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Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry

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ORIGINAL ARTICLE

ABSTRACT

Background. Calcific uraemic arteriolopathy (CUA, calciphylaxis) is a rare disease predominantly in dialysis patients and associated with high mortality. Painful skin ulcerations and calcification of cutaneous arterioles characterize calciphylaxis.

Methods. We established an observational, Internet-based registry allowing online notification for all German CUA cases. The registry recorded data about patient characteristics, biochemistry and therapies. Blood samples were stored in a central biobank.

Results. Between 2006 and 2015, 253 CUA patients were recorded: median age 70 [interquartile range (IQR) 61–76] years, 60% females and 86% ($n = 207$) dialysis patients, translating into an estimated annual incidence rate of 0.04% in German dialysis patients. Fifty-two per cent received vitamin K antagonists (VKAs) prior to CUA. Skin lesions were localized in 71% on the legs or gluteal region. In dialysis CUA patients median total serum calcium was 2.20 (IQR 2.06–2.37) mmol/L, phosphorus 1.67 (IQR 1.35–2.03) mmol/L, intact parathyroid hormone 147 (IQR 72–276) pg/mL and fetuin-A 0.21 (IQR 0.16–0.26) g/L (normal range 0.35–0.95). Median sclerostin, osteoprotegerin, TRAP5b, bone-specific alkaline phosphatase and c-terminal FGF23 levels were all elevated. The most frequently recorded therapeutic procedures in dialysis CUA patients were as follows: wound debridement (29% of cases), stopping VKA (25%), lowering calcium supply (24%), sodium thiosulphate (22%), application of vitamin K (18%), increase of dialysis duration/frequency (17%) and stoping active vitamin D (16%).

Conclusions. Approximately 50% of CUA patients used VKA. Our data suggest that uncontrolled hyperparathyroidism is not the key determinant of calciphylaxis. Therapeutic strategies were heterogeneous. The experience of the German registry will help substantially to initiate a large-scale multinational CUA registry.

Keywords: anticoagulation, calcification, calciphylaxis, cardiovascular, ESRD

INTRODUCTION

Calcific uraemic arteriolopathy (CUA), also known as calciphylaxis, is a rare disease (ORPHA292147) predominantly affecting patients with end-stage renal disease (ESRD) on dialysis [1, 2]. The exact incidence and prevalence are unknown. Although rare, two clinical and aetiological aspects qualify CUA as an exceptional research target in chronic kidney disease–mineral and bone disorder (CKD-MBD) [3]. First, the unmet clinical need of how to prevent and how to treat calciphylaxis is urgent since the condition is clinically devastating: debilitating pain, potentially large areas of skin ulcerations and markedly reduced quality of life dominate the clinical picture. Moreover, CUA is associated with a massive reduction in long-term survival [1, 2, 4]. Second, CUA might serve as a potential 'high-speed' template for general cardiovascular calcification processes in CKD involving larger arteries or heart valves. Therefore, CUA research might add valuable insights into the causative pathways of accelerated uraemic calcifying arteriosclerosis, since circumferential calcification in the medial layer of (in this case small cutaneous) arteries is also the histological hallmark of CUA [5].

Unfortunately, CUA treatment options are not evidence-based since prospective randomized controlled trials are barely possible in such a devastating, rare disease [1, 2]. Overcoming these limitations is not easy since centralizing clinical as well as research expertise in the field of CUA is difficult: the severe clinical condition and the high degree of comorbidities in the often elderly CUA patients complicate establishing tertiary referral centres (centres of expertise), requiring frequent long-distance travel. As an alternative, we established an Internet-based registry in 2006 (http://www.calciphylaxie.de). Within this online

registry, we invited treating physicians to register all cases of established or suspected CUA. The registry consists of a comprehensive database of various parameters, including patient characteristics, laboratory data, clinical background and presentation as well as therapeutic strategies. The aim of the registry was to collect data on potential risk factors and good clinical practice as well as the creation of a biobank allowing research biomarker analyses in the core facility [University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen].

