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Suitability of teriparatide and level of acceptance of pharmacotherapeutic recommendations in a healthcare management area

Adecuación de la teriparatida y grado de aceptación de las recomendaciones farmacoterapéuticas en un área de gestión sanitaria

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Abstract: *Objective:* To analyse the suitability of teriparatide prescriptions for osteoporosis treatment in a health management area, as well as the level of acceptance of pharmacotherapeutic recom- mendations made to physicians.
Design: A prospective interventional study conducted from fe- bruary 2015 to june 2015.
Setting: South Seville Health Management Area.
Participants: Patients receiving teriparatide.
Main measurements: Suitability of teriparatide prescriptions according to Clinical Practice Guidelines and level of acceptance of pharmacotherapeutic recommendations.
Results: Teriparatide prescriptions were unsuitable in 45 patients (68.2%); 11 due to no indication, 17 patients did not have previous treatments with first-line drugs, 6 due to contraindications and 9 patients were treated for more than 24 months with the drug. Besides, 4 prescriptions were unsuitable because of combination with other therapies. The acceptance of pharmacotherapeutic recommendations was 64.4%, leading to teriparatide discontinuation in 21 patients (72.4%), and a switch to alendronate or ibandronate in another 8 patients.
Conclusions: A high percentage of teriparatide prescriptions is unsuitable in our health care management area, but it has decreased after pharmacist intervention.

Keywords: Suitability, Teriparatide, Recommendation.

Resumen: *Objetivo:* Analizar la adecuación de la prescripción de teriparatida en el tratamiento de la osteoporosis en un área de gestión sanitaria, así como el grado de aceptación por el médico de las recomendaciones de intervención realizadas.
Diseño: Estudio prospectivo de intervención desde febrero de 2015 a junio de 2015.
Emplazamiento: Área de Gestión Sanitaria Sur de Sevilla. *Participantes:* Pacientes con prescripción activa de teriparatida. *Mediciones principales:* Adecuación de la prescripción de teriparatida y grado de aceptación por el médico de las recomendaciones farmacoterapéuticas.

Resultados: La prescripción de teriparatida fue inadecuada en 45 pacientes (68,2%). Once pacientes no cumplían los criterios de tratamiento, mientras que 17 no habían tenido prescrito previamente otro medicamento para la prevención de fracturas. Seis pacientes presentaban alguna contraindicación. En 9 pacientes la duración de la terapia fue superior a los 24 meses recomendados. Cuatro de ellas (dos ya inadecuadas) por combinación inadecuada con otros medicamentos. El grado de aceptación de las recomendaciones farmacoterapéuticas realizadas por farmacia fue del 64,4%, produciéndose en 21 pacientes (72,4%) la suspensión de teriparatida y en 8, el cambio a otro medicamento de primera línea: ibandrónico, en tres de ellos, y alendrónico, en el resto

Conclusiones: El número de pacientes con prescripciones in- adecuadas de teriparatida es elevado en nuestra área, pero ha disminuido tras realizar intervenciones con recomendaciones farmacoterapéuticas de adecuación del tratamiento.

Palabras clave: Adecuación, Teriparatida, Recomendación.

Introduction

Osteoporosis is a progressive and systemic condition, characterized by a reduction in mass and the deterioration of bone tissue microarchitecture, leading to an increase in the risk of fracture [1.] We have two main types of drugs for prevention and treatment of osteoporosis: antiresorptive and anabolic drugs. The effect of these drugs on the reduction of fractures has been demonstrated, clinically and by bone mineral density, in patients with diagnosed osteoporosis. However, there are no studies with a prospective comparison of the efficacy of these therapies. Antiresorptive agents include a wide drug armamentarium that act by inhibiting bone resorption (biphosphonates, raloxifene, bazedoxifene, calcitonin, denosumab, and strontium ranelate, hormonal replacement therapy). On the other hand, anabolic agents will increment bone formation by causing an increase of bone remodelling through action on osteoblasts, thus increasing bone mass and resistance [3,4] . This group includes two osteoanabolic drugs: parathyroid hormones and teriparatide.

