conjunction with adequate dialysis [9]. The most widely used phosphate binders are calcium-based, although they are frequently associated with hypercalcaemia and vascular calcification [9–11]. The newer, non-calcium-based phosphate binders, including sevelamer and lanthanum, may avoid this issue, and clear guidance is available about when calcium-based binders should not be used [9, 12].

Dyslipidaemia is a well-established risk factor in the general population [13]. Although lipid abnormalities are common in patients with CKD [4, 14], studies on the benefits of reducing cholesterol levels in dialysis patients have produced conflicting results [14, 15]. Nonetheless, the SHARP study found that reducing low-density lipoprotein cholesterol (LDL-C) levels reduced the risk of atherosclerosis in patients with CKD including dialysis patients [15].

Colestilan is a non-metallic phosphate binder that acts as an anion-exchange resin. Colestilan itself is not absorbed after oral administration, and it is able to bind dietary phosphate within the gastrointestinal tract and thus prevent absorption of the mineral [16]. Initial, Phase II, studies showed that it reduces serum phosphorus levels in dialysis patients with hyperphosphataemia without affecting serum calcium levels [16–18]. Colestilan also binds to bile acids, leading to a reduction in serum levels of LDL-C [19], and has been available for the treatment of hypercholesterolaemia since 1999 in Japan.

Based on the smaller, Phase II studies, colestilan showed potential as a treatment for hyperphosphataemia in patients on dialysis, and may also provide beneficial effects on lipid levels. Additional studies evaluating a wider range of doses, in a larger number of patients and covering multiple countries are needed to confirm and expand on these earlier studies. The aim of this Phase III study was to evaluate the efficacy of a range of fixed doses of colestilan compared with placebo for the control of serum phosphorus and LDL-C levels in patients with CKD stage 5 on dialysis.

MATERIALS AND METHODS

Study participants

The study enrolled patients aged ≥18 years with CKD stage 5 and both hyperphosphataemia and dyslipidaemia. Patients had to have a serum phosphorus level ≥1.94 mmol/L (6.0 mg/dL) and a serum LDL-C level ≥1.82 mmol/L (70 mg/dL) after washout of phosphate binders and lipid-lowering drugs. All patients were receiving thrice-weekly haemodialysis, daily automated peritoneal dialysis or continuous ambulatory peritoneal dialysis. Patients had to have a baseline dialysis fractional clearance of urea (Kt/V) value (single pool) ≥1.2 for those on haemodialysis or a weekly Kt/V value ≥1.8 for those on peritoneal dialysis, a calcium dialysate content of 1.00–1.75 mmol/L (2–3.5 mEq/L) and to be on a stabilized phosphate diet.

Key exclusion criteria included parathyroid hormone (PTH) level persistently >1000 pg/mL, serum LDL-C >4.94 mmol/L (190 mg/dL), serum triglycerides >6.76 mmol/L (600 mg/dL), serum albumin <30.0 g/L, significant gastrointestinal abnormalities or liver dysfunction, including liver function test values three times above normal. During the study, patients could not receive drugs that could affect phosphorus or lipid levels, other than study medication.

Study design and procedures

This Phase III, multicentre, randomized, double-blind, placebo-controlled, multiple fixed-dose trial was conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice guidelines, and the Declaration of Helsinki. The protocol and informed consent form were approved by the appropriate ethics committee or institutional review board for each site. All participants gave their written informed consent. Patients were enrolled from 100 sites in Hungary, Italy, Poland, Serbia, Macedonia, Ukraine, Russia and Malaysia.

After an 8-week washout period for lipid-lowering drugs, which also incorporated a 4-week washout period for phosphate binders, patients were randomized to receive colestilan at a fixed dose of 3, 6, 9, 12 or 15 g/day, or matching placebo, for 12 weeks. Randomization was performed according to a computer-generated central randomization code, which was designed within countries to ensure that each site enrolled approximately equal numbers of patients in each treatment group. Patients were randomized in blocks of 25 per country, with each block comprising four patients on each of the five active colestilan group, three patients on placebo 9 tablets and one patient each on placebo 12 and 15 tablets.

Study medication was split into three daily doses, taken with meals. Patients in the three lower dose groups and the corresponding placebo group all took nine tablets per day, comprising active and/or placebo tablets. Patients in the 12 and 15 g groups, and the corresponding placebo groups, received 12 or 15 tablets. The two high-dose groups were handled separately to the lower dose groups because of the potential impact on treatment compliance of such a large number of tablets per day, and to avoid subjecting all patients to such a regimen.

Study parameters

The co-primary endpoints were the mean change in serum phosphorus and the mean per cent change in serum LDL-C from baseline to Week 12 (or last observation carried forward, LOCF). Secondary efficacy endpoints included mean change from baseline to Week 12 for serum calcium, iPTH and LDL particle size; mean per cent change from baseline to Week 12 for serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, lipoprotein(a) and oxidized LDL. The proportion of responders was also evaluated. Safety parameters included adverse events, vital signs and laboratory values. Serum uric acid, C-reactive protein, glycosylated haemoglobin A1c (HbA1c) and vitamins B12, A, E, K and folic acid were also measured. Compliance with treatment was also assessed, with compliance defined as taking 80–120% of the study medication.

Statistical analyses

Assuming a 10% dropout rate, a maximum of 54 patients per group were needed to demonstrate a difference in change (or % change) between colestilan and placebo of ≥0.4 mmol/L (1.2 mg/dL) for phosphorus and ≥30% for LDL-C, with 90% power and a significance level of 5% (divided into $\alpha = 0.04$ for the analysis of phosphorus and $\alpha = 0.01$ for LDL-C). However, an overall target of 625 patients was set, in order to obtain additional safety information. Since a strong dose–response was expected, the type I error rate was divided within each parameter to give different P-values for the analysis of 3, 6 and 9 g ($\alpha = 0.03$ for phosphorus and $\alpha = 0.0075$ for LDL-C) and the analysis of 12/15 g ($\alpha = 0.01$ for phosphorus and $\alpha = 0.0025$ for LDL-C). The analyses were designed such that the 12 and 15 g groups were pooled for analysis in order to help limit the number of patients required, as the inclusion/exclusion criteria were expected to impact heavily on recruitment for the study.

Analyses compared the pooled 12/15 g group with pooled data for placebo 9, 12 and 15 tablets.

For the analysis of change in serum phosphorus and per cent change in serum LDL-C, a closed testing procedure was used to compare colestilan 3, 6 and 9 g with the placebo nine-tablet group, with comparison of lower doses only occurring if the difference at the dose above was significant. The pooled 12/15 g group was compared with pooled placebo (9, 12 and 15 tablets). The primary endpoints were tested using analysis of covariance (ANCOVA), with treatment and pooled country as factors and baseline value as a covariate, all of which were prespecified. Country was used as a stratification level in the randomization and therefore was included in the statistical analysis model as a factor. To ensure the number of subjects per country sufficient for the analysis model, data from small countries were pooled. This process was identified in the statistical analysis plan and the actual pooling was agreed at a blind data review meeting prior to database lock. The mean changes (least squares mean change), and differences in the mean changes between colestilan and placebo were calculated, with 95% confidence intervals (CIs). Secondary efficacy parameters were analysed using the same ANCOVA model. The primary efficacy analyses used the intent-to-treat population.

ORIGINAL ARTICLE

RESULTS

A total of 642 patients were randomized. The disposition of patients is summarized in Figure 1. Three patients were excluded from analysis because they did not receive medication or had no post-baseline efficacy data; therefore, the safety analysis population comprised 639 patients. Eight patients (one each in the colestilan 6 and 9 g groups, and two each in the colestilan 12 and 15 g and placebo nine-tablet groups) were excluded from the ITT population because of missing post-baseline serum phosphorus or LDL-C values, meaning that this population comprised 631 patients.

