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Original article

Treatment persistence and changes in fracture risk, back pain, and quality of life amongst patients treated with teriparatide in routine clinical care in France: Results from the European Forsteo Observational Study

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ABSTRACT

Objectives: The European Forsteo Observational Study assessed the clinical fracture incidence, back pain, quality of life (QoL), and treatment persistence amongst post-menopausal women, who were prescribed teriparatide in routine care in eight European countries. We present the results for France, with health-insurance reimbursement criteria channel teriparatide to women with severe disease and limit treatment to 18 months.

Methods: A representative sample of women initiating teriparatide in France was followed in routine care for 36 months. We described patients' characteristics at baseline and persistence to teriparatide (Kaplan–Meier analysis), fracture incidence, back pain, and QoL (EQ-5D) at baseline, 18 and 36 months follow-up (last-observation-carried-forward (LOCF) and mixed-models-for-repeated-measures (MMRM).

Results: One hundred and sixteen rheumatologists included 309 patients, of whom 290 (93.9%) had at least one follow-up visit. Women's mean age (standard deviation) was 74.5 years (7.4) and 296 (95.8%) had greater or equal to two vertebral fractures prior to teriparatide initiation. Clinical fracture incidence, mainly vertebral fractures, decreased around 6 months after teriparatide initiation, and was sustained at 36 months ($P = 0.013$) when most patients were treated by anti-resorptives. Back pain and EQ-5D measures improved significantly at 18 and 36 months ($P < 0.0001$) in the LOCF analyses but did not improve in the EQ-5D VAS measure after covariate adjustment in the MMRM model. Median treatment duration was 17.4 months.

Conclusion: French women initiating teriparatide in routine care had severe osteoporosis and showed good treatment persistence, consistent with France's insurance reimbursement criteria. Improvements in fracture risk and back pain began soon after treatment and was maintained at 36 months follow-up.

1. Introduction

Osteoporosis is a common disease, with almost 10% of women over 45 years old reporting this diagnosis in a recent population survey [1] and a predicted 15% increase in the number of women with osteoporosis in France between 2010 and 2020 [2]. Its clinical impact can be considerable: women with osteoporosis are at increased risk of vertebral and non-vertebral fractures [3], chronic back pain [4], and reduced quality of life (QoL) [5,6]. Osteoporosis also generates considerable costs to the French health system. A recent analysis of France's hospitalisation episodes database [7] estimated €415.4 million in direct costs to hospitals and a further €331.8 million in rehabilitation costs in 2008. Treatment aims to reduce the risk and burden of osteoporosis-related fractures [8].

Teriparatide, a recombinant human *N*-terminal fragment of parathyroid hormone, is a bone anabolic agent shown to increase bone mass and strength and reduces the incidence of vertebral and non-vertebral fractures in post-menopausal women with osteoporosis [9]. One of its authorized indications in Europe is the treatment of osteoporosis in post-menopausal women considered to beat high risk of fractures, for limited treatment duration, initially 18 months, and increased to 24 months in 2009 [10]. To

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qualify for reimbursement by the national health-insurance system in France, post-menopausal women with osteoporosis must have experienced at least two vertebral fractures prior to initiating teriparatide, which is reimbursed for 18 months only [11].

Although clinical trials are the basis for authorization and reimbursement decisions, observational studies are important sources of real-world evidence about drugs after approval [12]. They provide interesting data to prescribers, payers, regulators, and patients about drug utilization and impact in routine clinical care (effectiveness) [13]. Utilization data are important as they measure how a new medicine is reaching its target patient group. Effectiveness data evaluate clinical benefit in conditions of normal care, in contrast to "efficacy" measured in clinical trials. Effectiveness can differ from efficacy given the particular conditions imposed in clinical trials, such as strict inclusion/exclusion criteria and patient follow-up, which frequently do not reflect conditions of real-life practice [14].

The European Forsteo Observational Study (EFOS) was a prospective observational cohort study of women treated with teriparatide in eight western European countries. The study's primary objective was to determine the incidence of clinical vertebral and non-vertebral fractures in post-menopausal women with osteoporosis treated with teriparatide for 18 months, with a post-treatment follow-up of 18 months. The study's secondary objectives included evaluating persistence to teriparatide over time and measuring the change in back pain and quality of life (QoL) during and after teriparatide treatment [14]. The results for the full cohort pooled across countries have recently been published [15].

