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## Anti-osteoporotic treatment and COVID-19 risk: is there an association?

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**Abstract. Background.** Despite the recent ASBMR, AACE, Endocrine Society, ECTS&NOF guidelines for osteoporosis management in the era of COVID-19 the impact of antiosteoporotic drugs on disease risk and severity is insufficiently studied. **The purpose** of this study was to assess the COVID-19 risk for the patients receiving the parenteral bisphosphonate or Denosumab treatment, and the severity of its course in patients with systemic osteoporosis. **Materials and methods.** We performed the phone survey and studied the results of 195 patients (92 % women; mean age – 62.7 ± 10.8 years) with systemic osteoporosis depending on the current use of parenteral antiresorptive drugs (Zoledronic, Ibandronic acids, or Denosumab, n = 125) and compared the results with data of the patients with osteoporosis who did not use any anti-osteoporotic drugs previously (n = 70). **Results.** The group of patients with COVID-19 included 32.9 % of patients who did not receive previously any anti-osteoporotic treatment and 33.3 % of osteoporotic patients treated with parenteral antiresorptive drugs. The share of the patients taking the Zoledronic acid who fell ill with COVID-19 was 29.2 %, the share of those taking the Ibandronic acid was 34.4 %, and the share of those taking Denosumab was 42.9 %. We did not reveal any significant differences in the COVID-19 frequency and severity depending on the presence and type of parenteral anti-osteoporotic therapy. Additionally, there were no differences depending on the patients' age, gender, obesity, and other osteoporosis risk factors. The risk of COVID-19 in the patients with systemic osteoporosis did not differ depending on antiresorptive drug use, amounting (odds ratio (OR) 95 % CI) 1.1 (0.6-2.0), or on the use of the definite anti-osteoporotic drug (for the Zoledronic acid – 0.9 (0.4-2.0), the Ibandronic acid – 1.1 (0.5-2.3), and for the Denosumab – 1.6 (0.5-5.2). **Conclusions.** Parenteral anti-osteoporotic drugs (Zoledronic acid, Ibandronic acid, or Denosumab) do not have any influence on COVID-19 frequency and severity and can be recommended for the continuation of the treatment of patients with osteoporosis.

**Keywords:** COVID-19; antiresorptive drugs; osteoporosis; Zoledronic acid; Ibandronic acid; Denosumab

### Introduction

Nowadays, COVID-19 and its complications are considered an important medical issue with aggravated medico-social outcomes, both at the worldwide scale and in terms of various individual countries [1, 2]. COVID-19 arising from the SARS-CoV-2 virus infection was registered for the first time in China at the end of 2019; it reached a pandemic scope in May 2020 [1, 2]. In lately September of 2022, over 600 million subjects fell prey to the COVID-19 infection, with an overall death toll of 6.5 million [3]. The respective toll in Ukraine was 4.8 million infected and 105 thousand dead [2].

Unfortunately, the new pandemic with its high morbidity and mortality distracted society's attention from a number of extant chronic diseases. For a certain pe-

riod of time, it has also restricted the patient's access to high-quality healthcare due to the lockdown conditions. Among the muscular-skeletal disorders, systemic osteoporosis is one of the most prevalent chronic ones; its share progressing across the world due to the global population aging and the growing numbers of elderly and older patients. The treatment of osteoporosis and its complications requires long-lasting medication and non-medication therapy along with a dynamic re-assessment of fracture risks. However, the studies by the International Osteoporosis Foundation (IOF), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and National Osteoporosis Foundation (NOF) [4] testified to diminished public attention towards osteoporosis un-

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der the COVID-19 pandemics, resulting in a postponed initiation of antiosteoporotic therapy and reduced treatment compliance, as well as in the frequent “enforced drug holiday” in the osteoporotic treatment due to the restricted use of medications, namely parenteral forms of antiosteoporotic drugs, under the lockdown conditions.

One of the antiosteoporotic therapy’s restrictions was the patients’ fear of the side effects associated with the biological drug use (Denosumab, Romosozumab, etc.), namely an increased risk of infectious complications among the groups of medications used to treat a number of rheumatic diseases (Biologic disease-modifying antirheumatic drugs (bDMARDs)). In recent years, the reference sources feature very few findings on the antiosteoporotic drug effect on the COVID-19 risk [5, 6]. The data on their effect on the severity of disease, hospitalization risk, and treatment modifications, however, are not that numerous.

The **aim** of this study is to assess the COVID-19 risk for the patients receiving the parenteral bisphosphonate or Denosumab treatment, and the severity of its course in systemic osteoporosis patients.