Baseline demographic and clinical characteristics were similar across groups (Table 1). The majority of patients were receiving haemodialysis. Baseline mean Kt/*V* was in the range 1.37–1.49 across groups, and there were no notable changes in the adequacy of dialysis during the study. Almost all patients had been receiving a phosphate binder before the study and 11.4% of patients had been receiving lipid-modifying therapy, most commonly a statin.

Overall, 88–90% of patients in the colestilan 3, 6 and 9 g groups were compliant with study treatment (versus 91% of the placebo nine-tablet group). The rate of compliance in the 12 and 15 g groups was 84 and 74.5%, respectively (versus 91.5% in the pooled placebo group).

Calcium and phosphorus metabolism

The mean serum phosphorus levels during the study are shown in Figure 2. During the phosphate binder washout period, the mean phosphorus level increased from 1.75 mmol/L (5.4 mg/dL) to 2.35 mmol/L (7.3 mg/dL). After randomization, serum phosphorus decreased from baseline in all colestilan groups from Week 1 onwards, with a dose-dependent pattern evident for the 3, 6 and 9 g groups.

ANCOVA showed that colestilan 9 g was associated with a significantly greater mean reduction in serum phosphorus level from baseline to Week 12 than seen in the placebo nine-tablet group (co-primary endpoint; Table 2). The difference between colestilan 6 g and placebo reached a level of significance according to more orthodox P-values but did not reach a level of significance when multiplicity was taken into consideration and therefore statistical comparison of 3 g with placebo was not performed. The mean reduction in serum phosphorus in the pooled colestilan 12/15 g group was significantly greater than in the pooled placebo group (Table 2). In a per-protocol analysis, the reduction in serum phosphorus level with colestilan 6 g did reach a level of significance [difference in the mean change between colestilan 6 g and placebo −0.22 mmol/L (−0.67 mg/dL), P = 0.015].

The proportion of responders [defined as serum phosphorus ≤1.78 mol/L (5.5 mg/dL)] was significantly greater in the pooled colestilan 12/15 g group than the pooled placebo group (odds ratio 2.15, P = 0.007). There were no significant differences at lower doses using the prespecified criteria. The median time to first response was 4 weeks in the colestilan 12/15 and 9 g groups. In a prespecified subgroup analysis, patients with a baseline serum phosphorus level ≥2.42 mmol/L (7.5 mg/dL; *n* = 279) experienced a greater reduction in the mean serum phosphorus level at Week 12 than those with a baseline level <2.42 mmol/L (Figure 3).

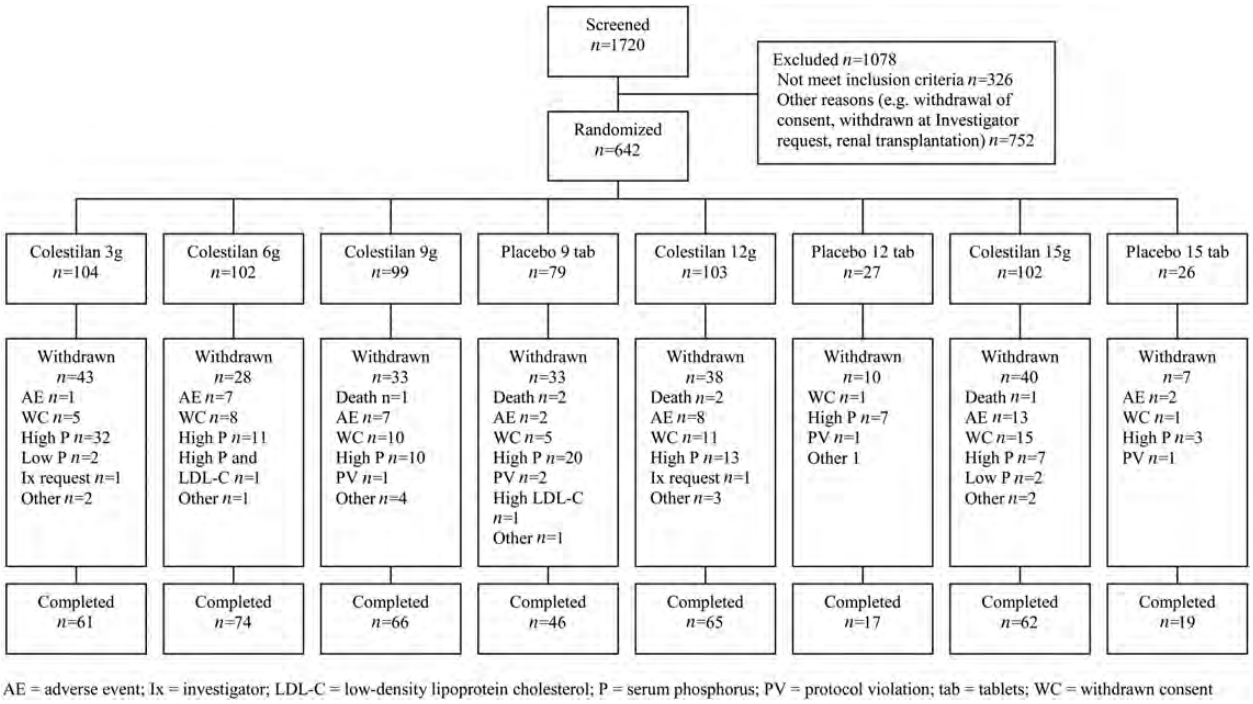
There were no significant differences between colestilan and placebo for the mean change in serum calcium or iPTH levels (Table 4). Calcium levels fell during the phosphate binder washout phase and were then relatively stable during the treatment period, remaining below the mean level recorded prior to the phosphate binder washout phase (Figure 4).

Lipid metabolism

The mean serum LDL-C levels during the study are shown in Figure 5. The mean level increased during the lipid-lowering drug washout period, from 2.2 mmol/L (87 mg/dL) to 2.9 mmol/L (111 mg/dL). Reductions from baseline in serum LDL-C levels were seen in all colestilan groups at all post-randomization visits. The mean per cent reductions in serum LDL-C levels at Week 12 followed a dose-dependent pattern in the colestilan 3, 6, 9 and 12 g groups.

As shown in Table 3, the mean per cent reduction in LDL-C level at Week 12 was significantly greater with colestilan 3, 6 and 9 g than in the placebo nine-tablet group, and significantly greater with pooled colestilan 12/15 g than with pooled placebo. Thus, this co-primary endpoint was reached.

The proportion of responders [defined as LDL-C <1.83 mmol/L (70 mg/dL)] was significantly greater in all colestilan groups than in the corresponding placebo groups, with odds ratios ranging from 6.22 for 3 g (P = 0.003) to 40.06 for 9 g (P < 0.001). A prespecified subgroup analysis found that the mean per cent reduction in LDL-C was greater in patients with a baseline serum LDL-C level ≥2.59 mmol/L (100 mg/dL)



AE = adverse event; Ix = investigator; LDL-C = low-density lipoprotein cholesterol; P = serum phosphorus; PV = protocol violation; tab = tablets; WC = withdrawn consent

FIGURE 1: Patient disposition.

than in those with a baseline serum LDL-C <2.59 mmol/L (Figure 6).

At Week 12, the mean per cent reductions in total cholesterol and in oxidized LDL were significantly greater with colestilan 3, 6, 9 g and pooled 12/15 g than with placebo (Table 4). There were no significant differences between colestilan and placebo for the mean per cent change in serum HDL-C, triglycerides or lipoprotein(a), or for mean change in LDL particle size (Table 4).

Other efficacy endpoints

At Week 12, colestilan 6, 9 g and pooled 12/15 g were associated with significant reductions in HbA1c compared with placebo, while uric acid levels decreased significantly in all colestilan groups compared with placebo (Table 5). There were no significant differences between groups for serum C-reactive protein.

