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Serological cardiovascular and mortality risk predictors in dialysis patients receiving sevelamer: a prospective study

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Abstract

Background. Cardiovascular morbidity and mortality are massively increased in patients with chronic kidney disease (CKD). Sevelamer hydrochloride has been shown to attenuate cardiovascular calcifications in CKD and end-stage renal disease (ESRD) patients. We assessed how sevelamer hydrochloride influences the evolution of serum fetuin-A and other serological factors predicting cardiovascular outcome and survival in haemodialysis patients.

Methods. Fifty-seven prevalent haemodialysis patients were included in a three-phase prospective interventional trial (A–B–A design; 8 weeks per phase). Sevelamer was only administered in the middle phase of the study. Within the other two phases, ≥90% of the patients received calcium acetate for phosphate binding. Detailed time courses of serum biochemistries were analysed in order to obtain detailed insight into the influence of sevelamer upon CKD–mineral and bone disorder (MBD) parameters as well as serum fetuin-A, fibroblast growth factor 23 (FGF23) and uraemic toxin levels [uric acid, indoxyl sulphate, hippuric acid, indole acetic acid, P-cresol and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF)].

Results. Forty-one patients finished the three prospective study phases (intention-to-treat analysis). After treatment with sevelamer, serum fetuin-A significantly increased (+21%), showing a delayed increase outlasting the third (non-sevelamer) study period. Total and low-density lipoprotein (LDL) cholesterol levels, as well as serum calcium, decreased significantly. The opposite occurred with albumin, C-reactive protein and intact parathyroid hormone (iPTH). FGF23, uric acid, indoxyl sulphate, hippuric acid, indole acetic acid, CMPF and serum phosphate did not change significantly during sevelamer treatment. In contrast, in parallel to sevelamer treatment, there was a significant rise in serum P-cresol.

Conclusions. In haemodialysis patients, treatment with sevelamer over 8 weeks was associated with a delayed yet long-lasting increase in serum fetuin-A levels. Increasing the serum level of fetuin-A, a negative acute-phase protein and systemic calcification inhibitor, might be one of the potential anti-calcification mechanisms of sevelamer. Since we failed to detect a decrease in systemic inflammation and uraemic toxins, the exact mechanisms by which sevelamer treatment affects serum fetuin-A remain to be determined.

Keywords: dialysis; fetuin-A; hyperphosphataemia; pleiotropic effects; sevelamer hydrochloride

Introduction

Excess morbidity and mortality are hallmarks of chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients [1]. Especially, the cardiovascular mortality risk is dramatically elevated in patients with CKD [1]. Accelerated and pronounced cardiovascular calcifications are typical for advanced chronic renal failure [2]. Chronic kidney disease–mineral and bone disorders (CKD–MBD) including hyperparathyroidism, hypercalcaemia and hyperphosphataemia contribute to the development of accelerated vascular calcification and cardiovascular disease in CKD patients [3,4]. Oral phosphate binder treatment plays a pivotal role in the current management of hyperphosphataemia and hyperparathyroidism in these patients [5]. For many years, calcium-containing phosphate binders have

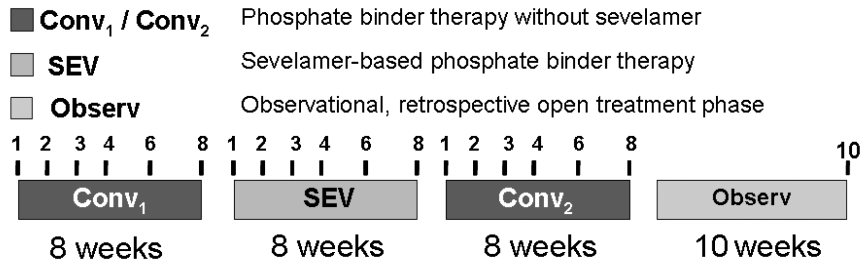

Fig. 1. Study design of the open-label prospective interventional trial with sevelamer. The prospective part of the study consisted of three phases ($Conv_1$, SEV, $Conv_2$) each lasting for 8 weeks. Two phases with 'conventional' phosphate binder regimens ('$Conv_1$' and '$Conv_2$', without sevelamer treatment) and a sevelamer ('SEV') treatment phase in between the other two. The prospective study period with three phases was followed up by an observational, retrospective open treatment phase. Figures indicate the week of blood drawing for routine laboratory parameters.

been the cornerstone of hyperphosphataemia treatment in CKD. However, a high calcium intake is suspected to contribute to vascular calcification [6–8].

The phosphate binder sevelamer hydrochloride (Genzyme Corporation, Cambridge, MA, USA) has been shown to reduce progression of vascular calcification in patients with CKD and ESRD in comparison with patients receiving calcium-based phosphate binders [9,10]. Besides reduced calcium loading, additional effects of sevelamer include lipid-lowering properties, anti-inflammatory activities and increases in calcification inhibitor levels (fetuin-A) [11–13]. These pleiotropic effects may play a key role in the vascular protective activities of sevelamer, because the substance is not absorbed from the gut and therefore is unlikely to exert any direct protective activities at the endothelium or vascular wall.

We performed a prospective interventional study in haemodialysis patients with sevelamer hydrochloride as phosphate binder to clarify the following questions: Firstly, we sought to investigate if sevelamer treatment in both diabetic and non-diabetic ESRD patients induces comparable increases of fetuin-A serum levels as previously described in non-diabetic CKD patients [13]. In this respect, we were especially interested in evaluating the exact time course of fetuin-A serum changes influenced by sevelamer. Secondly, we aimed at identifying additional potential beneficial serum marker changes following sevelamer treatment that could affect the cardiovascular risk profile in haemodialysis patients [e.g. changes in serum levels of fibroblast growth factor 23 (FGF23) and/or uraemic toxins].

