Assessing the Incidence of Osteosarcoma Among Teriparatide Users Via Linkage of Data From Medicare Part D and Multiple State Cancer Registries in the United States

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CONFLICT OF INTEREST

A. Gilsenan, K. Midkiff, D. Harris, L. McQuay, S. Hunter, and E. Andrews are employees of RTI Health Solutions, which received funding from Eli Lilly & Co. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. N. Kellier-Steele is a full-time employee of Eli Lilly & Co., the study sponsor, and holds stock in Eli Lilly & Co.

BACKGROUND

- Forteo® (teriparatide) is a recombinant human parathyroid hormone analog (1-34),[(rhPTH 1-34)] indicated for:
  - Treatment of postmenopausal women with osteoporosis at high risk for fracture
  - Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
  - Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
- In preclinical studies in rats, teriparatide caused a dose-dependent increase in the incidence of osteosarcoma.
- Osteosarcoma is a rare bone cancer in humans, with an estimated background incidence in adults aged 65 years and older of 3.9 cases per million population per year.
- This study is 1 of 5 surveillance studies initiated since initial drug approval in 2002 to evaluate a potential increased risk of osteosarcoma with teriparatide treatment.

OBJECTIVE

- Primary: To estimate the incidence rate ratio (IRR) of osteosarcoma among patients aged 65 years or older treated with teriparatide versus a cohort of matched comparators.
- Secondary: To describe characteristics and similarities of each cohort.

METHODS

Table 1. Study Design Overview

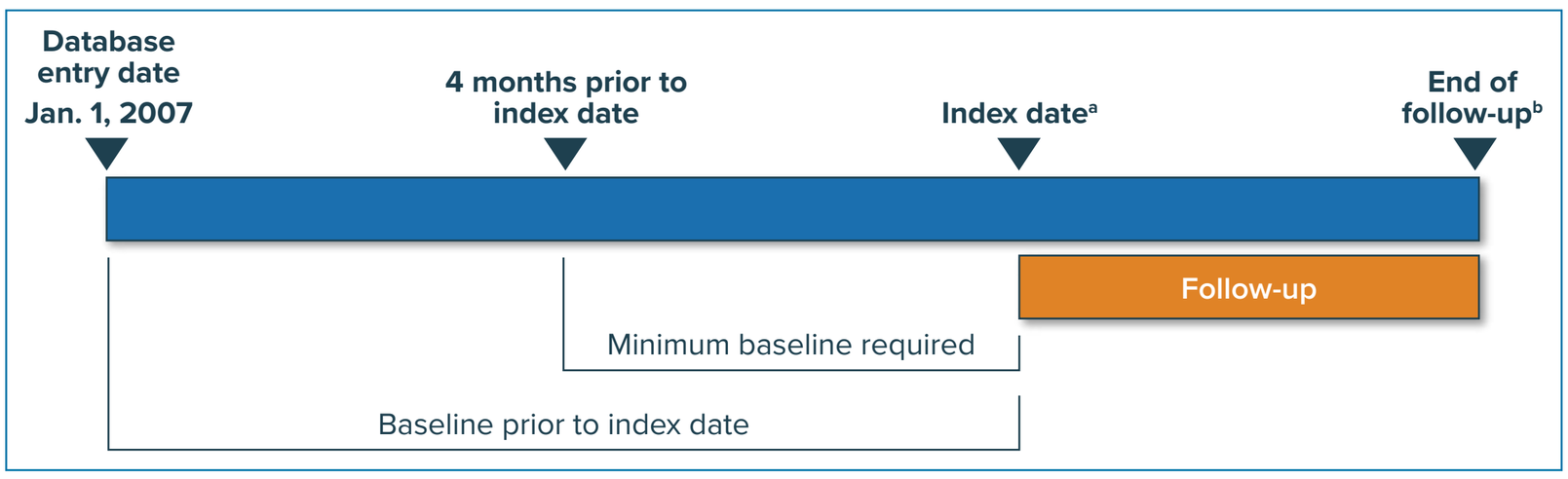
Study period	2007-2014
Population	US residents aged 65 years and older with at least 4 months of Medicare Part D coverage prior to index exposure
Exposure	Teriparatide (at least 1 filled prescription during the study period)
Outcome	Osteosarcoma[a]
Comparator	General population of Medicare Part D patients with a prescription for a medication other than teriparatide
Matching	Up to 4 comparators during calendar year and month of the index prescription matched on age, sex, 3-digit zip code and no. of therapeutic classes of medications in the past 4 months
Data sources	• Medicare Part D (exposure) • Population-based state cancer registries in the US (outcome) • Medicare Parts A, B, D (covariates for sensitivity analysis)
Linkage process	Cancer registries sent identifiable information to Medicare for deterministic linkage (Figure 2)
Main analysis	• IRR and 95% CI estimated using exact conditional Poisson regression • Assumed no induction or latency period between teriparatide exposure and the development of clinically detectable osteosarcoma • Adjusted for registry participation (i.e., coverage fraction)[b]
Sensitivity analysis	Completed for patients with Medicare Parts A and B where more baseline health status covariates were available