The aim of the present analyses is to provide a detailed and comprehensive summary of the first 9 years of data collection within the German calciphylaxis registry.

METHODS

The German calciphylaxis registry is accessible at http://www.calciphylaxie.de. It was established in December 2006 (first patient in). The nature of the registry is non-interventional and purely observational. For study participation, written informed consent of the patient is required. The storage of patient data is anonymous. The registry activity was approved by the University Hospital RWTH Aachen ethical committee (vote no. 10-024).

Most of the query items allow simple selection via drop-down menus. In contrast, the field with the question about applied treatment strategies allows a free text answer, since a drop-down list might incompletely reflect the real-world situation. Moreover, such a pre-selection may have created the impression of plausibility or a preference for a certain intervention. Incoming data underwent centralized plausibility checking and quality control. Numerical outliers were double-checked with the peripheral centre, and in case of doubts, ambiguous data, implausible data or incomplete data, such issues were discussed with the peripheral centre and the treating physician locally in charge. In case such a request could not clarify implausible data, such data or the entire data set was deleted from the database. Whenever possible, photo documentation and transfer of the images to the registry centre in Aachen was requested to allow second-opinion evaluation.

The registry team at the Aachen University Hospital requested full blood, plasma and serum sampling of the patients according to standard procedures and asked for immediate freezing at the peripheral study site. Long-term storage was done at −80°C immediately after arrival at the University Hospital Aachen.

The registry activities were supported by an unrestricted grant from Amgen (2006 until present) and Sanofi (2012 until present). The registry is under the patronage of the German National Society of Nephrology (DGfN) and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) CKD-MBD Scientific Working Group.

Marketing activities were undertaken by the study team to increase awareness of the registry and to increase motivation for participation. At the start of the registry, Amgen field staff distributed flyers about the aims and scope of the registry to virtually all German nephrologists. Since then, the study team has regularly presented data summaries at annual national as well as international nephrology congresses.

Laboratory measurements

The registry recorded online levels of serum albumin, total calcium, alkaline phosphatase, haemoglobin, serum creatinine, inorganic phosphate, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D [25(OH)D, calcidiol] and total protein. For those parameters, standard procedures were applied according to the laboratory routine in the peripheral centres. Total serum calcium was corrected for albumin content by the equation:

$$\text{Corrected total calcium(mg/dL)} = \text{Total calcium(mg/dL)} + 0.8 \times [4 - \text{Serum albumin(g/dL)}].$$

In order to increase comparability between biochemistry results, centralized laboratory analysis was performed using Aachen biobank samples for the following CKD-MBD parameters: iPTH, C-reactive protein (CRP) and calcidiol [25(OH)]. Additionally, non-routine (research) CKD-MBD parameters were measured from the same biobank samples: fetuin-A, osteoprotegerin (OPG), sclerostin, tartrate-resistant alkaline phosphatase 5b (TRAP5b), bone-specific alkaline phosphatase (BSAP) and c-terminal fibroblast growth factor 23 (c-FGF23).

Commercially available enzyme-linked immunosorbent assays (ELISAs) were used to determine levels of fetuin-A, OPG and BAP (TECOmedical AG, Sissach, Switzerland). PTH was measured as iPTH by an assay provided by Biomerica (Irvine, CA, USA). Serum sclerostin was assessed by the TECO Sclerostin EIA Kit, which is a 96-well immunocapture ELISA product. TRAP5b was assessed via ELISA (Quidel, San Diego, CA, USA). c-FGF23 was measured in plasma by an assay from Immutopics (San Clemente, CA, USA). CRP was measured by ELISA (Biomerica).

Statistical analysis

Descriptive statistics were performed for the entire cohort as well as for subgroups of patients: separate analyses were done for dialysis patients, for peritoneal dialysis (PD) patients and for haemodialysis (HD)/haemodiafiltration (HDF) patients stratified for gender.

Results are expressed as number (%) for categorical variables, as mean ± SD for normally distributed continuous variables and as median [interquartile range (IQR)] for continuous variables with skewed distribution. For differences between groups, Student's *t*-test and the Mann–Whitney *U* test were performed for normally and non-normally distributed variables, respectively.

