

# Vaccination for Coronavirus Disease 2019 (COVID-19) and Relationship to Osteoporosis Care: Current Evidence and Suggested Approaches

Elena Tsourdi,<sup>1,2</sup> Elaine W. Yu,<sup>3</sup> Suzanne M. Jan de Beur,<sup>4</sup> and Matthew T. Drake<sup>5,6</sup>

<sup>1</sup>Department of Medicine III, Universitätsklinikum Dresden, Dresden, Germany

<sup>2</sup>Center for Healthy Aging, Universitätsklinikum Dresden, Dresden, Germany

<sup>3</sup>Endocrine Unit, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

<sup>4</sup>Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>5</sup>Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA

<sup>6</sup>Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA

## ABSTRACT

The development of coronavirus disease 2019 (COVID-19) vaccines has proceeded at an unprecedented pace, with numerous trials conducted simultaneously across the world as a result of massive technological and financial resource expenditures. With multiple vaccines having now received regulatory approval, public health efforts to promote widespread vaccine dissemination are currently underway. There has been particular emphasis placed on vaccination of older populations, the age group in which COVID-19 infection has been most lethal. However, such widespread vaccination approaches have necessarily raised important questions related to potential interactions with underlying diseases and concomitant treatments among persons to be vaccinated. Osteoporosis is a chronic condition marked by reduced bone strength and an associated increased risk for fracture that generally requires sustained medical intervention(s). Osteoporosis is neither associated with a higher risk of COVID-19 infection nor by more pronounced disease severity following infection, such that individuals with osteoporosis need not be more highly prioritized for COVID-19 vaccination. Osteoporosis therapies do not interfere with the efficacy or side effect profiles of COVID-19 vaccines and should not be stopped or indefinitely delayed because of vaccination. Depending on the specific drug profile within an anti-osteoporosis medication category, minor adjustments to the timing of drug administration may be considered with respect to the patient's COVID-19 vaccination schedule. Herein we provide practical recommendations for the care of patients requiring treatment for osteoporosis in the setting of COVID-19 vaccination. © 2021 American Society for Bone and Mineral Research (ASBMR).

**KEY WORDS:** ABALOPARATIDE; BISPHOSPHONATES; COVID-19; DENOSUMAB; OSTEOPOROSIS; RALOXIFENE; ROMOSOZUMAB; SARS-CoV-2; TERIPARATIDE; VACCINE

## Introduction

At the time of this writing, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the causative virus for the coronavirus disease 2019 (COVID-19) pandemic, has infected more than 113 million people and resulted in over 2.5 million deaths worldwide.<sup>(1)</sup> In addition to the severe disease manifestations attributable to COVID-19 infection per se and its numerous associated complications, COVID-19 has had a tremendous impact on routine clinical and social practices, and has introduced heretofore unconsidered challenges for the management of many chronic medical conditions.<sup>(2)</sup> The international implementation of measures such as travel bans, quarantines, and isolation and social distancing has resulted in reduced physical activity and more sedentary behaviors, both

of which are associated with a loss of muscle mass and strength.<sup>(3)</sup> In addition, the redeployment of infrastructure and personnel for the acute management of patients with COVID-19 disease has resulted in suboptimal care for patients with osteoporosis and fragility fractures, including preventative measures.<sup>(4,5)</sup> The significant implications of the pandemic on musculoskeletal health have led professional societies and bone specialists to issue recommendations for pragmatic clinical management of osteoporosis and fractures.<sup>(6–8)</sup>

The discovery of the SARS-CoV-2 genotype laid the foundation for global efforts to develop treatment options, catalyzing numerous efforts globally to rapidly develop effective vaccines against COVID-19 at a pace not previously imagined.<sup>(9)</sup> Initial vaccine candidates in the portfolio of the COVID-19 Vaccine Global Access Facility (COVAX) comprised the categories of whole virus

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Address correspondence to: Matthew T. Drake, MD, PhD, Division of Endocrinology and Kogod Center on Aging, Mayo Clinic College of Medicine, Rochester, MN 55905, USA. E-mail: drake.matthew@mayo.edu

