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Original

Adherence to denosumab during the COVID-19 pandemic

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Abstract

Introduction: we aimed to analyze whether the SARS-CoV-2 pandemic has led to a decrease in denosumab (Dmab) adherence in the population, and assess the incidence of subsequent fractures in non-adherent patients.

Methods: we assessed all patients who should have required the administration of a dose of Dmab in Cantabria (Spain), during the lockdown Sociodemographic variables, risk factors for osteoporosis, data on Dmab administration, and the reason for drug discontinuation were collected. Furthermore, the development of a subsequent clinical fracture during the following year was also analyzed.

Results: a total of 2948 patients should have received a new dose of Dmab during the lockdown months, but 546 (18.5 %) discontinued the drug. The main reason for withdrawal was the patient's own doing (65 %). The incidence of clinical fractures in the overall group was low (n = 45; 1.46 %) with only 4 vertebral and 3 hip fractures being reported. When the group that did not receive more doses of Dmab or an alternate antiosteoporotic agent was analyzed (n = 147), it was revealed that 2 patients (1.36 %) sustained a vertebral fracture and another one (0.68 %) a hip fracture during the year following the last dose of the drug.

Conclusions: there was a non-negligible percentage of patients who did not receive the dose of Dmab on time during the lockdown period. However, the incidence of clinical vertebral and non-vertebral fractures was low, even in the non-compliant subjects who did not receive a different antiosteoporotic agent. None of the patients sustained multiple vertebral fractures at the 1-year follow-up.

Keywords:
Denosumab.
Adherence.
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INTRODUCTION

Osteoporosis is the most frequent metabolic bone disease and fragility fractures represent a major health problem (1,2). Among the available therapeutic schemes, denosumab (Dmab), a monoclonal antibody that acts as an inhibitor of the RANK ligand (RANKL), is usually administered via subcutaneous injection every 6 months, frequently in primary care centers. Dmab Discontinuation without subsequent antiosteoporotic therapy leads to significant changes in bone remodeling, the so-called "rebound phenomenon", and is associated with an increased risk of vertebral fractures (3,4).

The SARS-CoV-2 pandemic, which hit Spain with extraordinary virulence, has had a huge impact on the management of chronic diseases, including osteoporosis. The strict lockdown imposed by the Spanish government within the first months of the pandemic, changed the classic health care model, leading to an increase in telemedicine, delays in performing densitometric studies, and interruptions in drug supply and administration of parenteral drugs (5). Moreover, the potential risk of a flu-like reaction that could be mistaken for a COVID-19 infection after IV zoledronic acid administration (6) or fear of visiting the primary care center in association with the administration of Dmab represented an important dilemma for both clinicians and patients with osteoporosis (7).

Taking into account the above-mentioned considerations, we aimed to analyze whether the lockdown period has led to a decrease in adherence to Dmab and to study the features of non-adherent subjects. Besides, we also studied the potential development of subsequent clinical fractures in non-adherent patients vs those fully compliant with this monoclonal antibody.

PATIENTS AND METHODS

All patients from our region (Cantabria, Sppain) who should have required the administration of a dose of Dmab during the COVID-19 lockdown period in Spain, from March through June 2020 were included in the study. Nine patients were excluded because of incomplete data on the clinical chart. To detect non-compliant subjects, drug withdrawal in the pharmacy was analyzed and later checked in the patient's health history.

The study was conducted in Cantabria, a region in northern Spain, with a population of 581,641 inhabitants, an area of 5321 km^2, and a population density of 109 inhabitants per km^2. As Dmab is administered biannually, the data of those who received the last dose from September to December 2019 were collected. The study was approved by Cantabria Ethics Committee (No. 2022.004).

STUDY VARIABLES

Age, sex, the financial contribution of the patient to pharmacy costs, and the place of residence were collected as sociodemographic variables. An urban area was considered if the size of the population size exceeded 10,000 inhabitants.