## Materials and methods

### Study design

The study was conducted from May to December 2021 at the Outpatient Department of D. F. Chebotarev Institute of Gerontology of the National Academy of Medical Sciences of Ukraine, the Ukrainian scientific-medical Center of osteoporosis. It was a cross-sectional, phone survey which was approved by the Ethics Committee of the Institute (protocol №6 of 27.04.2021). All subjects signed the informed consent for antiosteoporotic treatment and supervision at the Center. Survey responses were collected, stored electronically, and analyzed.

### Population

We analyzed the data of 195 patients (180 women, 92 %) with systemic osteoporosis (mean age –  $62.7 \pm 10.8$  years, height –  $161.0 \pm 8.0$  cm, body weight –  $68.9 \pm 12.3$  kg, body mass index (BMI) –  $26.7 \pm 4.8$  kg/m<sup>2</sup>).

Prior to the antiosteoporotic therapy, all the patients had a confirmed diagnosis of systemic osteoporosis at the Ukrainian scientific-medical Center of osteoporosis. The diagnosis was performed by dual-energy X-ray absorptiometry. The patients got a complex treatment prescribed, comprising the parenteral antiresorptive drugs (Zoledronic acid, Ibandronic acid, or Denosumab) with sufficient Calcium and Vitamin D supplementation (at least 1000 mg/d Calcium and 400 IU/d Vitamin D).

The patients were divided into two groups: osteoporotic patients who have never taken antiosteoporotic treatment (group I,  $n = 70$ ) and osteoporotic patients receiving the parenteral bisphosphonate or Denosumab (group II,  $n = 125$ ). To assess the possible effect of antiresorptive drugs on the COVID-19 risk, the second group was divided into the following subgroups: A – subjects taking the Zoledronic acid (IV dose of 5 mg once a year,  $n = 48$ ); B – patients taking the Ibandronic acid (IV dose

of 3 mg/3 mL every three months,  $n = 63$ ); C – subjects taking Denosumab (percutaneous dose of 60 mg, twice a year,  $n = 14$ ; Table 1). The mean duration of antiosteoporotic treatment did not vary across the groups, accounting for 15 [7-27] months.

## Methods

The phone survey involved a number of items associated with the COVID-19 infection (the previous and current COVID-19 status, disease severity, method of diagnostic corroboration, particularities of treatment (ambulant / hospital ones), the fact of suspension/modification of antiosteoporotic therapy due to the COVID-19 infection, the fact of vaccination, the type of vaccine, etc.).

The analysis was performed depending on antiosteoporotic therapy use, age and sex of the patients, concomitant obesity, and other osteoporotic fracture factors.

The statistical analysis of findings was performed by the «SPSS-22» software. The sample was tested as to its conformity with the principle of normal distribution by the Kolmogorov–Smirnov test. The quantitative indices were presented as mean values and their standard deviations ( $M \pm SD$ ) or medians and quartiles ( $Me [25Q-75Q]$ ). We have assessed the differences of indices for two independent samples using the two-sample Student’s t-test or Mann–Whitney U-test for the independent samples. In the case of over two samples present, we have used the one-way ANOVA analysis along with the Scheffe Post Hoc Test. In order to assess the differences between the two categorical variables, we used the Chi-squared test ( $\chi^2$ ). The risk assessment was made by means of the Odds Ratio. The differences in indices were considered significant if  $p < 0.05$ .

## Results

The examined patients did not differ in terms of their age (Table 1), height, body weight, age of menopause, and duration of the postmenopausal period. However, the body mass index of subjects taking the Ibandronic acid was significantly higher than the one of patients who did not take any antiosteoporotic treatment ( $p = 0.03$ , by the one-way ANOVA analysis amended by Scheffe).

Among the examined patients, 23 from group I and 41 patients from group II fell ill with COVID-19 during the antiosteoporotic treatment. In most cases, the COVID-19 diagnosis was confirmed by the Polymerase Chain Reaction test (92.9 % of patients receiving Zoledronic acid, 81.0 % of patients receiving Ibandronic acid, and 83.3 % of patients receiving Denosumab).

We did not reveal any significant differences in COVID-19 frequency depending on the presence and type of parenteral antiosteoporotic therapy (Table 2). For instance, the group of patients with COVID-19 included 32.9 % of patients who did not receive any antiosteoporotic treatment in the past and 33.3 % of osteoporotic patients treated with parenteral antiresorptive drugs. The share of patients taking the Zoledronic acid who fell ill with COVID-19 was 29.2 %, the share of those taking the

Ibandronic acid was 34.4 %, and the share of those taking Denosumab was 42.9 %.

