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Álvaro Pérez-Martín[1], José Ramón López-Lanza[2], Javier Bustamante-Odriozola[1], José Ignacio Gutiérrez-Revilla[3], María José Agüeros-Fernández[4], Alejandro Pérez-Guijarro[1], José Manuel Olmos[5], Víctor Martínez-Taboada[6], José Luis Hernández[5]

[1]Centro de Salud Isabel II. Santander, Spain. [2]Centro de Salud Vargas. Santander, Spain. [3]Division of Pharmacy. Hospital Sierrallana. Torrelavega, Santander. Spain. [4]Centro de Salud Zapatón. Torrelavega, Santander. Spain. [5]Bone Metabolism Unit. Internal Medicine Department. Hospital Universitario Marqués de Valdecilla-IDIVAL. Universidad de Cantabria. Santander, Spain. [6]Rheumatology Division. Hospital Universitario Marqués de Valdecilla-IDIVAL. Universidad de Cantabria. Santander, Spain

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Correspondence:_Álvaro Pérez Martín. Centro de Salud Isabel II. C/ Isabel II, *n.º* 17. 39002 Santander, Spain
e-mail: alvaro.perez@scsalud.es

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ABSTRACT

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

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

Results: 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 decision (65 %). The incidence of clinical fractures in the overall group was low (n = 45; 1.46 %) with only 4 vertebral fractures and 3 hip fractures. When analyzing the group that did not receive more doses of Dmab or an alternate antiosteoporotic agent (n = 147), two patients (1.36 %) sustained a vertebral fracture and another

one (0.68 %) had a hip fracture during the year after 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 another antiosteoporotic agent. None of the patients sustained multiple vertebral fractures during the year of follow-up.

Keywords: Denosumab. Adherence. Osteoporosis. Fractures.

RESUMEN

Introducción: nuestro objetivo fue analizar si la pandemia por SARS-CoV-2 dió lugar a una disminución en la adherencia a Dmab y evaluar la incidencia de fracturas en pacientes no adherentes.

Métodos: se evaluaron todos los pacientes que deberían haber requerido la administración de una dosis de Dmab en Cantabria (España) durante el período de confinamiento. Se recopilaron variables sociodemográficas, factores de riesgo de osteoporosis, datos sobre la administración de Dmab y el motivo de la suspensión del medicamento. Además, se analizó el desarrollo de una fractura clínica durante el año siguiente.

Resultados: 2948 pacientes debieron recibir una nueva dosis de Dmab durante los meses de confinamiento, pero 546 (18,5 %) discontinuaron el fármaco. La principal razón para la suspensión fue la decisión del propio paciente (65 %). La incidencia de fracturas clínicas en el grupo total fue baja (n = 45; 1,46 %) con solo 4 fracturas vertebrales y 3 fracturas de cadera. Al analizar el grupo que no recibió más dosis de Dmab ni un agente antiosteoporótico alternativo (n = 147), dos pacientes (1,36 %) sufrieron una fractura vertebral y otro (0,68 %) tuvo una fractura de cadera, durante el año posterior a la última dosis del fármaco.

Conclusiones: hubo un porcentaje no despreciable de pacientes que no recibieron la dosis de Dmab, en la secuencia temporal correcta, durante el período de confinamiento. Sin embargo, la incidencia de fracturas vertebrales clínicas y no vertebrales fue baja, incluso en los sujetos no adherentes que no recibieron otro agente antiosteoporótico. Ninguno de los pacientes sufrió múltiples fracturas vertebrales durante el año de seguimiento.

Palabras clave: Denosumab. Adherencia. Osteoporosis. Fracturas.

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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 by subcutaneous injection every 6 months, frequently in Primary Care Health centers. Discontinuation of Dmab, without subsequent antiosteoporotic therapy, leads to significant changes in bone remodeling, the so-called "rebound phenomenon", and it 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 during the first months of the pandemic, changed the classic healthcare model, leading to an increase in telemedicine, delays in performing densitometric studies, and interruptions in drug supply and administration of parenteral medications (5). Moreover, the potential risk of a flu-like reaction that could be mistaken for a COVID-19 infection after intravenous zoledronic acid administration (6) or fear of visiting the primary care center for the administration of Dmab represented an important dilemma for both, clinicians and patients with osteoporosis (7).