A *post hoc* subgroup analysis suggested that the effect of colestilan on HbA1c was greater in patients with higher baseline HbA1c levels. In those with a baseline HbA1c ≥7.0% (range 8.03–10.60% across treatment groups; $n = 65$), colestilan was associated with reductions in HbA1c of −0.36% (12 g) to −1.38% (15 g), compared with an increase in the placebo groups (0.25% for placebo nine-tablet, 0.13% for pooled placebo). In contrast, among patients with a baseline HbA1c <7.0% (range 5.48–5.66%; $n = 566$), colestilan reduced HbA1c by only −0.01% (6 g) to −0.17% (12 g), compared with an increase of 0.08% for the placebo nine-tablet group and 0.06% for pooled placebo.

Analyses of efficacy parameters using the per-protocol population were generally consistent with those in the intent-to-treat population.

Safety parameters

Treatment-emergent adverse events were reported by 43.1 (6 g) to 58.4% (15 g) of the colestilan groups compared with 46.8 and 51.5% of the placebo nine-tablet and pooled placebo groups. Adverse events were generally mild or moderate in severity. Overall, the most frequently reported adverse events were gastrointestinal, and included nausea, vomiting, dyspepsia and diarrhoea (Table 6). Nausea and vomiting were the only adverse events reported by >10% of patients in any of the colestilan groups, and both showed a possible relationship with dose (Table 6). Three patients experienced gastrointestinal bleeding events (one in the colestilan 12 g group and two in the colestilan 15 g groups). Two were considered to be probably related to study medication and one as not related; all three recovered without sequelae.

Serious adverse events were reported by 1.0 (6 g) to 6.9% (12 g) of the colestilan groups compared with 5.1 and 6.1% of the placebo groups, and adverse events led to treatment discontinuation in 1.0 (3 g) to 12.7% (15 g) of colestilan recipients compared with 2.5 and 3.0% of the placebo groups. Analysis of laboratory parameters did not reveal any issues of concern. There were no clinically significant differences between the colestilan and placebo groups for other safety variables, including blood pressure, heart rate and weight. The mean values for vitamins E, A and folic acid decreased during the study in a dose-dependent manner, although levels generally remained within the reference range (see Supplementary data). Vitamins K and B12 also tended to decrease, but there was no clear dose-dependency (see Supplementary data).

Table 1: Demographic and clinical characteristics

Parameter	COL 3 g (n = 104)	COL 6 g (n = 102)	COL 9 g (n = 98)	Placebo 9 tablets (n = 79)	COL 12 g (n = 102)	COL 15 g (n = 101)	Placebo 9/12/15 tablets pooled (n = 132)	Total (n = 639)[a]
Age (years)								
Mean (SD)	49.9 (12.20)	48.7 (14.64)	47.3 (12.55)	47.9 (12.83)	49.5 (12.41)	50.7 (11.34)	48.5 (12.54)	49.1 (12.65)
Male, n (%)	56 (53.8)	48 (47.1)	50 (51.0)	47 (59.5)	54 (52.9)	55 (54.5)	77 (58.3)	340 (53.2)
Female, n (%)	48 (46.2)	54 (52.9)	48 (49.0)	32 (40.5)	48 (47.1)	46 (45.5)	55 (41.7)	299 (46.8)
Race, n (%)								
Caucasian	88 (84.6)	86 (84.3)	82 (83.7)	66 (83.5)	85 (83.3)	86 (85.1)	111 (84)	538 (84.2)
Asian	14 (13.5)	15 (14.7)	14 (14.3)	12 (15.2)	14 (13.7)	13 (12.9)	18 (13.6)	88 (13.8)
Black	0	0	0	0	1 (1.0)	0	0	1 (0.2)
Other	2 (1.9)	1 (1.0)	2 (2.0)	1 (1.3)	2 (2.0)	2 (2.0)	3 (2.3)	12 (1.9)
BMI (kg/m^2)								
Mean (SD)	25.4 (4.40)	25.1 (4.38)	25.6 (4.37)	25.4 (4.67)	25.8 (4.33)	26.6 (4.39)	25.8 (4.63)	25.7 (4.44)
Most common CKD aetiology, n (%)								
Glomerular kidney disease	40 (38.5)	36 (35.3)	38 (38.8)	31 (39.2)	35 (34.3)	39 (38.6)	58 (43.9)	246 (38.5)
Diabetic glomerulosclerosis	7 (6.7)	9 (8.8)	9 (9.2)	9 (11.4)	12 (11.8)	12 (11.9)	13 (9.8)	62 (9.7)
Cystic diseases	7 (6.7)	11 (10.8)	9 (9.2)	9 (11.4)	12 (11.8)	10 (9.9)	14 (10.6)	63 (9.9)
Vascular diseases	12 (11.5)	10 (9.8)	7 (7.1)	4 (5.1)	8 (7.8)	12 (11.9)	6 (4.5)	55 (8.6)
Time since CKD diagnosis (years)								
Mean (SD)	5.29 (4.43)	4.58 (4.09)	4.28 (3.69)	5.54 (4.54)	5.23 (4.35)	4.80 (3.92)	5.31 (4.17)	4.94 (4.12)
Dialysis, n (%)								
Haemodialysis	95 (91.3)	95 (94.1)	95 (97.9)	73 (94.8)	91 (91.0)	96 (97.0)	124 (95.4)	–
Peritoneal dialysis	9 (8.7)	6 (5.9)	2 (2.1)	4 (5.2)	9 (9.0)	3 (3.0)	6 (4.6)	–
Serum P, n (%)								
<2.42 mmol/L (7.5 mg/dL)	58 (55.8)	57 (55.9)	50 (51.0)	43 (54.4)	67 (65.7)	51 (50.5)	76 (57.6)	359 (56.2)
≥2.42 mmol/L (7.5 mg/dL)	46 (44.2)	45 (44.1)	48 (49.0)	36 (45.6)	35 (34.3)	50 (49.5)	56 (42.4)	280 (43.8)

Serum LDL-C *n* (%)								
<2.59 mmol/L (100 mg/dL)	34 (32.7)	40 (39.2)	37 (37.8)	32 (40.5)	37 (36.3)	39 (38.6)	49 (37.1)	236 (36.9)
≥2.59 mmol/L (100 mg/dL)	70 (67.3)	62 (60.8)	61 (62.2)	47 (59.5)	65 (63.7)	62 (61.4)	83 (62.9)	403 (63.1)
Diabetes mellitus								
Yes, *n* (%)	12 (11.5)	12 (11.8)	11 (11.2)	10 (12.7)	14 (13.7)	16 (15.8)	15 (11.4)	80 (12.5)
No, *n* (%)	92 (88.5)	90 (88.2)	87 (88.8)	69 (87.3)	88 (86.3)	85 (84.2)	117 (88.6)	559 (87.5)
HbA1c, *n* (%)								
<7.0% total Hb	96 (92.3)	90 (88.2)	88 (89.8)	70 (88.6)	90 (88.2)	91 (90.1)	119 (90.2)	574 (89.8)
≥7.0% total Hb	8 (7.7)	12 (11.8)	10 (10.2)	9 (11.4)	12 (11.8)	10 (9.9)	13 (9.8)	65 (10.2)

[a]Takes account of the fact that the 79 patients in the placebo nine-tablet group are also included in the pooled placebo group.
BMI, body mass index; CKD, chronic kidney disease; COL, colestilan; HbA1c, glycosylated haemoglobin; LDL-C, low-density lipoprotein cholesterol; P, phosphorus.

