Article

The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial

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Abstract

Background and objectives Uncontrolled secondary hyperparathyroidism (sHPT) in patients with ESRD is a risk factor for calcific uremic arteriolopathy (CUA; calciphylaxis).

Design, setting, participants, & measurements Adverse event reports collected during the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events trial were used to determine the frequency of CUA in patients receiving hemodialysis who had moderate to severe sHPT, as well as the effects of cinacalcet versus placebo. CUA events were collected while patients were receiving the study drug.

Results Among the 3861 trial patients who received at least one dose of the study drug, 18 patients randomly assigned to placebo and six assigned to cinacalcet developed CUA (unadjusted relative hazard, 0.31; 95% confidence interval [95% CI], 0.13 to 0.79; P=0.014). Corresponding cumulative event rates (95% CI) at year 4 were 0.011% (0.006% to 0.018%) and 0.005% (0.002% to 0.010%). By multivariable analysis, other factors associated with CUA included female sex, higher body mass index, higher diastolic BP, and history of dyslipidemia or parathyroidectomy. Median (10%, 90% percentile) plasma parathyroid hormone concentrations proximal to the report of CUA were 796 (225, 2093) pg/ml and 410 (71, 4957) pg/ml in patients randomly assigned to placebo and cinacalcet, respectively. Active use of vitamin K antagonists was recorded in 11 of 24 patients with CUA, nine randomly assigned to placebo, and two to cinacalcet, in contrast to 5%–7% at any one time point in patients in whom CUA was not reported.

Conclusion Cinacalcet appeared to reduce the incidence of CUA in hemodialysis recipients who have moderate to severe sHPT.

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Introduction

Calcific uremic arteriolopathy (CUA), often referred to as calciphylaxis, is a relatively rare syndrome, which carries a 1-year survival rate of only 45% (1–5). The central pathologic lesion in CUA is a calcified media of small and medium-sized arterial vessels of the skin and fat tissue, leading to progressive and extremely painful cutaneous ulcerations (1–5). Infections of such skin lesions represent the main reason for the high mortality of CUA (1–5). CUA rarely manifests in patients with normal kidney function (6), and most cases are confined to patients with advanced CKD and in particular ESRD (1). The exact prevalence of CUA in the dialysis population is unknown; estimates range from 1% to 4% of all patients with ESRD (7–9).

The pathogenesis of CUA is incompletely understood. Recent data suggest that CUA involves a cell-mediated, bone morphogenetic protein-2–driven osteogenic process with extensive subcutaneous extracellular matrix remodeling and deposition of hydroxyapatite (10). A cascade consisting of matrix remodeling, calcification, endothelial damage and thrombus formation,

luminal obstruction, and finally development of full-blown CUA has been postulated (10). Risk factors for CUA identified in clinical studies include CKD/ESRD, female sex, diabetes mellitus, obesity, and vitamin K antagonism (3–5,11,12). With respect to mineral bone disorders in CKD/ESRD, CUA prevalence is higher in patients with hyperphosphatemia and those receiving calcium-containing phosphate binders (3–5). Both low-turnover bone disease in ESRD and high-turnover bone disease associated with severe secondary hyperparathyroidism (sHPT) have been associated with CUA (13,14).

At present it is unknown whether specific therapies that decrease excessive parathyroid hormone (PTH) concentrations raise or lower the incidence of CUA. In the current analysis, we aimed to confirm or refute known risk factors for CUA and to test the hypothesis that a reduction in PTH with cinacalcet reduces the frequency of CUA in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial (www.ClinicalTrials.gov registration number: NCT00345839) (15,16).

