Study Update for a Postmarketing Case Series Study of Adult Osteosarcoma and Teriparatide in the United States

David Harris, MPH[1]; Kirk Midkiff, MPH[1]; Alicia Gilsenan, PhD[1]; Nicole Kellier-Steele, PhD[2]; David McSorley, MPH[1]; Elizabeth B. Andrews, PhD[1]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Eli Lilly & Co., Indianapolis, IN, United States

CONFLICT OF INTEREST

D. Harris, K. Midkiff, A. Gilsenan, D. McSorley, and E. Andrews are employees of RTI Health Solutions (RTI-HS), which received funding from Eli Lilly & Co. to conduct this study. The contract between RTI-HS and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organizations, including pharmaceutical companies. N. Kellier-Steele is a full-time employee of Eli Lilly & Co., the study sponsor, and holds stock in Eli Lilly & Co.

BACKGROUND

- Teriparatide is a recombinant human parathyroid hormone analog (PTH 1-34) approved in 2002 in the United States (US) for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. It is also approved for increase in bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. In 2009, the treatment indication was expanded to include treatment of men and women with glucocorticoid-induced osteoporosis who are at high risk for fracture.
- In preclinical studies in rats, teriparatide caused a dose-dependent increase in the incidence of osteosarcoma. Cases of osteosarcoma have been reported rarely in the postmarketing period. The association with teriparatide is unclear. Long-term surveillance studies are ongoing.
- Osteosarcoma is a rare bone cancer in humans, with an estimated background incidence in adults aged 40 years and older of 2.5 cases per million population per year.[1] Standardized to the age-sex distribution of patients receiving teriparatide,[2] the estimated incidence rate of osteosarcoma is 3.2 cases per million per year.
- As a condition of approval, the US Food and Drug Administration and the European Medicines Agency requested postapproval surveillance studies be conducted (Forteo Post-Approval Surveillance Study: Case Series). The study initiated in Europe lasted 10 years and has completed.[3] The US case series study is an ongoing, 15-year surveillance study and the subject of this poster.[4,5]

Forteo Post-Approval Surveillance Study: Case Series

- Initiated in 2003 to monitor for a signal of a possible association between teriparatide, an injectable treatment for osteoporosis, and adult osteosarcoma.
- Primary objectives: (1) to identify incident cases of osteosarcoma, if any, with a history of treatment with teriparatide; and (2) to identify and interview 33% of newly diagnosed cases of osteosarcoma in adults aged 40 years and older in the US.
- Secondary objective: To systematically collect, for descriptive epidemiology purposes, additional patient information, including demographics and data related to other risk factors for osteosarcoma.

OBJECTIVE

- To provide a study update as of March 31, 2017, including preliminary data and descriptive characteristics of patients aged 40 years and older with osteosarcoma in the US.

METHODS

- Incident cases of osteosarcoma diagnosed from 2003 to 2017 are identified through participating cancer registries in the US. Data collection will continue through the end of 2018.
- After consent, case information (including demographics, treatment with medications, and exposure to possible risk factors) is ascertained from the patient or proxy via a 25- to 30-minute telephone interview.
- A standardized incidence ratio (SIR) is calculated by dividing the observed number of patients with osteosarcoma exposed to teriparatide by the expected number of patients with osteosarcoma exposed to teriparatide that are estimated to be captured by the study.
  - The expected number of patients with osteosarcoma exposed to teriparatide is estimated by the product of the osteosarcoma background incidence rate, the estimated person-time at risk following exposure to teriparatide since drug launch, and the study interview rate.

Study Design

- Retrospective case series.

Eligibility Criteria

- Adults aged 40 years and older at the time of osteosarcoma diagnosis.
- Diagnosis of osteosarcoma (12 ICD-O-3 codes; no restriction on primary site of tumor) on or after January 1, 2003.

Case Identification Setting

- US cancer registries (population-based and comprehensive cancer treatment center cancer registries): cancer reporting is mandatory in all US states, and state registries collect cancer diagnoses for 96% of the US population. Registries receive reports from hospitals, pathology laboratories, physician offices, and mortality files.[6]
- As of March 31, 2017, a total of 29 US cancer registries had contributed data to the study (Figure 1).

