Long-term treatment strategies for postmenopausal osteoporosis

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Purpose of review
Osteoporosis guidelines do not usually provide specific recommendations regarding what medication is most appropriate for individual patients. Generic oral bisphosphonates are often considered first-line treatment for osteoporosis, but treatment duration is limited, based on potential long-term safety concerns, and there is no consensus about what to do after 5 years. There are no recommendations concerning long-term management of osteoporosis over 30 or more years of postmenopausal life.

Recent findings
This review attempts to specify medication choices and provide the best clinical management strategies for women at different stages of life and with different underlying disease severity. Because there is no evidence that considers the entire postmenopausal lifespan, much of the discussion here will be based on expert opinion. The review considers a role for estrogens and selective estrogen receptor modulators, oral and intravenous bisphosphonates, denosumab and the anabolic agents, teriparatide and abaloparatide.

Summary
Optimal sequential monotherapy, over an average of 30 postmenopausal years, should be able to minimize exposure to pharmacology while maximizing benefits on bone strength and minimizing imminent and long-term risk of fracture.

Keywords
anabolic and antiresorptive, goal-directed therapy, long-term strategies, treatment duration, treatment sequence

INTRODUCTION

Osteoporosis treatment rates have declined in the last decade even for the highest risk patients [1]; in the United States, and indeed worldwide, fewer than 25% of patients with major osteoporosis-related fractures, such as hip fractures, are treated for their underlying disease [2]. In part, this is related to a lack of understanding of the consequences of osteoporosis and what really constitutes the highest risk patients. Furthermore, both healthcare professionals and patients have a poor understanding of the benefits and risks of osteoporosis therapies. Treatment recommendations by many academic groups have not considered long-term treatment paradigms; in fact, some have recommended a 5-year treatment course with bisphosphonates or denosumab; then what? [3]

Postmenopausal osteoporosis is a chronic and progressive disease associated with low peak bone mass and/or rapid and persistent bone loss as a consequence of estrogen deficiency and aging. In addition, there are superimposed effects of many underlying chronic diseases and medications that contribute to excessive and/or imbalanced bone remodeling, with consequent further loss of skeletal mass and structure. Factors such as suboptimal nutrition and exercise as well as high-risk behaviors (smoking and excessive alcohol consumption) also play a role [4].

Many of our osteoporosis treatment guidelines have highlighted when treatment for osteoporosis is indicated, but not what medications should be utilized [4]. Oral bisphosphonates are often suggested as first-line treatments, sometimes with a suggested duration of 5 years, but with no subsequent suggestions for treatment in the near or distant future [3]. As many patients are diagnosed with osteoporosis or

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KEY POINTS

- Different osteoporosis medications may be most appropriate at different stages in a patient's lifetime.
- Osteoporosis treatment decisions must consider a 30-40-year postmenopausal lifespan.
- Logical transition of osteoporosis treatments will minimize risk and maximize benefit.
- High-risk patients, especially those with fractures, should be considered for first-line anabolic osteoporosis therapy.
- Comprehensive risk assessment should include vertebral imaging to identify vertebral fractures.

osteopenia in their 50s and average longevity encompasses 30 subsequent years, treatment strategies, which consider the entire lifespan, must be considered. Furthermore, goals of therapy differ across the lifespan and should be defined at different stages of life.

This article considers all of these factors in trying to help formulate long-term strategies for patients at different ages and stages of osteoporosis.

PREMENOPAUSAL WOMEN AND UNIVERSAL MEASURES

During youth, strategies are primarily related to lifestyle and are designed to optimize and maintain peak bone mass. These include maintaining a healthy weight, obtaining a diet that is calcium rich, with abundant fruits and vegetables and adequate vitamin D and/or sun exposure, maintaining regular menstrual function, engaging in regular weight bearing and muscle strengthening physical activity and avoiding smoking and excessive alcohol intake. These universal measures also apply to all groups of women (below) on medication for osteoporosis. Fall prevention strategies are also important for older women.

EARLY POSTMENOPAUSAL WOMEN WITHOUT FRACTURES (WOMEN IN THEIR 50S-MID/LATE-60S)

In middle-aged women with bone mineral density (BMD) above –2 at spine, total hip and femoral neck, and no other major risk factors, pharmacologic treatment can usually be avoided at least for a while. In patients who enter the menopause with low BMD (near or below osteoporosis range), medication should be used to prevent further deterioration of skeletal mass and structure, and can include estrogens, selective estrogen modulators (SERMSs) and the combination of estrogen and bazedoxifene (CEE/BZA) [5,6]. Estrogens and SERMs could be used in logical sequence from the 50s through the mid or late 60s, to help bridge the gap from menopause to older age when fracture risk is much higher, and more potent agents, with limited recommended durations of use, should be employed.

For patients with active hot flashes, low-dose estrogen/hormone treatment (as needed to treat the menopausal symptoms), or CEE/BZA is most appropriate [6]. At some point after about 5 years, a tapering of the estrogen dose might be warranted, particularly for those on hormone therapy (including progestins) where long duration treatment might increase risk of breast cancer [5]. For women on estrogen only and those on CEE/BZA, the duration of therapy can be longer, because of fewer safety concerns, but attempts to wean off these agents as women approach the decade of the 60s are still usually warranted.

For those who can successfully navigate off estrogen, raloxifene is a reasonable second choice. Raloxifene is also a good first choice for women in the 50s–60s who do not have menopausal symptoms and therefore do not require an estrogenic agent. Although there are no data confirming that raloxifene reduces risk of hip and all nonvertebral fractures, raloxifene will preserve bone mass, reduce risk of vertebral fracture and reduce risk of estrogen positive breast cancer. Hip fracture risk is exceedingly low in women in this age group, so the lack of hip fracture efficacy is not a significant limitation for these patients. Because raloxifene reduces breast cancer risk by about 50%, it would be highly recommended for women at elevated risk of breast cancer (family history, prior breast biopsies and/or extremely dense breast tissue).