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

PATIENTS AND METHODS

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

The study was carried out in Cantabria, a region in northern Spain, with a population of 581,641 inhabitants, an area of 5,321 km^2, and a population density of 109 inhabitants per km^2. As Dmab is administered biannually, the data of those patients who received the last dose from September to December 2019 were collected. The study was approved by the Ethics Committee of Cantabria (number 2022.004).

Study variables

Age, sex, the economic contribution of the patient to the cost of pharmacy, and the place of residence were collected as sociodemographic variables. An urban area was considered whether the population size was greater than 10,000 inhabitants.

Risk factors for osteoporosis including smoking, alcohol consumption, diseases or drugs affecting bone metabolism, previous medications, history of fractures, and the 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 patients who did not receive the corresponding dose of Dmab or who received it with a delay of more than one month, as well as the variation in Dmab pick-up in pharmacies, compared to the previous year were also assessed. Finally, we analyzed the occurrence of subsequent clinical fractures during the one-year follow-up

period. Data have been obtained from the clinical history of the patients. Nine 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 χ^2 or Fisher test, respectively, were used. A two-tailed p-value < 0.05 was considered significant in all the calculations.

RESULTS

During the study period, 2948 patients with osteoporosis should have received the correspondent dose of Dmab. Of them, 546 patients did not receive the subcutaneous injection, 18.5 % of the whole sample.

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

Figure 1 shows the distribution by cause of the non-compliant group. As can be seen, most of the patients left the treatment by their own decision. 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 observed in March, April, May, and June 2020 compared to the same months of the previous year. These figures represent

a 12.9 % decrease in the whole study period. Table III summarizes 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 for previous antiosteoporotic treatment and history of non-vertebral fractures (higher in women).

Table V summarizes the incidence of a subsequent fracture during the 1-year follow-up period 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 %]), two patients (1.36 %) sustained a vertebral fracture, and one (0.68 %) had a hip fracture during the year after 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 had 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 decision (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 who receive Dmab ($n = 2402$), 21 patients (0.87 %) sustained a vertebral fracture, 10 (0.41 %) had a hip fracture, and 4, other non-vertebral fractures (0.16) during follow-up. One patient (2.7 %) of the non-compliant group with alternative antiosteoporotic therapy sustained a vertebral fracture during the next year, and another one (2.7 %) had a hip fracture. Noteworthy, the non-compliant group without alternative antiosteoporotic therapy had 15 years more than the group with Dmab administration delay, 11 more than the non-compliant group that did receive alternative therapy, and 6 years more than the overall group. Given the high risk of fracture related to age in the non-compliant group without alternative treatment and the incidence of fracture in this group compared to

the other ones, it seems reasonable to assume 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, compared with the previous 6 months. The same trend was noted in this period regarding intravenous 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 attend the healthcare 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 implies a lesser delay in the drug administration than we found in the present study (59.6 %) (5). Moreover, these authors also found a lower percentage of switching to another antiosteoporotic treatment (4.2 %), although they observed a greater percentage of change to an oral bisphosphonate (2.2 %) (5).

Peeters et al. (11) surveyed 77 healthcare professionals in the Netherlands and found that 49 % of patients on denosumab were properly treated by their family physician, and 33.4 % were followed in the hospital outpatient clinics or at home by 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 the treatment without starting another antiosteoporotic agent. These data indicate a lesser percentage of withdrawal or Dmab administration delay than 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, delayed administration of subsequent Dmab doses by more than 16 weeks has been related to an increased risk for vertebral fracture compared with on-time dosing. Nevertheless, evidence for an increased risk of fractures at other anatomical sites with long delay is insufficient (9).

On these bases, Dmab should not be discontinued without switching to an alternative agent, usually bisphosphonates (4). This approach is 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).

We found no difference in the rate of clinical vertebral fractures or nonvertebral fractures after discontinuing denosumab. Although 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 %) compared to the compliant group (0.87 %), the differences were not statistically significant, mainly because only one patient had a vertebral fracture in this 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 patients who received the scheduled dose of Dmab. It may be possible that the low frequency of fractures following the non-administration of denosumab at the scheduled time may be due, in most cases, to switching to another drug. Indeed, in many cases, there was a delay in administration (exceeding 2 months from the indicated time) but not an abrupt discontinuation without an alternative anti-osteoporotic agent. Another possible explanation could be the reduction in physical activity, changes in lifestyle habits, and a lower number of falls due to 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 arm of the FREEDOM study, the risk of new clinical vertebral fractures was 2.6 % (1.6 % with two 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 % had non-vertebral fractures (13). The rate of fractures in both studies was quite similar to that observed in our study.