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(inactivated or weakened), viral vector (replicating and nonreplicating), nucleic acid (RNA, DNA), and protein-based (protein subunit, virus-like particle).<sup>(10)</sup> At the time of this writing, the European Medicines Agency (EMA) have approved two messenger RNA (mRNA)-based vaccines (BNT162b1 [BioNTech, Mainz, Germany | FosunPharma | Pfizer, New York, NY, USA] and mRNA-1273 [Moderna TX, Inc, Cambridge, MA, USA]) and one recombinant adenovirus vaccine (ChAdOx1 [University of Oxford/AstraZeneca]), while the US Food and Drug Administration (FDA) has approved the two former mRNA-based vaccines and one recombinant adenovirus vaccine (Ad26.COV2.S [Janssen Biotech, Inc, Horsham, PA, USA]), for the prevention of COVID-19 disease based on their efficacy and safety profile. Likewise, a recombinant adenoviral vector-based vaccine (Gam-COVID-Vac/Sputnik V [Gamaleya Research Institute, Moscow, Russia]) has been approved by the Russian Ministry of Health, and two inactivated vaccines (BBIBP-CorV [Sinopharm] and CoronaVac [Sinopharm]) have been approved by the National Medical Products Administration in China. Commonly described side effects of the both the recombinant adenoviral vector-based<sup>(11)</sup> and mRNA-based<sup>(12)</sup> COVID-19 vaccines include injection site reactions (i.e., localized pain, swelling, and/or erythema) and systemic flu-like symptoms (i.e., myalgia, headache, low-grade fever, and fatigue).

As a consequence of widespread public-health efforts to implement COVID-19 vaccinations as an intervention designed to end the pandemic through achievement of herd immunity, questions have arisen about their use in populations with multiple medical comorbidities. Chronic diseases, such as osteoporosis, are associated with generalized aging and are, therefore, highly prevalent among those most likely to be prioritized for initial vaccination. Recognizing the need to address this issue, the American Society for Bone and Mineral Research (ASBMR) formed a Steering Committee of bone specialists to review the available evidence and to provide clinical guidance for the COVID-19 vaccines in patients with osteoporosis. Given limited published data in the context of the very recent approval of vaccines against COVID-19, these recommendations are accordingly based primarily on expert opinion and will require tailoring to the status of specific localities, as well as reassessment both as additional COVID-19 vaccines, and more information related to their use in patients with osteoporosis, become available.

The main issues that need to be addressed regarding care decisions associated with COVID-19 vaccination in patients who require osteoporosis care are as follows.

### **Is There Rationale for COVID-19 Vaccine Prioritization in Patients with Osteoporosis?**

The limited initial supplies of all COVID-19 vaccines raise the question of how to prioritize available doses. Based on this concern, models that incorporate variables such as age, occupational and socio-economic factors, serostatus, and underlying comorbidities have been suggested.<sup>(13,14)</sup> Indeed, prevalent vertebral fractures have been identified as a predictor of poor outcomes among patients hospitalized with COVID-19.<sup>(15)</sup> Although it is possible that multiple severe vertebral fractures might lead to kyphosis and impaired respiratory mechanics, it is more likely that the presence of these osteoporotic fractures serves as a proxy for other age and cardiorespiratory comorbidities which more directly contribute to COVID-19 morbidity and mortality. Based on our understanding of COVID-19 infectivity

to date, osteoporosis per se does not appear to increase the risk for infection or complications with COVID-19; rather, we surmise that underlying disorders of skeletal metabolism such as osteoporosis are more likely to be identified in patients who require more advanced care for COVID-19 infection given that these patients are more frequently older. Thus, although osteoporosis generally correlates with increasing age,<sup>(16)</sup> and older age has also been shown to greatly affect prognosis in patients infected with COVID-19,<sup>(17)</sup> there is no current evidence for a direct link between osteoporosis and COVID-19 severity. Consequently, we do not believe that, independent of age, patients with osteoporosis should be prioritized for COVID-19 vaccination. Nevertheless, we accept that any decision to prioritize patients with osteoporosis for vaccination should be tailored to indications specific to each country. When considered in the context of other potential comorbidities in which osteoporosis is frequently also identified, such as diabetes mellitus, cardiovascular, rheumatologic, or hematological conditions, we refer to the statements of those respective societies.