Table 1. Patient characteristics of the 57 study beginners and of the 41 (72%) patients completing the study protocol

	n = 57	*n* = 41
Anthropomorphic data		
Gender (male)	36 (63%)	26 (63%)
Caucasians	56 (98%)	40 (98%)
Age (years)	65 ± 13	63 ± 14 [range 16.5–85]
Cardiovascular risk		
BMI (kg/m²)	26 ± 4	26 ± 4
Smoking		
Non-smoking	30 (53%)	22 (54%)
Current/former smokers	27 (47%)	19 (46%)
Hypertension	51 (89%)	37 (90%)
Diabetes mellitus	20 (35%)	15 (37%)
Coronary artery disease	40 (70%)	28 (68%)
Dialysis		
Mean dialysis vintage (years)	3.1 ± 2.6	3.0 ± 2.6 [range 0.1–6.5 years]
Median weekly dialysis time (h)	13.5	13.5
AV-fistula	50 (88%)	37 (90%)
Dialysis calcium concentration		
1.5 mmol/L	14 (25%)	9 (22%)
1.25 mmol/L	43 (75%)	32 (78)
Dialysis calcium 1.25 → 1.5 in phase SEV		10 (24%)
Medication		
Statin use	37 (65%)	26 (63%)
Active vitamin D	55 (97%)	40 (98%)
Cholecalciferol (1000 IU/day)	45 (79%)	33 (80%)
ACE-inhibitors/AT-II blockers	42 (74%)	30 (73%)
Current insulin use	18 (32%)	14 (34%)
Causes of ESRD		
Diabetic nephropathy	19 (33%)	12 (29%)
Glomerulonephritis	11 (19%)	10 (24%)
Nephrosclerosis	7 (12%)	6 (15%)
ADPKD	8 (14%)	5 (12%)
Other reasons	12 (21%)	8 (20%)

Given are mean ± standard deviation or number of patients with percentage in brackets. BMI, body mass index; ADPKD, autosomal dominant polycystic kidney disease; AV-fistula, arteriovenous fistula; ACE-inhibitors, angiotensin-converting enzyme inhibitors; AT-II, angiotensin-2.

Materials and methods

Study design

We performed an open-label prospective interventional trial in haemodialysis patients. Primary end point was the influence of sevelamer hydrochloride treatment upon the dynamics of fetuin-A serum levels over time. Secondary end points were potential changes in other prototypical CKD–MBD serum markers, lipid levels and uraemic toxins induced by sevelamer.

The study was conducted in an outpatient dialysis centre in Erkelenz, Germany, in cooperation with the Department of Nephrology at the University Hospital of the Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Germany. The prospective part of the study consisted of three consecutive phases: two phases with 'conventional' phosphate binder regimens ('$Conv_1$' and '$Conv_2$', without sevelamer) in conjunction with a sevelamer ('SEV') treatment phase between the other two phases. Each phase lasted 8 weeks (Figure 1). During the $Conv_1$ and $Conv_2$ phases, ≥90% of all patients received calcium-containing phosphate binders (see below). At the beginning of phase SEV, sevelamer hydrochloride was added at gradually increasing dosages, either as an *ad hoc* or as a stepwise substitute for calcium-containing phosphate binders aiming at phosphate levels <1.78 mmol/L. Sevelamer treatment was immediately stopped at the end of the SEV phase.

After conclusion of the prospective study period, an additional observation period (phase 'Observ', 10 weeks) was retrospectively added in which a phosphate binder treatment was prescribed at the discretion of the treating physician.

The study was approved by the local ethics committee of the University Hospital of the RWTH Aachen (no. EK002/04).

Table 2. Reasons for dropout during the different study phases

Gastrointestinal side effects of sevelamer [(n = 7 (12%)]
Death [n = 3 (5%), one in each phase]
Lost to follow-up [(n = 3 (5%)]
Prolonged hospital admission [n = 2 (4%)]
Diagnosis of cancer in one patient (2%)

Patients

All patients of the outpatient dialysis centre were eligible for the study. Overall, 95 patients were screened. Exclusion criteria were previous sevelamer hydrochloride treatment, inability or rejection to give informed consent, anticipated hospital admission within the upcoming weeks and absence of hyperphosphataemia >1.78 mmol/L (5.5 mg/dL) before initiation of the study or lack of necessity for phosphate-binder treatment within 1 month prior to inclusion. Fifty-seven haemodialysis (HD) patients (60% of all screened patients) started the study, after written and informed consent was provided, and participated in the first 2 weeks of the study protocol.

The enrolled patients were all chronic HD patients (three 4.0–5.0-h dialysis sessions per patient and week). Fifty-five (96%) were adult Caucasians, one Caucasian patient was 16.5 years and one patient was Asian. Forty-one patients (72% of all included patients) finished the three prospective study phases. For details of these 57 and 41 study patients, respectively, please refer to Table 1. The reasons for dropout are listed in Table 2. The 41 study patients completing all three phases of the study were not significantly different from the 57 patients who terminated the study after 2 weeks regarding age, gender, prevalence of diabetes, medication and underlying renal disease (Table 1). In the Observ phase, all 41 patients finishing phase $Conv_2$ were included.

Hypertension was defined as either blood pressure >140/90 mmHg or usage of antihypertensive drugs. The diagnosis 'coronary artery disease' was made due to history of myocardial infarction or corresponding results obtained in coronary angiography or by cardiac stress testing.

