



Are women with osteoporosis treated with denosumab at risk of severe COVID-19?

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Coronavirus disease 2019 (COVID-19), is a primarily respiratory infection [1] which not infrequently leads to a severe syndrome requiring hospitalization and assisted ventilation with high lethality [2] also causing very frequently and in some instances severe hypocalcemia [3, 4].

According to the last available age-related analysis of the Italian “Istituto Superiore di Sanità” (ISS) on June 26 2020, median age of the almost 240.000 confirmed cases of the SARS-CoV-2 infection was 61 years and almost 130.000 of them were females (54.2%). Specifically, about two thirds of the females who were proven to be infected were older than 50 years. Moreover, in a subgroup analysis, two thirds of the patients had symptomatic infection ranging from very mild/mild (48%) to severe (18%) infection [5].

Osteoporosis is a systemic skeletal disorder characterized by bone strength decrease and altered skeletal micro-architecture leading to an increased risk of vertebral and hip fractures [6]. In a cross-sectional, multicenter, cohort study evaluating 3247 postmenopausal women aged ≥ 50 and older in Italy the prevalence of osteoporosis, as assessed by BMD and NBHA criteria, was 36.6% and 57%, respectively [7].

Several pharmacological (antiresorptive such as bisphosphonates and denosumab and anabolic as teriparatide) and non-pharmacological (vitamin D and calcium) treatment options are available and highly effective in preventing fragility fractures for postmenopausal and other forms of osteoporosis [6, 8–10].

Denosumab is a human monoclonal antibody (IgG2 immunoglobulin isotype) which binding with high affinity and specificity to RANKL and induces rapid and profound inhibition of bone resorption for 6 months. Features

distinguishing denosumab from bisphosphonates are higher antiresorptive potency, rapid reversibility of antiresorptive effect, and better safety profile in patients with impaired renal function [8]. Denosumab has proven to be effective and is currently indicated in postmenopausal, glucocorticoid-, aromatase inhibitor-, and androgen deprivation-induced osteoporosis [11].

Another distinctive feature of denosumab as compared to bisphosphonates, is its possible action as an immune system modulator. In fact, risk of infections in denosumab users is a potential clinical concern [8]. Interestingly, in a recent meta-analysis [12] it was evaluated the risk of severe infections as side effects (SAEI) of treatment with denosumab. In this meta-analysis of 33 RCTs including 22.253 patients higher incidence of SAEI during denosumab treatment versus any comparator (RR, 1.21; 95% CI, 1.04–1.40; I² = 0%) was found. The risk resulted specifically higher for ear, nose, and throat (RR, 2.66; 95% CI, 1.20–5.91) infections [12]. However, despite these findings calling for caution, several recently published expert opinions on the management of osteoporosis recommended to maintain treatment with denosumab during the COVID-19 outbreak [13–16].

Therefore, we thought of clinical interest to quickly report on the incidence of symptomatic COVID-19 in denosumab vs. other available drug-treated osteoporotic populations attending our bone clinic in the Endocrine Division of San Raffaele Hospital Milano, one of the epicenters of COVID-19 pandemic in Italy since in the Lombardia region of which it is the main city almost 40% of total Italian cases of SARS-COV2 infection were reported according to last ISS report [5].

We conducted a telephone interview on a sample of 85 patients (aged ≥ 18 years) regularly followed in our bone center under pharmacologic antiosteoporotic treatment for postmenopausal osteoporosis ($n = 75$) or for aromatase inhibitor-induced bone loss in breast cancer ($n = 10$). All patients with osteoporosis were treated according to the indications for drug reimbursement of AIFA, the Italian Drug Agency. We excluded patients with comorbidities and

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concomitant therapies potentially influencing COVID-19 morbidity such as chronic kidney disease and glucocorticoid treatment [17, 18].

