

**Joint Guidance on Osteoporosis Management in the Era of COVID-19  
from the American Society for Bone and Mineral Research (ASBMR), American Association of  
Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS)  
and National Osteoporosis Foundation (NOF)**

**The guidance below has been created to assist clinicians in the management of patients with osteoporosis in the era of COVID-19.** The current pandemic has necessitated the implementation of social distancing strategies that have the potential to disrupt the medical care of patients with osteoporosis. We acknowledge that there is a paucity of data to provide clear guidance. Thus the below recommendations are based primarily on expert opinion.

**General Recommendations**

The initiation of oral bisphosphonate therapy can be done via telephone or video visit and should not be delayed in patients at high risk for fracture (for example: in patients who have recently sustained an osteoporotic fragility fracture).

Bone mineral density (BMD) examinations may need to be postponed when public health guidance recommends the halting of elective procedures.

When possible to do safely, patients who are already taking osteoporosis medications should continue to receive ongoing medications including oral and intravenous (IV) bisphosphonates, denosumab, estrogen, raloxifene, teriparatide, abaloparatide, and romosozumab. There is no evidence that any osteoporosis therapy increases the risk or severity of COVID-19 infection or alters the disease course (in either a positive or negative way). However, there are early signals that COVID-19 may be accompanied by an increased risk for hypercoagulable complications<sup>1,2</sup>, in which case caution should be used for estrogen and raloxifene, both of which may modestly increase thrombotic risk.<sup>3,4</sup>

To facilitate social distancing guidelines and to minimize patient exposure at phlebotomy centers, standard pre-treatment labs (such as calcium, 25-hydroxyvitamin D, and/or creatinine) prior to IV bisphosphonate and/or denosumab administration can be avoided if labs within the preceding year were normal and it is the clinical judgement of the medical provider that a patient's health has been stable. However, laboratory evaluation is recommended for patients with fluctuating renal function and those who are at higher risk of developing hypocalcemia, such as those with malabsorptive disorders, hypoparathyroidism, advanced renal dysfunction (chronic kidney disease stage 4 or 5), or taking loop diuretics.

**Alternative methods of delivering parenteral osteoporosis treatments**

We acknowledge that it may not be possible to safely provide parenteral osteoporosis treatments that are not self-administered (e.g. IV bisphosphonates, denosumab, or romosozumab) in all geographic locations during the current COVID-19 pandemic.

Alternative delivery methods include:

- Off-site clinics: Administration of treatments at locations geographically isolated from COVID-19 “hot-spots” should be considered whenever possible. However, recognize that this may disadvantage socioeconomically challenged communities if public transportation options are not available.
- Home delivery and administration: this is a feasible option if available and could include a visiting nurse, home health aide, home-visiting medical staff or family health care provider.
- Self-injection of denosumab (and/or romosozumab) has been proposed and is reportedly available in some locales. However, there are important medico-legal issues to consider surrounding the proper product handling and administration, including the small risk of drug-related hypersensitivity reactions in the absence of a medical provider, although steps to mitigate such potential risks may be in place in some communities.
- Drive-through administration of denosumab and/or romosozumab: this may also be logistically difficult to arrange. Further, it is recommended that patients be monitored by a medical provider for 15 minutes after injection in the unlikely event of a hypersensitivity reaction.

**Specific Recommendations for management of patients who are unable to receive ongoing non-oral osteoporosis medications during the COVID-19 pandemic**

We recommend frequent re-evaluation of patients in whom treatment was disrupted with the goal to resume the original osteoporosis treatment plan once circumstances allow.

**Denosumab (Prolia®)**

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 (such as weekly alendronate). For patients with underlying gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), achalasia or active peptic ulcer disease, consider monthly ibandronate or weekly/monthly risedronate. For patients with chronic renal insufficiency [estimated glomerular filtration rate (eGFR) levels < 30-35 mL/min], consider an off-label regimen of lower dose oral bisphosphonate (e.g. alendronate 35 mg weekly, or alendronate 70 mg every 2 weeks).