Medication

Administration of sevelamer hydrochloride. Sevelamer dose titration was performed every 2 weeks in the SEV phase aiming at the achievement of current Kidney Disease Outcomes Quality Initiative (K/DOQI) target levels for serum phosphate (<1.78 mmol/L, <5.5 mg/dL for CKD stage 5D). Sevelamer dosages were furthermore adapted to patient tolerance. Sevelamer was not given to any patient in the $Conv_1$ and $Conv_2$ study phases. The initial dosage of Renagel was 2400 mg [800 mg three times a day (t.i.d.)] in all patients at the start of phase SEV. Of the 41 patients finishing the study, the initial 800 mg t.i.d. Renagel dosage was unchanged in 19 (46%) during the entire SEV phase. Renagel dosage was increased in 17 (41%) patients [3 → 6 tablets in 10 (24%); 3 → 6 → 9 tablets in seven (17%)]. Renagel dosage was reduced in four (10%) patients (3 → 2 tablets) and altered between three and nine tablets in one patient. Patients were excluded from the study if intolerability (all gastrointestinal discomfort) persisted after reduction of the Renagel dosage to 800 mg t.i.d. (n = 7, 12%).

The 57 patients (intention-to-treat analysis group) were subdivided into three tertile groups (n = 19 each) according to the daily dosage of sevelamer at the end of phase SEV. The median daily dosages of these three groups were: high sevelamer dosage group: median six tablets per day; intermediate dosage group: three tablets per day; and the low dosage group combined either patients with two tablets of sevelamer per day or patients not taking sevelamer any more at the end of phase SEV.

After the end of the prospective study period (end of $Conv_2$), 29 of the 41 patients were switched back to sevelamer again (phase Observ) at the discretion of the treating physician. In the other patients, a calcium-containing phosphate binder regimen was continued.

Administration of calcium-containing phosphate binders. During phase $Conv_1$, 40 (98%) patients received calcium acetate as phosphate binder. The median daily dosage was 3000 mg calcium acetate. Overall, during phase SEV, 21 patients (51%) received, at least for a short period of time, calcium acetate in addition to sevelamer; among them, 10 patients (24%) during the complete SEV study period (median dosage 2750 mg per day), 2 (5%) for 3–6 weeks and 9 patients (22%) for 1 or 2 weeks within phase SEV. After the end of the SEV phase, calcium acetate was re-initiated in most patients with the last dosage of phase $Conv_1$. During phase $Conv_2$, overall 37 (90%) of the patients received calcium acetate (median dosage 2850 mg per day).

Additional medication. Aluminium-containing phosphate binders were given to six patients (15%) during each of the three study phases.

Of the 41 patients, 40 patients (98%) received active vitamin D [(39 oral daily calcitriol (0.25–0.75 µg), one patient oral alphacalcidol]. Thirty-three patients (80%) received cholecalciferol (1000 units per day) during phases $Conv_1$ and SEV, and 38 (93%) patients during phase $Conv_2$. Statin dosage [n = 26 (63%)] was not changed during the study. None of the patients received cinacalcet (Table 1).

None of the patients was on regular anti-inflammatory medications [e.g. non-steroidal anti-inflammatory drugs (NSAIDS)].

Laboratory analysis

Fasting morning blood samples were drawn after the long dialysis interval before initiation of dialysis. Blood was drawn for routine blood chemistry regularly during each of the three prospective study periods at Week 1, 2, 3, 4, 6 and 8. At the end of the Observ phase (Week 10), an additional last blood sampling was performed. Serum fetuin-A was measured during $Conv_1$ at Week 4 and 8; during SEV at Week 3, 6 and 8; during $Conv_2$ at Week 4 and 8; and at the end of phase Observ, respectively. Measurements for intact parathyroid hormone (iPTH), calcidiol, bone-specific alkaline phosphatase (BAP) and FGF23 were done in all three prospective phases at Week 4 and 8 each as well as at the end of the Observ phase.

All laboratory analyses were performed by investigators or dialysis staff unaware of the particular study phase being examined. Measurements of pH, base excess and bicarbonate levels were performed by bedside ABL80 FLEX blood gas analyser.

Measurements of alkaline phosphatase (AP), BAP, albumin, C-reactive protein (CRP), total serum calcium, inorganic phosphate, total cholesterol, high-density lipoprotein cholesterol (HDL-Chol), low-density lipoprotein cholesterol (LDL-Chol), iPTH and 25-OH vitamin D (calcidiol) were done externally in automated and standardized procedures. Photometry method was used to measure AP, total calcium and phosphate. Albumin and CRP were measured by nephelometry. Total cholesterol, HDL-Chol and LDL-Chol were measured enzymatically [cholesterol oxidase–*p*-aminophenazone (CHOD–PAP) method]. Electrochemiluminescence immunoassays were used to determine calcidiol, BAP and iPTH (Roche Diagnostics, Mannheim, Germany). Serum calcium–phosphorus product was calculated by multiplication of the two serum concentrations. Vitamin D deficiency was defined as a calcidiol level <20 µg/L [14]. Total serum calcium con-

Table 3. Serum fetuin-A and FGF23 in different study phases

Phase	$Conv_1$		SEV				$Conv_2$		Observ
Week	4	8	3	4	6	8	4	8	10
Fetuin-A (mg/L)	655 ± 195	634 ± 219	665 ± 196		663 ± 199	773 ± 223	761 ± 238	837 ± 217	726 ± 215
FGF23 (RU/mL)	7255 ± 8446	6715 ± 7361		6992 ± 7454		6017 ± 6906	5923 ± 6856	5710 ± 6649	6312 ± 7567

$Conv_1$ and $Conv_2$, 'conventional' phosphate binder regimens without sevelamer treatment; SEV, sevelamer treatment phase; Observ, observational, retrospective open treatment phase.

