Multiple vertebral fractures after suspension of denosumab. A series of 56 cases.

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November 30, 2020

Abstract

Background: Denosumab is a monoclonal antibody approved for the treat-ment of postmenopausal osteoporosis. The withdrawal of denosumab produc-es an abrupt loss of bone mineral density and may cause multiple vertebral fractures (MVF). Objective: To study the clinical, biochemical and densitometric characteristics in a large series of postmenopausal women who suffered MVF after deno-sumab withdrawal. Likewise, we try to identify those factors related to the presence of a greater number of vertebral fractures (VF). Patients and Methods: 56 patients (54 women) who suffered MVF after re-ceiving denosumab at least for 3 consecutive years and abruptly suspended it. A clinical examination was carried out. Biochemical bone remodeling markers (BBRM) and bone densitometry at the lumbar spine and proximal femur were measured. VF were diagnosed by MRI, X-ray or both at dorsal and lumbar spine. Results: 56 patients presented a total of 192 VF. 41 patients (73.2%) had not previously suffered VF. After discontinuation of the drug, a statistically signifi-cant increase in the BBRM was observed. In the multivariate analysis, only the time that denosumab was previously received was associated with the pres-ence of a greater number of VF ($p = 0.04$). Conclusions: We present the series with the largest number of patients col-lected to date. 56 patients accumulated 192 new VF. After the suspension of denosumab and the production of MVF, an increase in the serum values of the BBRM. The time of denosumab use was the only parameter associated with a greater number of fractures.

Introduction

Denosumab (DMAB), a monoclonal antibody against the receptor activator of nuclear factor k-B ligand

(RANKL), is a potent antiresorptive agent commonly prescribed in patients with postmenopausal osteoporosis. DMAB reduces bone resorption and improves bone mineral density (BMD) (1).The FREEDOM trial found reduced risk of fragility fracture, a study that lasted 10 years (2,3)

Unlike bisphosphonates, which have a residual effect on bone when deposited therein (4), discontinuing DMAB treatment may produce a rebound effect on markers of bone remodeling and a loss of bone mass to the extreme that their values are even below the existing values before starting treatment (5). Furthermore, since 2015, several case reports and series were published describing multiple vertebral fractures (MVF) in patients discontinuing DMAB, which are also characterized by being painful. (6–9). Recently, 3 cases have been described of patients who suffered a hip fracture after the suspension of denosumab (10) and also repeated fractures in the same patient (11). The mechanism by which this complication occurs is unknown, as is its exact incidence (11).

Most of the articles published to date describe isolated cases or series with few patients. In this study, we present a series of 56 patients who suffered multiple vertebral fractures after discontinuing DMAB as well as a study of their clinical, analytical and densitometric characteristics. This series includes the largest number of patients published so far, with the aim of identifying prognostic factors for higher risk patients and establish the most appropriate preventive actions.

Patients and Methods.

The study was carried out in Spain, between April 1, 2019 and January 31, 2020, coordinated by the working group on osteoporosis and mineral metabolism of the Spanish Society of Internal Medicine (SEMI). Patients who had previously received a minimum of one year of DMAB treatment, injecting at least 2 doses, having produced a minimum delay of 2 months from the moment of injection, were included. Patients must have suffered at least one fragility fracture after discontinuation of DMAB. This fracture was verified by a lateral radiography of the thoracic and lumbar spine, an MRI of the entire spine, or both. Genant's classification (12) was applied to diagnose vertebral fracture. Those patients with cancer, Paget's disease of bone or when the fracture was traumatic were excluded. The collection of clinical data was carried out with a questionnaire designed for this purpose.

Bone densitometry:

All patients had at least two dual X-ray absorptiometry (DXA) exams: one before or at the time of DMAB initiation and one after VF occurrence. Exams were carried out with different machines for different patients, but the same for each patient, allowing us to compare both exams. T-scores were calculated using normal values for the Spanish population. For biochemical determinations, fasting blood was drawn. The biochemical parameters: creatinine, total proteins, calcium and phosphorus were measured using standardized colorimetric methods. Immunochemiluminescence was used to determine the biochemical parameters of bone remodeling: P1NP, beta-crosslaps and osteocalcin.

VF diagnosis was confirmed by MRI assessed by a radiologist, except in four patients in which it was based on shape changes in X-ray exams as compared to recent previous images.

The study was carried out following the rules of the Declaration of Helsinki (13), the protocol approved by the Insular University Hospital of Gran Canaria Clinical Trials Committee. All patients were informed of the study objectives and gave their informed written consent.