Materials and Methods

Study Population and Design

In the EVOLVE trial, 3883 patients with sHPT receiving hemodialysis were randomly assigned 1:1 to receive cinacalcet (Sensipar or Mimpara, Amgen, Inc.) or placebo in addition to conventional therapies for CKD–mineral and bone disorder. Eligible participants were undergoing hemodialysis three times per week and had plasma PTH concentrations $\geq$300 pg/ml (31.8 pmol/L), serum calcium phosphate product $\geq$45 mg^2/dl^2 (3.63 mmol^2/L^2), and serum calcium $\geq$8.4 mg/dl (2.1 mmol/L). The dose of study drug was titrated every 4 weeks during the first 20 weeks and every 8 weeks during the subsequent follow-up period (from a starting dose of 30 mg to a maximum dose of 180 mg daily), depending on blood levels of PTH and calcium (17). The dialysis prescription, type/doses of phosphate binders, vitamin D sterols, calcium supplements and other medications, and other medical procedures were administered at the discretion of treating physicians. The trial assessed the effect of treatment with cinacalcet compared with placebo in addition to other conventional therapies (calcitriol or vitamin D sterols and phosphate binders) on the primary composite endpoint of all-cause mortality and major cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event). The study design, baseline characteristics of the participants, primary results, and effect of cinacalcet on severe unremitting hyperparathyroidism have been previously published (15–18). The intervention lasted up to 64 months. The trial was sponsored by Amgen, Inc. An academic Executive Committee with direct oversight of all final analyses and publications led the trial. The ethics committees at all participating sites approved the study, and all patients provided informed consent.

All adverse events, including CUA, were collected while patients were receiving the study drug. In contrast to the components of the primary composite outcome and selected secondary outcomes (i.e., stroke, parathyroidectomy, and clinical fracture), CUA adverse events were not adjudicated. The estimated incidence of CUA was based on the report of local investigators and was not necessarily confirmed by biopsy or other means. All demographic and laboratory data analyzed were collected as part of the primary study (15,16).

Statistical Analyses

All randomly assigned patients who received at least one dose of the study drug (n=3861; the safety analysis set) were included in these analyses. All CUA cases that occurred during the adverse event reporting period were reviewed and included. The observation period was from the first dose date of the study drug to initial CUA, excluding the time adverse events were not collected as per the protocol. A two-sided Gray test was used to compare the cumulative incidence function estimates of the survival time between the treatment groups. Fine–Gray subdistributional hazards regression models were used to calculate the relative hazard (cinacalcet versus placebo) and 95% confidence intervals (95% CIs). We performed unadjusted and multivariable analyses. The multivariable analysis was adjusted for baseline covariates using a backward selection procedure at a significance level of 0.10. Potential covariates included baseline patient and demographic characteristics, concomitant medication use, cardiovascular history, and laboratory measures.

