



COVID pandemic and denosumab adherence

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The coronavirus (COVID 19) pandemic has brought unprecedented disruptions to the provision of health care in every country of the world. Therefore, a number of measures have been implemented with the aim of containing the spread of the virus, the most dramatic being national lockdowns.

These measures challenged many national health systems, sometimes at the expense of patients with both acute and chronic diseases. For example, in order to counteract difficulties with osteoporosis, the American Society for Bone and Mineral Research provided clinical recommendations based on available evidence [1]. For denosumab, one of the most prescribed antiresorptive agents, the panel of experts “strongly recommend the temporary transition to an oral bisphosphonate for patients in whom continued treatment with denosumab is not feasible within 6 months of their most recent prior denosumab injection”. Another paper recommended home administration of denosumab, but this may not be possible in all settings [2].

To the best of our knowledge, there are no reports that have explored the impact of COVID 19 in a real world setting concerning continuation of denosumab treatment and adherence to the ASBMR recommendations. This is of utmost importance because of the well-known deleterious effects that may occur within the first several months following discontinuation. Many studies have shown that following denosumab discontinuation there is accelerated bone turnover, rapid loss of bone mineral density and increased rate of multiple vertebral fracture [3, 4]. Most importantly, a short off-treatment period of 2 to 10 months is enough to produce such catastrophic events [5]. This contrasts with

the relatively long-term effect following bisphosphonate withdrawal [6].

Here we report the experience of our referral centre concerning patient behaviour with denosumab adherence, before and during the pandemic period.

Table 1 reports our case series of 20 patients with vertebral fractures following denosumab discontinuation. Main demographic parameters, length of denosumab therapy, date of discontinuation, months elapsed between occurrence of vertebral fracture and denosumab discontinuation and ambulatory presentation are reported. For Italy, March 9, 2020, marked the beginning of the Italian national lockdown that completely limited, until May 4, free circulation. After that, these measures were in part eased, even though some limitations were still in place until June 14, at least in the Lazio region. Restrictive measures were re-imposed in the following periods depending on the number of infected persons, until June 2021.

It can be seen that the number of patients that came to our attention reporting vertebral fractures after denosumab discontinuation dramatically increased during the current year. Indeed, until 2019, we had observed only 8 cases in 7 years; in 2021 (and 2020), we observed 12 cases. According to these last 12 patients, this was mainly due to the inability of adhering to denosumab treatment for a number of reasons, the most important being the inability to access medical facilities during the pandemic period. This was due to mobility restrictions and fear of access to our hospital, selected for the management of COVID patients. We therefore believe that this should be listed among the side effects of the pandemic.

Finally, it is important to note that only patients with symptomatic vertebral fractures came to our attention. It is highly possible that the impact on fracture incidence due the pandemic is even greater than what we observed.

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Table 1 Case series of 20 patients with vertebral fractures following denosumab discontinuation

Patient	Sex	Age (years)	Length of denosumab therapy (months)	Date of discontinuation	Months interval (occurrence of fracture vs discontinuation)	Ambulatory presentation
A. G	F	64	42	February 2018	11	March 2019
A. R	F	63	66	July 2020	12	July 2021
B. P	F	75	24	April 2015	11	June 2016
B. L	F	65	18	December 2014	14	March 2016
B. A	F	83	54	December 2019	9	April 2021
C. A	F	60	60	June 2020	12	July 2021
C. P	F	59	48	December 2018	11	March 2021
C. G	F	69	36	March 2018	16	April 2021
C. L	F	60	18	March 2020	14	July 2021
D. L. E	F	74	24	September 2013	14	July 2018
D. M	F	56	66	July 2018	12	December 2019
F. R	M	72	18	December 2015	14	May 2018
F. L	F	71	18	February 2020	15	May 2021
G. S	F	78	36	July 2018	12	July 2019
M. C. L	F	67	24	June 2019	13	May 2021
P. T	F	79	24	August 2018	16	September 2021
R. A	F	73	18	November 2017	10	July 2019
S. P	F	70	42	May 2019	16	January 2021
V. M. L	F	81	30	July 2019	12	July 2021
V. T	F	65	36	March 2019	12	September 2021

Our letter calls attention to the need to emphasize optimal adherence to denosumab therapy and sharing information about discontinuation directly with patients.

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Data availability Upon reasonable request, the data can be shared.

Code availability None.

Declarations

Conflicts of interest SM served as speaker for Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Sandoz, Takeda and Kyowa Kirin. He also served in advisory board of Abiogen, Kyowa Kirin, Pfizer and UCB. Other authors declare no competing interests.

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