Risk factors for osteoporosis including smoking, alcohol consumption, diseases or drugs affecting bone metabolism, previous drug use, history of fractures, and use of calcium and/or vitamin D supplements were also collected, as well as serum 25-hydroxyvitamin D levels (ng/mL) and bone densitometry parameters. Dmab onset and last dose date, the initial prescribing physician, and the reason for drug withdrawal were also gathered from the clinical charts.

The number and characteristics of the patients who did not receive the corresponding dose of Dmab or who received it with a delay of more than 1 month, as well as the variation in Dmab pick-up in pharmacies vs the previous year were also assessed. Finally, we analyzed the occurrence of subsequent clinical fractures at the 1-year follow-up. Data were obtained from the patients' health history. A total of 9 patients from the non-compliant group were excluded from the analysis because they did not present sufficient valid data on their clinical charts.

STATISTICAL ANALYSIS

Results were expressed as numbers and percentages, mean ± standard deviation (SD), or median and interquartile range (IQR), as appropriate. To compare quantitative and qualitative variables Student t-test and the chi-square test or Fisher's exact test were used, when appropriate. A two-tailed p-value < 0.05 was considered significant in all calculations.

RESULTS

During the study period, a total of 2948 patients with osteoporosis should have received their correspondent dose of Dmab. Of these, 546 patients did not receive the subcutaneous injection (18.5 % of the entire sample).

The sociodemographic and clinical variables of the compliant and non-compliant groups are summarized in table I. The mean age was 76 years, female sex was predominant (*n* = 2732; 92.7 %), as well as the urban residence (*n* = 2165; 73.4 %) and a financial contribution < 10 % to the cost of the drug (*n* = 2639; 89.5 %). Significant differences were found regarding the contribution to the cost of Dmab in pharmacy (*p* = 0.009).

Figure 1 shows the distribution reason-wise of the non-compliant group. As can be seen, most patients discontinued their therapy on their own doing. Characteristics of Dmab prescription and reason for withdrawal in the group of patients who did not receive the drug at the scheduled time are shown in table II. Regarding pick-up Dmab data in pharmacies, -12.4%, -7.2%, -4.1%, and +10.8% were reported in March, April, May, and June 2020 vs the same months of the previous year. These figures represent a 12.9 % decrease in the entire study period. Table III shows the risk factors for osteoporosis and fragility fractures of the non-compliant group.

When stratifying these data by sex (Table IV), statistically significant differences were found for age, alcohol intake, and previous vertebral fractures (higher in men), and previous antiosteoporotic treatment and history of non-vertebral fractures (higher in women).

Table V summarizes the incidence of a subsequent fracture at the 1-year follow-up in the studied patients. When analyzing the group that did not receive more doses of Dmab (excluding deaths; *n* = 41, or 36 patients shifted to an alternate antiosteoporotic agent; *n* = 147 [27.4 %]), 2 patients (1.36 %) sustained a vertebral fracture, and 1 (0.68 %) a hip fracture during the year following Dmab discontinuation. All fractures occurred in women. The first patient with a vertebral fracture after Dmab discontinuation was an 85-year-old woman who had sustained multiple previous vertebral fractures, and the second case was a 77-year-old woman who had sustained a previous vertebral fracture. The reason for Dmab withdrawal was mainly the patient's own doing (76.2 %; *n* = 112), followed by the physician's decision (17 %; *n* = 25) and the odontologist´s advice (6.8 %; *n* = 10).