Because findings in the primary analysis of the EVOLVE trial (determining the effect of cinacalcet versus placebo on the primary composite endpoint through use of an unadjusted intention-to-treat analysis) were not statistically significant, analysis results with a P value <0.05 were deemed nominally statistically significant. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).
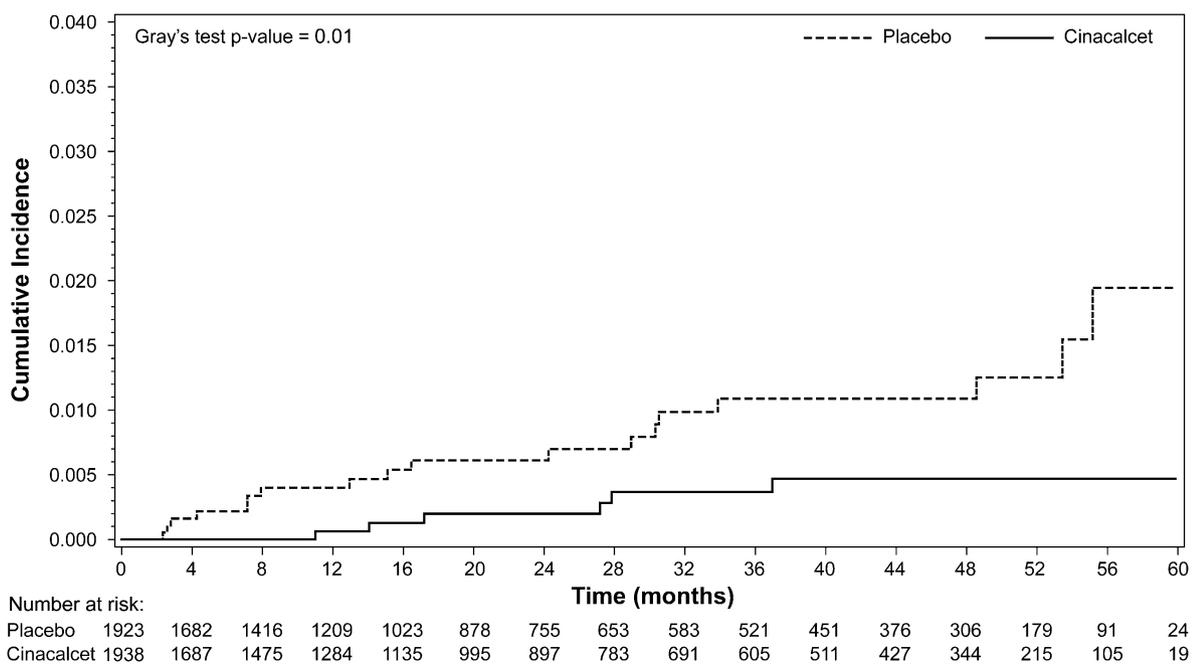

Figure 1. | **Cumulative incidence plot of time to calcific uremic arteriolopathy adverse event (safety analysis set).**

Table 1. Key baseline demographic and medical history characteristics by occurrence of calcific uremic arteriolopathy adverse event during the study (safety analysis set)