Table 4. Routine laboratory parameters at different weeks of study phases

Phase	$Conv_1$						SEV		
Week	1	2	3	4	6	8	1	2	3
CRP (mg/L)	10.1 ± 16.1	10.4 ± 18.0	11.0 ± 19.5	12.5 ± 35.5	10.6 ± 13.6	9.5 ± 10.9	11.9 ± 15.8	10.9 ± 15.5	10.6 ± 17.0
Ca^{2+} (mmol/L)	2.38 ± 0.19	2.37 ± 0.17	2.45 ± 0.15	2.36 ± 0.15	2.41 ± 0.17	2.42 ± 0.13	2.42 ± 0.19	2.36 ± 0.15	2.33 ± 0.16
PO_4^- (mmol/L)	2.07 ± 0.49	1.97 ± 0.55	2.09 ± 0.60	2.01 ± 0.55	2.04 ± 0.56	2.03 ± 0.63	2.07 ± 0.58	2.11 ± 0.58	1.98 ± 0.52
$Ca^{2+} \times P0_4^-$ ($mmol^2/L^2$)	4.92 ± 1.17	4.66 ± 1.32	5.09 ± 1.43	4.76 ± 1.34	4.92 ± 1.32	4.93 ± 1.55	5.02 ± 1.50	4.99 ± 1.41	4.62 ± 1.30
AP (U/L)	93 ± 50	94 ± 56	90 ± 52	92 ± 59	92 ± 51	93 ± 61	92 ± 63	95 ± 74	93 ± 75
Total cholesterol (mg/dL)	176 ± 39	173 ± 37	170 ± 40	171 ± 41	180 ± 42	182 ± 39	170 ± 46	177 ± 51	168 ± 45
LDL-Chol (mg/dL)	92 ± 26	93 ± 28	89 ± 32	95 ± 32	101 ± 34	94 ± 28	79 ± 32	87 ± 36	83 ± 33
HDL-Chol (mg/dL)	46 ± 13	46 ± 15	44 ± 14	43 ± 13	47 ± 15	47 ± 15	49 ± 16	48 ± 15	47 ± 15
Albumin (g/dL)	3.9 ± 0.3	3.9 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.3
BE	−3.1 ± 3.0	−3.4 ± 2.7	−2.4 ± 3.0	−3.2 ± 2.8	−3.3 ± 3.1	−2.9 ± 3.3	−4.7 ± 3.1	−4.6 ± 3.0	−5.1 ± 3.0
HCO_3^- (mmol/L)	21.7 ± 2.9	21.1 ± 2.7	21.8 ± 3.2	21.5 ± 2.8	21.2 ± 3.1	21.6 ± 3.2	19.9 ± 2.8	19.8 ± 2.8	19.6 ± 2.7
pH	7.36 ± 0.05	7.37 ± 0.04	7.38 ± 0.05	7.37 ± 0.04	7.37 ± 0.04	7.36 ± 0.05	7.35 ± 0.05	7.36 ± 0.05	7.35 ± 0.05

Values are given as mean ± standard deviation. $Conv_1$ and $Conv_2$, 'conventional' phosphate binder regimens without sevelamer treatment; SEV, sevelamer treatment phase; Observ, observational, retrospective open treatment phase; CRP, C-reactive protein; Ca^{2+}, total calcium; PO_4^-, phosphate; $Ca^{2+} \times PO_4^{3-}$, calcium–phosphate product; AP, alkaline phosphatase; HDL-Chol, HDL cholesterol; LDL-Chol, LDL cholesterol; BE, base excess; HCO_3^-, bicarbonate.

centrations were corrected for serum albumin concentration according to the following formula: corrected calcium (milligram per decilitre) = total calcium (milligram per decilitre) + 0.0704 × [34 − serum albumin (gram per litre)] [15].

For additional serum laboratory analysis (fetuin-A, FGF23 and uraemic toxins), serum was centrifuged and harvested according to standard procedures at +4°C, and frozen immediately afterwards at −80°C. Serum FGF23 was measured in duplicate with the C-terminal FGF23 (cFGF23) ELISA, which detects both intact FGF23 (iFGF23) and its C-terminal fragments (Immutopics, CA, USA). Serum analysis for fetuin-A was performed by nephelometry with a polyclonal anti-rabbit antibody as previously described [16].

Uric acid, indoxyl sulphate, hippuric acid, indole acetic acid and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF) were analysed with reversed phase high-performance liquid chromatography (RP-HPLC) as previously described. Briefly, after heat deproteinization, samples were filtered through a Centrifree® (Millipore, Brussels, Belgium), and the ultrafiltrate was injected on the RP-HPLC (Alliance 2695, Waters, Zellik, Belgium). Indoxyl sulphate and indole acetic acid concentrations were determined by fluorescence detection (excitation 280 nm, emission 340 nm). Uric acid, hippuric acid and CMPF were analysed by UV detection at 254 nm. Calibration curves of the five compounds were used to calculate the concentrations in each sample. Intra- and inter-assay coefficients of variation were <1.8% and <3.7%, respectively [17].