DISCUSSION

Colestilan is an anion-exchange resin that binds phosphate and bile acids in the gastrointestinal tract [16, 19]. It has been available in Japan for some years for the treatment of hypercholesterolaemia and familial hypercholesterolaemia. More recently, a clinical development programme of studies has been undertaken with colestilan as a non-calcium-containing phosphate binder for the treatment of hyperphosphataemia in patients with CKD stage 5 on dialysis. The current study demonstrates that colestilan reduces serum phosphorus and LDL-C levels (co-primary endpoints) significantly, over a range of doses, in dialysis patients who have both hyperphosphataemia and dyslipidaemia. Reductions were seen in both parameters as early as 1 week after commencing colestilan treatment.

The treatment of hyperphosphataemia is critical in patients with CKD. Chronic elevation of phosphorus levels can lead to secondary hyperparathyroidism and vascular calcification, and an association between hyperphosphataemia and increased morbidity and death has been demonstrated [4–7, 10, 20, 21]. Observational data from DOPPS suggest that the use of phosphate binders is associated with a reduced risk of mortality in dialysis patients [8], and a small randomized study has found a survival benefit with sevelamer compared with a calcium-based phosphate binder in non-dialysis CKD patients [22]. Many CKD patients on dialysis, despite receiving treatment, demonstrate elevated serum phosphorus levels [23]. Thus, guidelines do recommend further efforts to reduce serum phosphorus levels towards 1.13–1.78 mmol/L (3.5–5.5 mg/dL) in dialysis patients, to reduce the risk of subsequent morbidity [9, 12].

Short-term studies of colestilan in haemodialysis patients with hyperphosphataemia have been reported previously. In one study, colestilan 6 and 9 g/day reduced the mean serum phosphorus levels to a significantly greater extent than seen with placebo over a 3-week period [18]; in the other, colestilan 6 g per day reduced serum phosphorus significantly more than seen with placebo after 2 weeks [16]. Thus, initial short-term studies of colestilan in haemodialysis patients with hyperphosphataemia have confirmed that colestilan at 6–9 g/day significantly reduces the mean serum phosphorus levels over a 2–3-week period.

In the current study, the mean reduction in serum phosphorus level after 12 weeks was significantly greater with colestilan at doses of 9 g/day or above than with placebo. The reduction in phosphorus seen with colestilan 6 g, although being at a level of significance that would normally be considered meaningful, due to the nature of the statistical analysis of this dual endpoint study, it cannot be considered significant in the intent-to-treat analysis. However, this was significant in the per-protocol analysis, and the reduction achieved at this dose was clinically relevant. In addition, a responder analysis found that, compared with placebo recipients, a significantly greater proportion of patients treated with colestilan 12/15 g achieved a serum phosphorus level of ≤1.78 mmol/L (5.5 mg/dL). Of note, patients with a

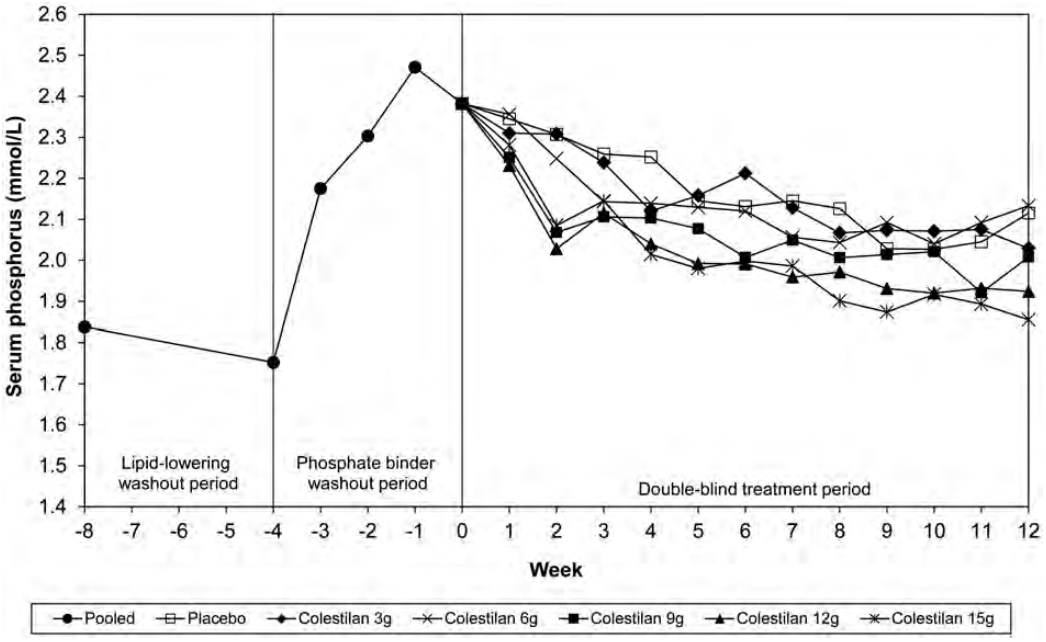


FIGURE 2: Mean serum phosphorus levels with colestilan (MCI-196) and placebo.

ORIGINAL ARTICLE

Table 2: Analysis of mean change in serum phosphorus level at Week 12

	Placebo 9 tablets ($n = 77$)	COL 9 g ($n = 97$)	COL 6 g ($n = 101$)	COL 3 g[a] ($n = 104$)	Placebo 9/12/15 tablets pooled ($n = 130$)	Pooled COL 12 + 15 g ($n = 199$)
Mean change[b] (mmol/L)	−0.07	−0.28	−0.23	−0.09	−0.06	−0.34
Difference between means[b]		−0.21	−0.17	−0.02		−0.28
95% CI[b]		−0.37, −0.05	−0.32, −0.01	−0.17, 0.13		−0.39, −0.18
P-value[b,c]		0.009	0.036	0.785		<0.001

[a]Formal statistical comparison of colestilan 3 g with placebo (closed testing procedure) was not performed.
[b]ANCOVA on change from baseline to Week 12 (LOCF), with treatment and pooled country as factors and baseline value as a covariate. Difference between means for colestilan – placebo.
[c]$\alpha = 0.03$ for colestilan 3, 6, 9 g versus placebo 9 tablets (closed procedure). $\alpha = 0.01$ for colestilan 12/15 g (pooled) versus pooled placebo.
COL: colestilan; PL: placebo.

higher baseline serum phosphorus level appeared to have a greater phosphorus reduction than those with a lower baseline level, which is consistent with findings from an earlier study [18].

Calcium-based phosphate binders can lead to an elevated serum calcium level, with an associated increase in the risk of vascular calcification [10, 11, 21]. In the current study, colestilan reduced serum phosphorus levels without modifying iPTH or calcium levels. Furthermore, during the study treatment period, serum calcium levels remained below those seen when patients were on pre-study phosphate binders, most of which were calcium-based.