Considering the overall group of patients on Dmab (*n* = 2402), 21 patients (0.87 %) sustained a vertebral fracture, 10 (0.41 %) a hip fracture, and 4, other non-vertebral fractures (0.16) at the follow-up. One patient (2.7 %) of the non-compliant group with alternative antiosteoporotic therapy sustained a vertebral fracture within the next year, and another one (2.7 %) a hip fracture. Of note, the non-compliant group without alternative antiosteoporotic therapy was 15 older vs the group with Dmab administration delay, 11 years older vs the non-compliant group that did receive alternative therapy, and 6 years older vs the overall

Table I. Sociodemographic variables of the compliant and non-compliant groups

		Compliant group (*n* = 2402)	Non-compliant group (*n* = 546)	*p*
Age (years)		75.8 ± 9.6	76.5 ± 10.6	0.15
Sex	Female	*n* = 2233 (93 %)	*n* = 499 (91.4 %)	0.20
	Male	*n* = 169 (7 %)	*n* = 47 (8.6 %)	
Residency	Urban	*n* = 1847 (76.9 %)	*n* = 318 (76.8 %)	0.94
	Rural	*n* = 555 (23.1 %)	*n* = 127 (23.2 %)	
Financial contribution to the cost of drug	< 10 %	*n* = 2167 (90.2 %)	*n* = 472 (86.4 %)	0.009
	> 40 %	*n* = 235 (9.8 %)	*n* = 74 (13.6 %)	

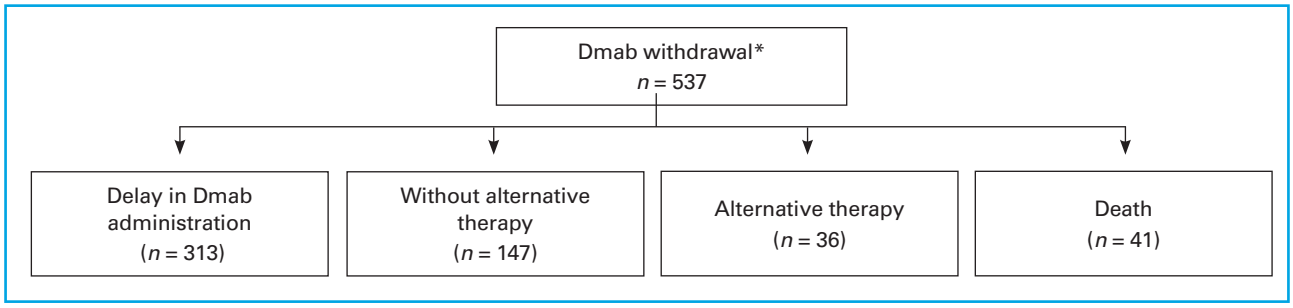

Figure 1. Flowchart of patients who discontinued Dmab. *A total of patients were excluded because they did not have sufficient valid data on their clinical charts.

Table II. Initial and final prescriber and cause of Dmab withdrawal in the non-compliant group

			n	%
Physician who starts treatment		Rheumatology	195	36.3
		Internal Medicine	142	26.4
		Primary Care	123	22.9
		Endocrinology	28	5.2
		Traumatology	19	3.5
		Gynecology	18	3.4
		Other	12	2.3
Physician who withdraws	**Primary Care**		16	23.9
	A different specialist		41	61.2
		Rheumatologist	19	46.3
		Internist	14	34.1
		Palliative care physician	3	7.3
		Other	5	12.3
	Odontologist		10	14.9
Cause of withdrawal		Patient´s own doing	353	65.7
		Postponed by the nurse	76	14.2
		Primary care physician	16	3
		A different physician	41	7.6
		Odontologist	10	1.9
		Death	41	7.6

**A total o 9 patients were excluded because they did not have sufficient valid data on their clinical charts.*

Table III. Risk factors for fracture in the non-compliant group

	n	%
Previous osteoporosis treatment	266	49.5
Alcohol intake	39	7.3
Current smoking	42	7.8
Secondary osteoporosis	136	25.3
Corticosteroid use	69	12.8
No. of previous treatment		
1	164	62.4
2	53	20.2
3	24	9.1
4	5	1.9
> 4	20	6.4
Oral pharmacological calcium intake	173	32.2
Oral vitamin D intake	422	78.6
Previous vertebral fracture	172	32.1
1	81	47.9
2	47	27.8
3	21	12.4
4	12	7.1
> 4	8	4.7