Characteristic	CUA (n=24)			No CUA (n=3837)			P Value[a]
	Placebo (N₁=18)	Cinacalcet (N₁=6)	Total (N₁=24)	Placebo (N₁=1905)	Cinacalcet (N₁=1932)	Total (N₁=3837)	
Median age (10%, 90% percentile) (yr)	54.5 (43.0, 71.0)	59.5 (32.0, 63.0)	56.0 (43.0, 63.0)	54.0 (35.0, 73.0)	55.0 (35.0, 74.0)	55.0 (35.0, 73.0)	0.99
Age category, n (%)							0.05
<65 yr	16 (88.9)	6 (100)	22 (91.7)	1435 (75.3)	1403 (72.6)	2838 (74.0)	
≥65 yr	2 (11.1)	0 (0.0)	2 (8.3)	470 (24.7)	529 (27.4)	999 (26.0)	
Race group, n (%)							0.28
White	11 (61.1)	4 (66.7)	15 (62.5)	1100 (57.7)	1115 (57.7)	2215 (57.7)	
Black	6 (33.3)	1 (16.7)	7 (29.2)	417 (21.9)	404 (20.9)	821 (21.4)	
Other	1 (5.6)	1 (16.7)	2 (8.3)	388 (20.4)	413 (21.4)	801 (20.9)	
Women, n (%)	11 (61.1)	4 (66.7)	15 (62.5)	754 (39.6)	802 (41.5)	1556 (40.6)	0.03
Median BMI (10%, 90% percentile) (kg/m²)	34.4 (24.7, 43.5)	28.5 (21.3, 37.3)	34.1 (23.1, 41.8)	26.3 (20.6, 36.6)	26.3 (20.4, 36.4)	26.3 (20.5, 36.5)	<0.001
BP (10%, 90% percentile) (mmHg)							
Systolic	163.0 (120.0, 184.0)	153.5 (137.0, 209.0)	162.5 (137.0, 184.0)	140.0 (110.0, 177.0)	140.0 (110.0, 176.0)	140.0 (110.0, 176.0)	<0.001
Diastolic	85.0 (67.0, 100.0)	80.0 (72.0, 130.0)	83.0 (70.0, 100.0)	80.0 (60.0, 100.0)	80.0 (60.0, 100.0)	80.0 (60.0, 100.0)	0.02
Tobacco use, n (%)							0.11
Never	6 (33.3)	3 (50.0)	9 (37.5)	1081 (56.7)	1077 (55.7)	2158 (56.2)	
Current	3 (16.7)	1 (16.7)	4 (16.7)	317 (16.6)	310 (16.0)	627 (16.3)	
Former	9 (50.0)	2 (33.3)	11 (45.8)	506 (26.6)	545 (28.2)	1051 (27.4)	
History of diabetes, n (%)	11 (61.1)	2 (33.3)	13 (54.2)	633 (33.2)	650 (33.6)	1283 (33.4)	0.03
Type 1	0 (0.0)	0 (0.0)	0 (0.0)	81 (4.3)	73 (3.8)	154 (4.0)	0.32
Type 2	11 (61.1)	2 (33.3)	13 (54.2)	553 (29.0)	577 (29.9)	1130 (29.5)	<0.01
History of cardiovascular disease, n (%)	18 (100)	6 (100)	24 (100)	1801 (94.5)	1842 (95.3)	3643 (94.9)	0.26
Hypertension	18 (100)	6 (100)	24 (100)	1746 (91.7)	1786 (92.4)	3532 (92.1)	0.15
Heart failure	9 (50.0)	2 (33.3)	11 (45.8)	443 (23.3)	444 (23.0)	887 (23.1)	<0.01
Peripheral vascular disease	8 (44.4)	0 (0.0)	8 (33.3)	313 (16.4)	313 (16.2)	626 (16.3)	0.03
CABG	1 (5.6)	2 (33.3)	3 (12.5)	152 (8.0)	133 (6.9)	285 (7.4)	0.35
PCI	1 (5.6)	0 (0.0)	1 (4.2)	130 (6.8)	130 (6.7)	260 (6.8)	0.61
Myocardial infarction	1 (5.6)	0 (0.0)	1 (4.2)	242 (12.7)	238 (12.3)	480 (12.5)	0.22
Stroke	1 (5.6)	1 (16.7)	2 (8.3)	192 (10.1)	160 (8.3)	352 (9.2)	0.89
Transient ischemic attack	1 (5.6)	0 (0.0)	1 (4.2)	73 (3.8)	98 (5.1)	171 (4.5)	0.95
Amputation	2 (11.1)	0 (0.0)	2 (8.3)	127 (6.7)	121 (6.3)	248 (6.5)	0.71
Atrial fibrillation	4 (22.2)	0 (0.0)	4 (16.7)	221 (11.6)	202 (10.5)	423 (11.0)	0.38

Table 1. (Continued)

Characteristic	CUA (n=24)			No CUA (n=3837)			P Value[a]
	Placebo (N₁=18)	Cinacalcet (N₁=6)	Total (N₁=24)	Placebo (N₁=1905)	Cinacalcet (N₁=1932)	Total (N₁=3837)	
History of parathyroidectomy, n (%)	3 (16.7)	1 (16.7)	4 (16.7)	84 (4.4)	90 (4.7)	174 (4.5)	<0.01
History of dyslipidemia, n (%)	12 (66.7)	3 (50.0)	15 (62.5)	744 (39.1)	768 (39.8)	1512 (39.4)	0.02

N_1 refers to number of patients in the safety analysis set; n percentages are based on N_1. CUA, calcific uremic arteriolopathy; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
[a]Wilcoxon rank sum test was used for continuous variables and chi-square test was used for categorical variables. Comparisons are between patients who experienced a CUA adverse event compared with those who did not.