Dyslipidaemia is common in patients with CKD [4, 14], and in dialysis patients, it is generally characterized by high triglyceride levels, low HDL-C levels and normal LDL-C levels, although one report noted that 55.7% of haemodialysis patients and 73.2% of peritoneal dialysis patients had an LDL-C ≥2.59 mmol/L (100 mg/dL) [4]. Although the 4D and AURORA studies failed to demonstrate that lowering LDL-C levels with a statin had a beneficial effect on cardiovascular outcomes in haemodialysis patients [24, 25]; more recently, the SHARP study found that treatment with simvastatin plus ezetimibe reduced the risk of atherosclerotic events in CKD patients, including those on dialysis [15]. The K/DOQI

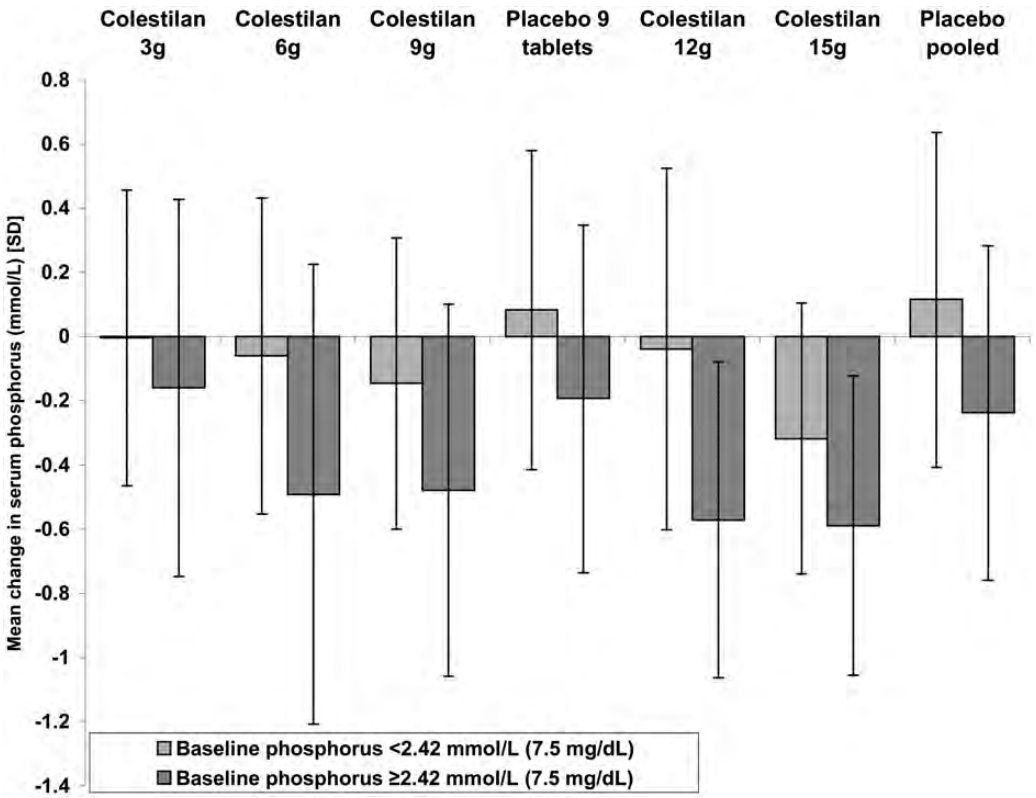


FIGURE 3: Mean change in serum phosphorus by baseline phosphorus level.

Table 3. Analysis of mean per cent change in serum LDL-C level at Week 12

	Placebo 9 tablets ($n = 77$)	COL 9 g ($n = 97$)	COL 6 g ($n = 101$)	COL 3 g ($n = 104$)	Placebo 9/ 12/15 tablets pooled ($n = 130$)	Pooled COL 12 + 15 g ($n = 199$)
Mean change[a] (%)	1.86	−27.61	−23.60	−15.91	4.09	−27.62
Difference between means[a]		−29.47	−25.46	−17.77		−31.71
95% CI[a]		−35.44, −23.51	−31.25, −19.66	−23.54, −12.00		−36.53 −26.89
P-value[a,b]		<0.001	<0.001	<0.001		<0.001

[a]ANCOVA on change from baseline to Week 12 (LOCF), with treatment and pooled country as factors and baseline value as a covariate. Difference between means for colestilan–placebo.
[b]$\alpha = 0.0075$ for colestilan 3, 6, 9 g versus placebo nine tablets (closed procedure). $\alpha = 0.0025$ for colestilan 12/15 g (pooled) versus pooled placebo.
COL, colestilan; PL, placebo.

guidelines for managing dyslipidaemias in CKD indicate that patients with stage 5 disease have a risk equivalent to that of coronary heart disease, and LDL-C should be reduced to <2.59 mmol/L (100 mg/dL) [4]. This recommendation is based on the Adult Treatment Panel III guidelines, an update of which includes an optional goal of <1.83 mmol/L (70 mg/dL) for high-risk patients [26].

In the current study, serum LDL-C level decreased with all doses of colestilan, whereas it increased in the placebo groups. At 12 weeks, the mean per cent reduction was significantly greater with all doses of colestilan compared with placebo. Furthermore, significantly more patients in each of the colestilan groups achieved an LDL-C level of <1.83 mmol/L (70 mg/dL) compared with the placebo groups. Colestilan was also

Table 4: Changes in secondary efficacy parameters (serum levels) at Week 12

	Placebo 9 tablets ($n = 77$)	COL 9 g ($n = 97$)	COL 6 g ($n = 101$)	COL 3 g ($n = 104$)	Placebo 9/12/15 tablets pooled ($n = 130$)	Pooled COL 12 + 15 g ($n = 199$)
Calcium (mmol/L)						
Mean change[a]	−0.04	−0.05	−0.01	−0.02	−0.01	−0.02
Difference[a] (95% CI)		−0.01 (−0.05, 0.04)	0.03 (−0.01, 0.08)	0.02 (−0.02, 0.07)		0.00 (−0.04, 0.03)
P-value[b]		0.816	0.174	0.380		0.863
Intact PTH (pmol/L)						
Mean change[a]	4.36	−2.71	2.19	5.98	4.41	0.68
Difference[a] (95% CI)		−7.07 (−17.01, 2.88)	−2.17 (−11.81, 7.46)	1.62 (−7.96, 11.20)		−3.73 (−10.70, 3.23)
P-value*		0.163	0.658	0.740		0.293
TC (mmol/L)						
Mean change (%)[a]	2.56	−20.17	−15.30	−9.68	4.26	−20.34
Difference[a] (95% CI)		−22.73 (−26.98, −18.48)	−17.87 (−21.99, −13.74)	−12.25 (−16.36, −8.13)		−24.60 (−28.06, −21.15)
P-value[b]		<0.001	<0.001	<0.001		<0.001
HDL-C (mmol/L)						
Mean change (%)[a]	1.31	1.56	2.84	−0.56	1.70	−1.29
Difference[a] (95% CI)		0.25 (−5.66, 6.17)	1.53 (−4.21, 7.27)	−1.87 (−7.60, 3.86)		−2.99 (−7.53, 1.54)
P-value[b]		0.933	0.600	0.522		0.195
TG (mmol/L)						
Mean change (%)[a]	9.21	6.41	8.73	11.76	10.27	3.14
Difference[a] (95% CI)		−2.80 (−15.82, 10.23)	−0.48 (−13.13, 12.17)	2.55 (−10.06, 15.16)		−7.12 (−16.27, 2.03)
P-value[b]		0.673	0.941	0.691		0.126
LDL-C particle size						
Mean change[a]	0.00	−0.01	−0.01	−0.01	0.00	−0.01
Difference[a] (95% CI)		0.00 (−0.01, 0.00)	0.00 (−0.01, 0.01)	−0.01 (−0.01, 0.00)		0.00 (−0.01, 0.00)
P-value[b]		0.341	0.740	0.218		0.526
Lipoprotein(a) (nmol/L)						
Mean change (%)[a]	4.49	0.97	−5.54	28.08	4.25	−2.27

Difference[a] (95% CI)		−3.52 (−54.91, 47.87)	−10.03 (−58.87, 38.80)	23.59 (−25.20, 72.38)		−6.52 (−16.12, 3.09)
P-value[b]		0.893	0.686	0.341		0.182
Oxidised LDL (U/L)						
Mean change (%)[a]	8.53	−16.48	−10.42	−1.20	6.67	−13.87
Difference[a] (95% CI)		−25.01 (−34.32, −15.70)	−18.95 (−28.00, −9.90)	−9.72 (−18.72, −0.73)		−20.54 (−29.34, −11.74)
P-value[b]		<0.001	<0.001	0.034		<0.001

[a]ANCOVA on change from baseline to Week 12 (LOCF), with treatment and pooled country as factors and baseline value as a covariate. Difference = difference between mean changes (colestilan–placebo).
[b]$\alpha = 0.05$ for colestilan 3, 6, 9 g versus placebo nine tablets and for 12/15 g (pooled) versus pooled placebo.
HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PL, placebo; PTH, parathyroid hormone; TC, total cholesterol; TG, triglycerides.

associated with significant reductions in total cholesterol level and oxidized LDL, but significant changes were not seen in other lipid parameters. Patients with higher baseline levels of LDL-C experienced the greatest reductions in LDL-C.

