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Factors related to bone forming inadequate response to treatment (teriparatide/PTH 1-84) in patients with severe osteoporosis. Preliminary results

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Summary
The aim of this study was to evaluate the long-term bone mineral density (BMD) response rate to osteoanabolic treatment in patients with severe osteoporosis and the factors related to "inadequate" response (IR).
Methods: 49 patients (46F:3M) with a mean age of 69.5±11.1 years treated with teriparatide (41) or PTH1-84 (8) during 18/24months were included (84% had vertebral fractures and 84% had previously received bisphosphonates). Previous skeletal fractures and antiosteoporotic treatment, risk factors and cause of osteoporosis were recorded in all patients. Bone turnover markers (BTM) and 25-OH vitamin D (25OHD) levels were assessed before and at 3, 6, 12 and 18/24 months. Lumbar and femoral BMD and spinal X-ray were assessed at baseline and at 12 and 18/24 months. IR was defined by a lumbar BMD change <3% at 18/24 months.
Results: 29% of patients showed IR to therapy. No significant differences were observed in age, baseline BMD and BTM and 25OHD levels between patients with or without IR. 92% of IR patients had been previously treated with bisphosphonates (vs 79%, p=0.34) during 7±4.8 years (vs 4.9±4.2 years, p=0.19). No significant differences were observed between groups in the magnitude of changes in BTM throughout the study.
Conclusions: 29% of patients with severe osteoporosis presented IR to osteoanabolic therapy. Although no predictive factors related to this finding were identified, previous prolonged therapy with bisphosphonates may play a role.

Key words: *osteoporosis, adequate response, teriparatide, PTH, bone metabolism, bone turnover markers.*

Introduction

The therapeutic effectiveness of most anti-osteoporosis treatments recommended in clinical practice guidelines and in clinical trials is high, especially when evaluated by measuring bone mineral density (BMD). However, in routine clinical practice, therapeutic failure is relatively common, particularly when assessed individually. In this sense, between 18 and 35% of patients treated with antiresorptive medications, mainly bisphosphonates (depending on the criteria) have a failure response and/or inadequate response to treatment[1-3]. Although non-adherence is often one of the main causes of inadequate response, other factors such as comorbidities, previous osteoporosis treatment, disease severity or vitamin D deficiency, among others, may influence response to antiosteoporotic treatment[1-3].

Similarly, bone forming treatment with parathyroid hormone (PTH) and/or teriparatide has been associated with a marked increase in BMD, as high as 10.5% at the lumbar spine after 18 months of treatment, and a decrease in the incidence of vertebral fractures (65%)[4-6]. It noteworthy that in this study (baseline testing), which included only patients with severe osteoporosis, teriparatide treatment was associated with a significant BMD increase in the lumbar spine (>3%) in 94% of patients at 18 months of treatment. Therefore, this agent is especially recommended for patients with severe osteoporosis and multiple fractures and/or inadequate response to other treatments[7]. However, as with antiresorptive treatments in clinical practice, some patients present a lack of response to this treatment, with figures ranging from 8% to 32%[8-10]. While the cause of this poor response to bone forming treatment is unclear, factors such as bone turnover and BMD baseline value, previous use of bisphosphonates and the initial response of bone turnover markers to treatment, have been linked to the magnitude of the BMD response to this long-term therapy[8,9,11,12]. In fact, some authors recommend quantifying the change in PINP values (a marker of bone formation) after starting teriparatide treatment. This indicates that if there is an increase of >10 ng/ml after 3 months of starting treatment, BMD will increase significantly in the long term[13-16].

Currently, both the incidence and factors related to inadequate response to bone forming treatment are poorly understood. Given the specific indications for this type of treatment, especially in patients with severe osteoporosis and multiple fractures, it is necessary to identify factors that may affect its therapeutic efficacy.

Therefore, the aim of this study was to analyze the long-term evolution of BMD after bone forming treatment (teriparatide or PTH 1-84) in patients with severe osteoporosis, and determine the frequency and factors associated with an inadequate response to treatment.

