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Editorial

Challenges in studying very rare cancer outcomes and infrequent exposures: example of teriparatide and osteosarcoma

When preclinical toxicology studies show a clear and dose-related association between a medication exposure and a specific tumor type, an obvious question is, what will happen in humans? Regulatory agencies often respond by requiring additional studies before approval or a safety study to address the possible medication-outcome association in the postmarketing environment. However, if the medication is not commonly used, and the tumor rarely occurs in the general population, the probability of being able to confirm anything other than a very large increase in risk in a treated population is low. For the symposium described in the Pinheiro et al. article in this issue, we illustrated this type of challenge using a program of research relating to teriparatide; we offer some observations here.

Teriparatide, a recombinant human parathyroid hormone analog, is an osteoanabolic used to increase bone mass for treatment of osteoporosis in specific populations with high fracture risk. This mechanism differs from other medications that aim to reduce bone resorption and turnover. In a clinical study of postmenopausal women, among 1326 women with a baseline and follow-up radiograph, researchers demonstrated a 65% reduction in new vertebral fractures in the teriparatide-treated group (5%) using the currently marketed dose compared with the placebo group (14%) [1]. Although not measured as outcomes in the clinical trials, vertebral fractures in general have been associated with increased short-term mortality, morbidity, and health care resource use [2]. In one 2-year (near-lifetime) preclinical study, in rats-administered teriparatide doses that created systemic exposures 3 to 60 times greater than that in humans, researchers found a dose-dependent increase in the incidence of osteosarcoma [3]. Subsequent studies demonstrated a “no-effect” dose in rats [4], and no bone tumors emerged in a long-term study of cynomolgus monkeys [5]. In addition, no cases emerged in humans in the clinical trial experience of over 2800 individuals; however, the U.S. product label of teriparatide contains a black box warning about the potential risk of osteosarcoma and recommends use in restricted populations and a treatment duration of no more than 2 years [6]. A published review of safety of teriparatide after 10 years of use concluded that no new safety issues had emerged that were not observed in clinical trials, and that the risk of osteosarcoma remained theoretical [7]. However, actual product use is relatively uncommon, with fewer than 40,000 patients prescribed Forteo (teriparatide) in Medicare part D in 2013 of 35 million patients enrolled [8]. Osteosarcoma in humans is a primary malignant bone tumor with an incidence of 4.2 per million for those aged 60 years and more [9]. Known risk factors are few, and most cases are diagnosed in patients without identified risk factors [10].

To design postauthorization safety studies of this theoretical association in humans, certain aspects of the population at risk and the rare nature of the outcome were key factors for consideration. For example, many of the resources available for drug safety studies in large populations are commercial health insurance claims databases containing records of filled prescriptions and outcomes that result in reimbursement for a physician visit or hospitalization. Because these databases primarily include employed persons, they do not include many teriparatide patients, most of whom are retirees aged more than 65 years. Another limitation of commercial claims is the nonspecific ICD-9 coding. Osteosarcoma is grouped into an ICD-9 code with a broad group of tumors that outnumber osteosarcoma in prevalence by a ratio of 9:1. Specific ICD oncology codes for osteosarcoma are used by cancer registries, but not by other databases commonly used in epidemiology studies [11]. Yet another limitation is the relatively short follow-up period included in commercial claims because employed individuals frequently change health insurance coverage.

The Surveillance, Epidemiology, and End Results Program–Medicare linked database, covering approximately 30% of the U.S. population in 2013, includes older individuals, uses ICD oncology codes, and permits long-term follow-up. However, because of the infrequency of osteosarcoma, this database was considered too small.

Three studies were implemented, all using cancer registries for osteosarcoma ascertainment due to the ability to differentiate osteosarcoma from other tumor types using ICD oncology codes. Two studies used a case-series design [12,13], and one used a prospective cohort design [14]. The case-series design was implemented in 2003 in the United States and in 2004 in five Nordic countries. Cancer registries covering over 60% of the U.S. population and nearly all the Nordic-country populations identified confirmed cases of osteosarcoma. Ascertainment of prior exposure and risk factors was made by telephone interview with the patient or proxy (United States) [12] or through abstraction of medical records (Nordic countries) [13]. In the United States, telephone interviews were validated for a sample of patients through chart abstraction, and concordance was high ($\geq$90%) for osteoporosis medications. We anticipated high levels of recall for teriparatide because of product characteristics: It is stored in a refrigerator and administered as a daily self-injection.

The case-series design was selected in preference to a case-control design in these two studies because of the inefficiency of including a control group, given the infrequent use of teriparatide. The analysis for these studies, therefore, compares the observed exposure with the expected exposure assuming no medication-

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outcome association, a standard analytic method in public health epidemiology. The analysis takes into account the age- and sex-adjusted background osteosarcoma incidence rates in the treated population, estimated teriparatide cumulative person-years at risk within the geographic areas covered (adjusted for mortality), and the interview rate.