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Table III (cont.). Risk factors for fracture in the non-compliant group		
	n	**%**
Previous non-vertebral fracture	146	27.2
Hip	43	29.9
Distal forearm	36	24.7
Rib	10	24.7
Humerus	5	3.4
Other	52	13.7
Serum 25OH D level (*n* = 317); mean ± SD (ng/mL)	27.9 ± 14.2	

Table IV. Sex-related sociodemographic and clinical variables of the non-compliant group				
		Male (*n* = 48)	**Female (*n* = 489)**	***p***
Age (years), mean ± SD		79.0 ± 11.2	75.5 ± 10.4	0.03
Residence (%)	Urban	52.1 (*n* = 25)	54.4 (*n* = 266)	0.88
Financial contribution to the cost of the drug (%)	Reduced (< 10 %)	93.8 (*n* = 45)	87.3 (*n* = 427)	0.28
Current alcohol intake (%)		18.8 (*n* = 9)	6.1 (*n* = 30)	0.004
Current smoking (%)		10.4 (*n* = 5)	7.6 (*n* = 37)	0.67
Secondary osteoporosis (%)*		18.8 (*n* = 9)	25.9 (*n* = 127)	0.36
Corticosteroid use (%)		12.5 (*n* = 6)	12.9 (*n* = 63)	0.88
Previous osteoporosis treatment (%)		22.9 (*n* = 11)	52.1 (*n* = 255)	0.0002
No. of previous antiosteoporotic agents (%)	1	12.5 (*n* = 6)	32.3 (*n* = 158)	0.007
	2	4.2 (*n* = 2)	10.4 (*n* = 51)	0.26
	3	2.1 (*n* = 1)	4.7 (*n* = 23)	0.64
	4	4.2 (*n* = 2)	0.6 (*n* = 3)	0.09
	> 4	0 (*n* = 0)	3.5 (*n* = 17)	0.38
Pharmacological calcium intake (%)		35.4 (*n* = 17)	31.9 (*n* = 156)	0.74
Pharmacological vitamin D intake (%)		72.9 (*n* = 35)	79.1 (*n* = 387)	0.42
Serum 25OH D level (ng/mL), (mean ± SD)		28.9±14.1	27.9±14.2	0.10
Presence of previous vertebral fracture (%)		50.0 (*n* = 24)	30.3 (*n* = 148)	0.008
No. of previous vertebral fractures (%)	1	14.6 (*n* = 7)	15.1 (*n* = 74)	0.91
	2	27.1 (*n* = 13)	6.9 (*n* = 34)	0.0001
	3	4.2 (*n* = 2)	3.9 (*n* = 19)	0.76
	4	4.2 (*n* = 2)	2.0 (*n* = 10)	0.66
	5	0 (*n* = 0)	1.6 (*n* = 8)	0.49
Previous non-vertebral fracture (%)		12.5 (*n* = 6)	28.6 (*n* = 140)	0.02
Site of previous non-vertebral fracture (%)	Hip	2.1 (*n* = 1)	8.6 (*n* = 42)	0.19
	Distal forearm	0 (*n* = 0)	7.4 (*n* = 36)	0.10
	Rib	0 (*n* = 0)	2.0 (*n* = 10)	0.66
	Humerus	0 (*n* = 0)	1.0 (*n* = 5)	0.93
	Ankle	2.1 (*n* = 1)	0.8 (*n* = 4)	0.93
	Knee	0 (*n* = 0)	0.4 (*n* = 2)	0.43
	Foot	0 (*n* = 0)	0.2 (*n* = 1)	0.15

**Secondary osteoporosis: hypogonadism, endocrine disorder (hyperparathyroidism, hyperthyroidism), GI, rheumatologic (rheumatoid arthritis), or organ transplantation.*