Patients and methods

Study Population

This retrospective study included all patients who followed a bone forming treatment (teriparatide or PTH 1-84) for 18 or 24 months in Bone Metabolism Unit of the Rheumatology Ward of the Clinic Hospital of Barcelona. Patients treated from 2006 to January 2014. All patients treated with teriparatide or PTH followed a clinical protocol that involved:

- *Analysis of risk factors for osteoporosis:* a family history of hip fracture, personal history of fractures, tobacco and alcohol consumption, dietary calcium intake (mg/day) and a history of kidney stones.

- *Assessment of the cause of osteoporosis, comorbidities and concomitant therapy:* including glucocorticoid treatment, and the presence, type and duration of the osteoporosis treatment previously received. Any patient treated for more than 5 years was considered to have undergone prolonged osteoporosis treatment.

- *Analytical determinations:* blood was taken between 8 and 10 am, after an overnight fast, at baseline (before the start of treatment) and at 3, 6, 12 and 18 or 24 months of treatment, performing biochemical profile including calcium, phosphate, creatinine, total alkaline phosphatase (FAT), levels of 25-hydroxyvitamin D (25OHD) and PTH, determined by standard techniques.

Also, the following biochemical markers of formation were determined: bone alkaline phosphatase (bone FA, IDS, Vitro) and aminoterminal propeptide of type I procollagen (PINP, automated method Cobas E411, Roche), and bone resorption: carboxy terminal telopeptide of type I collagen (CTx, automated method Cobas E411, Roche) and amino-terminal telopeptide of type I collagen (Osteomark NTxUrine, ELISA).

- *Quantification of BMD:* BMD of the lumbar spine and proximal femur (hip and femoral neck) was measured in all patients by dual X-ray absorptiometry (DXA, Lunar Prodigy, Radiation Corporation, Madison, Wisconsin, USA) at baseline and at 12 and 18 or 24 months of treatment. Densitometric risk categories (normal BMD, osteopenia and / or osteoporosis) were defined according to WHO criteria[17].

- *Radiological study:* X-rays of dorsal and lumbar spine (anteroposterior and lateral) were performed at baseline and at 12 and 18 or 24 months after commencing treatment. Baseline vertebral fractures were identified during follow-up, according to Genant criteria[18].

The study was carried out with the approval of the Hospital Ethics Committee.

Statistical analysis

"Inadequate response" was defined as a decrease or an increase in the lower lumbar BMD 3% at 18/24 months after treatment[9]. In addition, the percentage of patients with increased values of PINP >10 mg/ml at 3 months after starting bone forming treatment was analyzed[13]. Only patients who continued treatment with teriparatide vs PTH over 18/24 months were included.

The results were expressed as mean ± standard deviation of the mean (SD). Differences between

means of continuous variables were analyzed using the Mann-Whitney non-parametric test, and differences between proportions by Fisher test. The Wilcoxon test was used for comparison between paired variables. Pearson correlation coefficient was used to assess the association between variables. The p value <0.05 was considered statistically significant. Statistical analysis of the data was performed using SPSS software (version 18.0, Chicago, USA).

Results

Figure 1 shows the patients' flowchart. In all, 63 patients were included, of which 49 completed the 18/24 months of treatment. The clinical characteristics of the patients included are shown in Table 1. Briefly, 46 females and 3 males with a mean age of 69.5±11.1 years; 41 were treated with teriparatide and 8 patients with PTH 1-84 for 18 or 24 months. 84% of patients had previous vertebral fractures, with an average of 5 fractures per patient, and 84% had received previous treatment with bisphosphonates. The main cause of postmenopausal osteoporosis was in 32 patients (65%), followed by glucocorticoid osteoporosis (n=11; 22%) and miscellaneous in 6 patients.

In all, 29% of patients presented an inadequate response to treatment within 18/24 months. As shown in Table 1, there were no differences in age, baseline in BMD and markers of bone formation and resorption. No differences in 25OHD values were reported between patients with and without adequate response to treatment. Although there was no significant difference in the percentage of patients previously treated with bisphosphonates or in previous duration of the treatment between the two patient groups. Patients with inadequate response to bone forming treatment had previously undergone bisphosphonate therapy (92% vs . 79%, p=0.34) over a longer period (7±4.8 vs 4.9±4.2 years, p=0.19) (Table 1).