P-Cresol was measured with gas chromatography–mass spectrometry (GC–MS) as previously described [18]. Briefly, after heat–acid denaturation of the binding proteins, P-cresol was extracted in ethyl acetate and injected on the GC–MS (Trace GC–MS, Thermo Finnigan, San José, USA). As an internal standard, 2,6-dimethylphenol was used. Intra- and inter-assay coefficients of variation were 3.3% and 5.3%, respectively. We recently demonstrated a good agreement between this technique and HPLC methods for direct quantification of P-cresyl sulphate [19].

Statistical analysis

Results are expressed as mean ± standard deviation for quantitative data and as absolute and relative frequencies for qualitative data. Selected quantitative data are illustrated graphically by means of box plots. The statistical study analyses were conducted on the intention-to-treat population ($n = 57$).

The influence of sevelamer on CRP, serum calcium, serum phosphate, calcium–phosphate product, albumin, total cholesterol, LDL-Chol, HDL-Chol, base excess, bicarbonate, pH, BAP, iPTH, calcidiol and FGF23 was investigated using a repeated measures ANOVA model with factor phase ($Conv_1$, SEV, $Conv_2$) and weeks within phase. Contrasts were estimated to compare the $Conv_1$ phase with the SEV phase and the SEV phase with the $Conv_2$ phase. Additionally, model-based estimated marginal means and standard deviations are provided. All analyses were conducted in an explorative nature using a significance level of alpha = 0.05.

The influence of sevelamer on fetuin-A with consideration of the covariates CRP, calcium, phosphate, total cholesterol and albumin; the repeated factor phase ($Conv_1$, SEV, $Conv_2$); and weeks within phase (Week 4 and 8 in the $Conv_1$ and $Conv_2$ phase, respectively; Week 3, 6 and 8 in the SEV phase) was analysed using a repeated measures analysis of covariance (ANCOVA) model. Contrasts are estimated to compare the phases. To quantify the proportions of explained variance of the covariates and factors, the type III sum of squares was compared with the total sum of squares of the covariates and factors, plus the sum of squares of error. The results are presented in percent.

The influence of sevelamer on P-cresol, uric acid, indoxyl sulphate, hippuric acid, indole acetic acid and CMPF was investigated by comparison between the $Conv_1$ and SEV phases as well as SEV and $Conv_2$ by means of a paired *t*-test. Paired *t*-tests were also used to compare sevelamer dosage groups, diabetics *versus* non-diabetics, and patients taking or not taking aluminium-based phosphate binders regarding fetuin-A serum levels at the end of phase SEV.

Statistical analyses were performed using the software SAS (SAS Institute Inc., Cary, NC, USA, version 9.1.3.); graphical representations were created using the software R (R: a language and environment for statistical computing; R Foundation for Statistical Computing, version 2.6.1.).

Results

Table 3 (serum fetuin-A and FGF23), Table 4 (routine laboratory parameters) and Table 5 (uraemic toxins) provide mean ± SD values from laboratory analyses of blood biochemistry parameters over time.

Table 5. Uraemic toxins at the end of each study phase

	Phase		
	$Conv_1$	SEV	$Conv_2$
Uric acid (mg/dL)	5.99 ± 1.28	5.69 ± 0.93	6.06 ± 1.03
Indoxyl sulphate (mg/dL)	1.70 ± 1.10	1.80 ± 1.05	1.89 ± 1.23
Hippuric acid (mg/dL)	7.24 ± 6.28	7.05 ± 6.07	8.26 ± 6.88
Indole acetic acid (mg/dL)	0.21 ± 0.11	0.20 ± 0.10	0.22 ± 0.11
CMPF (mg/dL)	0.40 ± 0.29	0.42 ± 0.34	0.54 ± 0.55
p-Cresol (μmol/L)	187.1 ± 129.1	247.0 ± 141.5	187.9 ± 108.0

CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid.

Evolution of fetuin-A over time

Figure 2 illustrates the evolution of serum fetuin-A over time during the study phases: There was a delayed, but significant and sustained, increase of serum fetuin-A beginning at the end of the SEV phase and lasting until the end of the $Conv_2$ phase. The mean increase of serum fetuin-A between the $Conv_1$ (Week 4 and 8) and Week 8 off the SEV phase was 21 ± 23% (range −38% to +86%).

Comparing fetuin-A serum levels between the three dosage groups of sevelamer at the end of phase SEV revealed significantly lower fetuin-A serum levels in the low sevelamer dosage group (633 ± 103 mg/L) compared with other dosage groups ($P < 0.05$ each). There was no difference regarding serum fetuin-A between the intermediate and high dosage group (770 ± 223 and 808 ± 239 mg/L, respectively).

After the end of phase $Conv_2$ (end of the prospective study period), sevelamer treatment was re-initiated in 29 (71%) of the 41 patients and continued at least for some period of time during the next 10 weeks (= phase Observ). At the end of Observ phase, fetuin-A levels in the 29 patients with sevelamer were significantly higher than in the remaining 12 patients without sevelamer in the observational phase (altogether 18 weeks without sevelamer) (867 ± 227 *versus* 764 ± 181 mg/L, $P < 0.05$).

Fetuin-A levels during the three study periods as well as the evolution of serum fetuin-A over time were not significantly different between diabetic ($n = 20$) and non-diabetic patients ($n = 37$) as well as those not taking aluminium compared with those taking aluminium-based phosphate binders (data not shown).

