Cinacalcet Use and Risk of Gastrointestinal Bleeding in Secondary Hyperparathyroidism Patients Receiving Maintenance Hemodialysis

Tzu-Chieh Lin,[1] Haifeng Guo,[2] Paul Dluzniewski,[1] Yi Peng,[2] David Gilbertson,[2] Brian Bradbury,[1] Kimberly Nieman,[2] J. Michael Sprafka,[3] Jiannong Liu[2]

[1] Amgen Inc., Thousand Oaks, CA, USA; [2] Chronic Disease Research Group (CDRG), Hennepin Healthcare Research Institute, Minneapolis, MN US; [3] Independent

Disclosures

Lin TC, Dluzniewski P, and Bradbury B are employees and stockholders of Amgen Inc.; Guo H, Gilbertson D, Nieman K, and Liu J are employees of CDRG. CDRG receives research funds from Amgen. Sprafka JM is retired from Amgen.

Introduction

- Gastrointestinal (GI) bleeding contributes to hospitalization and death and is a frequent complication among dialysis patients.
- Increased risk of GI bleeding among dialysis patients is associated with kidney disease itself and with attendant comorbid conditions.
- Studies show that medications used by dialysis patients may increase the risk of GI bleeding.
- Cinacalcet use was hypothesized to increase GI bleeding risk in dialysis patients with secondary hyperparathyroidism (SHPT).
- This study assessed the association between cinacalcet use and risk of GI bleeding in hemodialysis (HD) patients with SHPT.

Methods

- We used the 2006-2010 USRDS database linked with patient medical records from a large US dialysis provider.
- The study included all US HD patients with SHPT receiving dialysis services from this provider, 2007-2010, who were:
  - Aged 18 years or older
  - Covered by Medicare Parts A, B, and D for ≥1 year
  - On dialysis for ≥90 days
- Patients with history of parathyroidectomy (PTX), kidney transplant, GI bleeding, or cinacalcet use within 1 year preceding the cohort entry date (the earliest date meeting all conditions above) were excluded.
- Patients were followed from cohort entry to the earliest date of death, PTX, GI bleeding, loss of Medicare coverage, change to peritoneal dialysis, transplant, or December 31, 2010.
- Outcome: GI bleeding event, including hospitalization with GI bleeding as primary diagnosis and death due to GI bleeding.
- This was a nested case-control study
  - Cases: patients with GI bleeding events during follow-up, event dates defined as index dates.
  - Controls, relative and case related: patients with no GI bleeding events before the index date of the corresponding case.
  - Incidence-density sampling match: up to four controls were matched to each case by age, sex, race, dialysis duration, and PTH level.
  - A control could become a case.
- Exposures were defined based on presence of a cinacalcet prescription in the Medicare Part D prescription event files:
  - Any use (yes/no) between cohort entry and index date.
  - Recency of use (within 61 days preceding index date [current], earlier than 61 days preceding index date [past], no use).
- Multivariable conditional logistic regression was used to estimate the odds ratios (ORs) and the corresponding 95% CIs for the association between cinacalcet use and risk of GI bleeding, adjusting for potential confounders including demographics, comorbid conditions, and medication use.
- Subgroup analyses were conducted by age, sex, race, dialysis duration, and PTH levels.