In post-menopausal women with osteoporosis and previous fracture, teriparatide significantly increased vertebral bone (8.6%) and femoral neck density (3.5%) when compared with placebo. On the other hand, it reduced the incidence of new vertebral (RR= 0.35; CI 95%: 0.22 to 0.55) and non-vertebral fractures (RR = 0.47; CI 95%: 0.25 to 0.88). However, there is no evidence on its effect for prevention of hip fracture [5] . Even though teriparatide is effective against fractures and it is a therapy option for osteoporosis treatment, it will cause adverse effects (nausea, headache, hypercalcaemia, etc.) and presents contraindications. Besides, studies on rats point out at an increase in the incidence of osteosarcoma with long-term administration of teriparatide; therefore, the therapy should not have a duration over the 24 months recommended [6] . The conclusion in clinical practice guidelines is that teriparatide should not be considered as a first line treatment [3,7] .

The widespread use of these drugs is not recommended in clinical practice; instead, an adequate diagnosis should be determined according to the outcomes of bone densitometry and the presence of risk factors

[3, 8,9.] Different studies have demonstrated that drugs for prevention and treatment of osteoporosis are sometimes prescribed without any established criteria for osteoporosis, not according to recommendations [10,11.]

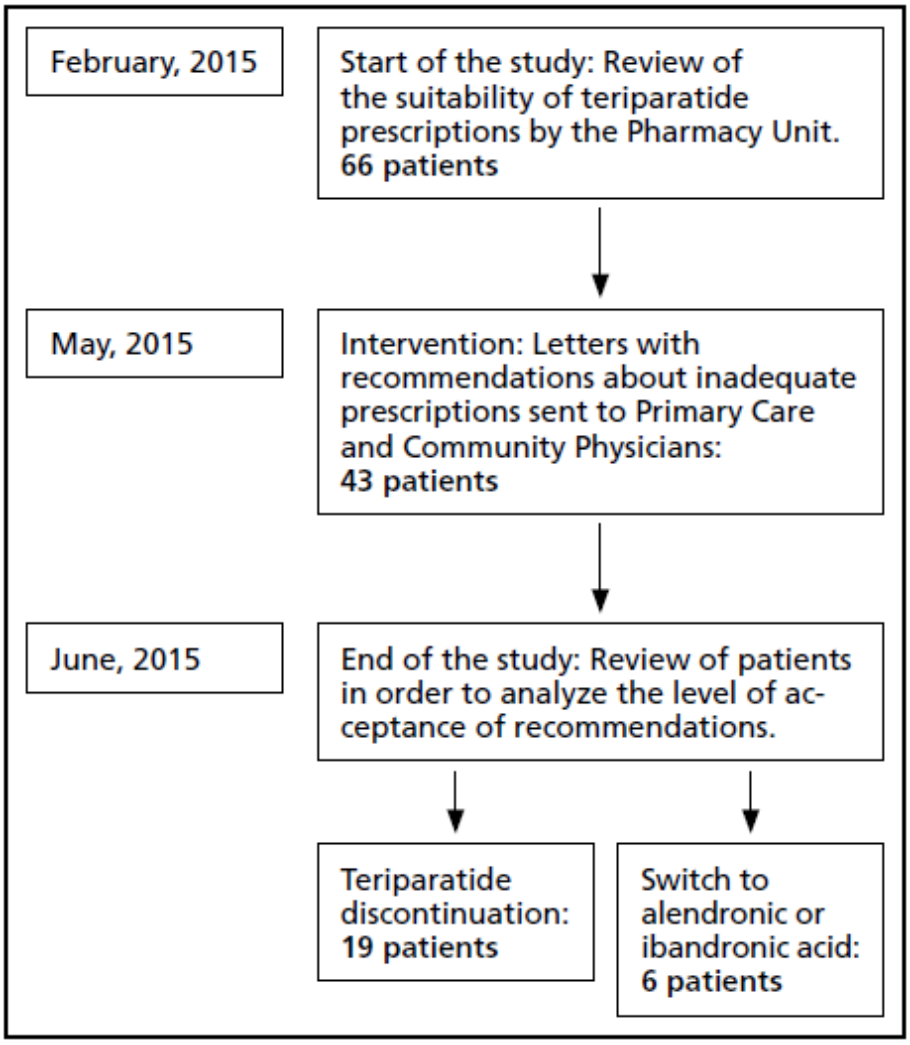
The objective of this study is to analyze the suitability of teriparatide prescription for osteoporosis treatment in a healthcare management area, as well as the level of acceptance by the physician of the interventions conducted for pharmacotherapeutical recommendations.

