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

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CONFLICT OF INTEREST

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

BACKGROUND

- Teriparatide is a recombinant human parathyroid hormone analog, 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 causality to teriparatide use 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 (Osteosarcoma Surveillance Study). 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]

US ADULT OSTEOSARCOMA SURVEILLANCE STUDY

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 an update on the results of the Osteosarcoma Surveillance Study, including descriptive characteristics of patients aged 40 years and older with osteosarcoma in the US.

METHODS

- Incident cases of adult osteosarcoma diagnosed on or after January 1, 2003, are identified through cancer registries in the US. After consent, case information (including demographics, treatment with medications, and exposure to possible risk factors) is ascertained from the patient or proxy via 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.

Study Design

- Retrospective case series

Eligibility Criteria

- Adults aged 40 years and older at time of osteosarcoma diagnosis
- Diagnosis of osteosarcoma (12 ICD-O-3 codes) on or after January 1, 2003

Case Identification Setting

- US cancer registries (population-based and comprehensive cancer treatment center cancer registries) were used to identify cases.
- Cancer reporting is mandatory in all states of the US, and state registries collect cancer diagnoses for 96% of the US population.
- Registries receive reports from hospitals, pathology laboratories, and physician offices and mortality files.[6]
- As of March 31, 2016, a total of 29 US cancer registries had contributed data to the study.

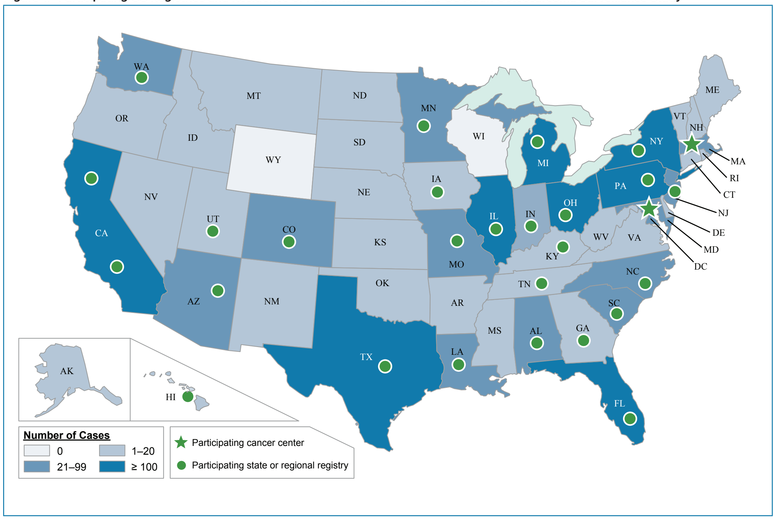
Data Collected From Cancer Registries

- 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
- Known risk factors for osteosarcoma: exposure to radiation, history of Paget's disease of bone
- Other possible risk factors for osteosarcoma: history of other cancers, injury or infection at tumor site, agricultural or occupational pesticide exposure, petrochemical exposure, family history of osteosarcoma

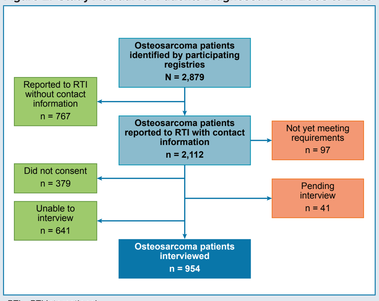
Figure 1. Participating US Registries and Residence of Patients Identified in the US Adult Osteosarcoma Surveillance Study



RESULTS

- Results for the SIR calculation have been updated since the abstract was submitted and are current to March 31, 2016, for patients diagnosed from January 1, 2003, to December 31, 2014.
- SIR calculation inputs
  - Numerator (observed)
    - Two patients had exposure to teriparatide prior to diagnosis of osteosarcoma.
  - Denominator (expected) = osteosarcoma background incidence rate × person-time at risk following exposure to teriparatide × study interview rate
    - The osteosarcoma background incidence rate is 3.2 cases per million population per year.
    - Person-time at risk following exposure to teriparatide since drug launch is estimated to be 4,229,000 person-years.
    - The interview rate (i.e., study coverage) is 24% (1,004/4,178).
    - Given these parameters, we would expect to see approximately 3.25 patients with osteosarcoma exposed to teriparatide.
  - SIR = observed ÷ expected = 0.62 (90% confidence interval [CI], 0.11-1.94)
  - Seven patients with an exposure to teriparatide would need to have been observed during the same period of time for the lower bound of the 90% CI to exceed 1.
- Descriptive results have been updated since the abstract was submitted and include data as of the most recent data lock, March 31, 2016, for patients diagnosed from January 1, 2003, to December 31, 2013.*

Figure 2. Study Accrual for Patients Diagnosed From 2003 to 2013



RTI = RTI International.