The share of patients who fell ill with COVID-19 did not differ depending on the parenteral antiresorptive drugs used, either in the group of females (31.3 % in the comparison group I, and 33.6 % in group II) or in the group of males (40 % in the comparison group I, and 30 % in the group II, respectively).

The risk of COVID-19 in the patients with systemic osteoporosis did not differ depending on antiresorptive drug use (Odd Ratio (OR) to 1.1 (95 % Confidence interval (CI): 0.6-2.0), or on the use of the definite antiosteoporotic drug. For those taking the Zoledronic acid, it was 0.9 (95 % CI: 0.4-2.0), for those taking the Ibandronic acid it consisted 1.1 (95 % CI: 0.5-2.3), and for those taking Denosumab, it was 1.6 (95 % CI: 0.5-5.2; Figure 1).

We have not received any significant differences as to the frequency of COVID-19 exposure depending on the age of the examined patients. For instance, among the subjects 50 years and older, there were 31.3 % of patients fell ill with COVID-19 in group I and 35.1 % of patients fell ill in group II (OR = 1.19 (95 % CI: 0.62-2.29)). Within the age group of 70 years and older, 33.3 % of patients who fell ill with COVID-19 did not take any

antiosteoporotic treatment (group I) and 37.9 % of patients who fell ill with COVID-19 took the parenteral antiosteoporotic drug (OR = 1.22 (95 % CI: 0.57-2.60)). The co-present obesity did not increase the COVID-19 frequency compared to the normal body weight (26.5 and 35.7 %, respectively); there was no difference registered in the group of obese patients who were not taking any antiosteoporotic treatment (36.4 %).

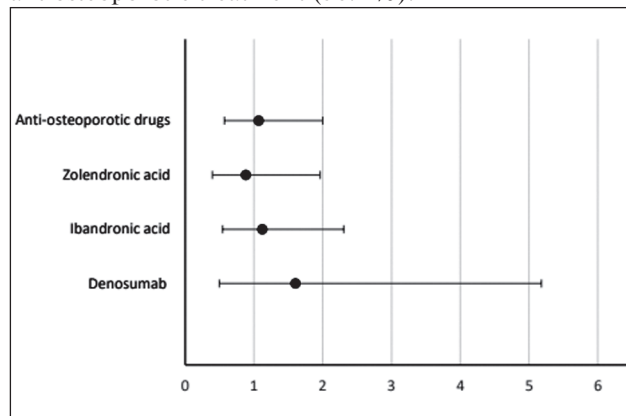


Figure 1. Odds Ratio and 95 % Confidence Interval of the COVID-19 risk among the patients taking the parenteral antiosteoporotic therapy

Table 1. Characteristics of the patients

| Indices                                  | Group I     | Group II    |             |             | F    | p    |
|--|-------------|-------------|-------------|-------------|------|------|
|  |             | A           | B           | C           |      |      |
| n  | 70          | 48          | 63          | 14          |      |      |
| Age, years                               | 63.8 ± 11.0 | 60.0 ± 12.4 | 63.4 ± 10.1 | 63.4 ± 4.5  | 1.35 | 0.26 |
| Sex (females / males), n                 | 65/5        | 43/5        | 58/5        | 14/0        | -    | -    |
| Height, cm                               | 162.2 ± 7.7 | 160.9 ± 8.5 | 159.4 ± 8.0 | 161.6 ± 7.5 | 1.37 | 0.25 |
| Body weight, kg                          | 67.4 ± 12.8 | 68.8 ± 11.8 | 71.2 ± 12.5 | 66.4 ± 9.5  | 1.30 | 0.28 |
| Body mass index, kg/m <sup>2</sup>       | 25.6 ± 4.6  | 26.7 ± 4.9  | 28.1 ± 5.1  | 25.5 ± 3.7  | 3.33 | 0.02 |
| Age of menopause (women), years          | 47.2 ± 11.2 | 46.8 ± 14.8 | 48.3 ± 11.3 | 47.7 ± 4.7  | 0.14 | 0.93 |
| Duration of postmenopause (women), years | 16.1 ± 7.8  | 14.9 ± 8.5  | 17.4 ± 8.6  | 15.6 ± 4.7  | 1.37 | 0.25 |

Notes: A – subjects taking the Zoledronic acid; B – patients taking the Ibandronic acid; C – subjects taking Denosumab. The indices presented as M ± SD, quantitative ones presented as n; comparison of indices was performed by the one-way ANOVA analysis.