### **Should General Bone Health Measures Be Continued During and After COVID-19 Vaccination?**

General bone health measures (i.e., calcium and vitamin D supplementation, weight-bearing exercises, maintenance of a balanced diet) are often prescribed in tandem with pharmacologic osteoporosis therapy and should not be interrupted at the time of vaccination or thereafter. Indeed, some, mostly observational, evidence exists for vitamin D as a facilitator of immunocompetence both with regard to innate and adaptive immunity in the setting of COVID-19.<sup>(8,18–20)</sup> Notably, large-scale randomized controlled trials examining the impact of vitamin D supplementation for prevention or treatment are required to document specific effects in the context of COVID-19; review of the US National Library of Medicine, Clinical Trials (<https://clinicaltrials.gov/>) website reveals that multiple such trials are currently in progress, although none appear to specifically examine interactions with COVID-19 vaccines. Similarly, exercise-induced immunomodulation has been acknowledged to be reflective of the interplay of intensity, duration, and frequency of exercise.<sup>(21)</sup> Moreover, it is well-recognized that malnutrition can negatively impact the immune system, resulting in suppression of the immune response and increasing susceptibility to pathogens such as SARS-CoV-2.<sup>(22)</sup> Accordingly, a diversified and balanced diet may contribute to improvement of the immune response to viral infections such as COVID-19, and by extrapolation to the immune response following COVID-19 vaccination.

### **Should Pharmacologic Osteoporosis Treatment Be Continued Before and After COVID-19 Vaccination?**

To date, there is no evidence that any osteoporosis therapy either increases the risk or severity of COVID-19 infection, alters the disease course (in either a positive or negative way), or interferes with the efficacy or side effect profile of COVID-19 vaccination. On the other hand, depending on the pharmacologic agent utilized, disruption of osteoporosis treatment could have significant implications on fragility fracture risk. Osteoporotic fractures continue to occur unabated throughout the COVID-19

pandemic, with fragility fractures comprising an even higher proportion of fractures than prior to the pandemic.<sup>(23,24)</sup> Thus, as a general rule, therapeutic regimens should not be permanently discontinued or indefinitely delayed because of vaccination. However, we acknowledge that depending on the specific profile of each anti-osteoporosis drug category, special adjustments may need to be considered with respect to vaccination timing. Accordingly, considerations related to each class of medications commonly utilized for the treatment of osteoporosis are discussed in the following sections. In the absence of clear data, these recommendations should be considered as suggestions, and not guidelines. Furthermore, in light of the current scarcity in vaccine availability, we recognize that vaccine dosing may need to be prioritized over potential slight alterations in standard osteoporosis regimens.

### Oral bisphosphonates

Oral bisphosphonates commonly used for osteoporosis treatment include alendronate, risedronate, and ibandronate. There is no reason to surmise that COVID-19 vaccination will lead to bisphosphonate intolerance or that bisphosphonate treatment will diminish COVID-19 vaccine effectiveness. When considered with the fact that oral bisphosphonates rarely cause an acute phase reaction,<sup>(25,26)</sup> there is no identifiable justification for their discontinuation during the vaccination period. Thus, we recommend that oral bisphosphonates should not be discontinued at the time of, or subsequent to, vaccination against COVID-19.

