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Research Article

Long Term Effect of Denosumab on Densitometry Evolution in Women Patients

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Abstract

Introduction: Osteoporosis is one of the most common bone disease in the world. The side effect associate to bone fractures increases the morbidity and mortality especially in aging women.

Recently, a monoclonal antibody directed against activator nuclear factor k B ligand receptor (RANKL) denominated Denosumab has been approved as an initial therapy for bone fracture high risk patients (e.g. aging, bisphosphonates intolerant or contraindicated).

Denosumab exert their effect inhibiting the osteoclasts function and decreasing the bone resorption. Several studies have demonstrated that Denosumab increased dual-energy X-ray absorptiometry (DXA) areal bone mineral density (aBMD) and decreased the bone turnover as well as the risk of new vertebral, non-vertebral, and hip fractures. However, the level of response to treatment with Denosumab among patients with or without osteoporosis in a long term evaluated by densitometry is unknown. The aim of this study is (a) to identify the proportion of women that decrease the bone density after starting the Denosumab treatment and (b) to identify factors associate to the decreasing bone density in women receiving Denosumab.

Materials and Methods: This retrospective, unicenter and real world study was conducted in the Gynaecology Unit of HM Hospitals during January 2013 to December 2015. Inclusion criteria: women older than 40 years old medicated with denosumab and with two consecutives densitometries.

T0 include all variables and the densitometry result immediately before the Denosumab treatment was prescribed. Then densitometries were routinely performed at 2 - 3 years, at 4 - 5 years and 6 - 7 years from treatment prescription. Treatment failure was considered when the second densitometry was lower than 2.7% regarding the previous.

Results: During the study period 834 patients have received Denosumab; The final sample included 365 patients of which 123 patients (33,6%) not reduce more than 2.7% at any time compared to the previous densitometry, (considering no decrease at the femoral or lumbar level).

When analyzing each one of the variables with its association to the failure of the treatment with Denosumab, none of the variables allows to predict which patient will respond or not to the treatment.

Conclusion: More studies are needed to validate these results and find other factors that may influence the response to Denosumab during long-term treatment and also assess the risk of fractures in patients who do not respond adequately to treatment.

Keywords: *Osteoporosis; RANKL; Dual-Energy X-Ray Absorptiometry (DXA); Areal Bone Mineral Density (aBMD)*

Introduction

Osteoporosis is one of the most common bone disease in the world. Only in the United States, it is responsible for 1.5 millions of bone fractures per year. Osteoporosis direct and indirect lifetime costs may excess the amount 20 billion dollars [1,2]. Likewise, side effect associate to bone fractures increases the morbidity and mortality especially in aging women [1].

Osteoporosis is characterized by low bone mass, microarchitectural disruption and increased skeletal fragility [3]. Oral bisphosphonates has been considered the first-line therapy for osteoporotic women as it demonstrated efficacy and safety [4-6]. Recently, a mono-

clonal antibody directed against activator nuclear factor k B ligand receptor (RANKL) denominated Denosumab has been approved as an initial therapy for bone fracture high risk patients (e.g. aging, bisphosphonates intolerant or contraindicated) [6-8].

Denosumab exert their effect inhibiting the osteoclasts function and decreasing the bone resorption [7]. Several studies have demonstrated that Denosumab increased dual-energy X-ray absorptiometry (DXA) areal bone mineral density (aBMD) and decreased the bone turnover as well as the risk of new vertebral, non-vertebral, and hip fractures [9-11]. Thus the Food and Drug administration and the European Medicine Agency have approve it for clinical use. However, the level of response to treatment with Denosumab among patients with or without osteoporosis evaluated by densitometry is unknown [7-11].

Aim of the Study

The aim of this study is (a) to identify the proportion of osteoporotic women that decrease the bone density after starting the Denosumab treatment and (b) to identify factors associate to the decreasing density in women receiving Denosumab.

Materials and Methods

This retrospective, unicenter and real world study was conducted in the Gynaecology Unit of HM Hospitals during January 2013 to December 2015. Inclusion criteria: women older than 40 years old, medicated with denosumab and with two consecutives densitometries or dual-energy X-ray absorptiometry (DXA). Exclusion criteria: medicated with Denosumab previous to be included in this study and lack of clinical or analytical variables.

Clinical and analytical variables were collected in a predefined form. T0 include all variables and the densitometry result immediately before the Denosumab treatment was prescribed. Then densitometries were routinely performed at 2 - 3 years, at 4 - 5 years and 6 - 7 years from treatment prescription. The bone load was reported by a T score which is a relative value of the patients load and the population. The T score range from negative to positive values and include the 0 and represent the number of standard deviations of the BMD with respect to the average value of the population of 20 to 39 years of the same sex. We calculate the difference in T score from Lumbar and Femoral bone between each two consecutive densitometry. Treatment failure was considered when the second densitometry was lower than 2.7% regarding the previous. Finally, denosumab failure was consider when the patient present at least one failure in lumbar and/or femoral densitometry during follow (Figure 1).