**Evidence**

Denosumab is a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), and RANKL plays a role in T-cell activation. Studies of denosumab in postmenopausal osteoporosis indicate an increased risk of skin and soft tissue infections.<sup>5</sup> No infection safety signals have been seen in studies of denosumab in patients receiving concurrent immunomodulatory treatment for rheumatoid arthritis<sup>6</sup> or in patients receiving concomitant chemotherapy for solid-organ tumors.<sup>7,8</sup>

There is evidence that denosumab discontinuation causes rebound high bone turnover and rapid bone loss within 1 year<sup>9,10</sup>, and increases the risk of multiple vertebral fractures

particularly among those with existing vertebral fractures.<sup>11</sup> Reports of vertebral fractures after denosumab discontinuation have occurred as early as 7 months after the last denosumab injection.<sup>12</sup>

The optimal regimen of bisphosphonate to mitigate the ‘rebound phenomenon’ that characterizes denosumab discontinuation is currently unknown. Limited evidence suggests that oral alendronate may provide protection from denosumab-discontinuation rebound bone loss, particularly in patients who have received only short period of previous denosumab treatment.<sup>13</sup> However, multiple vertebral fractures have been described in 2 patients provided with alendronate following treatment with denosumab for an average of 3.5 years.<sup>14</sup> There is conflicting evidence regarding whether zoledronic acid can prevent rebound bone loss following denosumab discontinuation, with most data showing that zoledronic acid was less effective in maintaining BMD when previous denosumab treatment exceeds 2 years.<sup>15-17</sup> Additional unknowns include the optimal bisphosphonate timing relative to denosumab discontinuation, and whether less potent antiresorptives (such as raloxifene) may prevent the high bone turnover state after denosumab discontinuation.<sup>18,19</sup>

#### **Teriparatide (Forteo®) or abaloparatide (Tymlos®)**

For patients in whom continued treatment with teriparatide or abaloparatide is not feasible, consider a delay in treatment. If this delay exceeds 2-3 months, consider a temporary transition to oral bisphosphonate.

#### **Evidence**

There is evidence that BMD progressively declines after teriparatide discontinuation.<sup>20</sup> Similar declines are expected with abaloparatide discontinuation. Hence, treatment with either skeletal anabolic agent should be followed by treatment with an antiresorptive agent to prevent bone loss.<sup>21</sup>

#### **Romosozumab (Evenity®)**

For patients in whom continued treatment with romosozumab is not feasible, consider a delay in treatment. If this delay exceeds 2-3 months, consider a temporary transition to oral bisphosphonate.

#### **Evidence**

There is evidence that bone loss occurs rapidly following romosozumab discontinuation, although there is no indication that discontinuation leads to increased fracture risk.<sup>22</sup> There is evidence that transitioning from romosozumab to alendronate can lead to continued gains in BMD.<sup>23</sup>

#### **Intravenous (IV) bisphosphonates**

For patients in whom continued treatment with intravenous (IV) bisphosphonates is not feasible, delays of even several months are unlikely to be harmful.

#### **Evidence**

There is evidence that the skeletal protective effects of bisphosphonate treatment linger for many months, and potentially years, after bisphosphonate administration.<sup>24-27</sup>

## **References**

1. **Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziapas G, Dimopoulos MA.** Hematological findings and complications of COVID-19. *Am J Hematol.* 2020 Apr 13. doi: 10.1002/ajh.25829. [Epub ahead of print]
2. **Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P.** COVID-19 related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost.* 2020 Apr 21. doi: 10.1055/s-0040-1710018. [Epub ahead of print]
3. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/022042lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf)
4. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2006/004782s147lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/004782s147lbl.pdf)
5. **Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY, Roux C, Malouf J, Bradley MN, Daizadeh NS, Wang A, Dakin P, Pannacciulli N, Dempster DW, Papapoulos S.** 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523.
6. **Lau AN, Wong-Pack M, Rodjanapiches R, Ioannidis G, Wade S, Spangler L, Balasubramanian A, Pannacciulli N, Lin CJF, Roy-Gayos P, Bensen WG, Bensen R, Adachi JD.** Occurrence of serious infection in patients with rheumatoid arthritis treated with biologics and denosumab observed in a clinical setting. *J Rheumatol.* 2018;45(2):170-176.
7. **Coleman R, Finkelstein DM, Barrios C, Martin M, Iwata H, Hegg R, Glaspy J, Periañez AM, Tonkin K, Deleu I, Sohn J, Crown J, Delaloge S, Dai T, Zhou Y, Jandial D, Chan A.** Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2020;21(1):60-72.
8. **Stopeck AT, Fizazi K, Body JJ, Brown JE, Carducci M, Diel I, Fujiwara Y, Martín M, Paterson A, Tonkin K, Shore N, Sieber P, Kueppers F, Karsh L, Yardley D, Wang H, Maniar T, Arellano J, Braun A.** Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer.* 2016;24(1):447-455.
9. **Miller PD, Wagman RB, Peacock M, Lewiecki EM, Bolognese MA, Weinstein RL, Ding B, San Martin J, McClung MR.** Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab.* 2011;96(2):394-402.
10. **Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, Grazette L, San Martin J, Gallagher JC.** Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab.* 2011;96(4):972-980.
11. **Cummings SR, Ferrari S, Eastell R, Gilchrist N, Beck Jensen JE, McClung M, Roux C, Törring O, Valter I, Wang AT, Brown JP.** Vertebral fractures after discontinuation of denosumab: a post

hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res.* 2018;33(2):190-198.