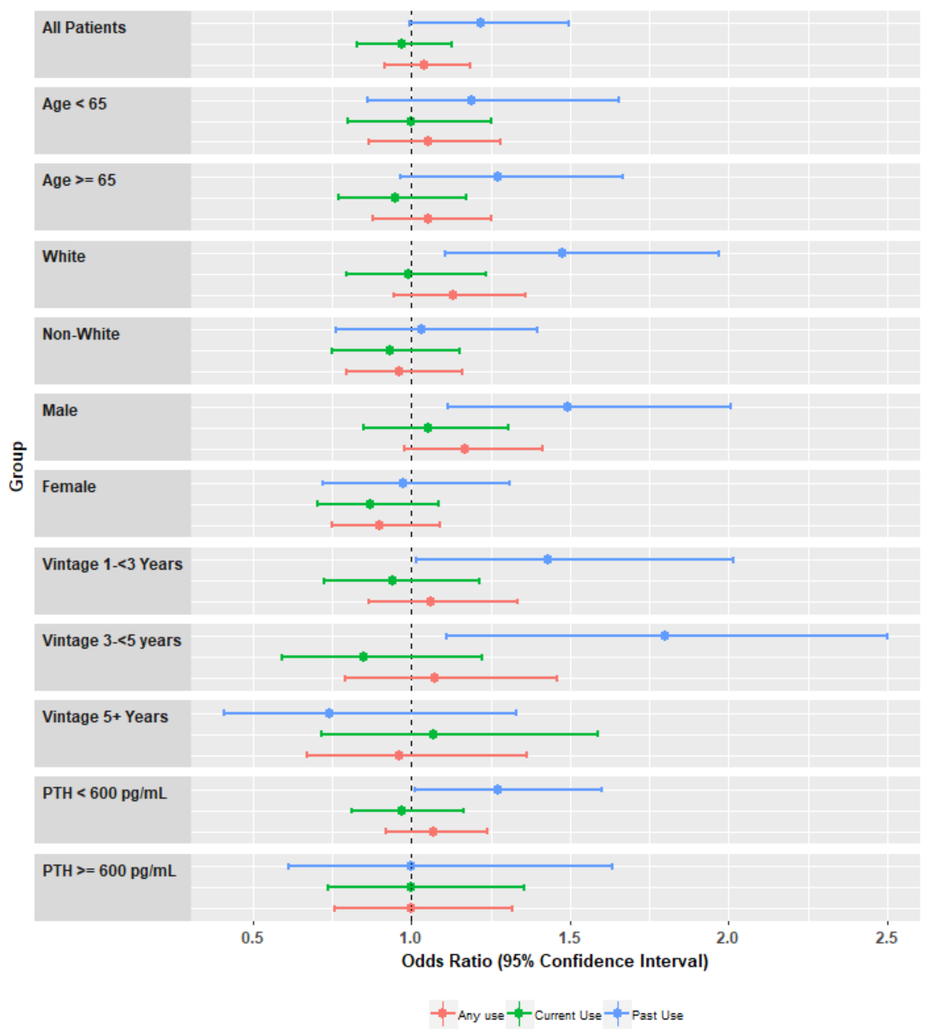
Results

- From 51,007 included patients, 2570 cases were identified.
- 2465 (96%) cases were matched to 9400 controls (2237 cases were matched to exactly four controls).
- Matched cases and controls were well balanced on matching variables (age 66.0 vs. 66.1 years; 52.0% vs. 52.1% female; 54.0% vs. 55.2% white; 2.5 vs. 2.3 years dialysis duration; 80.2% vs. 81.1% with PTH <600 pg/mL; differences were due to not every case being matched to four controls).
- Comorbid conditions and bleeding-related medication use were more prevalent in cases than in controls (Table 1).
- Cinacalcet use at any time before the index date was similar among cases and controls, 17.2% and 15.8%, respectively.
- The adjusted ORs and associated 95% CIs for the association between any, current, and past use and GI bleeding, relative to no use, were 1.04 (0.9-1.2), 0.97 (0.8-1.1), 1.22 (0.99-1.5), respectively (Figure 1).
- Results were similar across subgroups (Figure 1).

Table 1. Patient Comorbid Conditions and Other Medication Use in the Baseline Period before Entry Date

Variable	Matched Cases	Matched Controls
Overall	2465(100.00)	9400(100.00)
Comorbidity		
HDL	1268(51.44)	4645(49.41)
Necrosis	*	16(0.17)
Hepatitis	905(36.71)	2860(30.43)
cirrohosis	111(4.50)	160(1.70)
Asthma	218(8.84)	620(6.60)
COPD	659(26.73)	1914(20.36)
GI Cancer	31(1.26)	82(0.87)
Hematologic Cancer	39(1.58)	142(1.51)
Solid tumor Cancer	158(6.41)	553(5.88)
Systolic Heart Failure	179(7.26)	656(6.98)
Heart Failure	1260(51.12)	4250(45.21)
Diabetes Mellitus	1744(70.75)	6646(70.70)
CV Disease	515(20.89)	1635(17.39)
Thrombocytopenia	134(5.44)	373(3.97)
Low Serum Albumin	29(1.18)	96(1.02)
Calciphylaxis	220(8.92)	918(9.77)
CAD	1225(49.70)	3925(41.76)
PVD	220(8.92)	722(7.68)
Inflammatory GI	65(2.64)	159(1.69)
Diverticula GI	104(4.22)	232(2.47)
Lower GI	710(28.80)	1969(20.95)
Upper GI	762(30.91)	2100(22.34)
Surgery GI	59(2.39)	125(1.33)
Alcohol Use	51(2.07)	115(1.22)
Tobacco Use	242(9.82)	676(7.19)
Medication		
Warfarin	398(16.15)	1150(12.23)
Anticoagulant but not Warfarin	53(2.15)	124(1.32)
Antiplatelet	596(24.18)	1960(20.85)
Corticosteroid	372(15.09)	1133(12.05)
H2 Receptor Blocker	279(11.32)	998(10.62)
NSAID	253(10.26)	966(10.28)
Phosphatebinder	1404(56.96)	5226(55.60)
Protonpumpinhibitor	1188(48.19)	3974(42.28)
SNRI	91(3.69)	282(3.00)
SSRI	565(22.92)	1823(19.39)
Tertiarytricyclics	125(5.07)	333(3.54)
Other	86(3.49)	333(3.54)

Figure 1. Plot of ORs and 95% CIs: Cinacalcet Use vs No Use



Conclusions

- In this nested case control study of over 50,000 patients receiving HD, we found any use or current use of cinacalcet, a treatment commonly used to manage SHPT, did not associated with an elevated risk of GI bleeding.
- A modestly elevated risk of GI bleeding related to past cinacalcet use was found, which may be caused by residual confounding. Further investigation is necessary.

CDRG.org

Funded by a grant from Amgen