Results

CUA Incidence

Among the 3861 trial patients who received at least one dose of study drug, 24 patients developed CUA: 18 patients randomly assigned to placebo and six patients assigned to cinacalcet (unadjusted relative hazard, 0.31; 95% CI, 0.13 to 0.79; P=0.014). The median (10%, 90% percentile) time to CUA was 1.3 (0.2, 4.5) years in patients randomly assigned to placebo and 1.8 (0.9, 3.1) years in patients assigned to cinacalcet. Corresponding cumulative event rates (95% CI) at year 4 were 0.011% (0.006% to 0.018%) and 0.005% (0.002% to 0.010%), respectively (Figure 1).

Baseline Characteristics

Table 1 shows baseline characteristics of patients who were reported to have developed CUA and those of all other trial participants. Compared with the latter, patients who developed CUA were more likely to be younger and female; to have a higher Quételet (body mass) index (BMI); to have hypertension, diabetes mellitus, and/or dyslipidemia; and to have had a history of heart failure, peripheral vascular disease, or prior parathyroidectomy (with severe enough recurrence of sHPT to meet the trial inclusion criteria). In contrast, ethnicity, region of origin, dialysis vintage, dialysis access, dialysate calcium, tobacco use, history of fractures or coronary artery disease, and baseline laboratory values were not associated with CUA (Table 2).

Laboratory Findings Immediately Before CUA Manifestation

Laboratory findings most proximal to the reporting of CUA are shown in Table 3. Median (10%, 90% percentiles) plasma intact PTH at the time of CUA was 796 (225, 2093) pg/ml and 410 (71, 4957) pg/ml in patients randomly assigned to placebo and cinacalcet, respectively. Corresponding total serum calcium concentrations were 9.8 (8.5, 10.6) mg/dl and 9.7 (8.0, 11.6) mg/dl, respectively. Corresponding serum phosphate concentrations were 5.8 (4.5, 8.1) mg/dl and 6.3 (3.4, 10.2) mg/dl, and alkaline phosphatase values were 98 (67, 148) U/L and 190 (65, 648) U/L.

Concomitant Medications Immediately before CUA Manifestation

Table 4 shows the use of concomitant medications in patients reported to have developed CUA. Only one of 18 patients with CUA in the placebo group had received commercial cinacalcet (single 30-mg dose at 5 months before the onset of CUA). Vitamin K antagonists were actively prescribed in 11 of 24 (46%) patients with CUA: nine among those assigned to placebo and two among those assigned to cinacalcet. Four of 24 (17%) patients were receiving vitamin K antagonists at baseline; others started vitamin K antagonists during the trial. In contrast, among patients not developing CUA, vitamin K antagonist prescription ranged from 7.4% (284 of 3837 patients) at study year 1 to 5.1% (196 of 3837 patients) at study year 3. Because we did not collect complete data on concomitant medication use throughout the trial, we cannot be certain which patients were prescribed vitamin K antagonists and, if so, when during the trial. Thus, we could not include this variable in the regression model. Among patients diagnosed with CUA, data on vitamin K antagonist use were obtained from direct review of medical records.

Table 2.   Key baseline laboratory characteristics by occurrence of calcific uremic arteriolopathy adverse event during the study (safety analysis set)