12. **Gonzalez-Rodriguez E, Aubry-Rozier B, Stoll D, Zaman K, Lamy O.** Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors. *Breast Cancer Res Treat.* 2020;179(1):153-159.

13. **Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, Borenstein J, Kendler DL.** Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012;23(1):317-326.

14. **Lamy O, Fernández-Fernández E, Monjo-Henry I, Stoll D, Aubry-Rozier B, Benavent-Núñez D, Aguado P, Gonzalez-Rodriguez E.** Alendronate after denosumab discontinuation in women previously exposed to bisphosphonates was not effective in preventing the risk of spontaneous multiple vertebral fractures: two case reports. *Osteoporos Int.* 2019;30(5):1111-1115.

15. **Anastasilakis AD, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Makras P.** Zoledronate for the prevention of bone loss in women discontinuing denosumab treatment. A prospective 2-year clinical trial. *J Bone Miner Res.* 2019;34(12):2220-2228.

16. **Reid IR, Horne AM, Mihov B, Gamble GD.** Bone loss after denosumab: only partial protection with zoledronate. *Calcif Tissue Int.* 2017;101(4):371-374.

17. **Everts-Graber J, Reichenbach S, Ziswiler HR, Studer U, Lehmann T.** A single infusion of zoledronate in postmenopausal women following denosumab discontinuation results in partial conservation of bone mass gains. *J Bone Miner Res.* 2020; epub ahead of print: doi: 10.1002/jbmr.3962.

18. **Ebina K, Miyama A, Hirao M, Yoshikawa H, Hashimoto J, Kashii M, Nakaya H, Takahi K, Tsuji S, Tsuboi H.** Assessment of the effects of sequential treatment after discontinuing denosumab in 64 patients with postmenopausal osteoporosis. *J Bone Miner Res.* 2019;(S1):S259.

19. **Gonzalez-Rodriguez E, Stoll D, Lamy O.** Raloxifene has no efficacy in reducing the high bone turnover and the risk of spontaneous vertebral fractures after denosumab discontinuation. *Case Rep Rheumatol.* 2018;17:5432751.

20. **Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS.** Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. *J Clin Endocrinol Metab.* 2009;94(8):2915-2921.

21. **Leder BZ, Zapalowski C, Hu MY, Hattersley G, Lane NE, Singer AJ, Dore RK.** Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: results from the Phase 3 ACTIVEExtend trial. *J Bone Miner Res.* 2019;34(12):2213-2219.

22. **McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, Bolognese MA, Goemaere S, Bone HG, Zanchetta JR, Maddox J, Bray S, Grauer A.** Effects of 24 Months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel groups study. *J Bone Miner Res.* 2018;33(8):1397-1406.

23. **Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A.** Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med.* 2017;377(15):1417-1427.

24. **Ravn P, Weiss SR, Rodriguez-Portales JA, McClung MR, Wasnich RD, Gilchrist NL, Sambrook P, Fogelman I, Krupa D, Yates AJ, Daifotis A, Fuleihan GE.** Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. Alendronate osteoporosis prevention study group. *J Clin Endocrinol Metab.* 2000;85(4):1492-1497.
25. **Eastell R, Hannon RA, Wenderoth D, Rodriguez-Moreno J, Sawicki A.** Effect of stopping risedronate after long-term treatment on bone turnover. *J Clin Endocrinol Metab.* 2011;96(11):3367-3373.
26. **Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P, Leung PC, Man Z, Martinez RL, Tan M, Ruzicky ME, Su G, Eastell R.** The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2012;27(2):243-254.
27. **Grey A, Bolland MJ, Horne A, Mihov B, Gamble G, Reid IR.** Duration of antiresorptive activity of zoledronate in postmenopausal women with osteopenia: a randomized, controlled multidose trial. *CMAJ.* 2017;189(36):E1130-E1136.