The statistical analysis was performed with SPSS 21 (IBM, Armonk, NY, USA).

RESULTS

The entire registry cohort: clinical data

From December 2006 to March 2015 (100 months), 265 patients were recorded. Twelve patients were deleted from the database after negative plausibility control and feedback discussion with the referring physician revealing low probability of CUA or after an alternative diagnosis was established. Overall,

253 patients were finally classified as calciphylaxis. The median age of the CUA patients was 70 years (IQR 61–76; minimum 21 and maximum 88). The male/female ratio was 40–60%. Most (n = 252) patients were Caucasian, and one patient was Asian. The median annual notification rate in the complete years 2007–2014 was 30 cases per year [ranging from 24 (2012) to 35 (2009) per year]. In 210 cases (83%), a date for the occurrence of first symptoms was recorded, hence allowing calculation of days between onset of the disease and online notification to the registry. The median time interval was 28 days (IQR 13–60).

Overall, 19 centres recorded more than one patient into the registry. The maximum of registered patients per centre was five patients (period from 2008 to 2015).

A skin biopsy was performed in 45% of patients, whereas in 55% the diagnosis was established without histological examination of the specimen.

In 88% (n = 222) of cases, the treating physician stated the predominant anatomic site of cutaneous CUA manifestation. The dominant lesions were located on the legs in 179 (71%) cases. In the vast majority of these cases, the thighs were affected either alone or in combination with the lower legs. The trunk was the predominant location in 45 (18%) cases, with the abdominal wall and the hips being the most frequent locations. In 12% of cases, a dominant anatomic location was not recorded. The character of the skin lesions was described as ulcerative in 63% versus non-ulcerative in 37% [rate of return n = 199 (79%)].

In 66 (26%) cases, the referring physician speculated about the presence of an acute triggering event prior to calciphylaxis development. Physical trauma (e.g. fall, subcutaneous injections, injury, surgical wound, compression trauma and haematoma) was the single most recorded triggering event (n = 27).

The referring physician was asked to classify the presence/absence and degree of kidney disease prior to CUA development into categories (Table 1). The majority of patients were ESRD patients.

Cardiovascular comorbidities at baseline are listed in Supplementary data, Table S1, among which arterial hypertension, diabetes mellitus and coronary heart disease were most frequently recorded.

In 250 patients, data on previous or ongoing vitamin K antagonist (VKA) use at the time of CUA development were available. The overall proportion of patients on VKA was 130 (52%) versus 120 (48%) without previous VKA use (Supplementary data, Table S2). The patients were stratified according to the VKA prescription 'yes' versus 'no'. Those two groups did not reveal statistically significant differences in terms of anthropomorphic data, clinical data or biochemistry (data not shown).

Table 1. Stage of kidney disease at the time of CUA development

Status of kidney disease prior to CUA development (n = 253)	n (%)
Normal or mildly impaired renal function	7 (3)
CKD, non-dialysis	18 (7)
Functioning kidney graft	10 (4)
PD	25 (10)
Dialysis (HD + HDF)	193 (76)
ESRD (dialysis + transplantation)	228 (90)

The subgroup of CUA dialysis patients

For further analysis, especially regarding laboratory values and background medication usage, we focussed on dialysis patients. The group of dialysis patients was defined as HD/HDF patients (n = 193) and PD patients (n = 25) [n = 218 (86% of the entire cohort]. The HD/HDF patient group was split into males and females for further analysis. Table 2 provides an overview of the clinical data for the group of dialysis patients. We also recorded prescription of prototypic nephrology medication. Table 3 gives an overview of medication prescriptions in the dialysis subgroup of the entire cohort.

The laboratory values of the dialysis CUA patients are depicted according to the place of measurement, either in a peripheral treatment centre (Table 4) or results were obtained from the central biobank after measurement in the core lab (Table 5). In 180 dialysis patients, both albumin and total calcium levels were available, allowing for calculation of albumin-corrected calcium.