Statistical analysis *Univariate analysis.* Categorical variables are expressed as frequencies and percentages and continuous as mean and standard deviation (SD). Paired means were compared using the Wilcoxon test for paired data.*Poisson models.* The effect of each factor (X) on the number of vertebral fractures after DMAB (nVF) was analyzed by means of the Poisson model: nVFPoisson (μ), being:

$$\log(\mu) = \alpha + \beta X$$

Where μ is the expected number of vertebral fractures, which may depend on the X factor. When X is a binary variable indicating presence or absence of a character its values were coded as 1 (presence) and 0 (absence). From this model it follows:

$$\frac{\mu\left(X=t+1\right)}{\mu\left(X=t\right)}=exp\left(\beta\right)$$

Where $\mu\left(X=t\right)$ corresponds to the expected number of vertebral fractures when the factor X is in level t . Therefore, $\exp\left(\beta\right)$ correspond to the proportion of variation of the expected number of vertebral fractures for each unit that varies X.

Statistical significance was set at $p < 0.05$. Data were analyzed using the R package, version 3.6.1 (R Development Core Team, 2019).

Results

Table 1 shows the baseline characteristics of our study patients. A total of 56 patients were included, of which 54 were women (96.4%). The mean age was 68.1 ± 8.2 years. The most frequently observed concomitant diseases were arterial hypertension (32.1%), dyslipidemia (32.1%) and hypothyroidism (16.1%). Most of the patients had not previously suffered vertebral fractures (73.2%) and their risk of fracture calculated at 10 years using the FRAX risk assessment tool after having suffered multiple vertebral fractures was 11% for major fractures (95% CI 6.1% -16%) and 3.9% for hip fractures (1.2% -6.6%). Patients had been taking DMAB for a median of 30.5 months (95% CI: 24-43.5 months) and had injected a median of 6 doses (95% CI: 4-8 doses). 56 patients accumulated 192 new vertebral fractures.

Table 3 shows the reasons why DMAB was discontinued. Medical prescription was the main cause of suspending treatment, which occurred in 62.7% of cases.

Table 4 shows the biochemical values studied, including the biochemical markers of bone remodeling, obtained before and after DMAB suspension and the appearance of multiple vertebral fractures. Values of calcium, phosphorus, total proteins, vitamin D (25 hydroxycholecalciferol) and PTH do not change substantially, but the biochemical markers of bone remodeling increase significantly, both beta-crosslaps, P1NP and osteocalcin ($p < 0.006$ in all cases). The greatest increase occurs in the beta-crosslaps, from 0.071 to 0.520 ng/mL median, a 14-fold increase in baseline values. Osteocalcin values almost tripled while those of P1NP quadrupled.

Finally, Table 5 shows the logistic regression analysis to study the possible association between the various clinical, analytical and densitometric parameters and the number of vertebral fractures. The length of time of previous DMAB use is the only parameter that was associated in a statistically significant way ($p = 0.04$).

Discussion

Our study included a total of 56 patients and constitutes the largest number of cases collected in a single series. Previous studies presented a smaller number of cases. González-Rodríguez et al (7) collected 60 spontaneous vertebral fractures in 15 women with breast cancer who were undergoing treatment with aromatase inhibitors and in whom denosumab was discontinued. Fernández Fernández et al (14) described 49 vertebral fractures in 10 women and Florez et al (15) published a series of 7 women who had a median of 5 vertebral fractures. Another study collected the first 3 cases of hip fracture produced after abrupt DMAB discontinuation in the absence of other causes (10). Several systematic reviews have confirmed the magnitude of the problem (6,16-18). In this series, we publish the first two cases described in men.

The actual number of cases is probably much higher. The Spanish Agency for Medicines and Health Products (AEMPS), which collects adverse effects of drugs, described in 2019 a total of 64 patients with multiple vertebral fractures that were increased in a subsequent statement in 2020, 213 patients with multiple vertebral fractures and 50 hip fractures. There are several reasons that might explain why the magnitude of the problem is not preceived. We would mention: a) it is a complication not yet sufficiently known by the medical community in general, b) they are fractures that occur in patients who have osteoporosis, therefore,

they can be attributed to the disease rather than to the suspension of the drug, c) given that the drug is administered every 6 months, it is possible to forget it, especially when the questioning is directed at drugs that are taken orally, and d) for scientific journals, the publication of new cases do not provide anything noteworthy. So, in recent years, the number of publications on the matter has decreased, while the number of fractures has not.