Predictors of fetuin-A increase

Overall, 31 patients (76%) showed an increase of fetuin-A serum levels >10% between the end of the $Conv_1$ phase and the end of the SEV phase. Predictors of an increase in fetuin-A were analysed using an ANCOVA model (the predictive power is assessed by percent) including treatment phase, week of treatment phase, CRP, serum calcium, serum phosphorus, total cholesterol and albumin. Treatment phase (16.3%, $P < 0.0001$), week of treatment phase (15.1%, $P < 0.0001$), total cholesterol (3.1%, $P = 0.0007$) and albumin (1.9%, $P = 0.008$) all had a significant positive influence upon serum fetuin-A levels. CRP, serum calcium and serum phosphorus failed to exert a significant effect upon fetuin-A.

Evolution of routine and CKD–MBD laboratory parameters over time

Table 6 indicates which laboratory parameters exhibited statistically significant differences between the various phases in repeated measures ANOVA. Estimated marginal means and standard deviations are given. Compared to phase $Conv_1$, sevelamer treatment in phase SEV was associated with significant drops in serum calcium, calcium–phosphorus product, total cholesterol, LDL-Chol, base excess, pH and bicarbonate levels. In contrast, a significant increase during the phase SEV was detected for CRP, HDL-cholesterol, serum albumin and iPTH. Several patients revealed very high CRP levels (>20 mg/L) at the end of each study phase (Week 8): at phase $Conv_1$, four patients (9%); at phase SEV, 10 patients (24%); and at phase $Conv_2$, six patients (17%) ($P < 0.05$).

A comparison of lipid levels at phase $Conv_1$ (Week 8) with phase SEV (Week 8) showed a mean decrease of total cholesterol and LDL-Chol of −14 ± 16% and −16 ± 27%, respectively. HDL-Chol increased at the same interval by +6 ± 17%.

There were also significant changes detectable between phase SEV and $Conv_2$: Cessation of sevelamer was associated with a significant increase of calcium, calcium–phosphorus product, AP, BAP, total cholesterol, LDL-Chol, base excess, pH, bicarbonate and iPTH. On the other hand, HDL-Chol and albumin were significantly lower in phase $Conv_2$ compared to phase SEV.

Calcidiol did not change significantly over time. The prevalence figures of patients with vitamin D deficiency (defined as calcidiol <20 µg/L) were 40%, 43% and 43%, respectively, at Week 8 of each prospective study phase.

Regarding FGF23, there was a non-significant evolution over time detectable (Table 3).

Evolution of uraemic toxin serum levels

Paired *t*-test comparisons between the phases $Conv_1$ to SEV and SEV to $Conv_2$, respectively, revealed no significant changes for serum indoxyl sulphate, hippuric acid and indole acetic acid over time (Table 5). In contrast, there was

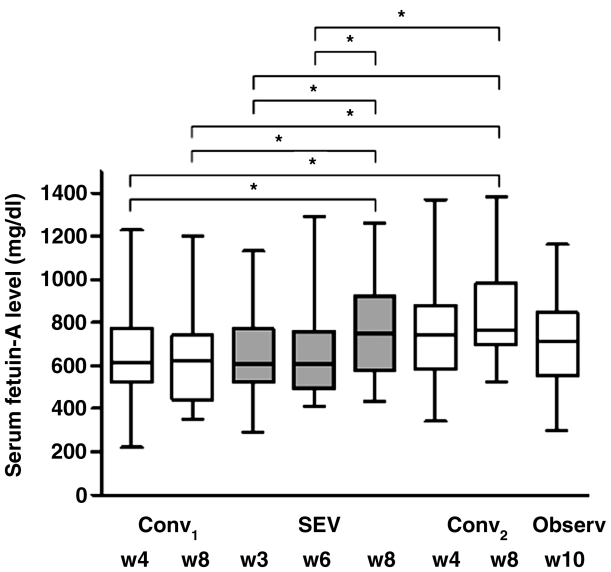

Fig. 2. Box plots indicating serum fetuin-A levels over time with sevelamer treatment. ($Conv_1$and $Conv_2$, 'conventional' phosphate binder regimens without sevelamer treatment. SEV, sevelamer treatment phase. Observ, observational, retrospective open treatment phase). Sevelamer treatment induced a late but sustained increase of serum fetuin-A levels from phase SEV Week 8 to phase $Conv_2$ Week 8. Significant differences between particular study weeks (pairwise analysis, $P < 0.05$) are indicated by asterisk (*). Box plots are depicted with median, standard deviation, 25th and 75th percentiles. For mean ± SD serum fetuin-A levels, please refer to Table 3.

Table 6. Model-based estimated marginal means, corresponding standard deviations and P-values for the comparison of phase $Conv_1$ *versus* Sev and phase Sev *versus* $Conv_2$, respectively