This article presents the results of the EFOS study for patients enrolled in French centers. The objectives of this pre-planned analysis of the France cohort were to describe the clinical profile of patients initiating teriparatide in France, as reimbursement conditions and so patient profile differ from other countries; to estimate the duration of treatment in real-life conditions in the French health system; and to measure the impact of teriparatide on patients' clinical outcomes.

2. Methods

2.1. Study design and population

EFOS was a prospective observational study of post-menopausal women diagnosed with osteoporosis who initiated teriparatide in the course of routine care. Its design has been described in detail elsewhere [15]. To achieve a sample of patients representative of those in routine practice in France, investigators were randomly selected from a national database of rheumatologists and asked to include consecutive patients initiating teriparatide. Women were followed for the duration of their teriparatide treatment and for a further 18 months after cessation of treatment. The only exclusion criteria were participation in a clinical trial and a contraindication to teriparatide. Inclusion took place from September 1, 2004 to April 30, 2005.

2.2. Data collection

Data were collected during routine consultations at the inclusion visit and then around 3, 6, 12, 18, 24 and 36 months after teriparatide initiation. The recommended treatment duration at the time of the study in all European countries was 18 months and so the last two visits (24 and 36 months) were considered post-treatment assessments. Physicians could stop teriparatide treatment at their discretion, consistent with normal practice. For women stopping teriparatide before 18 months follow-up, data collection took place 6 and 18 months after the end of treatment.

Data collected at baseline included patient demographics, clinical and medication history, risk factors for osteoporosis and falls, prior and current osteoporosis medications, most recent bone-mineral-density (BMD) measurement, back pain and QoL measures. Data collected during the follow-up included fractures since the previous visit, last BMD measurement, back pain and QoL measures. Incidence of clinical vertebral and non-vertebral fractures, the study's primary endpoint, was confirmed by review of X-rays or surgical reports. A new or worsened vertebral fracture was based on radiographic confirmation associated with signs and/or symptoms suggestive of vertebral fracture, such as acute or severe back pain. Back pain was assessed using a horizontal 100 mm visual analogue scale (VAS) from 0 (no pain) to 100 (worst possible pain) and a questionnaire measuring pain frequency, intensity, limitations of activity, and bed-rest because of pain during the month preceding the visit. QoL was measured by the European QoL (EQ-5D) questionnaire [16,17]. The Health State Value (HSV) was calculated from the EQ-5D using the UK algorithm.

2.3. Statistical analysis

We analyzed baseline data for all patients included in the study and follow-up data for all patients with at least one follow-up visit. We defined 18 months as the cut-off point between the teriparatide treatment and post-treatment periods, considering patients to be in these periods even if they stopped teriparatide before 18 months or continued after 18 months of treatment. The results therefore represent the effect of teriparatide in a patient population in routine care, integrating real-world deviations from ideal persistence to treatment.

Continuous variables were summarized by the mean and standard deviation (sd) or median and interquartile range (IQR). Categorical variables were described by counts and percentages. Persistence to teriparatide was estimated by the time until treatment cessation using the Kaplan–Meier method. Clinical fracture risk was described in six-monthly intervals following teriparatide initiation by the incidence rate given as the number of fractures by 10,000 patient years with 95% confidence intervals (95% CI) calculated from 10,000 bootstrap samples by the percentile method. Logistic regression models were used to estimate the odds ratios (ORs) of fracture and 95% CI, comparing the first 0-to-6-month interval with each of the follow-up 6-month time periods. To account for repeated observations within patients, the models were estimated using generalized estimating equations (GEE) with an unstructured correlation matrix [18]. The adjusted models included age, prior bisphosphonate use, and fractures in the 12 months before initiating teriparatide as co-variables.

Changes in the back pain VAS and the EQ-5D VAS scores were analyzed by a mixed regression model for-repeated measures (MMRM), adjusting only for baseline score. The analysis was repeated by additionally adjusting on the following covariates: number of previous fractures, age, rheumatoid arthritis, prior bisphosphonate therapy duration, and any fracture in the 12 months before starting teriparatide. *P*-values and 95% CIs for the adjusted mean changes from baseline obtained after controlling for the covariates (least-square [LS-] means) are given.

As a supportive non-parametric approach, which relies on fewer assumptions than the MMRM analysis, the back pain VAS and the EQ-5D VAS changes from baseline were analyzed with the sign test using the last-observation carried-forward (LOCF) approach. The same approach and test was applied also to each of the back pain questionnaire items and the EQ-5D domain scores. Change from baseline of the EQ-5D HSV score was analyzed by the Wilcoxon sign-rank test using the LOCF approach and the number of days in bed owing to back pain was analyzed with the Wilcoxon sign-rank test.