[a] 9180/3 Osteosarcoma NOS (not otherwise specified), 9181/3 Chondroblastic osteosarcoma, 9182/3 Fibroblastic osteosarcoma, 9183/3 Telangiectatic osteosarcoma, 9184/3 Osteosarcoma in Paget's disease of bone, 9185/3 Small cell osteosarcoma, 9186/3 Central osteosarcoma, 9187/3 Intraosseous well differentiated osteosarcoma, 9192/3 Parosteal osteosarcoma, 9193/3 Periosteal osteosarcoma, 9194/3 High-grade surface osteosarcoma, 9195/3 Intracortical osteosarcoma.

[b] Coverage fraction = number of cases reported by the participating registries from 2007 to 2014 divided by the total number of osteosarcoma cases occurring in the US during 2007-2014.

CI = confidence interval; US = United States.

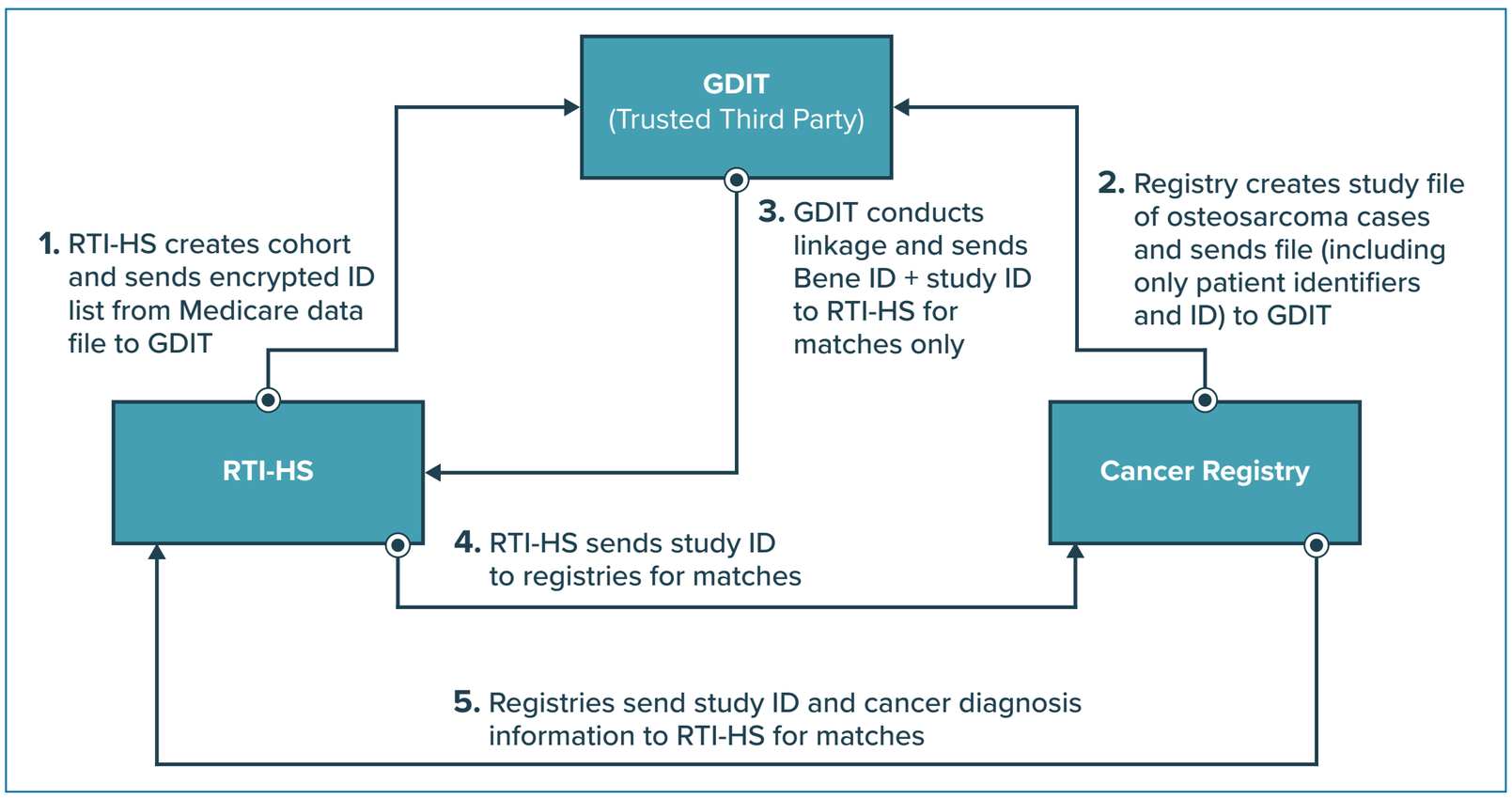
Figure 1. Study Initiation Period, Index Date and Follow-up Time