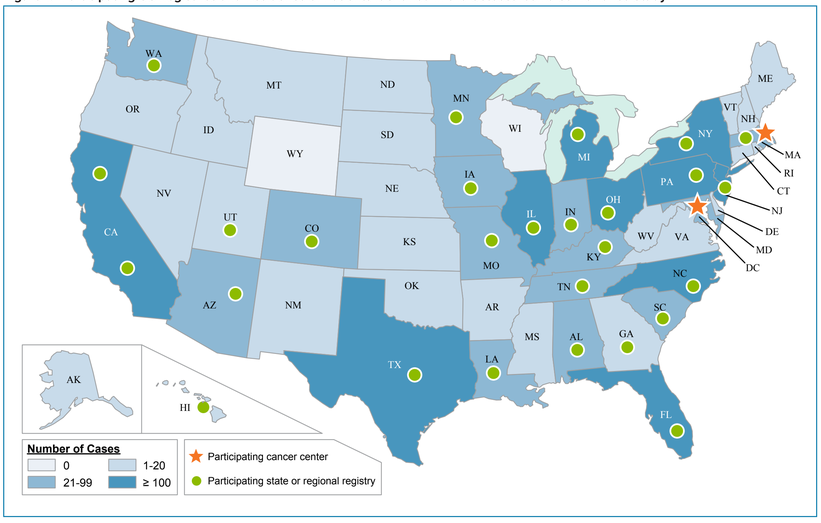
Data Collected From Cancer Registries

- Patient demographics: age, sex, race, and vital status.
- Cancer information: date of diagnosis, cancer site, morphology, grade.

Data Collected From Patient (or Proxy) by Telephone Interview

- Drug exposure: prior use of teriparatide, prior use of other medications for osteoporosis.
- Factors that may increase the risk of osteosarcoma: exposure to radiation, history of Paget disease of bone, history of other cancers, injury or infection at the site of the tumor, agricultural or occupational pesticide exposure, petrochemical exposure, and family history of osteosarcoma.

Figure 1. Participating US Registries and Residence of Patients Identified in the Osteosarcoma Surveillance Study



RESULTS

- As of March 31, 2017, interviews were completed for 1,046 patients diagnosed with osteosarcoma between 2003 and 2014 (Figure 2) for a study interview rate of 25%. The person-time at risk following exposure to teriparatide since drug launch is estimated to be 4,229,000 person-years.
- The expected number of osteosarcoma cases among patients treated with teriparatide = 3.38.
- Two reports of teriparatide use prior to diagnosis were identified.
- Given the two observed cases, the SIR = observed (2) ÷ expected (3.38) = 0.59 (90% confidence interval, 0.11-1.86).
- Patients with osteosarcoma interviewed for the study were predominantly non-Hispanic whites, with a mean age at diagnosis of 61 years (Figure 3).
- The distribution of possible risk factors for adult osteosarcoma is included in Table 1.
- Osteosarcoma not otherwise specified (NOS) was the most common tumor type, followed by chondroblastic osteosarcoma and fibroblastic osteosarcoma, representing 90% of the cumulative distribution of cases (Table 2).
- The most common tumor sites, in order, were the leg bones, skull/face/mandible, and the pelvis/coccyx (Figure 4).

Figure 2. Study Accrual for Patients Diagnosed From 2003 to 2014

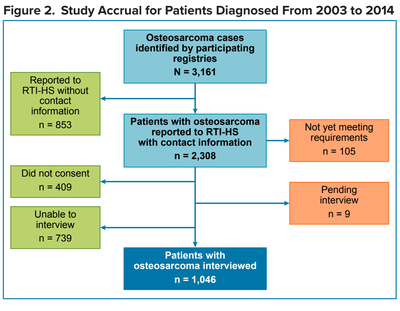
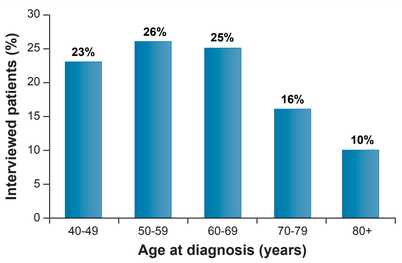
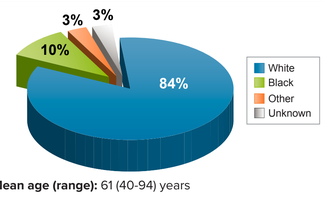


Figure 3. Demographic Characteristics of Adult Patients With Osteosarcoma Interviewed for the US Adult Osteosarcoma Surveillance Study (N = 1,046)