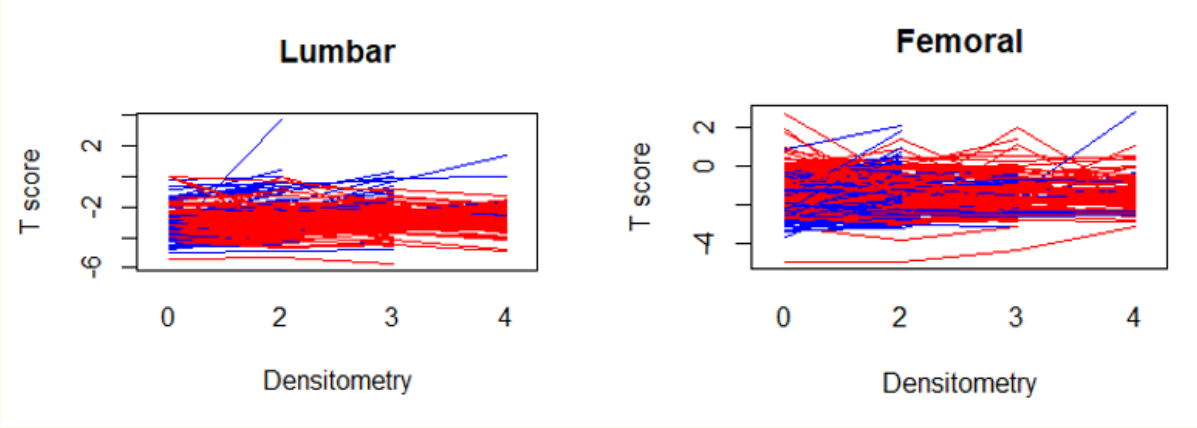

Figure1: *Evolution of main variables during the study period.*

Statistical analysis

Continuous variables are reported mean and standard deviation or medium and p25-P75 according to it distribution. Categorical variables are reported as absolute frequency with percentage. Denosumab failure versus response was compared. Continuous variables were compared with T test or Man Whitney variables with a p value < 0.1 in the univariate analysis P value < 0.05 was considered significant.

Results

At t2 densitometry was performed in 35 patients, at t4 in 206 patients and at t6 126 patients.

As the main finding of the patients who perform consecutive densitometry, 123 (33,6%) they did not reduce more than 2.7% at any time compared to the previous densitometry, (considering no decrease at the femoral or lumbar level).

When analyzing each one of the variables with its association to the failure of the treatment with Denosumab, none of the variables allows to predict which patient will respond or not to the treatment.

	All patients (n = 365)	Failure (n = 242)	Respond (n = 123)	p
Main characteristics				
Age	64.9 (59.4, 70.3)	64.9 (60.2, 70.7)	64.1 (58.4, 69.75)	0.376
Menopausal Age	50 (47, 52)	50 (47, 52)	50 (48, 52)	0.115
Years since menopause	16 (11, 24)	17 (11, 25)	15 (10, 21)	0.096
Hormone replacement therapy (years)	1 (0, 5)	1 (0, 5)	1 (0, 4)	0.226
Years since menopause without treatment	9 (4, 15)	9 (3, 15)	10 (5, 16)	0.129
Weight (kg)	57.3 (52, 63)	57 (52, 62)	59 (53, 64)	0.054
Height (cm)	160 (155, 164)	160 (155, 164)	160 (156, 163)	0.949
IMC, kg/m^2	22.82 (21.06, 24.92)	22.77 (20.96, 24.89)	22.83 (21.09, 24.92)	0.79
25-OH-vitamin D, ng/mL	31.4 (24.62, 38.73)	31 (24.92, 37.85)	32.5 (24.32, 40.98)	0.424
CTX, ng/mL	0.4 (0.28, 0.52)	0.38 (0.26, 0.51)	0.42 (0.3, 0.53)	0.214
P1NP, ng/mL	50.12 (38.19, 64.46)	48.42 (35.96, 62.94)	52.66 (41.47, 68.52)	0.063
Calcio, mg/dl	164.8 (110.24, 239.76)	164.3 (110.77, 243.18)	168.16 (110.48, 229.34)	0.772
Alkaline phosphatase, UI/L	55 (42, 70)	54.5 (42, 72)	56 (41, 70)	0.86
Densitometry (Tscore)				
Femoral t0	-1.56 (-2.1, -0.98)	-1.44 (-2, -0.86)	-1.75 (-2.32, -1.2)	0.001
Femoral t2 t3	-1.4 (-1.91, -0.89)	-1.45 (-1.96, -0.97)	-1.33 (-1.86, -0.72)	0.195
Femoral t4 t5	-1.52 (-2.1, -0.88)	-1.56 (-2.1, -0.96)	-1.3 (-1.95, -0.46)	0.226
Femoral t6 t7	-1.52 (-1.98, -0.82)	-1.59 (-1.97, -0.82)	-1.47 (-1.98, -1.32)	0.946
Lumbar t0	-3.08 (-3.47, -2.76)	-3.05 (-3.46, -2.71)	-3.13 (-3.5, -2.84)	0.23
Lumbar t2 t3	-2.75 (-3.2, -2.33)	-2.84 (-3.29, -2.44)	-2.51 (-3.04, -2.09)	0
Lumbar t4 t5	-2.7 (-3.16, -2.24)	-2.79 (-3.16, -2.33)	-2.36 (-2.64, -1.67)	0.005
Lumbar t6 t7	-2.71 (-3.13, -2.12)	-2.76 (-3.27, -2.21)	-1.91 (-2.4, -1.63)	0.006