Biochemistry data regarding calcium, phosphate and iPTH were stratified according to target ranges defined in the Kidney Disease Outcomes Quality Initiative (KDOQI) or Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Supplementary data, Table S3 and Table 6).

We analysed the recorded data from the free text field regarding therapeutic strategies in the questionnaire. Data were recorded in 165 cases (76%; in the other 24% of patients no data were recorded) (Table 7).

Table 2. Clinical parameters in the dialysis patients with calciphylaxis (n = 218)

Parameter	All HD/HDF patients, n = 193	PD, n = 25	Male HD/HDF, n = 72	Female HD/HDF, n = 121
Age (years)	70 (62–76)	64 (55–74)	69 (61–76)	71 (64–77)
Caucasians	All	All		
Females	121 (63%)	12 (48%)		
Time between onset to diagnosis (days)	24 (11–50)	24 (12–42)	30 (14–60)	21 (10–46)
Time interval since start of dialysis to CUA diagnosis (months)	30 (7–56)	46 (29–69)	25 (4–50)	34 (7–64)
Kt/V[a]	1.4 (1.3–1.7)	n.a.	1.3 (1.2–1.5)	1.5 (1.3–1.7)
Previous fracture	23 (12%)	2 (8%)	5 (7%)	17 (14%)
Previous parathyroidectomy	19 (10%)	4 (16%)	6 (8%)	13 (11%)

Values are given as median (IQR) or n (%).
[a]Kt/V: multiple of the volume of plasma cleared of urea divided by the distribution volume of urea.

Table 3. Medication use in the group of dialysis patients at the time of CUA development[a]

Medication[a]	All HD/HDF, patients, $n = 193$		PD, $n = 25$		Male HD/HDF, $n = 72$		Female HD/HDF, $n = 121$	
	Yes	No	Yes	No	Yes	No	Yes	No
Active vitamin D (calcitriol, paricalcitol, others)	102 (53%)	87 (45%)	15 (60%)	9 (36%)	41 (57%)	30 (42%)	61 (50%)	57 (47%)
Cinacalcet	50 (26%)	137 (71%)	12 (48%)	12 (48%)	20 (28%)	49 (68%)	30 (25%)	88 (73%)
Any phosphate binder (PB)[b]	149 (77%)	41 (21%)	20 (80%)	4 (16%)	56 (78%)	15 (21%)	93 (77%)	26 (21%)
Calcium-containing PB[b]			11 (44%)		19 (26%)		35 (29%)	
Sevelamer[b]			7 (28%)		21 (29%)		31 (26%)	
Lanthanum carbonate[b]			1 (4%)		13 (18%)		18 (15%)	
Other PB[b]			2 (8%)		7 (10%)		20 (17%)	
VKAs	98 (51%)	93 (48%)	15 (60%)	9 (36%)	33 (46%)	38 (53%)	65 (54%)	55 (45%)
Erythropoietin and other Erythropoiesis-stimulating agents, ESAs	160 (83%)	29 (15%)	21 (84%)	2 (8%)	57 (79%)	13 (18%)	103 (85%)	16 (13%)

[a]Due to missing values, patient figures may be smaller than the entire subgroup and cumulative percentage figures may not reach 100%.
[b]Single use as well as part of combination therapy.

Table 4. Locally obtained biochemical parameters at the time of blood drawing after online notification in dialysis CUA patients ($n = 218$)

Parameter (unit)	Normal range	All HD/HDF patients, $n = 143–184$	PD, $n = 19–25$	Male HD/HDF, $n = 51–70$	Female HD/HDF, $n = 92–114$
Albumin (g/L)	35–55	34 (29–38)	29 (24–34)	34 (29–40)	35 (29–38)
Alkaline phosphatase (U/L)	65–220	112 (80–168)	100 (91–133)	108 (73–158)	112 (81–168)
Total calcium (mmol/L)	2.30–2.60	2.20 (2.06–2.37)	2.20 (2.05–2.28)	2.20 (2.10–2.37)	2.22 (2.06–2.40)
Haemoglobin (g/L)	male: 14–18 female: 12–16	103 (94–115)	96 (87–104)	105 (96–122)	102 (94–111)
Serum phosphorus (mmol/L)	0.77–1.55	1.65 (1.31–2.04)	1.80 (1.38–2.00)	1.65 (1.42–2.13)	1.67 (1.30–2.02)
Protein (g/L)	66–83	66 (60–71)	65 (60–70)	68 (62–71)	64 (58–70)