Variables	Unit	$Conv_1$	SEV	$Conv_2$	Observ	$Conv_1$ *vs* SEV	SEV *vs* $Conv_2$
CRP	mg/dL	12.0 ± 0.9	15.6 ± 1.0	14.4 ± 1.1	11.8 ± 2.1	0.0044	>0.05
Ca^{2+}	mmol/L	2.39 ± 0.01	2.34 ± 0.01	2.41 ± 0.01	2.40 ± 0.01	<0.0001	<0.0001
PO_4^{3-}	mmol/L	2.02 ± 0.02	1.99 ± 0.02	2.02 ± 0.02	2.15 ± 0.05	>0.05	>0.05
$Ca^{2+} \times PO_4^{3-}$	$mmol^2/L^2$	4.84 ± 0.04	4.68 ± 0.05	4.89 ± 0.06	5.19 ± 0.12	0.0252	0.0057
AP	U/L	95 ± 2	99 ± 2	106 ± 2	120 ± 4	>0.05	0.0019
Total cholesterol	mg/dL	174 ± 1.5	161 ± 1.7	171 ± 1.9	166 ± 3.7	<0.0001	<0.0001
LDL-Chol	mg/dL	93 ± 1.2	77 ± 1.4	94 ± 1.5	91 ± 2.9	<0.0001	<0.0001
HDL-Chol	mg/dL	45 ± 3.5	47 ± 4	45 ± 4.5	45 ± 0.9	0.0002	0.0033
BE		−3.1 ± 0.1	−4.7 ± 0.2	−3.1 ± 0.2	−3.2 ± 0.3	<0.0001	0.0001
HCO_3^-	mmol/L	21.5 ± 0.1	19.8 ± 0.1	21.3 ± 0.2	20.7 ± 0.3	<0.0001	<0.0001
pH		7.37 ± 0.00	7.35 ± 0.00	7.37 ± 0.002	7.36 ± 0.004	<0.0001	<0.0001
Albumin	g/L	4.1 ± 0.01	4.2 ± 0.02	4.04 ± 0.91	3.91 ± 0.03	<0.0001	<0.0001
iPTH	pg/mL	244 ± 7	281 ± 9	309 ± 9	332 ± 13	0.0012	0.0157
BAP	U/L	15.2 ± 1.0	17.6 ± 1.2	21.2 ± 1.3	26.5 ± 3.1	>0.05	0.0293
Calcidiol	µg/L	22.6 ± 0.4	22.8 ± 0.6	22.8 ± 0.6	25.5 ± 0.7	>0.05	>0.05

$Conv_1$ and $Conv_2$, 'conventional' phosphate binder regimens without sevelamer treatment; SEV, sevelamer treatment phase; Observ, observational, retrospective open treatment phase; CRP, C-reactive protein; Ca^{2+}, total calcium; PO_4^-, phosphate; $Ca^{2+} \times PO_4^{3-}$, calcium–phosphate product; AP, alkaline phosphatase; HDL-Chol, HDL cholesterol; LDL-Chol, LDL cholesterol; BE, base excess; HCO_3^-, bicarbonate; BAP, bone alkaline phosphatase.

a significant increase from phase $Conv_1$ to SEV (P = 0.0085) for P-cresol and a corresponding drop from phase SEV to $Conv_2$ (P = 0.0003). There was a trend towards lower uric acid levels during phase SEV compared to $Conv_1$, but only the increase from phase SEV to $Conv_2$ reached statistical significance (P = 0.0105). Similarly, CMPF levels were significantly higher in phase $Conv_2$ than in phase SEV (P = 0.0111).

Discussion

The major finding of the present prospective study is that the administration of the non-calcium-containing phosphate binder sevelamer over 8 weeks was associated with a significant increase of serum fetuin-A levels in haemodialysis patients. Between 6 and 8 weeks after initiation of sevelamer, fetuin-A serum levels started to rise. More interestingly, fetuin-A levels remained relatively high for an additional 8 weeks despite cessation of sevelamer. According to the ANCOVA model applied, treatment phase and week exerted the strongest detectable effect upon fetuin-A serum levels pointing towards a direct effect of sevelamer administration on fetuin-A serum levels. The present study is therefore in line with a previous report by Caglar and co-workers [13] but amends and surpasses this study in several important respects. The study by Caglar *et al*. was performed in CKD stage 4 patients not yet on dialysis and excluded patients with the highest cardiovascular risk (such as those with prevalent coronary heart disease and diabetes) [13]. We have now reproduced these findings in an 'unselected' haemodialysis patient cohort. Moreover, only two serum measurements were performed by Cagler *et al*., while the present study could elaborate the effect of treatment time upon fetuin-A increase. Moreover, we stratified the patients according to different sevelamer dosages, and our data suppose a dose dependency of sevelamer action upon serum fetuin-A levels.

Our data indicate that the majority of patients treated with sevelamer increased their fetuin-A serum levels by at least 10% within 8 weeks. This rise may be beneficial, since an increase in serum fetuin-A of 0.1 g/L was associated with a hazard ratio of 0.87 [95% confidence interval (CI) 0.80–0.93; P = 0.001] for all-cause mortality and a hazard ratio of 0.90 (95% CI 0.81–1.00; P = 0.09) for cardiovascular (CV) mortality in a previous dialysis cohort study [16]. We consider fetuin-A as an important study surrogate end point in treatment studies in ESRD patients, since it is a systemic calcification inhibitor [20,21] with well-known positive associations with survival in ESRD patients [16,22]. In parallel to the fetuin-A increase in the study by Caglar *et al.* [13], the administration of sevelamer was associated with a significant increase of flow-mediated vasodilatation (FMD) compared to placebo. FMD improvement in turn may be the result of less atherosclerotic vascular disease following sevelamer administration [13].

The second important issue addressed in our study is the influence of sevelamer upon additional serological survival factors in ESRD patients (e.g. inflammation, lipid levels, uraemic toxins, FGF23). Since sevelamer is not absorbed from the gut, the effects upon fetuin-A serum levels are most likely indirect effects, e.g. upon hepatic fetuin-A synthesis. We know that fetuin-A is a negative acute-phase protein. However, in contrast with previous studies [13,23,24], sevelamer did not induce a decrease of CRP levels in the present study. The unexpected increase of mean CRP in phase SEV was mainly caused by a high percentage of patients, in whom CRP levels at Week 8 of sevelamer treatment exceeded 20 mg/dL, potentially pointing towards acute intercurrent uncontrolled infections rather than subclinical inflammation. Since no other indicators of systemic inflammation [e.g. interleukin (IL)-6] were determined in our study, we presently can only speculate that chronic modification of the systemic (micro-) inflammatory state in dialysis patients by sevelamer contributes to serum fetuin-A changes.