Material and Methods

A prospective interventional study conducted from February, 2015 to June, 2015 in the Healthcare Management Area of South Seville, including a Primary Care district formed by 20 healthcare centres and a specialty hospital. Patients with an active prescription for teriparatide from January,1st to February, 28th, 2015, were included for review by the Pharmacy Unit of this area, with the objective of analyzing the suitability of their prescriptions. Those patients who did not continue under treatment at the time of the review were excluded.

The variables collected were: age, gender, date of treatment initiation with teriparatide, and treatment duration, dosing regimen, previous osteoporotic fracture, previous treatment with other medications for fracture prevention, T and/or Z score in the most recent bone densitometry, and suitability of prescription.

Teriparatide prescription was considered adequate if any of the criteria for osteoporosis treatment was met



(Table 1) [3,12]. According to clinical practice guidelines3,6, prescription was also considered inadequate if, even though treatment criteria were met, patients had not been previously treated with another medication considered first line for prevention of fractures. Moreover, prescription was also unsuitable if the maximum dose (20 micrograms administered once a day) and/or duration of treatment (24 months) were exceeded; or there was concomitant treatment with some drug for prevention of fractures, or some contraindication.

Table 1

Algorithm for treatment decision in osteoporosis. Adapted from the Guidelines for Clinical Practice for Osteoporosis and Prevention of Fractures caused by Bone Brittleness. 2010 [3]

Table 1. *Algorithm for treatment decision in osteoporosis. Adapted from the Guidelines for Clinical Practice for Osteoporosis and Prevention of Fractures caused by Bone Brittleness. 2010*[3]

Age < 65 years	
Vertebral fracture	T-score < -1 SD
Non-vertebral fracture	T-score < -1 SD
No fracture	T-score < -2.5 SD
	T-score between -2.5 and -1 SD and risk factors
Age > 65 years	
Vertebral or hip fracture	Regardless of Z-score value
Other type of fracture	Z-score < -1 SD
No fracture	Z-score < -1 SD

SD: standard deviation
T-score: value comparing BMD vs. the mean value among the young adult population of the same gender.
Z-score: value comparing BMD vs. the mean value among the population with the same age and gender.

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With the aim to analyze if there was any contraindication, the values of creatinine, alkaline phosphatase and calcaemia previous to treatment were collected; moreover, patient clinical records were reviewed. Treatment contraindications were those described in the product specifications6: hypersensitivity to the molecule or any of the drug excipients; pregnancy and breastfeeding; pre-existing hypercalcaemia; severe renal impairment; bone metabolic conditions (including hyperparathyroidism and Paget disease of bone) other than osteopo- rosis; unexplained elevations of alkaline phosphatase; patients who had previously received external radiation or localized radiotherapy on their skeletal system; bone tumours or bone metastasis.

In case of unsuitability, letters individualized by patient were sent to GPs, indicating the cause of this lack of adequacy, as well as pharmacotherapeutical recommendations for teriparatide prescription. At the end of the study, the active prescriptions of patients were consulted, and there was a registry of the level of acceptance of the

interventions of pharmacotherapeutical recommendations for treatment discontinuation or change, made by the Pharmacy Unit.