Values are given asmedian (IQR); n indicates the number of patients in whom the biochemical parameters were recorded (n = a – b indicates the range between the minimum and maximum numbers of patients with available data for each parameter).

Table 5. Centrally obtained (Aachen biobank) biochemical research parameters at the time of blood drawing after online notification in dialysis CUA patients

Parameter	All HD/HDF patients, $n = 123$	PD, $n = 14$	Male HD/HDF, $n = 45$	Female HD/HDF, $n = 78$
Study centre research parameters[a]				
Fetuin-A (g/L)	0.21 (0.16–0.27)	0.17 (0.16–0.22)	0.21 (0.17–0.28)	0.22 (0.16–0.28)
iPTH (pg/mL)	143 (66–275)	201 (115–329)	167 (87–275)	130 (62–272)
Calcidiol, 25(OH)D (ng/mL)	22.3 (11.7–34.3)	15.5 (12.1–20.3)	24.8 (12.2–32.3)	20.8 (11.2–33.4)
OPG (pmol/L)	19.2 (15.1–23.8)	20.4 (14.8–27.2)	19.2 (16.0–23.9)	18.9 (15.1–23.3)
Sclerostin (ng/mL)	0.94 (0.64–1.53)	1.51 (0.84–2.3)	1.01 (0.68–1.54)	0.94 (0.61–1.54)
TRAP5b (U/L)	3.8 (2.6–5.3)	5.0 (4.1–9.4)	3.8 (2.6–4.8)	3.7 (2.6–5.7)
Bone-specific AP (U/L)	36.5 (25.8–57.2)	33.8 (27.5–54.9)	39.0 (20.3–65.3)	36.0 (27.9–55.5)
c-FGF23 (RU/mL)	1760 (819–9092)	6709 (4546–18 977)	2796 (583–11 481)	1592 (833–7643)
CRP (mg/L)	43.9 (12.3–99.3)	84.4 (22.3–173.8)	53.1 (13.6–105.5)	38.5 (11.8–92.8)

[a]Normal ranges or mean values according to the manufacturer's instructions: fetuin-A: 0.35–0.95 g/L; iPTH: 10.4–66.5 pg/mL; calcidiol: >30 ng/mL (target range); OPG: 5.7 ± 0.42 pmol/L; sclerostin: pre-menopausal 0.59 ± 0.23 ng/mL, post-menopausal 0.66 ± 0.22 ng/mL, male 0.83 ± 0.22 ng/mL; TRAP5b: pre-menopausal 0.54–3.23 U/L, post-menopausal 1.15–4.14 U/L, male 0.61–3.45 U/L; bone-specific AP: pre-menopausal 11.6–29.6 U/L, post-menopausal 14.2–42.7 U/L, male 15.0–41.3 U/L; c-FGF23: pre-menopausal 20.9–91.1 RU/L, post-menopausal 44.0–139.9 RU/L, male 33.7–96.5 RU/L; CRP: 0.07–8.2 mg/L.

DISCUSSION

We report data from a long-term nationwide online CUA registry that represents the largest CUA cohort documented so far. Overall, the German CUA registry allows presentation of far-reaching data regarding the clinical picture, additional background data, comprehensive data on biomarkers (CKD-MBD standard as well as research biomarkers) as well as applied therapeutic strategies.

We recorded a stable notification rate of ∼30 dialysis patients per year, which equals an annual incidence of ∼0.04%, assuming that the number of German dialysis patients has been ∼70 000 during the registry period. Thus, our data do not support estimated incidence figures as high as 4–5% among dialysis patients [6]. Also, we need to acknowledge that we have to accept a potentially high estimated number of unreported cases.