The effect of colestilan on several other metabolic parameters was also evaluated. Specifically, colestilan reduced HbA1c and uric acid levels significantly compared with placebo. In line with the findings for serum phosphorus and LDL-C, patients with a higher baseline HbA1c derived the greatest benefit from colestilan treatment. Both diabetes and hyperuricaemia have been associated with an increased risk of cardiovascular events in some, although not all, studies in patients with CKD stage 5 [27–30], and the ability to improve glycaemic control and uric acid levels in dialysis patients with diabetes or hyperuricaemia could potentially be an additional benefit of colestilan.

Lipid and glucose homoeostasis are inter-related through several metabolic pathways, including bile acid-activated nuclear hormone receptor signalling pathways [31]. By altering the effects of various nuclear receptors, bile acid sequestrants such as colestilan can lead to improved glycaemic control, in addition to their lipid-lowering effects [31]. The mechanism by which colestilan reduces uric acid levels is not known. Possibilities to consider include reduced protein intake, weight loss, increased excretion or binding of uric acid [32]. Dietary protein was not assessed in the current study, but there were no differences in blood urea nitrogen levels between the colestilan and placebo groups. There were also no notable differences in weight or in the adequacy of dialysis between groups.

Patients with CKD stage 5 often have to take multiple medications and it was possible that compliance could have been an issue in the study, given the number of tablets that had to be taken, particularly in the two highest dose groups. However, overall compliancy rates were high in the 3, 6 and 9 g groups, although they were slightly lower in the 12 and 15 g groups.

Colestilan was generally well tolerated in this study, with most adverse events being of mild or moderate severity. The most common adverse events were gastrointestinal, which is to be expected with an oral agent that is not absorbed. Nausea and vomiting were the most frequently reported events. Colestilan has the potential to bind to fat-soluble vitamins in the gastrointestinal tract and reduce their absorption. Vitamins A, D and E have large reserves in the body, but vitamin K could potentially be prone to depletion. In the current study, levels of vitamins A, E (α-tocopherol) and K tended to decrease, but evidence of some dose-dependency was seen only for vitamins A and E.

In conclusion, colestilan is effective at reducing serum phosphorus and LDL-C levels in patients with CKD stage 5 on dialysis who have hyperphosphataemia and dyslipidaemia, and is generally well tolerated. Colestilan reduces phosphorus without increasing serum calcium levels. It also reduces total cholesterol, oxidized LDL, HbA1c and uric acid levels. These findings suggest that colestilan is an effective treatment for hyperphosphataemia, and has additional beneficial effects on

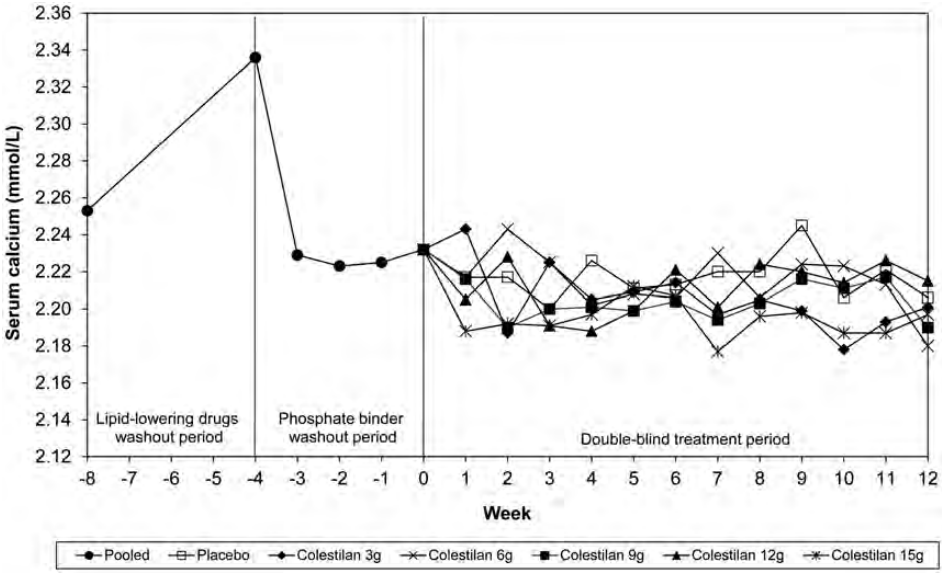


FIGURE 4: Mean serum calcium levels with colestilan (MCI-196) and placebo.

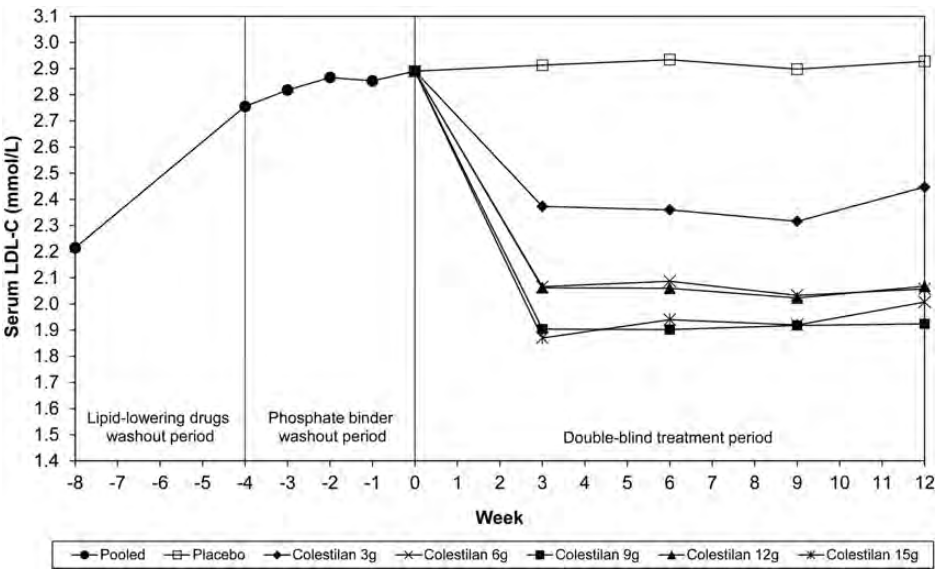


FIGURE 5: Mean serum LDL-C levels with colestilan (MCI-196) and placebo.

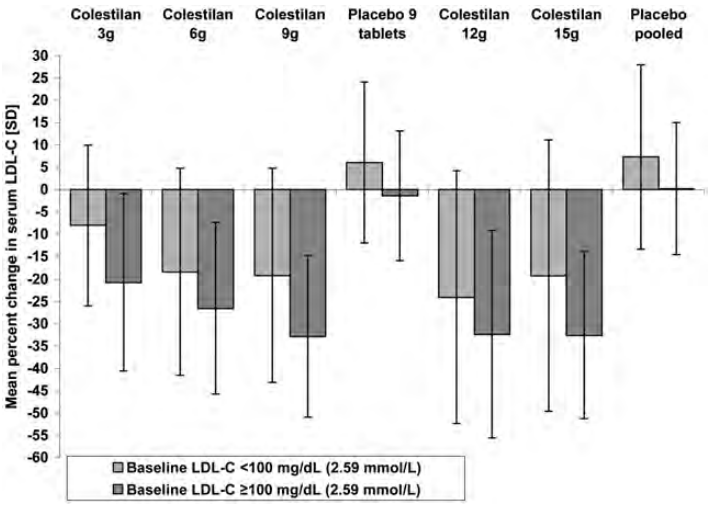


FIGURE 6: Mean percent change in serum LDL-C by baseline LDL-C level.