As expected, significant differences in the evolution of BMD between the two groups of patients (Figure 2) were observed. Thus, patients with inadequate response to treatment showed a loss of BMD in both lumbar spine (lumbar BMD: -2.7% at 12 months, p=0.646; 3.4% at 24 months, p=0.021) and proximal femur (BMD total femur. -2.8% at 12 months, p=0.261; 0.6% at 24 months, p=0.475 femoral neck BMD: -1.7% to 12 months, p=0.477; -3.12% at 24 months, p=0.333), whereas patients with adequate response showed a significant increase in lumbar spine BMD (12 months 9.4%, p<0.001 ; 24 months: 12.8%, p<0.001) and femoral BMD (total femur 12 months: 4.02%, p=0.008; 24 months: 4.5%, p=0.001; femoral neck 12 months: 2.7%, p=0.049; 24 months: 6.8%, p<0.001).

No significant differences were observed in the evolution of the markers of bone formation and resorption between both groups of patients throughout the study (Table 2). No differences were observed in the percentage of patients with increased PINP values >10 ng/mL at 3 months treatment in both groups of patients (inadequate response: 82% adequate response vs 91%, p=0.422), or the evolution of values 25OHD during follow-up (Table 2).

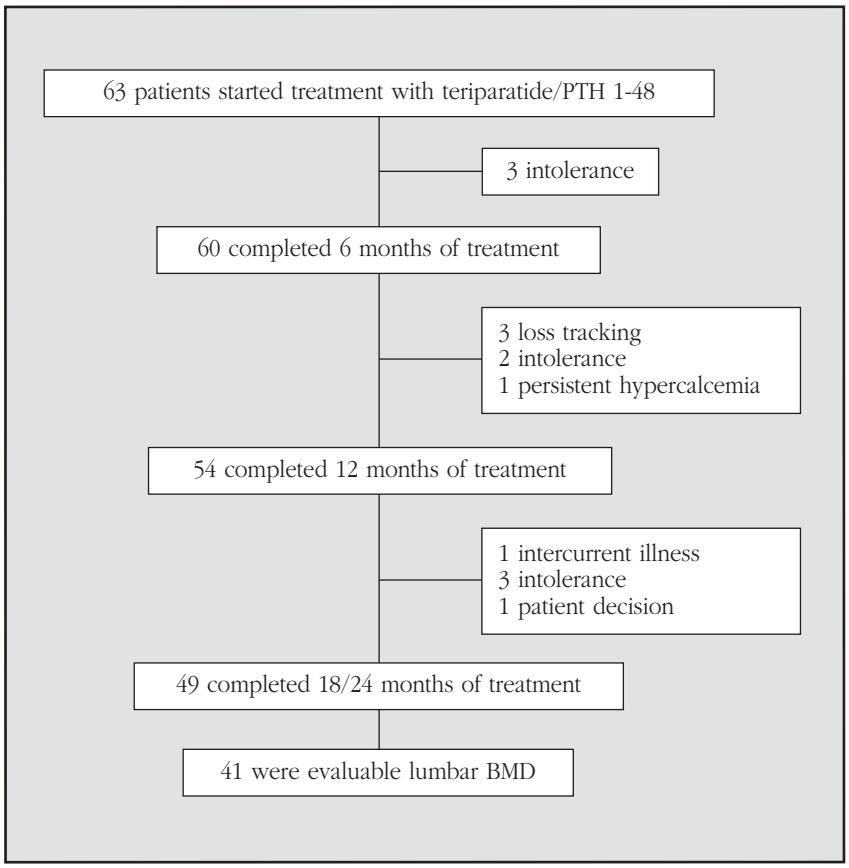
The incidence of fragility fractures (≥2) was similar in both groups of patients (14% vs 16%, p=ns). The change in lumbar spine BMD and/or femoral to 18/24 months was not associated with changes in the value of markers of formation and/or resorption at the start of treatment (3 and 6 months of treatment) (data not shown).

