The Effect of Cinacalcet on Calciphylaxis Events in Haemodialysis Patients in the EVOLVE Clinical Trial

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RESULTS

Uncontrolled secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease is a risk factor for cinacalcet therapy failure. Adverse event signals collected during the EVOLVE Trial were used to determine the frequency of CUA in patients receiving hemodialysis with moderate to severe SHPT. In total 3860 patients were randomized to placebo and 3860 patients were randomized to Cinacalcet. Among the 3860 trial patients, 18 patients in the placebo and 22 patients in the Cinacalcet group developed CUA (relative hazard 0.25, 95% confidence interval (CI) 0.08–0.80). CUA event rates (95% CI) at year 1 were 1.0% (0.8%, 1.3%) in patients randomized to placebo and 1.5% (1.0%, 2.4%) in patients randomized to Cinacalcet. By multivariable analysis, other factors associated with CUA included female sex, higher body mass index, higher diastolic blood pressure, and history of dipeptidyl peptidase-4 inhibitors. Obese patients (≥30 kg/m²) had higher CUA event rates (95% CI) at year 4 compared to non-obese patients (0.98% (0.51%, 1.61%) vs. 0.72% (0.47%, 1.10%), p-value < 0.001.

METHODS

In the EVOLVE, 3860 patients with SHPT receiving hemodialysis were randomized to receive cinacalcet or placebo supplements in addition to their regular therapy to reduce PTH levels. The effects of cinacalcet versus placebo. CUA events were collected while receiving hemodialysis with moderate to severe SHPT in patients with end-stage renal disease is a risk factor for calcific uremic arteriolopathy (CUA; calciphylaxis). We aimed to test the hypothesis that a reduction in PTH with cinacalcet reduces the frequency of CUA in patients receiving hemodialysis with moderate to severe SHPT.

RESULTS

Laboratory Findings Immediately Prior to CUA Manifestation

| Variable            | Placebo (N = 18) | Cinacalcet (N = 22) | P-value
|---------------------|------------------|---------------------|---------
| NT-proANP (pg/mL)  | 15 (10, 38)      | 21 (10, 44)        | 0.097   |
| uBNP (pg/mL)       | 56 (38, 94)      | 117 (44, 221)      | 0.021   |
| Renal artery stenosis (%) | 20 (11, 33)    | 28 (13, 42)        | 0.105   |

Comitant Medications Immediately Prior to CUA Manifestation

| Drug                  | Placebo (N = 18) | Cinacalcet (N = 22) | P-value
|-----------------------|------------------|---------------------|---------
| Statin use (%)        | 100 (100)        | 96 (100)            | 0.949   |
| Calcium-containing phosphate binder use (%) | 67 (67)          | 83 (83)             | 0.277   |
| Vitamin K antagonist use (%) | 72 (72)         | 100 (100)           | 0.001   |

DISCUSSIONS

We provide the first suggestion from a prospective trial that any therapeutic strategy could reduce the risk of CUA.

REFERENCES


SUMMARY

• The overall exposure-adjusted rate of 5.2 per 1000 patient-years in our total population is relatively low.
• Calciphylaxis became a relevant therapeutic target after the introduction of cinacalcet. We provide the first suggestion from a prospective trial that any calcimimetic strategy could reduce the risk of CUA.

Laboratory Findings Immediately Prior to CUA Manifestation

| Test                  | Placebo (N = 18) | Cinacalcet (N = 22) | P-value
|-----------------------|------------------|---------------------|---------
| Vitamin B12 (nmol/L)  | 166 (115, 216)   | 167 (112, 219)      | 0.921   |
| Albumin (g/dL)        | 3.4 (2.7, 3.8)   | 3.2 (2.8, 4.1)      | 0.398   |
| Serum phosphorus (mg/dL) | 5.8 (4.5, 8.1)  | 6.3 (3.4, 10.2)     | 0.049   |
| Hematocrit (%)        | 41 (34, 46)      | 40 (33, 46)         | 0.034   |
| Calcium (mg/dL)       | 9.7 (8.1, 11.4)  | 9.7 (8.1, 11.4)     | 0.989   |
| Serum potassium (mg/dL) | 5.4 (4.1, 6.6)  | 5.4 (4.1, 6.6)      | 0.989   |

CUA (Calciphylaxis) Study

• The frequency of vitamin K antagonist use is about 7–8 fold higher in patients who develop CUA and not undergoing CUA. On this account one third of the CUA patients started vitamin K antagonists during the trial.

CONCLUSION

We provide the first suggestion from a prospective trial that any therapeutic strategy could reduce the risk of CUA.

DISCLOSURES

As EVOLVE executive committee members, the Floege, Chertow, and Parfrey have received consulting fees from Amgen, Abbott, Fresenius Medical Care, Genzyme, and Roche Pharmaceuticals, and lecture or meeting support from Amgen, Fresenius Medical Care, Genzyme, and Roche Pharmaceuticals. Drs. Parfrey and Floege have received honoraria from Amgen, Sercis, for board membership or scientific advisory board participation, and have received travel support from Amgen, Sercis, as board members of the American Society of Nephrology Kidney Week 2014; Philadelphia, PA; 11-16 November 2014.