Table 2. Share of patients with osteoporosis depending on COVID-19 presence, availability of anti-osteoporotic therapy, and its types

| Groups      | COVID-19 (-) | COVID-19 (+) | χ <sup>2</sup> (p) |
|-------------|--------------|--------------|--------------------|
| Group I     | 47 (67.1)    | 23 (32.9)    | -                  |
| Group II    | 84 (67.2)    | 41 (32.8)    | < 0.001 (0.99)     |
| Sub-group A | 34 (70.8)    | 14 (29.2)    | 0.18 (0.82)        |
| Sub-group B | 42 (66.7)    | 21 (33.3)    | 0.003 (0.95)       |
| Sub-group C | 8 (57.1)     | 6 (42.9)     | 0.52 (0.47)        |

Notes: findings presented as n (%); differences of the indices assessed with the Chi-squared test.

The COVID-19 severity depending on the type of antiosteoporotic treatment was not revealed any significant differences across the groups. 85.7 % of subjects receiving the Zoledronic acid were treated as outpatients; the corresponding indices of subjects receiving the Ibandronic acid were 81.0 and 83.3 %. 9.5 % of subjects receiving the Ibandronic acid required the glucocorticoids prescription as a component of the COVID-19 treatment while the patients taking the Zoledronic acid or Denosumab did not require any additional glucocorticoid prescription at all.

The enforced “drug holiday” in the antiosteoporotic treatment was confirmed by 38.1 % of subjects receiving the Ibandronic acid and 33.3 % of subjects taking Denosumab, and neither patient receiving the Zoledronic acid. The modification of antiosteoporotic medication was registered by 28.6 % of patients taking the Ibandronic acid and 16.7 % of patients taking Denosumab, and neither patient taking the Zoledronic acid. All the patients receiving the parenteral Ibandronic acid had it replaced with a per os form, as well as a patient taking parenteral Denosumab.

## Discussion

The COVID-19 pandemic provoked by the SARS-CoV-2 virus is a worldwide problem associated nowadays with a high degree of mortality, hospitalization, and work-related disability. It is unfortunate that COVID-19 distracted the public attention from a number of chronic diseases, namely systemic osteoporosis, and aggravated the high-quality healthcare provision due to the lockdown restrictions. The recent IOF, ESCEO, and NOF surveys [4] of healthcare personnel from 53 countries were delving into the healthcare services provision for osteoporotic patients and specific features of the antiosteoporotic treatment during the COVID-19 pandemic. The surveys revealed tectonic shifts in patient management, namely the increase in phone and video consultation frequency (by 33 and 21 %, respectively) and the diminishing of “in-person” visits (3 %). The researchers have confirmed the watershed changes in the antiosteoporotic medication prescription. Less than a third (28 %) of the surveyed osteoporotic patients continued taking the medications prescribed earlier, 3 % obtained new prescriptions, 63 % continued taking the previously prescribed medications with new drugs added, and 4 % discontinued the prescribed medication use unless they concerned the emergency cases.

The most frequently mentioned causes of antiosteoporotic regimen cessation are the suspension of treatment due to the anti-COVID-19 therapy, concern about the side effects of biological drugs (Denosumab, Romosozumab, etc.), failure to obtain the parenteral injections/infusions due to the lockdown measures and closure (restricted access) to the healthcare institutions. The subjects taking Denosumab are also expressing their concerns about the possible increase in infectious complication risks [5, 6].

There are a few recent studies published on COVID-19 risk associations [5, 6]. For instance, the study held in

Spain did not confirm an increased COVID-19 risk among patients taking antiosteoporotic medications [5]. The Relative Risk (RR) amounted to 0.58 (95 % Confidence Interval (CI): 0.28-1.22) for those subjects receiving Denosumab, to 0.62 (95 % CI: 0.27-1.41) for those subjects receiving the parenteral Zoledronic acid and 0.64 (95 % CI: 0.37-1.12) for those subjects receiving the Calcium monotherapy. The authors have never confirmed any significant effect of per os bisphosphonates and Vitamin D on the COVID-19 risk.

In a small study by A.M. Formenti et al. [6], there was no confirmed COVID-19 risk registered among the postmenopausal women taking Denosumab. This claim implies the safety of antiosteoporotic medication use during the pandemic.