The mean age of our series was 68.1 years, somewhat older than those described in other series, such as that of Barcelona, where the median age was 65 years (15), and that of Madrid with a mean of 66.4 years (14). In the González-Rodríguez series (7), the mean age was lower, 62.3 years, but they were other types of patients, women with breast cancer and not postmenopausal osteoporosis. In a systematic review in which 24 cases were collected, the mean age was 64.1 years (6).

Our patients had received a median of 6 doses, with DMAB having been used a median of 30.5 months. These results coincide with those published in other series and reports of individual cases (6–8,10,14–16,19–23). In a "real world" study, the risk of fracture when discontinuing DMAB treatment has been calculated to increase markedly when the third injection is given (16). The time it takes for fractures to occur after the last dose of DMAB showed a median of 11 months in our study, which represents a 5-month delay, since the drug is administered every six months, although in one case it occurred after the delay of a month and a half. In different reported cases, this period ranges from 2 to 13 months (6,8,14,15).

Probably the appearance of fractures will depend on two factors, the severity of the disease and the withdrawal of the drug. The severity of the disease could be determined through the FRAX or by the presence of previous fractures. The 10-year risk of fracture calculated by the FRAX tool showed a median of 11% for major fracture and 3.9% for hip fracture. Although there is a debate on the optimal threshold to perform a therapeutic intervention (24–26), the high risk of fracture has been established at 20% for the major fracture and 3% for the hip fracture (27). In our study, the fracture risk at 10 years showed a median of 11% for the major fracture and 3.9% for the hip fracture. FRAX has rarely been estimated in the publications of other cases.

The other factor involved is the discontinuation of the drug. One of the reasons DMAB was discontinued came about after reported improvement in treatment with BMD, leading to the misconception that osteoporosis was cured. Following this line, the idea of the "treat to target" was developed according to which, when reaching a certain T-score value, the drug could be suspended, without verifying the results of this suspension (28–30).This led to the discontinuation of DMAB due to medical recommendation in 41.1% of cases. Closely related to this idea is the concept of therapeutic holidays wrongly applied to DMAB (31,32). On the other hand, given that the association between the use of denosumab and osteonecrosis of the jaws has been described (33–35), the suspension of denosumab was carried out by the dentist's indication in 21.5% of the patients. Our results coincide with those reported in other series (7,8,22).

The deleterious effect of DMAB suppression is determined by the sudden increase in remodeling that can lead to a deterioration in bone strength and facilitate the appearance of fractures. This fact had been previously described, although an increase in fractures had not been observed. After discontinuing DMAB, beta-crosslaps increase significantly, from a median of 0.071 ng/mL to 0.520 ng/mL ($p < 0.001$). To a lesser extent, but also significantly, the markers of bone formation increase, the P1NP that goes from 25.3 ng/mL to 101.2 ng/mL, $p = 0.006$ and osteocalcin from 10.7 ng/mL to 28.1 ng/mL. This indicates an increase in all bone remodeling in which osteoclastic activity clearly predominates, as has also been described in other series (20,36,37). We have not observed changes in serum levels of creatinine, calcium, phosphorus, total protein, vitamin D, measured as 25-hydroxyvitamin D, or in PTH.

Finally, we carried out a logistic regression analysis to try to identify which factors could be associated with the presence of a greater number of fractures, obtaining a statistically significant association with the time in which denosumab was previously used ($p = 0.04$).

Among the limitations of our study is the sample size, which is due to the difficulty in identifying these patients. On the other hand, since there is no control group, we have not been able to establish what the

clinical, analytical or densitometric factors could be associated with the appearance of fractures. The strength of the study is determined by the high number of fractures associated with a full number of complementary tests.

To sum up, we present a series of 56 patients in which the abrupt discontinuation of DMAB caused a total of 192 vertebral fractures, the increase in bone removal probably being manifested through a considerable increase in biochemical markers of bone remodeling, especially those of resorption, which causes this effect.