Our cohort of CUA patients is characterized by a striking predominance of dialysis patients. It is generally accepted that non-renal CUA is even rarer than dialysis-related CUA [7]. We

Table 6. Proportion of dialysis patients (PD, HD and HDF) within and outside biochemistry target ranges according to KDIGO guidelines 2009 (serum calcium and phosphorus were measured in transferring centres, iPTH was measured in a core lab) (laboratory data were obtained at the time of registry inclusion)

Parameter	*n*	Target range KDIGO[a]	Below	Within target range	Above target range
Serum calcium	207	2.30–2.60 mmol/L	133 (64%)	65 (31%)	9 (4%)
Albumin-corrected calcium	180		74 (42%)	79 (44%)	27 (15%)
Serum phosphorus	201	0.77–1.55 mmol/L	12 (6%)	68 (34%)	121 (60%)
iPTH, study core lab	138	133–600 pg/mL[b]	65 (47%)	65 (47%)	8 (6%)
iPTH, peripheral centre	197	n.a.[c]	n.a.	n.a.	n.a.

[a]KDIGO suggests normal range for calcium and phosphate as the target range.
[b]Target range is defined as PTH levels between 2- and 9-fold of the upper limit of normal range (=66.5 pg/mL).
[c]Calculation of the target range is not applicable since assays and consecutively normal PTH levels vary between centres.

acknowledge that our registry and our scientific activities primarily address the German nephrology community, and therefore we might have missed cases seen by other medical specialists. Additionally, lack of awareness of the disease might have contributed to a difficult to quantify number of hidden cases. On the other hand, our registry approach might carry the risk of including a few false-positive cases, which cannot be excluded completely due to the absence of systematic diagnostic standards for calciphylaxis and decentralized patient care within the registry.

All available data, including the present registry, indicate that ESRD predisposes patients to develop CUA. The registry allows comprehensive analyses of CKD-MBD parameters; at the time of CUA diagnosis, serum calcium levels in affected dialysis individuals were clinically unremarkable. Total serum calcium levels were indeed quite low, looking at the distribution of calcium levels according to the historical KDOQI target ranges or according to the current KDIGO target ranges. Hypercalcaemia above the upper limit of normal (2.60 mmol/L) was present in only 15% of CUA dialysis patients in terms of albumin-corrected calcium. In contrast, serum phosphate levels were more often above target ranges (42% for the KDOQI range and 60% for the KDIGO range), reflecting the well-documented prevalence of hyperphosphatemia in dialysis patients. Of note, these laboratory data were obtained about 1 month after CUA development. Hence, the current disease burden and nutritional status may have influenced the recorded calcium and phosphate levels.

More strikingly, the PTH levels in our dialysis CUA cohort were unexpectedly low, which deserves thorough comments and further evaluation. Relatively low PTH levels are in line with previous case–control series, which could not document uncontrolled hyperparathyroidism being a risk factor for CUA development [1]. The fact that our CUA cohort exhibited low PTH levels is also reflected by the low rate of co-medication with cinacalcet in our cohort: 71% of our patients did not receive cinacalcet at the time of CUA diagnosis. Adynamic bone disease might predispose to CUA development since the buffering capacity for an excess of circulating minerals is thought to be impaired [8]. One potential reason for low PTH levels in dialysis patients is oversuppression of hyperparathyroidism prior to CUA development. However, such a discussion about iatrogenic adynamic bone disease remains speculative in the absence of bone histomorphometry and serial bone metabolism data. Both BSAP and TRAP5b markedly exceeded the normal range in our cohort, but such levels cannot reliably exclude the presence of localized transient osteoporosis. Our notion of overall predominantly 'low' PTH levels in the CUA cohort is not in contrast with findings from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial [9], indicating that cinacalcet treatment was associated with a significant decrease of CUA incidence compared with the control arm. In the EVOLVE trial, the median PTH levels prior to CUA development were 796 pg/mL in the placebo arm and 410 pg/mL in the cinacalcet arm. Of note, the EVOLVE trial included preselected patients with advanced hyperparathyroidism at baseline, while a nationwide approach such as the registry is unlimited by any exclusion criteria. So, the EVOLVE design presumably missed the predominant PTH range for calciphylaxis development and fuels speculation about an optimal intermediate