Recently there were a number of articles that analyzed the risks and possibility of osteoporosis treatment in the era of COVID-19 [7-9]. According to the recent ASBMR, AACE, Endocrine Society, ECTS&NOF recommendations [10], there was no evidence corroborating the fact that any antiosteoporotic therapy increases the COVID-19 risk or severity, modifies the course of the disease. However, according to a study in 2022, patients who received anti-osteoporotic drugs had lower mortality from COVID-19 than the national rates for the same age [11].

As is known COVID-19 may be associated with an aggravated risk of hypercoagulable complications, which may be relevant as far as Hormone replacement therapy (HRT) or Raloxifene use is concerned [12]. On the other hand, raloxifene could be among the best candidates to prevent mortality in severe COVID-19 patients [13]. Unfortunately, raloxifene is not registered in our country, so we could not currently assess its impact on the risk of COVID-19.

By the expert opinion, the patients receiving parenteral bisphosphonates may suspend the medication use for several months without any negative effect; the patients receiving Denosumab may be recommended a possible suspension of use. If the suspension lasts over 1 month (7 months after the previous injection), one should consider a temporary shift to the per os bisphosphonates [14]. However, there are also studies that consider the possibility of delaying denosumab injection for up to 9 months [15].

This study has the following *limitations*: its design (phone survey) and a small sample. The long-term observations of osteoporotic patients receiving their respective treatment during the pandemic times will allow us to obtain a wider scope of knowledge about the COVID-19 risk among patients suffering from osteoporosis and its complications.

## Conclusions

Parenteral antiosteoporotic drugs (Zoledronic acid, Ibandronic acid, or Denosumab) do not have a significant influence on COVID-19 frequency and severity and can be recommended for the continuation of treatment of patients with osteoporosis.



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**Authors' contribution.** N. V. Grygorieva — research concept and design, analysis of the data, editing of the text; M. A. Bystrytska — collection of data, analysis of the results; N. V. Zaverukha — collection of data, writing and editing of the article; A. S. Musienko — collection and analysis of the data, editing of the article.

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## Антиостеопоротичне лікування та ризик COVID-19: чи існує зв'язок?

**Резюме. Актуальність.** Незважаючи на нещодавні рекомендації ASBMR, AACE, Endocrine Society, ECTS&NOF щодо лікування остеопорозу в епоху COVID-19, вплив антиос-

теопоротичних препаратів на ризик і тяжкість захворювання вивчений недостатньо. **Метою** дослідження було оцінити ризик COVID-19 у хворих з остеопорозом, які отримують

парентеральне лікування бісфосфонатами або деносумабом, а також тяжкість його перебігу у вищезазначеного контингенту. **Матеріали та методи.** Ми провели телефонне опитування та проаналізували дані 195 пацієнтів (92 % жінок; середній вік  $62,7 \pm 10,8$  року) із системним остеопорозом залежно від поточного застосування парентеральних антирезорбтивних препаратів (золедронова кислота, ібандронова кислота або деносумаб,  $n = 125$ ) і порівняли результати з даними хворих з остеопорозом, які раніше не застосовували жодних антиостеопоротичних препаратів ( $n = 70$ ). **Результати.** Серед обстежених на COVID-19 захворіли 32,9 % осіб, які не отримували будь-якого антиостеопоротичного лікування в минулому, та 33,3 % хворих з остеопорозом, які отримували лікування парентеральними резорбентами ( $p > 0,05$ ). Серед осіб, які приймали золедронову кислоту, захворіли 29,2 %, ібандронову кислоту — 34,4 %, деносумаб — 42,9 %. Вірогідних відмінностей у частоті та тяжкості COVID-19 залежно від наявності

та типу антиостеопоротичної терапії не було виявлено. Крім того, не встановлено відмінностей показників залежно від віку пацієнтів, їх статі, наявності ожиріння та інших факторів ризику остеопорозу. Ризик COVID-19 у пацієнтів із системним остеопорозом не відрізнявся залежно від застосування антирезорбтивних препаратів: відношення шансів (OR) становило 1,1 (95% ДІ 0,6–2,0), або від застосування певного антиостеопоротичного препарату (для золедронової кислоти — 0,9 (95% ДІ 0,4–2,0), ібандронової кислоти — 1,1 (95% ДІ 0,5–2,3) та для деносумабу — 1,6 (95% ДІ 0,5–5,2)). **Висновки.** Парентеральні антиостеопоротичні препарати (золедронова або ібандронова кислоти, деносумаб) не впливають на частоту та тяжкість COVID-19 і можуть бути рекомендовані для продовження лікування хворих на остеопороз під час COVID-19.

**Ключові слова:** COVID-19; антирезорбтивні препарати; остеопороз; золедронова кислота; ібандронова кислота; деносумаб