Patient selection was conducted with the FARMA® prescription invoicing database through the MicroStrategy® computer application, both from the Andalusian Healthcare System (SAS). These programs collect data from prescription and dispensation of medication and healthcare products by the different healthcare professionals.

Data collection was conducted by consulting the electronic clinical record and the computer system for electronic prescription "*DIRAYA receta XXI*". The statistical program IBM SPSS Statistics® 20.0 for Windows (IBM Corp., Armonk, NY) was used for data analysis. A descriptive analysis was conducted through mean and standard deviation (SD), or median and interquartile range (IQR), in case of asymmetry, for quantitative variables, and through frequencies and proportions for qualitative variables.

Outcomes

Sixty-six (66) patients were identified with active prescription of teriparatide, with a mean age of 74.1 years (SD= 7.9); 87.9% of them were female. The median treatment duration was 10 months (IQR: 7-13). For all patients, the dosing regimen was 20 micrograms once a day. For 53 patients (84.1%) there was a personal history of previous osteoporotic fracture stated in their clinical record; in the majority of cases this was vertebral (88.7%), and in the rest, it was a hip fracture (11.3%). The majority (86.8%) of patients with a previous fracture were >65-year-old. Forty-four (66.7%) patients had been previously treated with another medication for prevention of fractures (Table 2). Only seven patients had undergone a bone densitometry, and diagnostic criteria of osteoporosis had been met in all cases.

Teriparatide prescription was inadequate in 45 patients (68.2%) (Table 3). Eleven patients did not meet treatment criteria, while seventeen had not been previously prescribed another medication for prevention of fractures. For nine patients, the duration of therapy exceeded the recommended 24 months; with a mean 28.2 months (SD= 4.8). Six patients presented some contraindication, due to the presence of hypercalcaemia (11.3 mg/dl) in one patient, severe renal impairment in two patients, and elevation of alkaline phosphatase in four patients. However, there were no lab test results available for 25.8% of patients, either previous or during treatment, and therefore the proportion of contraindication might have been higher. The mean previous calcaemia was 9.5 mg/dl (SD= 0.8); creatinine levels were 0.8 mg/dl (SD= 0.2), and the level of alkaline phosphatase was 87.6 U/l (SD= 35). During review, four patients with concomitant prescription of biphosphonate and teriparatide were detected (two of them were already inadequate for other reasons); in two cases, ibandronic acid was prescribed, and alendronic acid in the other two.

The pharmacotherapeutical recommendations made about inadequate prescriptions were accepted in 29 patients (64.4%); teriparatide was discontinued for 21 patients (72.4%), and 8 patients (27.6%) were switched to another first line medication: ibandronic acid in three patients, and alendronic acid in the rest.

Table 2
Previously prescribed drugs for prevention of fractures

Table 2. *Previously prescribed drugs for prevention of fractures*

Drug	N (%)
Alendronic acid	30 (68.2)
Risedronic acid	8 (18.2)
Ibandronic acid	2 (4.5)
Strontium ranelate	2 (4.5)
Raloxifene	1 (2.3)
Zoledronic acid	1 (2.3)

In those patients without criteria for osteoporosis treatment, there was a 54.5% acceptance of pharmacotherapeutical recommendations, and teriparatide was interrupted in 6 out of 11 cases. The intervention was only accepted in 33.3% of those cases (2 out of 6) where there was a contraindication. When teriparatide had been prescribed as first line, and therefore was unsuitable, there was a 52.9% acceptance (9 out of 17); only two of the cases were switched to an oral biphosphonate. However, acceptance was higher (88.9%) in those patients with treatment duration over 24 months (8 out of 9), only two patients were switched to biphosphonates. In the case of those four patients with an unsuitable combination with another drug, teriparatide was discontinued in two cases, and biphosphonates in the other two.