Figure 3. Demographic Characteristics of Adult Osteosarcoma Patients Interviewed for the US Adult Osteosarcoma Surveillance Study (N = 954)

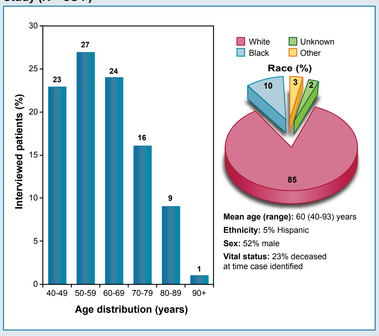


Figure 4. Osteosarcoma Site For Interviewed Patients (N = 954), as of March 31, 2016

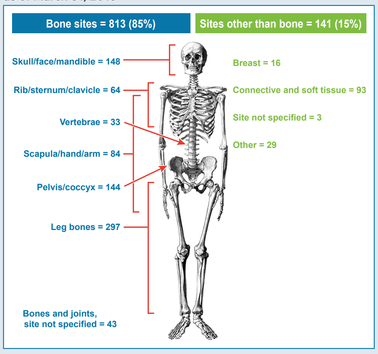


Table 1. Self-Reported Prevalence of Exposures (and Characteristics) Among Interviewed Patients (N = 954)

Exposure/Characteristic	n (%)
Lifestyle exposures	
Drank alcohol during 12 months before diagnosis	608 (64)
Smoked ≥ 100 cigarettes in their lifetime	472 (49)
Treatment, injury, and infection exposures	
Previous injury or infection at tumor site	164 (17)
Prior radiation treatment	184 (19)
Environmental exposures	
Agricultural pesticide exposure	229 (24)
Occupational petrochemical exposure	112 (12)
Occupational radiation exposure	63 (7)
Personal and family history	
Personal history of other cancers	257 (27)
Family history of osteosarcoma	47 (5)
Personal history of Paget's disease of bone	46 (5)

Note: Known risk factors are highlighted in red.

Table 2. Distribution of Morphology Among Interviewed Cases (N = 954)

Morphology	n (%)
9180 Osteosarcoma NOS	679 (71)
9181 Chondroblastic osteosarcoma	115 (12)
9182 Fibroblastic osteosarcoma	63 (7)
9192 Parosteal osteosarcoma	30 (3)
9186 Central osteosarcoma	20 (2)
9183 Telangiectatic osteosarcoma	16 (2)
9184 Osteosarcoma in Paget's disease	15 (2)
9185 Small cell osteosarcoma	7 (1)
9193 Periosteal osteosarcoma	4 (< 1)
9194 High-grade surface osteosarcoma	3 (< 1)
9187 Intraosseous well-differentiated osteosarcoma	2 (< 1)
9195 Intracortical osteosarcoma	0 (0)

NOS = not otherwise specified.

*Due to a 9- to 18-month case identification and reporting lag time, patients diagnosed in 2014-2016 are not included in figures or tabular displays. No such patients reported prior teriparatide use.

DISCUSSION AND CONCLUSIONS

- There have been two reports of teriparatide treatment before an osteosarcoma diagnosis. Seven reports would need to have been seen during the same period for the lower bound of the SIR CI to exceed 1. The current SIR is **0.62 (90% CI, 0.11-1.94) in this ongoing study**.
- Regarding descriptive characteristics among the 954 patients interviewed:
  - Osteosarcoma NOS was the most common tumor type, followed by chondroblastic osteosarcoma and fibroblastic osteosarcoma, representing 90% of the cumulative distribution of cases.
  - Most common tumor sites, in order, were the leg bones, skull/face/mandible, and the pelvis/coccyx.
  - Of the osteosarcomas reported by the cancer registries and interviewed by RTI, 141 (15%) occurred in a site other than bone.
- These interim results describe the distribution of possible risk factors among adult patients with osteosarcoma from a population-based case series and contribute to the knowledge about the long-term safety of teriparatide treatment.

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