Table V. Occurrence of a subsequent fractures at the 1-year follow-up

	Overall (*n* = 2939)*	Compliant group (*n* = 2402)	Delay in Dmab administration (*n* = 313)	Non-compliant group with alternative therapy (*n* = 36)	Non-compliant group without alternative therapy (*n* = 147)
Age (years; mean ± SD)	78.9 ± 8.2	79.3 ± 7.6**	70.5 ± 19.1**	74.0 ± 11.9**	85.0 ± 2.8
Total fractures (*n*)	43	35	2	3	3
Clinical vertebral fracture (*n*)	25	21	1	1	2
Overall clinical vertebral fractures (%)	0.85	0.87	0.31	2.7	1.36
Hip fractures (*n*)	13	10	1	1	1
Overall hip fractures (%)	0.44	0.41	0.31	2.7	0.68
Non-vertebral fractures (*n*)	5	4	0	1	0
Overall non-vertebral fractures (%)	0.17	0.16	0	2.7	0

**A total of 9 patients were excluded because they did not present sufficient valid data on the clinical chart. **p < 0.0001 vs the non-compliant group without alternative therapy.*

group. Given the high risk of age-related fracture related in the non-compliant group without alternative treatment and the incidence of fracture in this group vs the other ones, it seems reasonable to suggest that there is no increased risk of fractures.

DISCUSSION

Our study found that there was a non-negligible percentage of patients (18.5 %) who did not receive the correspondent dose of Dmab during the lockdown due to the COVID-19 pandemic in Cantabria, Spain.

Kocijan et al. (8) found a decrease in the prescription of this monoclonal antibody in Austria from March (22 %) and April (23 %) 2020 vs the previous 6 months. The same trend was noted in this period regarding IV zoledronate (36 % and 49 % decrease vs the previous year).

Fuggle et al. (5) noted that 43% of 209 health professionals from different parts of the world reported difficulties in treating osteoporosis during the COVID-19 pandemic. The main issues were problems obtaining the drug, delays in the administration of parenteral agents, and the reluctance of patients to go to their health center. In the specific case of parenteral drugs, 46% were administered appropriately, 3% had to switch these treatments to an alternative area, 21% delayed treatment until there was a lower risk of COVID-19, 13% switched to an oral drug, 8% were administered at home and 9% had some other issues such as self-administration of the dose by the patient at home. Primary care physicians prescribed Dmab in 15% of the cases, which involves shorter delays in drug administration than the one we found in the present study (59.6%) (5). Additionally, these authors also found a lower percentage of switching to a different antiosteoporotic treatment (4.2 %), although they saw a greater percentage of change to an oral bisphosphonate (2.2 %) (5).

Peeters et al. (11) surveyed a total of 77 health care professionals in The Netherlands and found that 49% of patients on Dmab were properly treated by their family physician, and 33.4% were followed in the hospital outpatient clinics or at home via self-injection. Some 6.3% of patients reported a delay in Dmab administration, 8.3% were taught via video conference to self-administer the drug, and 1% discontinued treatment without starting another antiosteoporotic agent. These data indicate a lower percentage of withdrawal or Dmab administration delay than the one we found (5.0% and 10.6%, respectively).

Dmab discontinuation causes rebound high bone turnover and rapid bone loss within the first year, increasing the risk of major osteoporotic fractures, especially multiple vertebral fractures, particularly among subjects with previous vertebral fractures (3). Besides, the delayed administration of subsequent Dmab doses by more than 16 weeks has been associated with an increased risk for vertebral fractures vs on-time dosing. Nevertheless, evidence for an increased risk of fractures at different anatomical sites with long delays is insufficient (9).

Based on all this, Dmab should not be discontinued without switching to an alternative agent, usually bisphosphonates (4). This approach was very important during the SARS-CoV-2 pandemic, and the Joint Guidance on Osteoporosis Management in the Era of COVID-19 from the ASBMR, AACE, Endocrine Society, ECTS & NOF recommended that "for patients in whom

continued treatment with denosumab is not feasible within 7 months of prior denosumab injection, strongly consider transition to oral bisphosphonate if possible" (www.asbmr.org).