Discussion

Our study brings to light the existence of a high level of inadequate prescription of teriparatide for osteoporosis treatment. On the other hand, the interventions conducted through pharmacotherapeutical recommendations based on clinical practice guidelines have been effective, with a moderate level of acceptance.

There are various studies in our setting that have analyzed an adequate management of osteoporosis; however, no study has been focused on teriparatide. Díez *et al.* [13] evaluated the suitability of osteoporosis diagnosis and treatment according to the 2001 clinical practice guidelines by the Spanish Society of Bone and Mineral Metabolism Research

(SEIOMM); this was high both in the Primary Care setting (71%) as in the hospital setting (78%). Like the present study, Martínez *et al.* [14] analyzed the adequacy of prescription for antiresorptive drugs according to the criteria by the Osteoporosis Guidelines by the Spanish Society of Primary Care and Community Medicine (SEMFYC), taking into account T and Z scores from densitometries and risk factors; this study demonstrated

Table 3
Causes for unsuitability of treatment with teriparatide, and acceptance of pharmacotherapeutical recommendations

Table 3. *Causes for unsuitability of treatment with teriparatide, and acceptance of pharmacotherapeutical recommendations*

Causes for unsuitability (N)			Acceptance of recommendations (N)	
			Teriparatide discontinuation	Switch to biphosphonate
Criteria for osteoporosis treatment not met		11	6	-
Criteria for osteoporosis treatment are met	No previous treatment with other medications for first line fracture prevention	17	7	2
	Duration over 24 months	9	6	2
	Contraindication	6	2	-
	Concomitant treatment with another drug for fracture prevention	4*	2*	2

*Two patients were also unsuitable due to another cause.

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that only 13.7% of prescriptions were inadequate. This disparity of data vs. what we have observed can be due to the fact that, in both studies, two thirds of prescriptions were for drugs considered first line treatment, such as biphosphonates. Other study has shown outcomes similar to ours, though slightly lower; the conclusion was that the quality of prescription for antiresorptive drugs was below the desirable level, because a low proportion of treatments (23.9%) are initiated with a clinical history record of bone densitometry and/or previous history of osteoporotic fractures [15] . In a study conducted in a Primary Care region, 53% of treatments for osteoporosis with wrong indication were observed, according to the Guidelines for Osteoporosis Management in Primary Care of Osakidetza; these data affect both Primary Care and other specialties [16] . Zwart *et al.* [10] used the same criteria for osteoporosis treatment as our study, though lower levels of suitability were shown (8%). We only have one study [17] assessing the suitability for a single type of drug, strontium ranelate, for osteoporosis treatment; and it was low (27.2%). Similarly to our study, pharmacotherapeutical recommendations for suitability were made, and there was a high acceptance of these interventions (87.5%); these data are superior to those observed by us, and this can be due to the fact that the pharmacotherapeutical recommendations made by these authors were mostly based on pharmacovigilance notes issued by the Spanish Agency of Medicines and Medical Devices.

One of the limitations of this study is the bias caused by insufficient entries in clinical records, though we only found 16.7% of patients without data for osteoporosis diagnosis. This fact has also been reported by other authors, such as Felipe *et al.* [18], who also reached the conclusion in his study that almost half of treatments for osteoporosis has not been adequately indicated, based on clinical record data. Another limitation is that no analysis was conducted on the causes for lack of acceptance of the interventions conducted by the Pharmacy Unit, because the end of the study coincided with the holiday season.

The future line of research must be directed towards encouraging training on osteoporosis management among professionals, because of the high level of unsuitability observed, as well as establishing periodical audits for prescriptions.

Based on the outcomes obtained, we can state the conclusion that there is a high number of patients with inadequate prescriptions for teriparatide in our area, but this has been reduced after conducting interventions with pharmacotherapeutical recommendations for treatment suitability.

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