Table 7. Recorded therapeutic strategies in 165 CUA dialysis patients (76% of the entire dialysis CUA cohort) [multiple answers possible; single answers in *n* = 16 (10%) cases]

Intensifying dialysis therapy	
Increase of dialysis duration and/or frequency	16.9%
Switch from haemodialysis to haemodiafiltration	0.8%
Switch from PD to HD	1.5%
Reduction of calcium supply/intake	
Lowering/stopping of calcium-containing PB	23.8%
Lowering dialysis bath calcium concentration	1.5%
Reduction/stop active vitamin D treatment including VDRA	16.2%
Vitamin K metabolism	
Stop VKA treatment	25.4%
Give vitamin K	17.7%
Secondary hyperparathyroidism	
Initiate cinacalcet	10.8%
Stop cinacalcet	2.3%
Parathyroidectomy	2.3%
Initiate native vitamin D	2.3%
Calcification inhibition	
Apply STS	21.5%
Give bisphosphonates	2.3%
Fresh frozen plasma	1.7%
Tissue oxygen supply	
Revascularization (surgical and angioplasty)	3.8%
Antibiotics	16.1%
Surgical wound management	
Including necrosectomy, debridement and skin transplantation	29.2%
Others	
Application of glucocorticoids	3.1%
Prostaglandin infusion	0.7%

(protective) PTH range. Taken together, for all classical CKD-MBD parameters (calcium, phosphate, calcium–phosphate product and PTH), further CUA studies should investigate the time course (trend analysis) in the months prior to CUA.

Interpretation of the innovative research biomarkers is limited due to the absence of a control group. Remarkably, fetuin-A levels were much below the normal range in our CUA dialysis patients. Deficiency of fetuin-A may be expected in a dialysis cohort with high CRP levels and overall low protein and albumin levels. Cause or effect of low fetuin-A levels cannot be established from our data, and both interpretations are possible. Interestingly, we also observed median sclerostin levels above the normal range in our CUA patients. The potential role of sclerostin as a marker or mediator of vascular calcification is a matter of ongoing debate [10]. If sclerostin alone or in combination with the various alternative bone markers, which proved to be above the normal range in our calciphylaxis cohort (OPG, BSAP and TRAP5b), might help in identifying patients at particular risk for developing calciphylaxis remains undetermined.

The high prevalence of VKA treatment is striking. Vitamin K activates matrix Gla protein (MGP) via gamma-carboxylation [1]. Fully active MGP is a prerequisite for maintaining vascular wall integrity by avoiding calcification. Hence, the application of a VKA such as warfarin and phenprocoumon (most often Marcumar® in Germany) is thought to interfere with calcification defence mechanisms and promote vascular wall calcification [11]. There are no confirmed data available about the exact prevalence of a VKA application in dialysis patients in Germany, but valid estimates point towards ∼10% of patients. This suggests that our 50% VKA treatment prevalence might be a factor of 5-fold increased prevalence of VKA in CUA patients compared with non-CUA dialysis patients. This finding is in line with a previous report from Japan that calculated a factor (hazard ratio) of 10 according to a case–control approach [12]. We should point out that the assumption of VKA being causally linked to CUA development has already influenced treatment strategies (see below).

A recent state-of-the-art review by Nigwekar *et al.* [13] nicely summarized current treatment strategies in CUA patients, showing several analogies, but also discrepancies, with our registry data—the latter reflecting the real-world treatment situation in Germany.