Although we found no differences in the rate of clinical vertebral or nonvertebral fractures after Dmab discontinuation, we observed a crude higher percentage of vertebral fractures in the group of patients who discontinued Dmab and switched to other alternative therapy (2.7%) vs the compliant group (0.87%). The differences reported were not statistically significant, mainly because only 1 patient sustained a vertebral fracture in the latter group. There was also a slight, albeit non-significant increase in the group of withdrawal patients without alternative therapy (1.36%) while in those who delayed the dose the incidence of fractures was very similar to that of patients who received the scheduled dose of Dmab. It may be that the low frequency of fractures following the non-administration of Dmab at the scheduled time may be due, in most cases, to switching to a different drug. Indeed, in many cases, a delayed administration was reported (exceeding 2 months from the indicated time) but not an abrupt discontinuation without an alternative anti-osteoporotic agent. Another possible explanation could be the reducted physical activity, changes in lifestyle habits, and lower number of falls associated with the lockdown. However, we do not have collected these data to adequately analyze its influence on this outcome.

Regarding non-vertebral fractures, specifically hip fractures, the incidence of this type of fractures was also very low and non-significant across the study groups.

Noteworthy, in the placebo group of the FREEDOM study, the risk of new clinical vertebral fractures was 2.6% (1.6% with 2 or more vertebral fractures), 1.2% for hip fractures, and 8% for non-vertebral fractures (12). Furthermore, in a post-hoc analysis of the FREEDOM study of 1001 patients who discontinued Dmab during the study, 5.6% sustained vertebral fractures and 2.3% non-vertebral fractures (13). The rate of fractures in both studies was quite similar to that observed in our study.

In the FREEDOM extension study, Cosman found in the discontinuation group a crude annualized incidence of vertebral fracture of 11.8% (n = 56) and 7.2% (n = 34) in multiple vertebral fractures [9.5 % (n = 31) in the placebo group for vertebral fractures and 3.7 % (n = 12) for multiple vertebral fracture (14)].

In the COVID-19 era, we should reconsider the management strategies of patients with osteoporosis, highlighting and implementing therapeutic compliance. To achieve this, the methods of providing medical care must also be adapted, either by increasing virtual follow-up consultations or by facilitating a multidisciplinary approach with other health professionals. Although telemedicine reduces costs, waiting times, or trips, it also increases the uncertainty of physicians and patient and a possible medical and legal vulnerability (5).

The study has several limitations. First, the study was conducted in a specific area from northern Spain and included Caucasian people. Therefore, data could not be extrapolated to other geographical areas or ethnicities. Second, data have been reviewed from clinical charts, and the overall time on Dmab or the precise reasons for Dmab withdrawal cannot be well-defined in some cases. Third, the number of fractures was small and the short period of follow-up could be a limitation of the study since the long-term incidence of fractures was not assessed. Fourth, we only have data on clinical vertebral fractures, which required radiology. Finally, we do not have data on Dmab withdrawal during other periods before or after the lockdown.

In conclusion, the lockdown of the Spanish population within the first months of the SARS-CoV-2 pandemic in our health care field of expertise led to almost an 18% rate of Dmab discontinuation due to delayed administration, switch to a different antiosteoporotic agent, or definitive withdrawal without prescribing an alternative therapy. With the limitations inherent to this kind of study design, the interruption of Dmab during this COVID-19 pandemic was not followed by a significant increase in clinical and non-vertebral fractures vs the results of the FREEDOM study. None of the patients sustained multiple vertebral fractures at the 1-year follow-up Despite these data, we consider that current scientific recommendations should be adopted in cases of Dmab withdrawal. In the COVID-19 era, clinicians should conduct more intensive and long-term follow-ups of osteoporotic patients on Dmab to prevent the fractures associated with the discontinuation of this monoclonal antibody.

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