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Predictors of teriparatide treatment failure in patients with low bone mass

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ABSTRACT

Introduction: While teriparatide is the only skeletal anabolic agent approved in the United States, treatment failure is a major concern which complicates its clinical utility. We sought to identify factors that predict response failure in patients with low bone mass.

Method: We performed a retrospective study of adults with osteopenia or osteoporosis (T-scores < -1.0 and -2.5 SD below normal, respectively, at the total hip or lumbar spine) treated with teriparatide at the Mayo Clinic (Rochester, Minnesota) between November 2002–December 2012. Trained study investigators blinded to patient outcomes collected electronic medical record data. Potential response failure predictors were identified using univariate analysis. Multivariable logistic regression modeling was used to identify independent predictors of treatment failure based on either osteoporotic fragility fracture or BMD response.

Results: During the 10-year period, 494 patients received teriparatide treatment and met eligibility criteria. Thirty-five patients had osteoporotic fractures, while 172 did not achieve a ≥ 3% BMD increase. Among predictors as defined by BMD change, both prior bisphosphonate treatment [odds ratio (95% confidence interval), 1.50 (1.01–2.24)] and vitamin D therapy [1.50 (1.01–2.22)] were significantly ($P < 0.05$) associated with teriparatide treatment failure. By contrast, no predictors were associated with treatment failure when fracture was the endpoint.

Conclusion: These data suggest that prior bisphosphonate or vitamin D exposure may predict response failure to teriparatide therapy. Although these findings may, in part, reflect increased severity or longer duration of disease, this knowledge should help guide clinicians and patients when therapy choices are made.

1. Introduction

Osteoporosis affects more than 20 million Americans and is associated with approximately 1.5 million fractures annually (Finkelstein et al., 2003). Thus, osteoporosis represents a major health problem that will only worsen as the population ages. The osteoporotic skeleton is characterized by diminished bone mineral density (BMD), reduced bone quality, and increased fragility, all of which increase susceptibility to fractures (Anon., 1993).

Teriparatide [recombinant human parathyroid hormone (PTH)] is a recombinant molecule composed of the amino-terminal 34 amino acids of human PTH (Body et al., 2002). FDA-approved in November 2002, teriparatide is the only currently available skeletal anabolic agent in the United States, and is most frequently reserved for patients with severe osteoporosis or in whom other treatment modalities have failed (Ragucci & Shrader, 2011; Andrews et al., 2012). Daily subcutaneous injection of teriparatide both stimulates osteoblast generation and limits osteoblast elimination by apoptosis (Body et al., 2002), ultimately resulting in new bone formation with increases in both bone mass and strength (Yu et al., 2011). A randomized controlled trial (RCT) conducted by Neer et al. (2001) in 2001 reported that teriparatide significantly increased BMD and reduced both vertebral and non-vertebral fractures when administered (once daily) subcutaneously at doses of either 20 or 40 micrograms (μg).

A potential drawback associated with teriparatide use is response failure. Gallagher et al. (2006) reported this problem in a review of three RCTs that included postmenopausal women treated with teriparatide, in comparison to either placebo or treatment with the bisphosphonate, alendronate. Interestingly, when administered subcutaneously at a daily dose of either 20 or 40 μg, the response rate to

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teriparatide, as defined by a minimum increase in lumbar spine BMD from baseline of 3%, ranged from 87 to 94% (Gallagher et al., 2006). Nevertheless, the authors were unable to detect any differences in baseline characteristics between patients who responded versus those who did not. In a more recent study, Heaney & Watson (2011) reported that the response rate to teriparatide may be more variable and somewhat lower, with positive BMD response rates of 44.8% and 82.5% at the lumbar spine and total hip, respectively.

Considering that teriparatide treatment is associated with significant cost and treatment burden that includes daily injections, it is of upmost importance to identify predictors of treatment failure. Therefore, we aimed to establish the impact of an array of baseline characteristics and osteoporosis-related exposures on the response to teriparatide treatment in patients with low BMD, and to identify factors that significantly predict treatment failure.

2. Material and methods

2.1. Study participants and setting

This study was a retrospective analysis carried out using the unique electronic medical record system at the Mayo Clinic, a tertiary care teaching institution located in Rochester, Minnesota. The study protocol was approved by the Mayo Clinic Institutional Review Board and all patients provided authorization for review of their medical records for research in accordance with Minnesota privacy law (St Sauver et al., 2012). To be eligible for study inclusion, patients were required to have received teriparatide (for at least 12 months) at Mayo Clinic between 1 November 2002 and 31 December 2012. We included patients >18 years old who were diagnosed with low bone mass (osteopenia or osteoporosis with T-scores less than 1.0 and 2.5 SD below normal respectively, at either the total hip or lumbar spine). Medical records with missing outcome data were excluded from analysis. Patients were not otherwise excluded based on specific baseline medical conditions or medications. Outcomes evaluated were the occurrence of osteoporotic fracture and BMD treatment failure (defined as a less than 3% increase from baseline at either the total hip or spine).