Cosman in the FREEDOM extension study 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, while in the placebo group it was 9.5 % ($n = 31$) for vertebral fracture 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.

Telemedicine reduces costs, waiting times, or trips, but also increases the uncertainty of the physicians and patient and a possible medical and legal vulnerability (5).

The study has several limitations. Firstly, the study was conducted in a specific area in northern Spain and included Caucasian people, therefore, data could not be extrapolated to other geographical areas or ethnicities. Secondly, 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. Thirdly, 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. Fourthly, we only have data on clinical vertebral fractures, which have 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 during the first months of the SARS-CoV-2 pandemic in our healthcare area led to almost 18 % of Dmab discontinuation, due to delay in administration, switch to another 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 period was not followed by a significant increase in clinical vertebral and non-vertebral fractures compared to the results of the FREEDOM study. None of the patients sustained multiple vertebral fractures during the year of 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 carry out more intensive and long-term monitoring of osteoporotic patients on Dmab to prevent the fractures associated with the discontinuation of this monoclonal antibody.

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

		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 %)	
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 %)	

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
	Another 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 decisión	353	65.7
		Postponed by nursing	76	14.2
		Primary care physician	16	3
		Another physician	41	7.6
		Odontologist	10	1.9
		Death	41	7.6

*Nine patients were excluded because they did not present sufficient valid data on clinical charts.

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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
Number 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
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. Sociodemographic and clinical variables of the non-compliant group according to sex.

		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
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
Number 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

Number 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), gastrointestinal, rheumatologic (rheumatoid arthritis), or organ transplantation.

Table V. Occurrence of a subsequent fracture during the 1-year follow-up period

	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
Clinical vertebral fracture over total patients (%)	0.85	0.87	0.31	2.7	1.36
Hip fracture (*n*)	13	10	1	1	1
Hip fracture over total patients (%)	0.44	0.41	0.31	2.7	0.68
Non-vertebral fracture (*n*)	5	4	0	1	0
Non-vertebral fracture over total patients (%)	0.17	0.16	0	2.7	0

*Nine patients were excluded because they did not present sufficient valid data on the clinical chart. ** $p < 0.0001$ compared to the non-compliant group without alternative therapy.

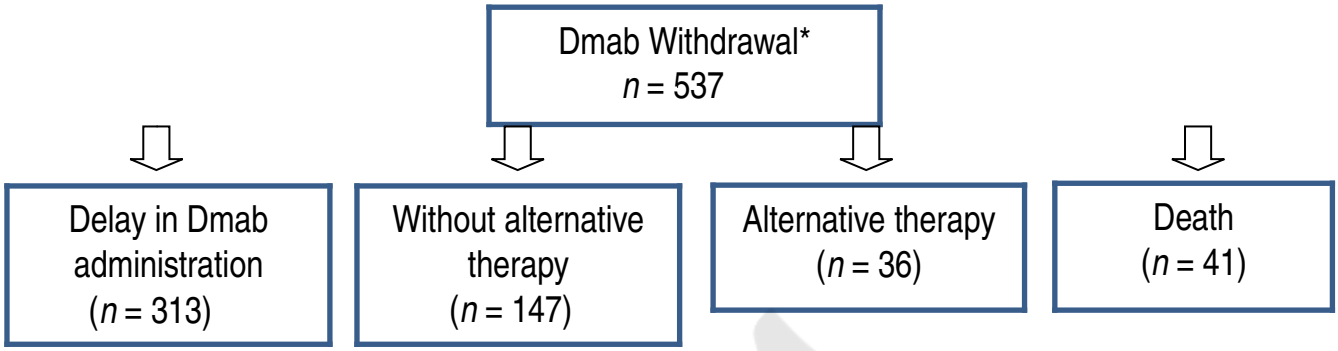

Figure 1. Flowchart of patients who discontinued Dmab. *Nine patients were excluded because they did not present sufficient valid data on clinical charts.

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