- **Mean age (range):** 61 (40-94) years
- **Ethnicity:** 5% Hispanic
- **Sex:** 52% male
- **Vital status:** 22% deceased at the time the case was identified

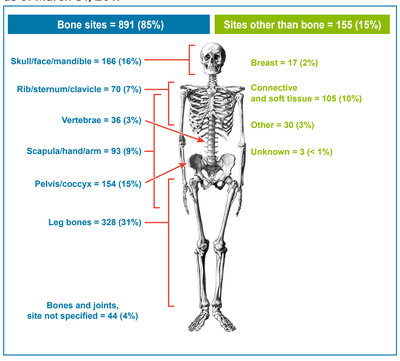
Table 1. Self-Reported Prevalence of Exposures (and Characteristics) Among Interviewed Patients and Proxies (N = 1,046)

Exposure/Characteristic	n (%)
Lifestyle exposures	
Drank alcohol during 12 months before diagnosis	658 (63%)
Smoked ≥ 100 cigarettes in their lifetime	512 (49%)
Treatment, injury, and infection exposures	
Previous injury or infection at tumor site	173 (17%)
Prior radiation treatment	202 (19%)
Environmental exposures	
Agricultural pesticide exposure	246 (24%)
Occupational petrochemical exposure	121 (12%)
Occupational radiation exposure	72 (7%)
Personal and family history	
Personal history of other cancers	278 (27%)
Family history of osteosarcoma	51 (5%)
Personal history of Paget disease of bone	46 (4%)

Table 2. Distribution of Morphology Among Interviewed Cases (N = 1,046)

Morphology	n (%)
9180 Osteosarcoma NOS	735 (70%)
9181 Chondroblastic osteosarcoma	136 (13%)
9182 Fibroblastic osteosarcoma	70 (7%)
9192 Parosteal osteosarcoma	32 (3%)
9186 Central osteosarcoma	21 (2%)
9183 Telangiectatic osteosarcoma	18 (2%)
9184 Osteosarcoma in Paget disease	15 (1%)
9185 Small cell osteosarcoma	8 (1%)
9193 Periosteal osteosarcoma	6 (1%)
9194 High-grade surface osteosarcoma	3 (< 1%)
9187 Intraosseous well-differentiated osteosarcoma	2 (< 1%)
9195 Intracortical osteosarcoma	0 (0%)

Figure 4. Osteosarcoma Site for Interviewed Patients (N = 1,046), as of March 31, 2017



DISCUSSION AND CONCLUSIONS

- Based on interim calculations of the SIR, no signal of an increased risk of osteosarcoma with teriparatide use has been seen in the first 12 years of this 15-year study. Eight cases would need to have been seen during the same period for the lower bound of the SIR to exceed 1.
- The interim assessment of data from this ongoing study contribute to the knowledge about the long-term safety of teriparatide treatment.

REFERENCES

1. Surveillance, Epidemiology, and End Results (SEER) Program. Rate of osteosarcoma from SEER*Stat Database. National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch. Released April 2013, based on the November 2012 submission.
2. Eli Lilly and Company. IMS LRx data. Teriparatide patient age-gender distribution: launch through Oct 2008. Data on file. March 2009.
3. Midkiff KD. Forteo/Forsteo post-approval osteosarcoma surveillance study (Study B3D-MC-GHBX). Postauthorization safety study information. June 2014. Available at: http://www.encepp.eu/encepp/openAttachment/studyResult/8539. Accessed June 29, 2016.
4. Andrews EB, Gilsenan AW, Midkiff K, Sherrill B, Wu Y, Mann BH, et al. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res. 2012;27(12):2429-37.
5. Midkiff KD, Andrews EB, Gilsenan AW, Deapen DM, Harris DH, Schymura MJ, et al. The experience of accommodating privacy restrictions during implementation of a large-scale surveillance study of an osteoporosis medication. Pharmacoepidemiol Drug Saf. 2016 Aug;25(8):960-8.
6. Centers for Disease Control and Prevention. National Program of Cancer Registries (NPCR). April 2016. Available at: http://www.cdc.gov/cancer/npcr/about.htm. Accessed June 27, 2016.

CONTACT INFORMATION

David Harris, MPH
Research Epidemiologist

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1 919.541.7493
Fax: +1 919.541.7222
E-mail: dharris@rti.org