We could, however, confirm previous findings [9,10,13] about lipid profile changes: We found a decrease of total and LDL-Chol accompanied by an increase of HDL-Chol. This finding is particularly remarkable since about two-thirds of our patients were already on statins. These figures regarding LDL-Chol and total cholesterol are comparable with previous studies where similar figures were detected [9,10,13]. A significant mean decrease suggests overall adequate adherence to the study medication. It is interesting to note that, in contrast with fetuin-A, lipid levels returned to pre-sevelamer levels within 1 week after cessation of sevelamer. We therefore speculate that the cause for the increase in fetuin-A is not just simple binding of intraluminal negative regulators of fetuin-A synthesis by sevelamer. Rather, this delayed time course (in both directions) points towards more complex interactions between sevelamer and fetuin-A which remain to be clarified.

We could not verify a significant effect of sevelamer upon serum FGF23 [25], a phosphaturic hormone regarded as a central regulating factor in phosphate homeostasis [26]. Our data confirm that FGF23 levels are massively elevated in patients on haemodialysis [27]. Gutierrez *et al*. have recently shown that high FGF23 levels in dialysis patients are associated with reduced survival [26]. The modest, non-significant trend for lowering FGF23 levels with sevelamer treatment in our study is in contrast with a previous report [25]. However, in the study of Koiwa *et al.* [25], there was a more pronounced drop in serum phosphorus levels detectable after 4 weeks of sevelamer treatment (from 5.9 ± 1.2 to 5.0 ± 1.2 mg/dL). Thus, it needs to be determined whether the reduction in FGF23 was due to sevelamer *per se* or due to a more vigorous phosphate control. Our data support the hypothesis that, with stable phosphate levels, the particular type of phosphate binder plays a minor role regarding FGF23 levels in ESRD.

Uraemic toxins have gained substantial interest in recent years due to their potential hazardous role in excessive mortality among ESRD patients. Uraemic toxins compromise a heterogeneous group of substances (middle molecules, water-soluble molecules and protein-bound molecules) with potential harmful effects when accumulating during chronic kidney disease [28]. Based upon previous *in vitro* data [29] showing that sevelamer could bind *p*-cresol, we speculated that the administration of sevelamer was associated with a drop of gut-derived uraemic toxins in humans on dialysis [30]. Previous animal experiments, however, have shown that none of the investigated uraemic toxins (uric acid, indoxyl sulphate, indole acetic acid, hippuric acid and CMPF) was influenced by sevelamer treatment in uraemic mice [31]. Moreover, the present study revealed an increase of total P-cresol after 8 weeks of sevelamer treatment that resolved to baseline levels 8 weeks after withdrawal. The pathophysiology behind this increase is not clear. We speculate that sevelamer-induced changes in the colonic microenvironment (microbial flora, transit time) may play a role. In any case, this finding needs confirmation and additional investigation, since an increase of P-cresol must be considered as an unwanted side effect in the light of the association of free P-cresol with reduced survival in ESRD patients [32]. However, the effects of sevelamer upon uraemic toxins are even more complex looking at the increase of two uraemic toxins after sevelamer cessation (uric acid and CMPF).

Considering the albumin increase with sevelamer treatment, a limitation of the present study is that we did not assess protein-unbound (free) fractions of uraemic toxins.

Overall, we could show that sevelamer is associated with various effects on the complex interplay of (cardiovascular) risk factors in dialysis patients amongst which the increase in fetuin-A is likely beneficial in terms of vascular calcification. A direct causal relation between sevelamer administration and the changes in serum markers remains to be determined. We elaborated partly inconsistent and contradictory changes in humoral risk factors in our study. Therefore, the net effect upon uraemic vascular disease in uraemic patients also remains to be determined.

In summary, our study adds novel data to the research field of pleiotropic sevelamer actions in dialysis patients beyond phosphate binding. One of these non-classical actions of sevelamer is the increase of serum fetuin-A, now also confirmed in patients on dialysis. According to our data, the rise in fetuin-A is long-lasting. Two mechanisms potentially explaining the fetuin-A increase dropped out: Neither reduced systemic inflammation nor reduced circulating uraemic toxins were elaborated. Our data regarding changes of uraemic toxins after sevelamer treatment need further investigation.

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Conflict of interest statement. V.M.B. has received research grants and/or speaking honoraria from ABBOTT, Genzyme, Amgen, Roche, Shire. M.K. has received research grants and/or speaking honoraria from ABBOTT, Genzyme, Amgen, Fresenius Medical Care, Shire. J.F. has received research grants and/or speaking honoraria from ABBOTT, Genzyme, Amgen, Roche, Shire. W.J.D. has received grants and/or speaker honoraria from Genzyme and Amgen. P.E. has received grants and/or speaking honoraria from Genzyme and Amgen. B.M. is the recipient of a doctoral fellowship (FWO-Vlaanderen, grant no. 1.1.382.06N). R.V. received research grants from Genzyme, Roche and Amgen. The other authors have not declared a conflict of interest. These data were presented in extracts at the congress of the American Society of Nephrology 2005 and at the congress of the ERA-EDTA 2006.

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Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients

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Abstract

Background. Vascular calcification has detrimental consequences on chronic kidney disease (CKD) patients, yet its pathogenesis is not fully understood. Fibroblast growth factor-23 (FGF-23) is involved in the regulation of mineral metabolism which may in turn affect vascular calcifica-