[a] Date of teriparatide prescription for exposed cohort; date of prescription for any drug (other than teriparatide) for comparator cohort.

[b] Osteosarcoma diagnosis, death, or end of study period.

Figure 2. Linkage Method



Bene ID = beneficiary identifier; GDIT = General Dynamics IT.

Note: GDIT is a trusted third party for Medicare data.

RESULTS

- A file with a total of 153,316 patients in the teriparatide cohort and 613,247 patients in the comparator cohort (91% female; mean age at index, 77) was linked to a file with 811 osteosarcoma cases from 26 participating state cancer registries (covering 68% of US cases aged 65+ and diagnosed 2007-2014).
- Mean duration of treatment with teriparatide was 10 months.

Main Results

Table 2. Incidence Rate Ratio and 95% Confidence Interval, Adjusted for Number of Participating Registries

Statistic	Teriparatide Cohort (n = 153,316)	Comparator Cohort (n = 613,247)
Number of matched osteosarcoma cases by linkage to participating registries	0	n < 11[a]
Total person-time of observation (years)	585,955	2,212,036
Total person-time of observation adjusted for registry coverage fraction (68%)	397,000	1,498,715
Incidence rates per 1,000,000 person-years, (95% CI)	0.0 (0.0, 9.3)	Suppressed (1.5, 8.7)
IRR (95% CI)	0.0 (0.0, 3.2)	

[a]To protect patient privacy, non-zero cell counts < 11 cannot be disclosed.

Descriptive Results for Patients With Medicare Parts A, B, and D

- As anticipated, corticosteroid use, use of osteoporosis drugs, and history of fracture were higher in the teriparatide cohort compared with the comparator cohort prior to index date; however, the mean Charlson Comorbidity Index score was similar (Table 3).
- A higher proportion of teriparatide users had 3 or more inpatient or outpatient visits in the 4 months prior to index date compared with the comparator cohort (Table 3).
- Among risk factors relevant to developing osteosarcoma, the teriparatide subcohort and comparator subcohort were similar with regard to radiation treatment and history of Paget's disease of the bone (Table 3).

Table 3. Descriptive Characteristics for the Teriparatide and Comparator Cohorts in Subset of Patients With Medicare Parts A, B, and D Coverage

Characteristic	Teriparatide Cohort (n = 105,794)	Comparator Cohort (n = 297,509)
Osteoporosis indicators		
Use of corticosteroid drugs prior to index date	39%	31%
Use of other osteoporosis drugs prior to index date	59%	26%
Health status proxies		
History of vertebral or hip/pelvic fracture	23%	8%
≥ 3 inpatient and outpatient visits in the 4 months prior to index date	42%	31%
History of cancer	35%	34%
Mean Charlson Comorbidity Index score (SD)	3.8 (3.25)	3.8 (3.31)
Risk factors		
Prior radiation	3%	4%
History of Paget's disease of the bone	0.6%	0.4%

SD = standard deviation.

DISCUSSION AND CONCLUSIONS

- The incidence of osteosarcoma among teriparatide-treated patients aged 65 years or older in the US ranges from 0 to 3.2 times the incidence of osteosarcoma in US patients aged 65 years or older treated with other medications.
- Given the low incidence of osteosarcoma, this range of effect is inconsistent with a large absolute increase in risk for osteosarcoma.
- The findings from the sensitivity analysis did not alter the study findings.

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