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Table 1. Characteristics of the population studied

	Media ± SD
Number	56
Age (years)	68.1 ± 8.2
Weight (kg)	60.7 ± 12.3
Height (m)	1.6 ± 0.1
BMI (Kg/m^2)	25.1 ± 4.6
	Number (%)
Sex female	54 (96.4)
Diabetes mellitus	3 (5.4)
Arterial hypertension	18 (32.1)
Dyslipemia	18 (32.1)
Hypothyroidism	9 (16.1)
Concomitant use of calcium and vitamin D	41 (73.2)
Prevalence of fractures before the appearance of multiple vertebral fractures	*Prevalence of fractures before the appearance o*
No vertebral fracture	41 (73.2)
1 vertebral fracture	4 (7.1)
2 vertebral fractures	2 (3.6)
3 vertebral fractures	1 (1.8)
4 vertebral fractures	2 (3.6)
Non-vertebral fractures	5 (8.9)
Hip fracture	1 (1.8)

Table 2. Ten years risk of fracture (FRAX) after the appearance of multiple vertebral fractures, number of fractures and data related to the use and withdrawal of denosumab.

	Median CI 95%
FRAX (Major) pre multiple vertebral fractures	11.0 (6.1 - 16.0)
FRAX (Hip) pre multiple vertebral fractures	3.9 (1.2 - 6.6)
Time using denosumab (months)	30.5 (24.0 - 43.5)
Number of dose (n)	6.0 (4.0 – 8.0)
Time after last dose of denosumab and multiple vertebral fractures (months)	11.0 (7.5 - 13.5)
Number of vertebral fractures after denosumab withdrawal (n)	3 (2 – 4)
Number of vertebral fractures accumulated (n)	192

Table 3. Reason for denosumab withdrawal

Reason	**Number (%)**
Medical recommendation	23 (41.1)
Dentist recommendation	12 (21.5)
Oversight, forgotten	5 (8.9)
Fatigue	5 (8.9)
Secondary effects	5 (8.9)
Others	6 (10.7)

Table 4. Biochemical parameters including bone remodeling markers pre and post denosumab withdrawal and the appearance of multiple vertebral fractures.

Parameter	Pre-withdrawal	Post-withdrawal	p value	Quotient (Post/Pre)
Creatinine (mg/dL)	0.710 (0.660 ; 0.790)	0.700 (0.600 ; 0.810)	0.499	-
Calcium (mg/dL)	9.5 (9.2 ; 9.8)	9.7 (9.2 ; 10.0)	0.075	-
Phosphorus (mg/dL)	3.5 (3.125 ; 3.775)	3.6 (3.25 ; 3.85)	0.298	-
Total proteins (g/L)	7.1 (6.9 ; 7.28)	7.0 (6.6 ; 7.2)	0.183	-
Betacrosslaps (ng/mL)	0.071 (0.052 ; 0.312)	0.520 (0.440 ; 1.090)	**< 0.001**	14.7 (2.1 ; 19.7)
P1NP* (ng/mL)	25.3 (15.1 ; 44.7)	101.2 (74.2 ; 191)	**0.006**	6.5 (2.7 ; 9.9)
Osteocalcin (ng/mL)	10.7 (8.4 ; 14.1)	28.1 (21.41 ; 33.0)	**0.003**	3 (2.4 ; 3.44)
Vitamin D** (ng/mL)	29.7 (25.9 ; 39.8)	31 (26.4 ; 44.8)	0.770	-
PTH (pg/mL)	50.1 (39; 60)	46.8 (36.6 ; 56.2)	0.500	-

Data are medians (IQR)

* Type I procolagen amino-terminal peptipe ** 25 hydroxicholecalciferol (25-HCC)

Table 5. Association of the number of vertebral fractures with each one of the showed factors, adjusted by age*.

Factor	Relative risk (95% CI)	p-value
Time using denosumab per month	1.009 (1.000 - 1.017)	**0.044**
Diabetes mellitus	0.701 (0.319 - 1.541)	0.381
Arterial hypertension	0.856 (0.613 - 1.193)	0.362
Dyslipemia	0.794 (0.574 - 1.098)	0.169
Hypothyroidism	1.054 (0.708 - 1.569)	0.795
DXA lumbar spine-before	2.546 (0.578 - 11.221)	0.225
DXA lumbar spine-post	0.348 (0.087 - 1.394)	0.144
Creatinine Post	0.617 (0.234 - 1.623)	0.333
Calcium post	0.970 (0.900 - 1.046)	0.433
Phosphorus Post	0.973 (0.809 - 1.171)	0.775
Total proteins Post	0.862 (0.598 - 1.243)	0.431

(*) Each relative risk was obtained by means of a Poisson regression, being the dependent variable the number of vertebral fractures and the covariates, the corresponding factor and the age.

Addendum 1. Other researchers:

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