Discussion

Preliminary results of this study demonstrate that a relatively high percentage of patients with severe osteoporosis present an inadequate response to bone forming treatment when analyzed by measuring BMD. Thus, about 30% of patients included in this study had an inadequate response, with no significant increase in BMD at 18/24 years of treatment. However, it should be noted that these patients had multiple fractures associated with osteoporosis and also had undergone previous treatment with bisphosphonates for several years. Although we found factors related to inadequate response to bone forming treatment, patients with this type of response had a tendency to have had prior bisphosphonate treatment more often and longer, with an average of 7 years of treatment.

However, in most patients (70%) a marked increase in BMD at 18/24 months of treatment, around 12% at the lumbar spine and proximal femur 4.5% was observed. This outcome is similar in scale to data published previously[4,6], but differs in the incidence of inadequate response compared to those studies. Thus, only 6% of patients included in the study of Neer et al.[6] had an inadequate response to teriparatide treatment, a finding that was observed in about 30% of our patients. In addition, this group of patients not only experienced an increase in BMD after bone forming treatment, but presented a loss of bone mass in the lumbar spine and proximal femur of -3.4% and -0.6% respectively. Although the causes of this increased incidence of treatment failure remain unclear, it is possible that the severity of the disease and previous treatment with bisphosphonates have contributed in part to these results. In this sense, our patients had a more severe osteoporosis, with an average of 5 vertebral fractures per patient, double the baseline studies, and often (>80%) had undergone previous treatment with bisphosphonates, a fact that was observed in only 14-16% of patients in reference studies 6. In fact, recent studies also indicate an increased incidence of inadequate response after bone forming treatment, rising to 32% of patients in the study by Chen et al.[9]. This suggests that baseline BMD and bone remodeling (especially low PINP values) and previous treatment with bisphosphonates could influence the magnitude of therapeutic response to these agents[8-11,18]. In our study, although differences in the rate and duration of prior bisphosphonate treatment between both groups of patients were not significant, over 90% of patients

Figure 1. Flow chart of patients included



with inadequate response to treatment had had prior bone forming treatment with bisphosphonates for an average 7 years, suggesting a possible inhibitory effect of this type of treatment.

As noted previously, several studies point to the role of bone remodeling markers[8,9,11,12,15,16,19] to predict the level of response to long-term bone forming treatment[9,12,19], especially when the PINP bone formation marker is used[12,16]. In a post-hoc study, Eastell et al.[13] note that by quantifying the change in PINP at 3 months of starting teriparatide treatment allowed for the indentification of long-term patients who presented a significant BMD increase, particularly if the increase was greater than 10 ng/mL[9,12-16]. In our study, we observed a marked increase in the values of all bone remodeling markers after starting bone forming treatment. The magnitude of the increase was similar in both groups of patients during follow-up. We did not detect significant differences in the percentage of patients who experienced an increase of serum PINP (>10 ng/mL) after starting the bone forming treatment between both groups of patients.

Some of this study's limitations include the small number of patients and its characteristics as a retrospective study. However, as initially indicated, this preliminary analysis includes a sample of patients treated in a specialized, bone metabolism unit. All patients were evaluated based on a standardized therapeutic protocol in which serial determination of biomarkers and densitometric, radiological and clinical monitoring was carried out, allowing close monitoring of the clinical course in this group of patients.

In conclusion, although these are preliminary results in a small number of patients, our study shows that about 30% of patients with severe osteoporosis presented an inadequate response to long-term bone forming treatment. Although this study has not identified predictors of this type of response, it is possible that prolonged prior bisphosphonate therapy may be related to the findings. These results indicate the need to analyze this in a greater number of patients.

Conflict of interest: No conflict of interest by the authors.