A total of 42 patients responded to the survey (no. 35 with postmenopausal osteoporosis and no. 7 with osteoporosis due to aromatase inhibitor therapy). All patients were adequately informed of the aims of the interview and gave their oral informed consent. Ten were treated with bisphosphonates (9 patients on alendronate and 1 on clodronate; median age 71, range 54–84 years; median treatment duration 7 months), 26 with denosumab (median age 72, range 32–92 years; median treatment duration 18 months) and 6 with teriparatide (median age 73, range 60–83 years; median duration of treatment 6.5 months). All subjects reported a good compliance to prescribed anti-osteoporosis drugs and were on vitamin D oral supplements (26% of subjects were on treatment with calcifediol; 74% were treated with cholecalciferol). Regarding vitamin D status, last available (within the previous 6–8 months) mean serum 25 OH vitamin D values were similar between groups: 40 (± 16.6 SD) ng/mL in denosumab group, 32 (± 17 SD) ng/mL in bisphosphonate group, and 36 (± 13.1 SD) ng/mL in teriparatide group. Despite supplementation, 9.5% of subjects showed vitamin D deficiency (defined as serum 25 OH vitamin D level < 20 ng/mL) and 4.8% presented severe deficiency (25 OH vitamin D level < 12 ng/mL) [19, 20]. Half of the patients with hypovitaminosis D was in the bisphosphonate group and the other half in the denosumab group. No patients in the teriparatide group had hypovitaminosis D. Among those treated with denosumab, two subjects (8%) presented vitamin D deficiency and only one (4%) had severe deficiency. Similar distribution was found among bisphosphonate-treated subjects.

All patients were asked the following questions concerning the 3-month period from February 21 to May 24, 2020: 1. clinical symptoms of upper airway infection or diagnosis of pneumonia, 2. COVID-19 positive testing, hospitalization, and related clinical course; 3. Falls or clinical fractures.

In the bisphosphonate group one patient (10%), a nurse, reported a self-limited episode (7 days) of fever (with peak at 39°) and cough. In the light of her specific activity, likely to be at high risk of infection, she was tested for SARS-COV2 and resulted positive. Her last available 25 OH vitamin D level was 33 ng/mL. None of the other patients was tested positive for SARS-COV2 or was hospitalized for COVID-19, and two patients (20%) reported one episode of fall without fractures or other clinical consequences.

In the denosumab group one patient (3.8%) reported self-limited symptoms (3 days) of mild fever (with peak at 38°) and cough, theoretically related with respiratory tract infection during the pandemic, but a SARS-COV2 specific swab was not performed. She was a housewife. Her last available 25 OH vitamin D level was 30 mg/mL.

None of the patients treated with denosumab was hospitalized for COVID-19 and one patient (3.8%) reported one episode of fall without fractures or other clinical consequences.

In the teriparatide group, none of the patients had systemic or respiratory symptoms, was tested positive for SARS-COV2 or was hospitalized for COVID-19, and no patients reported episodes of fall or any clinical fractures.

The two subjects who had symptoms of respiratory tract infections, respectively, on denosumab and bisphosphonates, had not respiratory comorbidities such as COPD. The one on denosumab had subclinical hypothyroidism and depressive disorder. The one on bisphosphonates had arterial hypertension and a previous history of surgery and radiotherapy treatments for breast cancer.

Our preliminary data suggest that women older than 50 years under pharmacologic treatment for postmenopausal or aromatase inhibitor-induced osteoporosis do not seem to be at high risk of symptomatic/severe COVID-19. Moreover, despite higher respiratory tract infection risk reported by RCTs and meta-analysis [11], denosumab treatment did not seem to represent a specific risk factor for COVID-19 in our surveyed population.

Our data give some initial real-life evidences supporting to opinions published so far [13–15] which recommended to continue denosumab as all other antiosteoporotic treatments during COVID-19 pandemic and consequent lockdown also due to the high risk of fractures that can be additionally driven by COVID-19 per se [16]. Our data need to be confirmed in larger possibly prospective trials and may not be extended to patients taking denosumab for indications other than postmenopausal or aromatase inhibitor-induced osteoporosis. Interestingly, all the patients were taking vitamin D as part of their antiosteoporotic treatment as recommended by guidelines [20]. Since vitamin D may have immune stimulating actions and can protect against respiratory infections [21], it has been previously suggested that widespread hypovitaminosis D may predispose to COVID-19 [22], and vitamin D treatment may have beneficial effects in the pandemic [23]. Therefore, it can be hypothesized that our patients with osteoporosis may be protected from SARS-COV2 by vitamin D independently of the pharmacologic antiosteoporotic treatments. Finally, it cannot be excluded that a selection bias may have occurred in the choice of our patients for denosumab treatment excluding a priori those with recurrent or at increased risk for respiratory infections.

Data availability

All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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