Overall, our data confirm the clinical experience that treatment is multimodal. In terms of homologies, wound care (non-invasively and surgically) is a mainstay of therapy, accompanied by systemic antibiotic therapy. Real-world care considers a reduction in calcium supply via reduced oral intake, less active vitamin dosages and lowering dialysis bath calcium as effective. PTH-lowering interventions (cinacalcet and parathyroidectomy) are a rarely used treatment option in Germany. German nephrologists increased the frequency and duration of dialysis sessions in a substantial proportion of cases, although CKD-MBD parameters were formally 'controlled' (with the exception of highly prevalent hyperphosphatemia).

Modification of the anticoagulation regime by stopping VKA and/or vitamin K replenishment was a common treatment option [14]. Pain management and other supportive care measures such as nutritional consulting have not been regularly recorded in the German registry. We speculate about 'false-negative' results here because physicians might not have regarded this as specific CUA interventions.

The issue of sodium thiosulphate (STS) application warrants some additional comments. Case series published, e.g. by Nigwekar *et al.* [15], have fuelled the discussion about potentially positive effects of STS in CUA patients. Accordingly, STS is part of the treatment summary provided by Nigwekar *et al.* [13]. However, evidence regarding a positive risk:benefit ratio of STS in CUA is low, given the fact that no controlled, prospective data are available [1]. STS is indeed applied in about a fifth of patients in Germany. We speculate that this percentage is a reliable estimate of the real-world situation (meaning a low number of false-negative recordings), as physicians might be especially prepared and motivated to communicate STS as specific CUA treatment. Regarding CUA treatment, we cannot draw conclusions about any therapeutic effect of any intervention, since systematic follow-up visits were not part of the registry protocol. Hence, it remains speculative if any single intervention (such as the application of STS) or any multimodal treatment approach influences outcomes in these patients.

A relevant limitation of our registry is the cross-sectional nature with single-spot recording of data—so, we cannot comment on biomarker trends and upcoming warning signs prior to CUA outbreak. The latter is of particular interest in terms of average low PTH levels, which we recorded at the time of diagnosis. Moreover, the registry did not record long-term outcomes in terms of potential treatment effects or survival. The international European Calciphylaxis Network initiative (http://www.eucalnet.net)—a multinational European calciphylaxis registry—is aimed at biochemistry trend analyses and outcome assessment to overcome this limitation [16].

In summary, we consider three issues raised by the registry as important. Our data confirm that CUA qualifies as a truly rare disease. A novel finding is that median PTH levels among dialysis patients are low. VKA usage is highly prevalent in CUA patients, pointing towards the need to investigate the potential beneficial effects of early VKA withdrawal and vitamin K replenishment.

SUPPLEMENTARY DATA

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

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CONFLICT OF INTEREST STATEMENT

We declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

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ORIGINAL ARTICLE

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Immunogenicity and safety of quadrivalent human papillomavirus types 6/11/16/18 recombinant vaccine in chronic kidney disease stage IV, V and VD

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ABSTRACT

Background. Up to >80% of sexually active adults will become infected with human papillomavirus (HPV) during their lifetime. Persistent HPV infection can result in cervical, vulvovaginal, penile and anogenital cancer. Clinical studies have shown the efficacy of three doses of quadrivalent HPV-6/11/16/18 L1 virus-like particle (VLP) vaccination, at Day 0, Month 2 and Month 6, to lower the occurrence of HPV infection and its complications. However, immunogenicity and safety of the HPV vaccine have not been proven in the chronic kidney disease (CKD) population.

Methods. Sixty CKD stage IV, V and VD patients were enrolled for quadrivalent HPV-6/11/16/18 vaccination. A dose of vaccine was given at Day 0, Month 2 and Month 6. Each dose contained 20 μg HPV-6 L1 VLP, 40 μg HPV-11 L1 VLP, 40 μg HPV-16 L1 VLP and 20 μg HPV-18 L1 VLP, along with 225 μg of amorphous aluminum hydroxyphosphate sulfate adjuvant. HPV type-specific antibody response to neutralizing epitopes on HPV-6/11/16/18 was performed by multiplexed, competitive Luminex® immunoassays (cLIA) at Day 0 and Month 7.