Table 5: Changes in additional pre-specified efficacy parameters (serum levels) at Week 12

	Placebo 9 tablets ($n = 77$)	COL 9 g ($n = 97$)	COL 6 g ($n = 101$)	COL 3 g ($n = 104$)	Placebo 9/12/15 tablets pooled ($n = 130$)	Pooled COL 12 + 15 g ($n = 199$)
HbA1c (% total Hb)						
Mean change[a]	0.06	−0.14	−0.15	−0.08	0.08	−0.19
Difference between means[a] (95% CI)		−0.21 (−0.38, −0.04)	−0.21 (−0.38, −0.05)	−0.15 (−0.31, 0.02)		−0.27 (−0.40, −0.13)
P-value[b]		0.014	0.011	0.078		<0.001
Uric acid (μmol/L)						
Mean change[a]	4.81	−32.36	−26.10	−13.19	5.18	−40.85
Difference between means[a] (95% CI)		−37.17 (−54.93, −19.42)	−30.91 (−48.14, −13.68)	−18.00 (−35.10, −0.89)		−46.02 (−61.32, −30.73)
P-value[b]		<0.001	<0.001	0.039		<0.001
CRP (mg/L)						
Mean change[a]	0.04	−1.94	−2.13	−1.47	−0.72	−0.27
Difference between means[a] (95% CI)		−1.98 (−4.44, 0.48)	−2.17 (−4.59, 0.25)	−1.51 (−3.89, 0.88)		0.45 (−2.13, 3.03)
P-value[b]		0.114	0.078	0.214		0.731

[a]ANCOVA on change from baseline to Week 12 (LOCF), with treatment and pooled country as factors and baseline value as a covariate. Difference between means for colestilan–placebo.
[b]$\alpha = 0.05$ for colestilan 3, 6, 9 g versus placebo nine tablets and for 12/15 g (pooled) versus pooled placebo.
CRP, C-reactive protein; HbA1c, glycosylated haemoglobin.

Table 6: Treatment-emergent adverse events experienced by ≥5% of patients in any group

	COL 3 g (*n* = 104)	COL 6 g (*n* = 102)	COL 9 g (*n* = 98)	Placebo 9 tablets (*n* = 79)	COL 12 g (*n* = 102)	COL 15 g (*n* = 101)	Placebo 9/12/15 tablets pooled (*n* = 132)	Overall (*n* = 639)
All TEAEs, *n* (%)	49 (47.1)	44 (43.1)	49 (50.0)	37 (46.8)	55 (53.9)	59 (58.4)	68 (51.5)	324 (50.7)
Nausea	4 (3.8)	9 (8.8)	12 (12.2)	0	20 (19.6)	20 (19.8)	0	65 (10.2)
Vomiting	2 (1.9)	4 (3.9)	8 (8.2)	2 (2.5)	12 (11.8)	6 (5.9)	2 (1.5)	34 (5.3)
Dyspepsia	4 (3.8)	8 (7.8)	7 (7.1)	1 (1.3)	5 (4.9)	9 (8.9)	1 (0.8)	34 (5.3)
Diarrhoea	5 (4.8)	5 (4.9)	6 (6.1)	5 (6.3)	4 (3.9)	5 (5.0)	7 (5.3)	32 (5.0)
Hypertension	3 (2.9)	6 (5.9)	7 (7.1)	1 (1.3)	2 (2.0)	5 (5.0)	4 (3.0)	27 (4.2)
Abdominal distension	0	3 (2.9)	2 (2.0)	1 (1.3)	7 (6.9)	6 (5.9)	4 (3.0)	22 (3.4)
Hypocalcaemia	2 (1.9)	2 (2.0)	3 (3.1)	2 (2.5)	6 (5.9)	2 (2.0)	3 (2.3)	18 (2.8)
Constipation	3 (2.9)	1 (1.0)	6 (6.1)	0	0	5 (5.0)	2 (1.5)	17 (2.7)
Abdominal pain upper	1 (1.0)	3 (2.9)	0	1 (1.3)	3 (2.9)	6 (5.9)	2 (1.5)	15 (2.3)
Decreased appetite	2 (1.9)	1 (1.0)	1 (1.0)	0	6 (5.9)	4 (4.0)	1 (0.8)	15 (2.3)

COL, colestilan; TEAE, treatment-emergent adverse event.

other metabolic parameters associated with cardiovascular risk, notably LDL-C.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

The authors thank all participants and contributors to the study, in particular the members of the Data Safety Monitoring Board: M. Ketteler (Coburg, Germany), G.D. Murray (Edinburgh, UK), T.B. Drüeke (Amiens, France) and the investigators: Hungary: I. Mezei (Hatvan), L. Major (Esztergom), S. Ferenczi (Gyor), G. Varga (Ajka), K. Magyar (Baja), P. Voros (Budapest); Italy: A. Albertazzi (Modena), M. Morosetti (Ostia), F. Locatelli (Lecco), G. Villa (Pavia); Macedonia: G. Spasovski (Skopje); Malaysia: C.H. Ching (Alor Setah), B. Thevarajah (Kota Kinabalu), I. Vaithilingam (Taiping), K. Rahmat (Melaka), H.H. Tan (Kuching), Z. Nordin (Kuala Terengganu), B.L. Goh (Kajang), S.M. Teo (Ipoh), W.S. Yusuf (Seremban), W.R. Seman (Kuantan), H.W. Lee (Kota Kinabalu), N. Zulkarnain Sim (Klang); Poland: M. Nowicki (Lodz), M. Kuczera (Rybnik), Z. Hruby (Wroclaw), R. Malecki (Warszawa), Z. Wankowicz (Warszawa), A. Rydzewski (Warszawa), M. Switalski (Plock), Kurzawska-Firlej (Poznan); Russia: A. Zuev (Petrozavodsk), S. Lebedev (Moscow), N. Khadikova (St Petersburg), A. Vatazin (Moscow), A. Gurevich (St Petersburg), K. Staroselsky (St Petersburg), V. Shilo (Moscow), A. Strokov (Moscow), G. Timokhovskaya (St Petersburg), V. Zlokazov (Ekaterinburg), V. Anashkin (Moscow), O. Barbarash (Kemerovo), K. Gurevich (St Petersburg), A. Nazarov (Ekaterinburg), E. Shutov (Moscow), E. Kolmakova (St Petersburg), A. Zemchenkov (St Petersburg), N. Tomilina (Moscow), A. Yampolskiy (Krasnodar), V. Marasaev (Yaroslavl), D. Pichkov (Nishniy Novgorod), N. Lineva (Nishniy Novgorod), Y. Konstantinov (St Petersburg), D. Perlin (Volzhskiy), V. Doru-Tovt (St Petersburg), S. Abramenkov (Moscow), O. Balkarova (Moscow), I. Novoseltsev (Mytishchi), G. Dyubanova (Novosibirsk), O. Tarasova (Ivanovo), L. Tkalich (Tomsk), A. Borsukov (Smolensk), N. Strakhova (Rostov-on-Don), A. Bevzenko (Khabarovsk), A. Evseev (Vladivostok), G. Shostka (St Petersburg), M. Melnichenko (Tver), N. Nezdoymina (Chelyabinsk), S. Ivliev (Krasnoyarsk), D. Elfimov (Tumen), L. Lysenko (Moscow), V. Serebrennikov (Novokuznetsk), E. Chernyavskaya (Omsk), K. Zelenin (Arkhangelsk), V. Babich (Novorossiysk), A. Serin (Chita), I. Shtykalova (Armavir), I. Rozhkova (Kaluga); Serbia: N. Dimkovic (Belgrade), S. Pljesa (Belgrade), M. Poskurica (Kragujevac), V. Djordjevic (Nis), I. Mitic (Novi Sad), Z. Kovacevic (Belgrade), M. Radovic (Belgrade); Ukraine: I. Kuchma (Kiev), M. Kolesnyk (Kiev), I. Dudar (Kiev), L. Pyrih (Kyiv), L. Martnyuk (Ternopil), V. Lesovoy (Kharkiv), T. Kostynenko (Mykolaiv), O. Legun (Ivano-Frankivsk), V. Stryzhak (Uzhgorod), N. Prylypko (Uzhgorod), S. Korneyeva (Uzhgorod), A. Lyulko (Uzhgorod). The study was

funded by Mitsubishi Pharma Europe Ltd. Editorial assistance was provided by K. Croom, with financial support from Mitsubishi Pharma Europe Ltd.