Characteristic	CUA (n=25)			No CUA (n=3858)			P Value[a]
	Placebo (N_1=19)	Cinacalcet (N_1=6)	Total (N_1=25)	Placebo (N_1=1916)	Cinacalcet (N_1=1942)	Total (N_1=3858)	
Intact PTH (pg/ml)	515 (285, 1339)	857 (344, 2755)	579 (333, 2121)	692 (364, 1693)	694 (363, 1699)	693 (364, 1695)	0.18
Corrected calcium (mg/dl)	9.9 (9.0, 10.6)	10.5 (9.7, 10.8)	10.1 (9.5, 10.6)	9.8 (9.0, 10.7)	9.8 (9.0, 10.7)	9.8 (9.0, 10.7)	0.08
Phosphorus (mg/dl)	6.4 (4.6, 9.5)	6.6 (4.8, 8.2)	6.4 (4.8, 8.8)	6.2 (4.9, 8.4)	6.3 (4.9, 8.3)	6.2 (4.9, 8.4)	0.45
25(OH)D (ng/ml)	14.5 (6, 38)	20.5 (14, 26)	15 (8, 28)	18 (8, 39)	17 (8, 37)	17 (8, 37)	0.44
Alkaline phosphatase (U/L)	91 (59, 151)	129 (59, 500)	91 (59, 166)	108 (65, 232)	107 (64, 248)	108 (65, 24)	
Bone alkaline phosphatase (µg/L)	17.53 (9.60, 32.89)	31.51 (10.29, 139.66)	20.96 (10.21, 38.21)	22.92 (11.56, 66.81)	23.09 (11.52, 70.52)	23.02 (11.53, 68.11)	0.12
N-telopeptide (nmol/L)	141.6 (45.6, 280.4)	620.9 (134.4, 1414.1)	196.2 (52.8, 692.8)	249.6 (79.3, 821.0)	261.0 (81.0, 925.4)	255.3 (80.6, 884.9)	0.13
Hemoglobin (g/dl)	11.9 (8.4, 13.2)	11.7 (9.1, 12.7)	11.7 (9.1, 12.7)	11.8 (10.0, 13.8)	11.7 (10.0, 13.5)	11.8 (10.0, 13.6)	0.62
Albumin (g/dl)	3.6 (3.1, 4.0)	3.5 (3.3, 4.2)	3.6 (3.1, 4.0)	3.7 (3.2, 4.1)	3.7 (3.2, 4.1)	3.7 (3.2, 4.1)	0.30
Total protein (g/dl)	7.0 (6.2, 7.7)	6.8 (5.8, 7.1)	6.9 (6.2, 7.5)	7.0 (6.3, 7.7)	6.9 (6.3, 7.7)	6.9 (6.3, 7.7)	0.44
Bicarbonate (mEq/L)	18.8 (14.4, 26.0)	23.3 (18.9, 24.9)	19.3 (14.7, 24.9)	20.4 (15.8, 25.6)	20.3 (15.7, 25.4)	20.3 (15.7, 25.5)	0.63
Creatinine (mg/dl)	9.7 (4.7, 13.6)	10.9 (7.7, 12.8)	10.0 (6.4, 13.2)	9.9 (6.7, 13.9)	9.9 (6.6, 13.9)	9.9 (6.7, 13.9)	0.77

Values are expressed as median (10%, 90% percentile). N_1 refers to number of patients in the safety analysis set; n percentages are based on N_1. CUA, calcific uremic arteriolopathy; PTH, parathyroid hormone; 25(OH)D, 1,25-dihydroxyvitamin D.
[a]Wilcoxon rank-sum test was used for continuous variables and chi-square test was used for categorical variables. Comparisons are between patients who experienced a CUA adverse event compared with those who did not.

Table 3. Laboratory values before onset of calcific uremic arteriolopathy adverse event

Variable	Placebo (n=18)	Cinacalcet (n=6)
Intact PTH (pg/ml)	796 (225, 2093)	410 (71, 4957)
Serum calcium (mg/dl)	9.8 (8.5, 10.6)	9.7 (8.0, 11.6)
Serum phosphorus (mg/dl)	5.8 (4.5, 8.1)	6.3 (3.4, 10.2)
Alkaline phosphatase (U/L)	98 (67, 148)	190 (65, 648)
Bone alkaline phosphatase (μg/L)	15.56 (7.97, 33.62)	44.01 (15.97, 188.97)
N-telopeptide (nmol/L)	205.2 (36.8, 490.5)	491.4 (109.9, 1471.4)
Hemoglobin (g/dl)	11.4 (8.3, 13.2)	11.6 (6.7, 13.1)
Albumin (g/dl)	3.4 (2.7, 3.8)	3.2 (2.8, 4.1)
Total protein (g/dl)	6.9 (6.4, 7.9)	6.9 (5.9, 7.3)

Values are expressed as median (10%, 90% percentile). PTH, parathyroid hormone.