### Intravenous bisphosphonates

The development of a postinfusion inflammatory reaction, particularly in treatment-naive patients, is a well-recognized side effect of intravenous bisphosphonate administration. Although the immunological basis for such acute phase reactions is not entirely understood, it appears at least partially attributable to the indirect activation of  $\gamma\delta$  T cells, with subsequent release of interferon- $\gamma$  and tumor necrosis factor alpha (TNF- $\alpha$ ) into the systemic circulation.<sup>(27)</sup> Because acute phase reactions are a reported side effect of both recombinant adenovirus vector-based<sup>(11)</sup> and mRNA-based<sup>(12)</sup> COVID-19 vaccines, it would seem prudent to stagger the timing of administrations of an intravenous bisphosphonate and a COVID-19 vaccine. It is important to re-emphasize that no data currently exists to suggest that concurrent administration of these two treatments might alter the side effect profile and/or reduce the efficacy of either the bisphosphonate or COVID-19 vaccine. However, based on empirical evidence and an understanding of bisphosphonate pharmacologic and COVID-19 disease-specific biology, we suggest a 1-week interval to allow for distinguishing between putative acute phase reactions resulting from either intravenous bisphosphonate administration or COVID-19 vaccination. Furthermore, given that the median acute phase reaction duration has been estimated to be 3 days after zoledronic acid infusion,<sup>(28,29)</sup> if a patient has received intravenous bisphosphonate infusion and continues to have symptoms consistent with an acute phase reaction which extend beyond 3 days following intravenous bisphosphonate administration, evaluation for COVID-19 (or other) infection should be considered, because prolonged reaction to intravenous bisphosphonate therapy is unlikely to be the etiology of such symptoms. Of note, patients who had previously tolerated intravenous bisphosphonate therapy without significant acute

phase reactions are unlikely to develop a postinfusion inflammatory reaction in subsequent infusions.

It should be also be noted that infusion of the aminobisphosphonate zoledronic acid, has a sustained effect on maintenance of bone mineral density (BMD) and suppression of bone turnover markers (BTMs).<sup>(30,31)</sup> Furthermore, randomized controlled trials that have examined dosing intervals of zoledronic acid which are less frequent than once yearly have indicated potential protection against fractures.<sup>(32–34)</sup> Thus, if necessary, in patients who have received previous treatment with zoledronic acid, subsequent infusions may be delayed for up to several months given the drug's prolonged skeletal biologic half-life.

### Denosumab

Denosumab is a humanized monoclonal antibody that binds to and inhibits receptor activator of nuclear factor  $\kappa$ -B ligand (RANKL). Although RANKL has a well-recognized role in osteoclast biology, it is also expressed in humans within cells of the immune system, where it plays a role in T-cell activation.<sup>(35)</sup> Thus, taking into account the role of innate immunity and specifically T-cell activation in the host response to SARS-CoV-2,<sup>(36)</sup> an impairment of the T-cell-driven immunological response to COVID-19 vaccination through denosumab-mediated RANKL inhibition cannot be ruled out. On the other hand, early data appear to suggest that denosumab use is not associated with any increase in COVID-19 incidence.<sup>(37)</sup> Moreover, no evidence exists that denosumab inhibits the development of innate immunity for influenza (or any other) vaccine. Although denosumab treatment is associated with an increased risk of skin and soft tissue infections and injection site reactions,<sup>(38,39)</sup> the concomitant use of denosumab in patients with rheumatoid arthritis receiving treatment with biologic agents,<sup>(40–42)</sup> or in patients with solid-organ malignancies receiving chemotherapy,<sup>(43,44)</sup> was not associated with an increased risk for systemic infection. A recent meta-analysis confirmed that denosumab treatment was not associated with an increased risk for respiratory infections in osteoporosis patients.<sup>(45)</sup> It should be noted, however, that denosumab can cause dermatologic reactions, including dermatitis and eczema.<sup>(38,39)</sup> Thus, we suggest an interval of 4 to 7 days between treatment with denosumab and COVID-19 vaccination to allow for the potential occurrence of injection site reactions. Moreover, the injection of denosumab should be administered in the contralateral arm or at an alternative site (abdomen or upper thigh).

It is particularly important to recognize that the timing of denosumab administration is critical to optimize skeletal effects and conversely to limit the negative skeletal consequences that can occur when denosumab treatment is delayed or discontinued. These effects, consisting of rapid osteoclastogenesis, a dramatic increase in bone resorption, rapid bone loss, and an increased risk for multiple vertebral fractures, have now been well described.<sup>(46)</sup> Of note, vertebral fractures after denosumab discontinuation have been reported as early as 7 months following the last denosumab injection.<sup>(47)</sup> Thus, although denosumab timing may need to be slightly adjusted to account for vaccine timing, we strongly recommend that denosumab injections should not be delayed more than 7 months after the previous denosumab dose.