CONFLICT OF INTEREST STATEMENT

F.L. is or was a member of advisory boards for Abbott, Amgen, Genzyme, Mitsubishi Pharma Europe Ltd and Shire. G.S. was a member of advisory boards for Mitsubishi Pharma Europe Ltd and has been supported as lecturer by Genzyme, Abbott, Shire and Amgen. N.D. was a member of an advisory board for Mitsubishi Pharma Europe Ltd and has been supported as lecturer by Genzyme, Baxter, Roche, Fresenius and Cilag.

REFERENCES

1. United States Renal Data System. USRDS 1997 annual data report: VI causes of death. Am J Kidney Dis 1997; 30: S107–S117
2. Vanholder R, Massy Z, Argiles A *et al.* European Uremic Toxin Work Group. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant 2005; 20: 1048–1056
3. Collins AJ, Li S, Ma JZ *et al.* Cardiovascular disease in end-stage renal disease patients. Am J Kidney Dis 2001; 38(4 Suppl 1): S26–S29
4. Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003; 41 (4 Suppl 3): I–IV, S1–91
5. Raggi P, Boulay A, Chasan-Taber S *et al.* Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002; 39: 695–701
6. Block GA, Klassen PS, Lazarus JM *et al.* Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15: 2208–2218
7. Kestenbaum B, Sampson JN, Rudser KD *et al.* Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005; 16: 520–528
8. Lopes AA, Tong L, Thumma J *et al.* Phosphate binder use and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS): evaluation of possible confounding by nutritional status. Am J Kidney Dis 2012; 60: 90–101
9. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42: S1–S201
10. Guérin AP, London GM, Marchais SJ *et al.* Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant 2000; 15: 1014–1021
11. Block GA, Wheeler DC, Persky MS *et al.* Effects of phosphate binders in moderate CKD. J Am Soc Nephrol 2012; 23: 1407–1415
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2009; S1–S130
13. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421
14. Cheung AK. Is lipid control necessary in hemodialysis patients? Clin J Am Soc Nephrol 2009; 4: S95–S101
15. Baigent C, Landray MJ, Reith C; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–2192
16. Kurihara S, Tsuruta Y, Akizawa T. Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. Nephrol Dial Transplant 2005; 20: 424–430
17. Date T, Shigematsu T, Kawashita Y *et al.* Colestimide can be used as a phosphate binder to treat uraemia in end-stage renal disease patients. Nephrol Dial Transplant 2003; 18 (Suppl 3): iii90–iii93
18. Locatelli F, Dimkovic N, Pontoriero G *et al.* Effect of MCI-196 on serum phosphate and cholesterol levels in haemodialysis patients with hyperphosphataemia: a double-blind, randomized, placebo-controlled study. Nephrol Dial Transplant 2010; 25: 574–581
19. Nakaya N, Goto Y; MCI-196 Study Group. Colestilan: a new bile acids sequestrant resin. A review of its clinical study in hypercholesterolaemia in Japan. Atherosclerosis 2000; 151: 134–135
20. Block GA, Hulbert-Shearon TE, Levin NW *et al.* Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31: 607–617
21. Goodman WG, Goldin J, Kuizon BD *et al.* Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000; 342: 1478–1483
22. Di Iorio B, Bellasi A, Russo D; INDEPENDENT Study Investigators. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clin J Am Soc Nephrol 2012; 7: 487–493
23. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphataemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. Am J Kidney Dis 2000; 35: 1226–1237
24. Wanner C, Krane V, März W; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238–248
25. Fellström BC, Jardine AG, Schmieder RE; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395–1407
26. Grundy SM, Cleeman JI, Merz CN; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol 2004; 44: 720–732

27. Sturm G, Lamina C, Zitt E *et al.* Association of HbA1c values with mortality and cardiovascular events in diabetic dialysis patients. The INVOR study and review of the literature. PLoS One 2011; 6: e20093
28. Neri L, Rocca Rey LA, Lentine KL *et al.* Joint association of hyperuricemia and reduced GFR on cardiovascular morbidity: a historical cohort study based on laboratory and claims data from a national insurance provider. Am J Kidney Dis 2011; 58: 398–408
29. Suliman ME, Johnson RJ, García-López E *et al.* J-shaped mortality relationship for uric acid in CKD. Am J Kidney Dis 2006; 48: 761–771
30. Latif W, Karaboyas A, Tong L *et al.* Uric acid levels and all-cause and cardiovascular mortality in the hemodialysis population. Clin J Am Soc Nephrol 2011; 6: 2470–2477
31. Reasner CA. Reducing cardiovascular complications of type 2 diabetes by targeting multiple risk factors. J Cardiovasc Pharmacol 2008; 52: 136–144
32. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. J Pharmacol Exp Ther 2008; 324: 1–7

Received for publication: 30.11.2012; Accepted in revised form: 5.2.2013

Nephrol Dial Transplant (2013) 28: 1888–1898
doi: 10.1093/ndt/gfs593
Advance Access publication 27 January 2013

ORIGINAL ARTICLE

Impact of frequent hemodialysis on anemia management: results from the Frequent Hemodialysis Network (FHN) Trials

Daniel B. Ornt[1],
Brett Larive[2],
Anjay Rastogi[3],
Mohamad Rashid[3],
John T. Daugirdas[4],
Ann Hernandez[3],
Manjula Kurella Tamura[5],
Rita S. Suri[6],
Nathan W. Levin[7],
and Alan S. Kliger[8],
the Frequent Hemodialysis Network Trial Group

Correspondence and offprint requests to: Daniel B. Ornt; E-mail: daniel.ornt@rit.edu

[1]College of Health Sciences and Technology, Rochester Institute of Technology, Rochester, NY, USA,
[2]Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH, USA,
[3]Division of Nephrology, David Geffen School of Medicine, Los Angeles, CA, USA,
[4]Division of Nephrology, University of Illinois at Chicago, Chicago, IL, USA,
[5]Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA, USA,
[6]London Health Sciences Center, University of Western Ontario, London, Ontario, Canada,
[7]Renal Research Institute, New York, NY, USA and
[8]Hospital of Saint Raphael and Yale University, New Haven, CT, USA

Keywords: anemia, erythropoietin, frequent, hemodialysis, nocturnal

ABSTRACT

Background. The extent to which anemia management is facilitated by more frequent hemodialysis (HD) is controversial. We hypothesized as a preselected outcome that patients receiving HD six times (6×) compared with three times (3×) per week would require lower doses of erythropoietin-stimulating agents (ESA) and/or achieve higher blood hemoglobin (Hb) concentrations.

Methods. Subjects enrolled in the Frequent Hemodialysis Network (FHN) daily and nocturnal trials were studied. As the primary outcome for anemia, the dose of ESAs was recorded at 4-month intervals and the monthly dose of intravenous iron (IV Fe) was reported. Serum iron, transferrin saturation and