Table 1: *Main features of the whole cohort and univariate analysis between patients that respond or failure to the Denosumab prescription. CTX: C-Terminal Telopeptide, P1NP: Procollagen Type 1 N-Terminal Propeptide.*

Comorbidites	All patients (n = 365)	Failure (n= 242)	Respond (n = 123)	p
Menopause	256 (0.7)	172 (0.71)	84 (0.68)	0.669
THS	66 (0.18)	45 (0.19)	21 (0.17)	0.831
ACHO	90 (0.25)	57 (0.24)	33 (0.27)	0.577
Osteoporosis previous treatment	220 (0.6)	154 (0.64)	66 (0.54)	0.084
Smoke	68 (0.19)	45 (0.19)	23 (0.19)	1
Caffeine intake	220 (0.6)	147 (0.61)	73 (0.59)	0.885
Physical activity	240 (0.66)	155 (0.64)	85 (0.69)	0.398
Chronic back pain	174 (0.48)	118 (0.49)	56 (0.46)	0.636
Previous bone fracture	169 (0.46)	112 (0.46)	57 (0.46)	1
Osteoporosis family history	79 (0.22)	58 (0.24)	21 (0.17)	0.168
Hyperthyroidism	1 (0)	1 (0)	0 (0)	1
Diabetes	4 (0.01)	2 (0.01)	2 (0.02)	0.606
Malabsorption syndrome	2 (0.01)	2 (0.01)	0 (0)	0.552
Cancer	18 (0.05)	10 (0.04)	8 (0.07)	0.463
Prolactinoma Pituitary Tumor	2 (0.01)	2 (0.01)	0 (0)	0.552
Connective tissue disease	2 (0.01)	1 (0)	1 (0.01)	1
Chronic hepatic disease	4 (0.01)	4 (0.02)	0 (0)	0.305
Cerebrovascular disease	14 (0.04)	6 (0.02)	8 (0.07)	0.081
Chemotherapy	10 (0.03)	5 (0.02)	5 (0.04)	0.315
Radiotherapy	11 (0.03)	5 (0.02)	6 (0.05)	0.193
Lost of heigh 3cm	43 (0.12)	33 (0.14)	10 (0.08)	0.17
Medication at treatment prescription	15 (0.04)	11 (0.05)	4 (0.03)	0
Steroids	20 (0.05)	14 (0.06)	6 (0.05)	0.907
Immunosuppressive agents	2 (0.01)	2 (0.01)	0 (0)	0.552
Thiazides	7 (0.02)	6 (0.02)	1 (0.01)	0.431
Statins	66 (0.18)	39 (0.16)	27 (0.22)	0.22
Antiepileptic Drugs	4 (0.01)	2 (0.01)	2 (0.02)	0.606
Thyroid drugs	49 (0.13)	29 (0.12)	20 (0.16)	0.332
Anticoagulants	6 (0.02)	4 (0.02)	2 (0.02)	1
Gonadotropin releasing hormone analogue	1 (0)	1 (0)	0 (0)	1
Oral antihyperglycemic agents	1 (0)	0 (0)	1 (0.01)	0.337
Aromatase inhibitors	7 (0.02)	3 (0.01)	4 (0.03)	0.232
Raloxifeno/bazedoxifeno	112 (0.31)	70 (0.29)	42 (0.34)	0.367
Ibandronato/Risedronato/Alendronato	145 (0.4)	105 (0.43)	40 (0.33)	0.058
Teriparatida	6 (0.02)	5 (0.02)	1 (0.01)	0.668
Strontium ranelate	32 (0.09)	26 (0.11)	6 (0.05)	0.094
Calcitonin	7 (0.02)	6 (0.02)	1 (0.01)	0.431

Table 2: *Main comorbidities of the whole cohort and univariate analysis between patients that respond or failure to the Denosumab prescription.*

Variables	p value
Years since menopause	0.780
Weight, kg	0.865
P1NP, ng/mL	0.119
Cerebrovascular disease	0.057
Osteoporosis previous treatment	0.480
Ibandronato/ Risedronato/Alendronato Treatment	0.136

Table 3: *Multivariate analysis.*

Discussion

In our study we have reported that 33.6% of the patients receiving Denosumab presented a positive response (never decrease their bone load more than 2,7% respect previous densitometry).