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Table 1. Baseline characteristics of patients included

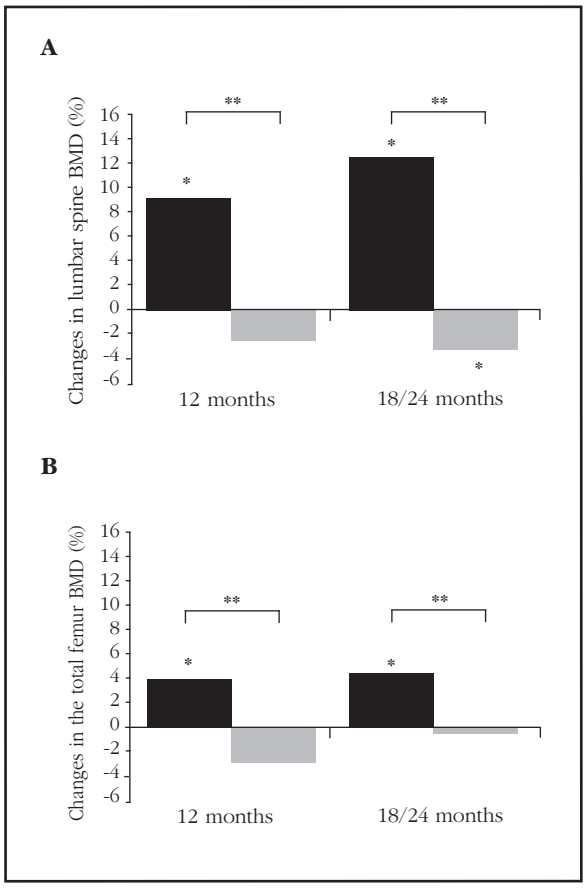
	All patients (n=49)	Appropriate response (n=29)	Inadequate response (n=12)	p
Women/Men (n)	46/3	27/2	12/0	0.351
Age (years)	69.5±11.1	68±11	70±11	0.641
BMI (kg/m^2)	26±5	25±5	27±5	0.483
Treatment				
Teriparatide/PTH 1-84 (n)	41/8	25/4	10/2	0.813
Duration of treatment (months)	21±3	21±3	20±3	0.47
Skeletal fractures				
Previous vertebral fractures (%)	84	86	75	0.386
Number of prior vertebral fractures (n)	5±4	5±4	4±4	0.832
Baseline BMD				
Lumbar (g/cm^2)	0.775±0.161	0.733±0.146	0.812±0.166	0.197
Total femur (g/cm^2)	0.701±0.121	0.674±0.087	0.701±0.157	0.474
Prior osteoporosis treatment				
Patients with previous BF (%)	84	79	92	0.339
Duration of previous BF (years)	5.8±4.5	4.9±4.2	7±4.8	0.195
BF discontinuation time (months)	3.2±7.3	2.8±6.8	3.1±8.6	0.635
Comorbidities				
Glucocorticoid treatment (%)	22	21	17	0.767

BMI: body mass index; BMD: mineral bony density; BF: bisphosphonates.

Table 2. Evolution of biochemical parameters and bone turnover markers at 3 and 6 months of bone forming treatment in patients with adequate response (RA) and inadequate (RI) treatment

	Basal		3 months		6 months	
	RA	RI	RA	RI	RA	RI
Calcium (mg/dL)	9.7±0.6	9.8±0.4	9.9±0.7	9.5±1.8	9.9±0.7	9.9±0.5
AP bone (ng/mL)	14.9±7.4	14.1±4.7	23.3±13.7	23.7±13.8	34.5±36.2	45.3±43.3
PINP (ng/mL)	45±42	36±33	132±140	126±156	184±127	191±227
CTx (ng/mL)	0.42±0.38	0.24±0.07	0.85±0.76	1.06±1.72	1.02±0.5	1.16±1.14
NTx (ng/mL)	55±43	41±24	98±82	98±99	107±63	111±72
25OHD (ng/mL)	32±17	27±10	22±11	22±5	25±12	23±4

Figure 2. Changes in BMD in the lumbar region (A), and total femur (B) in patients with adequate response (black bar) and inadequate response (gray bar) at 12 and 24 months into the treatment



*p<0.05 compared to baseline value.
**p<0.05 comparing both groups of treatment response.

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