Table 4. Concomitant medication use before onset of calcific uremic arteriolopathy adverse event

Variable	Placebo (n=18)	Cinacalcet (n=6)
Vitamin D sterol use (%)	72	100
Median IV paricalcitol-equivalent dose (10%, 90% percentile) (μg/wk)	15 (6, 24)	10 (5, 45)
Phosphate binder use (%)	100	100
Calcium-containing phosphate binder use (%)	67	83
Study drug dose		
Patients (n)	N/A	5
Median dose (10%, 90% percentile) (mg/d)		30 (30, 180)
Commercial cinacalcet dose		
Patients (n)	1	NA
Median dose (10%, 90% percentile) (mg/d)	30[a]	
Statin use (%)	100	100
Warfarin or other oral anti-coagulant use (%)	50	33
Erythropoietin agents (%)	100	100
Iron use (%)	78	83

n refers to number of patients in the safety analysis set. Percentages are based on n. IV, intravenous; N/A, not available.
[a]Single dose at 5 months before calcific uremic arteriolopathy onset.

Risk Factors for CUA

After adjustment for baseline characteristics, the relative hazard (cinacalcet versus placebo) was 0.25 (95% CI, 0.10 to 0.67). Baseline factors independently associated with a higher rate of CUA included random assignment to placebo, female sex, higher BMI, higher diastolic BP, history of dyslipidemia, history of parathyroidectomy, and former tobacco use (Table 5).

Discussion

Within the EVOLVE trial, 24 of 3861 enrolled patients who received at least one dose of the study drug developed CUA. The overall exposure-adjusted rate of 0.3 per 100 patient-years in our total population is relatively low. In the literature, a prevalence of 1%–4% was reported among nonselected patients receiving maintenance dialysis (1,3,19). It is unlikely that CUA was substantially underreported, given the severity of the diagnosis. Rather, our data suggest that the CUA risk in our selected population of relatively young patients with advanced sHPT may be lower than that of a non-selected maintenance hemodialysis population.

Our central observation was that a cinacalcet-based therapeutic regimen in hemodialysis patients with advanced sHPT reduced CUA incidence by 69%–75%, considering unadjusted or adjusted data, respectively. This observation makes EVOLVE the first randomized controlled of this intervention to show a reduced risk of CUA. To date, the therapeutic approach undertaken to prevent or ameliorate CUA has been deduced from case-control studies that identified risk factors for CUA in patients with ESRD, including hyperphosphatemia, peritoneal dialysis (rather than hemodialysis), diabetes mellitus, obesity, and the use of vitamin K antagonists (3–5,11,12). The role of sHPT in the pathogenesis of CUA is not well understood. In some cases with extremely high plasma PTH concentrations, subtotal or total parathyroidectomy was effective in ameliorating CUA (1). In other reports, lower levels of PTH ("oversuppression") which are associated with low bone turnover, were also associated with CUA (1). In the EVOLVE population, a relatively young group of patients with moderate to severe sHPT, cinacalcet therapy appeared to reduce the risk of CUA. Among patients randomly assigned to placebo (in other words, patients

Table 5. Multivariate regression using Fine-Gray subdistributional hazards model of calcific uremic arteriolopathy adverse events (safety analysis set)

Multivariate Model	Hazard Ratio (95% CI)	P Value
Treatment (cinacalcet versus placebo)	0.25 (0.10 to 0.67)	<0.01
Male sex (reference, female)	0.33 (0.14 to 0.75)	<0.01
Body mass index (per kg/m^2)	1.09 (1.05 to 1.13)	<0.001
Diastolic BP (per 10 mmHg)	1.50 (1.19 to 1.90)	<0.001
History of dyslipidemia	2.15 (0.90 to 5.15)	0.09
History of parathyroidectomy	5.79 (1.79 to 18.70)	0.003
Baseline tobacco use (reference, never use)		
Current	1.79 (0.54 to 5.89)	0.34
Former	3.04 (1.19 to 7.74)	0.02