## Teriparatide/abaloparatide

Teriparatide exerts no prolonged skeletal effects after its discontinuation,<sup>(48)</sup> and given the similarity in physiologic mechanism of action between teriparatide and abaloparatide, it is presumed that the same also applies to abaloparatide. Neither medication has been associated with an increased risk of infections or immunomodulatory effects, nor has either been described to cause acute phase reactions. Both teriparatide and abaloparatide may induce local injection site reactions, but because the sites of administration do not involve the same site as COVID-19 vaccine (which is typically delivered in the upper arm), this is not expected to cause confusion. Therefore, both teriparatide and abaloparatide can and should be continued in patients undergoing vaccination against COVID-19.

## Romosozumab

Romosozumab is a humanized monoclonal antibody that binds to and inhibits the activity of sclerostin, an osteocyte-produced inhibitor of the Wnt signaling pathway. It is provided in the form of two concomitant subcutaneous injections once monthly for 12 months, after which it is followed by another (typically anti-resorptive) osteoporosis therapy to sustain the anticipated skeletal anabolic effects.<sup>(49)</sup> Although the pro-inflammatory cytokines TNF- $\alpha$  and interleukin-1 $\beta$  (IL-1 $\beta$ ) have been shown to induce sclerostin expression,<sup>(50,51)</sup> there is no evidence for an increased risk of infection or for acute phase reactions with romosozumab treatment.<sup>(52)</sup> Because upper arm injection site reactions such as pain, swelling, and erythema have been reported as an adverse effect of both romosozumab<sup>(52)</sup> and COVID-19 vaccination,<sup>(11,12)</sup> an interval of 4 to 7 days between provision of these injections, or alternatively injection of romosozumab in the abdomen (except for a 2-inch area around the navel) or thigh if administered concomitantly with COVID-19 vaccination, can be considered.

## Raloxifene

Raloxifene has recently been shown to inhibit interleukin 6 (IL-6) signaling at therapeutic doses, suggesting a putative role for raloxifene in preventing the cytokine storm that can accompany COVID-19 infection, and suggesting a potential for drug repurposing in the treatment of SARS-CoV-2 infection.<sup>(53,54)</sup> Moreover, there is no known interaction between raloxifene and COVID-19 vaccines. Raloxifene therapy does not cause an acute phase reaction and should not be discontinued at the time of, or subsequent to, COVID-19 vaccination.

## Conclusion

To meet the historic challenge posed by the COVID-19 pandemic, vaccines have been developed through a rapid and coordinated global effort. Osteoporosis is not likely to directly impact the incidence or outcomes of SARS-CoV-2 infection, and therefore patients do not warrant higher prioritization for vaccination against COVID-19 due to their osteoporosis. Standard nonpharmacologic approaches for optimization of bone health include maintenance of vitamin D supplementation, maintenance of adequate physical activity, and adherence to a balanced diet; these strategies should be continued because of their musculoskeletal benefits and their potential roles as facilitators of immunocompetence. Based on current evidence, osteoporosis

therapies do not increase the risk or severity of COVID-19 infection and do not interfere with the efficacy or side effect profile of COVID-19 vaccines. Oral bisphosphonates, as well as the self-administered skeletal anabolic agents, teriparatide and abaloparatide, should not be discontinued during vaccination. We recommend an interval of 1 week between intravenous bisphosphonate infusion and COVID-19 vaccination because of the possibility of treated patients developing an acute phase reaction as a result of administration of either agent. In terms of denosumab and romosozumab, it seems prudent to allow for an interval of 4 to 7 days between these drugs and vaccination because of putative injection site reactions. Given the relative paucity of COVID-19 vaccine dosages available worldwide, COVID-19 vaccination should be prioritized over any slight delays that may be needed to provide either denosumab or romosozumab according to their standard dosing intervals.

We hope that these recommendations provide practical guidance for the care of patients with osteoporosis during this unprecedented pandemic and in the setting of widespread dissemination of COVID-19 vaccinations.

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## Author contributions

Elena Tsourdi: Conceptualization; writing-original draft; writing-review & editing. Elaine Yu: Conceptualization; writing-review & editing. Suzanne Jan de Beur: Conceptualization; writing-review & editing. Matthew Drake: Conceptualization; writing-original draft; writing-review & editing.

## Peer Review

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## Data availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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