This 33.6% of patients respond to treatment with Denosumab preventing bone resorption and reduce the risk of fractures as demonstrated by the FREEDOM study [11].

This is one of the studies to evaluate the response to long-term treatment with objective measurement parameters (BMD) with densitometry or dual-energy X-ray absorptiometry (DXA) although some studies also consider fractures as an event of interest [12] it is of fundamental importance because once a fracture occurs, some complications, including decreases of activities of daily living (ADL) and cognitive functions, develop, which lead to an increased mortality risk for several years.

In the setting of osteoporosis targets are less well defined but BMD or fracture risk are logical therapeutic targets [12-14].

Bone Marker Standards Working Group have identified PINP and CTX-I in blood to be the reference markers of bone turnover for the fracture risk prediction and monitoring of osteoporosis treatment. Although used in clinical research for many years, bone turnover markers (BTM) have not been widely adopted in clinical practice primarily due to their poor within-subject and between-lab reproducibility [14,15].

This study also aims to assess the effectiveness of treatment with Denosumab, not as a recovery of bone mass already lost in already manifest osteoporosis, but as a bone mass maintainer in non-osteoporotic patients. With this we want to descriptively evaluate the percentage of patients in whom treatment with Denosumab is effective in maintaining bone density over time.

It has been described that treatment with Denosumab for 10 years is associated with a continuous increase in BMD, and a low incidence of fractures and acceptable tolerance and safety [11], even in those patients who are still considered to be at high risk of fracture after 5 years [12].

However, there is evidence of a fall in BMD after the cessation of Denosumab. In some patients, this may be accompanied by an increased risk of multiple vertebral fractures, although there is currently no evidence to suggest that the risk of single vertebral fractures or non-vertebral fractures increases after stopping Denosumab. Therefore, it is important to warn patients and doctors that they should not interrupt Denosumab treatment without evaluating and considering an alternative therapy, especially in those patients considered to be at high risk of fracture [15,16].

It seems important to consider then the therapeutic alternatives and the individual conditions of each patient and their comorbidities when choosing a treatment.

In the general population, fracture prevention using bisphosphonates is well established. With bisphosphonates has been shown to decrease the incidence of fractures by approximately 50% in postmenopausal women with osteoporosis and is considered a first-line drug for primary osteoporosis [4-6]. However, bisphosphonate used as a treatment in patients with special conditions such as hemodialysis patients or patients who need another treatment alternative (presenting adverse events or changing antiosteoporotic therapy) The effects of bisphosphonates in hemodialysis patients are still unclear. In contrast, Denosumab, a fully humanized monoclonal IgG2 antibody against the receptor activator of nuclear factor-κB ligand (RANKL) [16-18], is not eliminated by the kidneys. Therefore, in patients with renal insufficiency, denosumab is easier to use than other anti-osteoporotic drugs such as alendronate, which are eliminated through the kidney [18,19].

In our study, we looked for the variables associated with the failure of Denosumab treatment and we obtained no significant association with the variables studied that give us the possibility of predicting which patients will respond satisfactorily to treatment. This is important since, according to our results, 1/3 of the patients will respond with a tendency to not decrease BMD > 2.7 in the period studied.

As negatives points of the study we emphasize that being descriptive and retrospective, we were able to lose important data when evaluating important characteristics in patients that may have influenced the response to treatment.

On the other hand, the number of patients studied may not be enough to draw conclusions about the relevant variables in the satisfactory response or not to treatment with Denosumab. It is also important not only to objectively measure the levels of densitometry, but also to focus on the quality of life and adverse events that patients may present during treatment.

Future studies should validate these results and find a possible scientific explanation to other factors that may influence the response to Denosumab during long-term treatment and also assess the risk of fractures in patients who do not respond adequately to treatment.

Conclusion

In our study we have reported that 33.6% of the patients receiving Denosumab presented a positive response. We obtained no significant association with the variables studied and the failure to the treatment so more studies are needed to validate these results and find other factors that may influence the response to Denosumab during long-term treatment and also assess the risk of fractures in patients who do not respond adequately to treatment.

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