2.2. Data source

All data were retrieved from the Mayo Clinic Life Sciences System (MCLSS), an exhaustive clinical data warehouse which stores patient demographics, diagnoses, clinical notes, and hospital, laboratory, flow sheet, and pathology data gathered from various clinical and hospital source systems within the institution (Alsara et al., 2011). To conduct the search in MCLSS, we used the query-building tool provided by MCLSS, Data Discovery and Query Builder (DDQB), which allows a thorough interrogation of MCLSS for the intended data (Alsara et al., 2011). To ensure the reliability of this tool, we manually retrieved fracture data from medical records of 20 randomly selected patients. Inter-rater agreement (k) between the tool and manual extraction was excellent ($k = 0.95$).

2.3. Definitions of treatment failure

Clinical response failure was defined as sustaining one or more osteoporotic fractures (i.e., hip, spine, distal forearm, proximal humerus) after the patient has been treated with teriparatide for at least 6 months. Osteoporotic fractures, also known as fragility or minimal-trauma fractures, were defined by convention as occurring from low-energy trauma such as a fall from a standing height or less, and due to no more than moderate trauma (e.g., motor vehicle accidents) (Rebolledo et al., 2011). Radiographic response failure was defined as <3% increase in BMD from baseline at the spine, total hip or both when measured at least 12 months following teriparatide initiation (Gallagher et al., 2006). BMD measurements were obtained at time of teriparatide initiation. For study inclusion, subjects must have had a repeat BMD determination performed 12–24 months following treatment initiation. To adjust for this variation in follow-up length from time of treatment initiation, we calculated the average between-measurement time (referred to as follow-up duration) and included this variable in the regression model.

2.4. Ascertainment of study variables

Outcome variables were collected by study investigators who retrieved information about fracture occurrence as well as baseline and follow-up BMD measurements from the electronic medical record of the Mayo Clinic. BMD was assessed by dual-energy X-ray absorptiometry (DXA) at the total lumbar spine, total hip and femoral neck using a Lunar Prodigy scanner (General Electric Healthcare, Waukesha, WI), as described previously (Dy et al., 2012). To reduce measurement errors, standard practice at Mayo Clinic is to report the average of 2 scans performed during each assessment. In addition, the average least significant change (LSC) in BMD for all technicians is included in order to avoid the need for patients to have scans performed on the same machine by the same technician each time an assessment is performed. The LSC is defined as the smallest amount of change between two BMD measurements over time that must be exceeded before a change can be considered the result of a true difference in a patient's BMD and not due to either DXA or patient factors with 95% confidence (Shepherd & Lu, 2007).

Predictor variables were identified a priori, and were collected from the electronic medical records using DDQB. Based on opinions received from a panel of content experts, in addition to a comprehensive literature search (i.e. previous studies, meta-analyses and review articles written by experts in the bone and osteoporosis fields), we were able to identify several variables that could be potential predictors of response failure. These factors included: 1) demographics: age and sex; 2) anthropometric measurements: height, weight and body mass index (BMI); 3) habitual exposures: alcohol intake and cigarette smoking; 4) co-morbidities: hypertension, diabetes, cancer, chronic renal disease, chronic liver disease; 5) baseline medications and supplements (i.e. bisphosphonates, corticosteroids, calcium, phosphate, proton pump inhibitors, vitamin D); and 5) biochemical parameters (i.e. bone alkaline phosphatase, C-terminal telopeptide of type I collagen (CTX), 25-hydroxyvitamin D, parathyroid hormone) at baseline and after treatment completion.

2.5. Statistical analysis

Data for the predictor variables are presented as means and standard deviations (SD) for variables with normal distribution, and medians and interquartile ranges (IQR) for those with skewed distributions, as appropriate. Categorical variables are presented as frequencies and percentages. Unpaired Student's t-tests were used to compare continuous variables with normal distribution, and the Mann–Whitney U test otherwise. For comparison of categorical variables, chi-square tests were used.

Candidate predictors of response were identified using univariate logistic regression. Predictors that achieved a level of significance equal to a P-value of <0.05 were selected for inclusion in the multivariate model to predict treatment failure (at least one fracture versus no fractures; or less than a 3% increase in total hip and or spine BMD from baseline versus 3% or more). To determine the independent impact of each variable on the response to teriparatide treatment, multivariable logistic regression models were created. We included risk factors identified from univariate models as covariates and either fracture or BMD response failure as dependent variables. For all analyses, a P-value < 0.05 was considered statistically significant. Analyses were performed using STATA, version 12.1 (StataCorp LP, College Station, TX, USA).