1. ABSTRACT

Title

The use, safety, and effectiveness of Prolia in clinical practice among Chinese women with postmenopausal osteoporosis ─ Taiwan and Hong Kong

Keywords

Real-world evidence, postmenopausal osteoporosis, Prolia, hip fracture, osteonecrosis of the jaw, atypical femur fracture, hypocalcemia

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Prolia®, [redacted]

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Research Question and Objectives

Among postmenopausal Chinese women with osteoporosis treated in clinical practice, the objectives were to:

1. Evaluate the effectiveness of denosumab for the reduction of clinical osteoporotic fractures, and
2. Characterize the safety of denosumab.

Study Design

The study included both a comparative analysis for effectiveness and a descriptive analysis for safety. Effectiveness was evaluated among women initiating Prolia by comparing the incidence of hip fractures (the primary endpoint), clinical vertebral fractures and non-vertebral fractures (secondary endpoints), between 2 cohorts:

a) patients persistent to therapy (ie, received 2 or more doses of Prolia), starting at 6 months + 45 days after initial Prolia administration and followed until the earliest date of discontinuation of Prolia, fracture endpoints, end date of data source, or death versus

b) patients non-persistent to therapy (ie, received only 1 dose of Prolia), starting at 6 months + 45 days after initial Prolia administration and followed until the earliest date of re-initiation of any osteoporosis medication, fracture endpoints, end date of data source, or death.

Statistical techniques (propensity score [PS] matching) were then applied to match patient cohorts at baseline with respect to risk factors for fracture. To assess the robustness of results and to address the potential impact of unmeasured confounding, both subgroup analyses and sensitivity analyses using inverse probability of treatment weights (IPTW) and high-dimensional propensity score (hdPS) were specified within the protocol.

Safety was evaluated among women initiating Prolia beginning at the first date of Prolia administration and continuing through the earliest date of Prolia discontinuation, death, or the end of the study period. Safety endpoints aligned with 3 important identified risks in the Global Risk Management Plan for Prolia.

Setting and Data Source

The setting included all public medical care delivered by health care systems in Taiwan and Hong Kong. Taiwan has 23.5 million people, of which 3.6 million are postmenopausal women (aged 55 years and over) (Census, 2018). Hong Kong has 7.2 million people, of which 1.3 million are postmenopausal women (Census, 2018).

Within this setting, 2 databases provided anonymized, patient-level data on demographics, administration of biological medicines, drug dispensing, diagnoses received at hospitalization or outpatient consultation, and mortality. One database was the Health Insurance Research Database of the Taiwan Bureau of Health Insurance, which serves the population through a single-payer health insurance program for medical and dental care. Nearly 99% of the population of Taiwan is enrolled in this program. The second database was the electronic medical records of the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority, which serves a population of 7 million through 41 hospitals and more than 100 outpatient clinics. This database includes data on approximately 80% of all hospital admissions in Hong Kong. Data for this study included Taiwan data through December 2016 and Hong Kong data through August 2018.

The Taiwan dataset, being the larger dataset of Prolia patients by an order of magnitude, was prespecified as the primary data source to support study conclusions. The same study design and methods (ie, use of common protocol) were applied to the Hong Kong dataset to qualitatively assess consistency of the Hong Kong results with the Taiwan results.

Variables

The use of Prolia, endpoints for effectiveness and safety, and covariates were identified through drug administration codes, drug dispensing codes, and diagnoses codes received by the patient at the time of clinical care. As a measure of validity, the primary endpoint, hip fracture in the Taiwan database, 2 physicians individually reviewed the radiographic reports of 300 randomly selected patients with a hip fracture diagnosis. Of these 300 patients, 298 were confirmed to have sustained a hip fracture (ie, a positive predictive value of 99.3%). The secondary endpoints were clinical vertebral fracture and non-vertebral (hip, humerus, wrist, and distal forearm) fracture. Safety endpoints were osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF) as indicated by a subtrochanteric or shaft of femur fracture, and hypocalcemia requiring emergency room evaluation or hospitalization. Covariates known to confer fracture risk included:

demographic characteristics, history of comorbidities, history of medication use, and history of health-seeking behavior.

Subject and Study Size

The study size was dependent on the number of patients treated with Prolia in clinical practice. To ensure that women included in the study were receiving Prolia for the indication of PMO, all women with a history of Paget's disease or malignancy were excluded.

For the comparative analysis of effectiveness, the Taiwan study population included 38 906 women. The mean age was 77 years, 17% had prior hip fracture, and 35% had prior bisphosphonate therapy. Of the 38 906 women, 25 059 (64%) were included in the persistent cohort (ie, received 2 or more doses of Prolia) and 13 847 (36%) were included in the non-persistent cohort. The Hong Kong study population included 2835 women. The mean age was 78 years, 14% had a prior hip fracture, and 37% had prior bisphosphonate therapy. Of the 2835 women, 2379 (84%) were included in the persistent cohort and 456 (16%) were included in the non-persistent cohort.

Results

In the Taiwan dataset, 686 hip fractures were observed. The crude incidence rates of hip fracture were 0.88 cases and 1.74 cases per 100 person-years in the persistent and non-persistent cohorts, respectively. In the primary analysis, before PS matching, most (46 of 59) demographic and risk factors for fracture used as covariates were similar between the 2 study cohorts. After PS matching, the study cohorts were balanced for all covariates. With the PS matched cohorts, Prolia reduced the risk of hip fracture, clinical vertebral fracture, and non-vertebral fracture by 38% (hazard ratio, 0.62 [95% CI: 0.52, 0.75]), 37% (hazard ratio, 0.63 [95% CI: 0.52, 0.75]), and 38% (hazard ratio, 0.62 [95% CI: 0.53, 0.73), respectively. Consistent results were observed in subgroups (age, previous bisphosphonate exposure, and fracture history) and sensitivity analyses using IPTW and hdPS.

In the Hong Kong dataset, 41 hip fractures were observed. While based on a relatively smaller sample size, crude incidence rates of hip fracture were similar to that observed in the Taiwan dataset. In Hong Kong, the crude incidence rates of hip fracture were 0.89 cases and 1.68 cases per 100 person-years in the persistent and non-persistent cohorts, respectively.

In the Taiwan dataset, the observed incidence rates of ONJ, AFF, and hypocalcemia, were 9.6 (95% CI: 7.4, 12.4), 12.5 (95% CI: 9.9, 15.7), and 9.4 (95% CI: 7.2, 12.2) cases per 10 000 person-years, respectively. In the Hong Kong dataset, the incidence rates of safety endpoints were similar to those observed in the Taiwan dataset, for each of the 3 endpoints.

Discussion

This observational study, which characterized the effectiveness and safety of Prolia in clinical practice in Taiwan and Hong Kong among postmenopausal Chinese women with osteoporosis, showed clinically meaningful risk reduction for hip fracture, clinical vertebral fracture, and non-vertebral fractures for the Prolia persistent cohort compared with the non-persistent cohort matched on baseline characteristics. [redacted]

Marketing Authorization Holder

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