In the U.S. case-series study, midway through the planned duration, 1448 persons with osteosarcoma diagnosed in 2003–2009 were identified by participating cancer registries (estimated to be 62% of all adult cases in the United States for that time period) [12]. Of those, 549 patients or proxies were interviewed; no valid reports of prior teriparatide exposure were identified. Interviewed patients were similar to noninterviewed patients with regard to mean age, sex, race, geographic distribution, tumor type, and site of tumor. At that time, the study had adequate power to detect a risk, if it occurs, of one additional case per 78,000 treated patients per year (i.e., a 5-fold increase in risk), without regard to latency. Since the reporting of these data at the workshop described by Pinheiro et al, two cases have been reported with prior teriparatide exposure, when three such cases would have been expected based on the background rate and geographic coverage of the study. The U.S. study is expected to be able to detect a two-fold or three-fold increase in risk, if it exists, by the end of the 15-year study period.

At the conclusion of the 10-year Nordic study, no patient diagnosed with osteosarcoma was identified with prior teriparatide exposure. Given the infrequent occurrence of osteosarcoma and teriparatide use relative to the population size of these countries in the age group of interest, the study was expected to identify patients with osteosarcoma previously treated with teriparatide only if teriparatide was associated with a large increased risk. For example, if a single case of osteosarcoma with prior teriparatide treatment had been observed, it would indicate a 12-fold (90% confidence interval, 0.6-fold to 55-fold) increase in the risk of osteosarcoma associated with treatment compared with the background rate. This hypothetical 12-fold increase would translate to an absolute risk difference of one additional case of osteosarcoma per 47,000 teriparatide-treated patients per year [15].

An ongoing patient registry was established in the United States in 2009 in which all new teriparatide patients are invited to enroll. To maximize enrollment, patient involvement is minimal, and there is no physician involvement. Patients sign a one-time-only registration form confirming their exposure to teriparatide and also supplying some identifying information necessary to carry out linkage with individual state cancer registry databases. Patients are followed for development of osteosarcoma through annual linkage with participating U.S. cancer registries. These registries cover over 90% of the U.S. population aged 18 years and older. Enrollment is scheduled to continue through 2017, and linkage will continue through 2024. If the study included 1.7 million patient-years of follow-up at the final linkage with cancer registries, five cases of osteosarcoma would be expected. As of March 31, 2016, 54,804 people had enrolled [14]. Annual linkages through 2015 have not yet identified any incident cases of osteosarcoma. Although the registry includes a very large number of enrollees, the likelihood of achieving the target 1.7 million patient-years of follow-up is low.

These three studies provide different methods to address the very difficult challenge of studying an uncommon exposure in an older population to detect a signal of a possible increase in the risk of a rare tumor. Taken together, the interim data provide considerable assurance in reducing the uncertainty around a possible meaningful increased risk of osteosarcoma associated with teriparatide. Strengths and limitations of each design were presented during the symposium and are beyond the scope of this editorial. The designs represented the best methods available and feasible at the time the studies were initiated.

What additional design or data sources available today could further reduce the uncertainty about this exposure-outcome association? Several options are worth considering. Large databases are needed to find enough exposed individuals. However, even the large Sentinel System (with 178 million individuals by the end of 2012) would currently not have enough patients in the age range of interest [16]. Because Medicare prescription drug coverage began in 2006 and includes a majority of patients aged 65 years and more, this source is promising. However, ascertainment of osteosarcoma is not possible in Medicare data (or the Sentinel System) alone because of the imprecise coding schemes available in claims, which could obscure any true association between teriparatide and osteosarcoma. Linkage with cancer registries would facilitate the ascertainment of primary osteosarcoma cases using the more precise coding system. However, because no national cancer registry exists, linkage is possible only through research agreements with individual state cancer registries, each having unique requirements and restrictions [17]. Furthermore, the current environment, in which extreme sensitivity, and in some cases legislation, limits the ability to share patient-level identifying data to allow linkages for research makes implementation of this approach challenging. Although such linkage collaborations are possible, they do not represent a scalable and practical solution for future monitoring of multiple drugs, biologics, and devices that have signals of possible associations with rare cancers. We were among the many researchers at this workshop who urged federal agencies to tackle these challenges and work toward solutions, such as a national registry or simplified application process (as described in the paper by Deapen in this issue).

The practical limitations inherent in research involving infrequent exposures and rare outcomes must be considered before embarking on future such research programs. It would be important to establish appropriate expectations around the target level of potential increased risk that studies should be designed to detect or rule out. That level of risk should be meaningful to the patient in the context of the benefits achieved through therapy. In the case of teriparatide, how would the average patient view the reduction in fracture risk and attendant morbidity and mortality attributable to treatment, compared with a potential and hypothetical future (given latency) risk of osteosarcoma? Current data suggest that risk is less than five-fold higher than the general population risk for this very rare outcome, or, in absolute terms, less than 1 of 78,000 patients per year. The public good, in terms of knowledge and resources, may be better served by measuring the patients' risk tolerance before undertaking long-term safety surveillance studies designed to measure a potential risk that may be considered acceptable (or not) in comparison to benefits of treatment.

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