Treatment heterogeneity in comparative effectiveness of teriparatide vs bisphosphonates: multi-database cohort study

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1 Introduction

Osteoporosis is a common condition characterised by decreased bone density and associated with increased risk for fragility fractures, which affects almost 30% of women aged ≥ 50 years [1]. It was estimated that in 2005, over 2 million incident fractures occurred in the United States, with hip fractures accounting for more than 70% of the costs. By 2025, annual fractures and costs could rise by almost 50% [2].

Fracture prevention is thus the key focus of anti-osteoporotic therapy, reducing the disease burden both for the affected patient but also on the population level. Several pharmacological agents are available for primary and secondary prevention. The choice of anti-osteoporotic agent largely depends on history of fragility fracture and anticipated fracture risk. Oral bisphosphonates (BP) are first line treatments for postmenopausal patients with increased fracture risk in clinical guidelines (#AACE/ACE 2020) as for their favourable cost-effectiveness and safety profile. Teriparatide, a parathyroid hormone analogue administered as a daily injection, was approved by the FDA in 2002 as the first anabolic agent for treatment of severe postmenopausal osteoporosis. While clinical trials among patients with previous vertebral fractures showed a substantial risk reduction for new vertebral fracture comparing teriparatide to placebo [3] and risedronate [4], its efficacy on low-incident major osteoporotic fractures, especially hip fractures, is less well established: Previous randomised trials assessing hip fracture comprised only few events, thus not providing sufficient power to show differences between treatment groups when studying comparative effectiveness. A recent meta-analysis by Diez-Perez and colleagues assessed the effect of teriparatide on hip fracture, indicating a significant 80% risk reduction compared to placebo and a non-significant 46% risk reduction when compared to active controls [5].

With teriparatide-containing biosimilars being launched in recent years, treatment costs dropped significantly. Subsequently, the discussion of cost-effectiveness in patients with less severe forms of osteoporosis is restarting. Therefore, evaluation of the effectiveness in hip fracture prevention is required. In particular, observational studies assessing comparative effectiveness in a real-world setting are required, as effectiveness may differ from clinical trial as for differences in patient's persistence and adherence to their anti-osteoporotic treatment. While hip fracture is a comparatively rare outcome, it is unambiguously defined and reliably recorded in routinely collected data, allowing for a direct comparison to results from clinical trial meta-analyses. While results from non-controlled, observational studies suggest that teriparatide may reduce the risk of hip fractures [6,7], this is the first observational study assessing teriparatide in hip fracture risk reduction compared to oral bisphosphonate users in postmenopausal women using multiple large real-world databases.

2 Methods

2.1 Study design

We performed a retrospective new user cohort study to estimate the effectiveness of teriparatide compared to oral bisphosphonates in patients with osteoporosis[8]. We included female participants above the age of 50 with established osteoporosis (any condition occurrence of hip, wrist, spine or shoulder/humerus fracture in their history, prior to treatment initiation) and at least 365 days of continuous observation period before the index event. Patients were considered to be new-users if they received no anti-osteoporosis drugs (raloxifene, bazedoxifene, denosumab, abaloparatide, romosozumab) 365 days prior to treatment initiation with teriparatide or an oral bisphosphonate.

Our primary efficacy outcome was hip fracture. Vertebral fracture and a composite major osteoporotic fracture, defined as hip, vertebral or wrist/forearm/proximal humerus fracture, were our secondary efficacy outcomes. We excluded patients that had experienced the outcome under study any time prior to treatment initiation. Patient time-at-risk started 1 day after treatment initiation and finished 730 days after treatment initiation.

2.2 Data sources

We ran our analyses on three US observational databases mapped to OMOP-CDM version. More specifically:

- **IBM MarketScan Medicare Supplemental Database (MDCR)** is a claims database representing retirees in the United States with primary or Medicare supplemental coverage.
- **Optum De-Identified Clinformatics® Data Mart Database – Date of Death (Optum-DOD)** is a claims database including members of private health insurance.
- **Optum de-identified Electronic Health Record Dataset (Optum-EHR)** is an EHR database including Humedica's Electronic Health Record.

2.3 Statistical analyses

We carried out two sets of analyses. First, we derived overall treatment effect estimates of teriparatide compared to oral bisphosphonates regarding the three outcomes of interest. To account for potential measured confounding we developed separate large-scale propensity score models within each database based on LASSO logistic regression using the same predefined set of measured covariates [9]. We estimated treatment effects using Cox proportional hazards models with treatment as the sole covariate fitted in the 1:4 propensity score-matched subset of the

considered patient population. Results from different databases were summarized using random effects meta-analysis.

For the second set of analyses, we used the standardized framework for risk-based assessment of treatment effect heterogeneity, that follows the directives of the PATH statement [10,11]. Following data extraction, the framework was applied in two steps. First, we derived individualized risk predictions for the three efficacy outcomes. We built the prediction models using LASSO logistic regression on the propensity score matched (1:4) subpopulation of the pooled treatment arms, aiming to remove any effect of measured confounding that may cause differential fit of our models across treatment arms. We considered the same large set of candidate covariates as for the development of the propensity score models.

For each outcome we used the derived prediction models to divide the population in 4 equally-sized subgroups, based on the quarters of the predicted risk distribution. Within each of these risk-based subgroups we developed a new propensity score model. Our analyses were performed on the propensity score matched (1:4) subset of the risk subgroup subset. We derived relative effect estimates using Cox proportional hazards models only with treatment as a predictor. Absolute effect estimates were calculated based on the difference of the Kaplan-Meier estimates, on day 730 after treatment initiation.

Residual study bias from unmeasured confounding can still be present in observational studies, which often may not be visible when evaluating propensity score adjustment. To account for that, we considered a set of 126 negative control outcome experiments, where a null effect was assumed to be true. We used the estimated relative effects for these outcomes to derive an empirical approximation to the true null distribution, which was then used to calibrate the hazard ratios and their 95% confidence intervals for the 3 outcomes of interest [12,13].

3 Results

4 Discussion

5 References

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6 Tables and figures