Baseline variables were included using backward elimination. Heart failure and diabetes mellitus were removed during the backward elimination procedure at a significance level of 0.10. Additional baseline variables of age, vitamin K antagonist use, vitamin D sterol use, and peripheral vascular disease were evaluated but not included in the multivariate regression model using the backward elimination procedure because they did not meet the entry criteria, $P<0.25$ in a univariate model. 95% CI, 95% confidence interval.

generally treated with vitamin D sterols and phosphate binders), the median plasma PTH concentrations were higher in the weeks and months proximal to the recognition of CUA than at baseline. The number of patients randomly assigned to cinacalcet who developed CUA was very small. However, in the latter, CUA developed in the setting of very high and very low plasma PTH concentrations, suggesting that factors other than PTH alone play a role in CUA pathogenesis.

Predisposing factors, which occurred more often in our patients who experienced CUA than in the overall EVOLVE population, were consistent with the literature and included female sex (3,4), obesity (5), and diabetes mellitus (3). Recent case-control studies also reported that administration of warfarin was associated with a 4- to 11-fold risk for CUA in patients receiving dialysis (11,12). Our study further supports a role of vitamin K antagonism in precipitating CUA given that the frequency of vitamin K antagonist use was about 7- to 8-fold higher in patients who developed CUA than in those not developing CUA; about one third of the patients who developed CUA started vitamin K antagonists during the trial. Similarly, in a CUA registry (http://www.calciphylaxis.net), almost 50% of the patients were receiving vitamin K antagonists at CUA manifestation (1). The mechanism may involve the inactivation of the major vascular wall calcification inhibitor, matrix Gla protein, which depends on vitamin K for its bioactivity (20). Our observations thus further support a restrictive policy of vitamin K antagonism in patients receiving dialysis (21).

The role of other comedications in serving as "triggers" for CUA is less well established. A case-control study has suggested that statins reduce CUA risk and that calcitriol, but not paricalcitol, increases this risk (3,12). In EVOLVE, all 24 patients who developed CUA were receiving statins in the weeks and months before CUA was reported. This may reflect the severity of diabetes, atherosclerotic vascular disease, or other conditions in these patients; there is insufficient evidence to link statin use with CUA on the basis of these findings. Likewise, almost all patients with CUA were receiving vitamin D sterols, but

these were used very commonly among all patients, and only a small fraction developed CUA.

Strengths of our analysis include data obtained from a large, prospective, randomized trial, as well as a diverse population assessed for a broad range of baseline clinical characteristics and serial laboratory determinations. Limitations include the relatively small number of CUA events despite the large trial size, which makes it more difficult to precisely determine the magnitude of the treatment effect or the relative and absolute importance of clinical factors other than cinacalcet treatment that influence CUA risk. Another limitation is that the diagnoses of CUA events were based on physician's assessment, without biopsy confirmation in all cases. However, the advisability of skin biopsy in CUA is controversial, given concerns that the biopsy may precipitate further lesions (1). Because of relatively poor adherence with cinacalcet, we may have underestimated the therapeutic effect on CUA (however, adverse events were no longer captured after discontinuation of study drug, and thus we have no information on how many CUA events have developed in such patients). Most important, the trial was not designed to detect a reduction in the rate of CUA, and the power to detect such a difference, using reasonable assumptions, was low. Thus, the findings might be "false positive" despite relative hazards that were quite low and reached levels of nominal statistical significance.

In summary, upon carefully examining safety/adverse event data from the EVOLVE trial, the largest and longest randomized clinical trial conducted in the hemodialysis population, we confirmed important associations among a variety of known risk factors for CUA, including diabetes mellitus, obesity, and the use of vitamin K antagonists. We also found a 69%–75% risk reduction in CUA among patients randomly assigned to cinacalcet, the first suggestion from a prospective trial that any therapeutic strategy could reduce the risk of CUA.

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