If a woman does not respond well to raloxifene, for example, if BMD declines significantly, then a short-term oral bisphosphonate might be warranted. Treatment for 3–4 years is likely to produce BMD stability, after which a medication holiday for a few years could be attempted, with continued monitoring and reassessment of risk annually. For those women who cannot take estrogen therapy/hormone therapy or raloxifene, oral bisphosphonate therapy for a few years is reasonable as long as it is not continued long term. For women with particularly low hip BMD (below –3 or –3.5), even in this young age group, a 3–4 year course of bisphosphonate treatment might also be reasonable to prevent further deterioration for women who are not yet ready to embark on a more definitive therapy with anabolic medication or denosumab.

WOMEN IN THEIR LATE 60S AND BEYOND

Mild osteoporosis, no other risk factors

For patients with moderate osteoporosis (BMD T-Score in the range of –2.9 to –2.5, without fractures) in their late 60s and beyond (or younger women who cannot take estrogens/SERMS), bisphosphonates will improve and/or maintain BMD and reduce risk of fracture throughout the skeleton. In these women, it is estimated that there is about a 50% probability that women will attain a T-Score above osteoporosis range with 3–5 years of bisphosphonate [7▪]. It is reasonable to start with an oral bisphosphonate once monthly or once weekly and move to intravenous zoledronic acid once yearly if there are tolerability and/or compliance issues. For older women or those with contraindications to oral bisphosphonates or simply for those who prefer to avoid regular 'pill taking', intravenous zoledronic acid can be the bisphosphonate of choice. After a 3–5-year course of bisphosphonate treatment, if treatment goals are met, with no fractures and BMD above –2.5 at the main skeletal sites, a medication break is reasonable [8,9]. Because they bind to skeletal mineral, bisphosphonates will provide residual protection from fractures even after discontinuation of the medication. Patients must be monitored during a medication holiday for clinical fracture occurrence, height loss, which might suggest an incident vertebral fracture, BMD loss and possibly biochemical turnover marker increase. Another short course (3 years) of bisphosphonate treatment might be warranted in those who begin to lose BMD [with losses that exceed least significant change (3–4% in the spine, 4–6% in the hip and femoral neck)]. Biochemical marker increments above least significant change might also be a sign that bisphosphonates should be started again, but there are really no confirmatory data at this time. Certainly, if a fracture occurs on therapy, medication treatment must be intensified and anabolic therapy is most appropriate at this stage.

Mild osteoporosis without fractures but with other major risk factors

Because fracture risk is higher in this group of patients, a more potent medication is warranted; denosumab is particularly appropriate here. This type of patient might not be severe enough to warrant anabolic therapy, but the target BMD here might be higher than in the person with no other major risk factors [7▪]. Although denosumab is not anabolic (does not stimulate bone formation), it does result in continued BMD accrual over 10 years. However, it needs to be continued indefinitely or, if stopped, replaced with a different osteoporosis agent [10]. Therefore, this needs to be considered in decisions regarding when to start denosumab.

The long-term continued increase in BMD with denosumab in both spine and hip throughout 10 years of administration [11▪] is distinctly different from what is observed with long-term bisphosphonate administration, where BMD plateaus after 3–4 years [12]. Over 10 years of denosumab treatment, average BMD increased 21.7% in the spine and 9.2% in the total hip. These changes represent T-Score increases of almost 2 for the spine and almost 1 for the hip. The hip BMD attained, while patients are being treated with denosumab is a predictor of future fracture risk [13]. Therefore, a 'normalized T-Score', for example of –2, or perhaps higher in people with other risk factors, is a sign of minimized future risk. It might be desirable to transition off denosumab in these patients; however, the optimal approach to withdraw denosumab while maintaining BMD and skeletal integrity is not yet known [14▪]. Observations so far indicate that bisphosphonate treatment upon withdrawal of denosumab reduces but does not eliminate bone loss [15]. Stopping denosumab without starting another antiresorptive medication is dangerous and has been associated with multiple vertebral fractures [16▪,17,18–22].

WOMEN AT ANY AGE WITH RECENT OSTEOPOROTIC FRACTURE OR MULTIPLE OSTEOPOROTIC FRACTURES OR VERY LOW BMD (BELOW –3 OR –3.5)

In postmenopausal patients who present with a history of osteoporosis-related fracture, particularly if the fracture was recent, anabolic therapy should be considered first-line therapy. This is particularly important in patients with recent fracture (within the preceding 2 years); absolute fracture risk is particularly high immediately after the first incident event, approaching 20% in the first 2 years [23▪,24–26]. Patients who have had multiple fractures are also at particularly high risk of subsequent fracture [27]. In order to comprehensively determine if a patient falls within these high-risk categories, vertebral imaging must be done to find vertebral fractures, which most often occur without acute localizing symptoms at the time of the event [28▪]. We recommend that women at age 65 who have a spine, total hip or femoral neck T-Score –1.5 or lower, have a vertebral imaging test as well as a bone density test [4,29,30].

In these highest risk patients, rapid fracture risk reduction is required. With antiresorptive agents, nonvertebral fracture risk reductions are usually not

demonstrated before 3 years of therapy and the magnitude of risk reduction does not exceed 20–25% [31,32]. Furthermore, with bisphosphonates, fracture risk reductions, particularly for the nonvertebral skeleton, are difficult to demonstrate after 3–4 years and BMD plateaus at that time [33]. For patients who remain within the osteoporosis range by BMD, fracture risk remains high [8,34] and it is not clear that continued treatment with bisphosphonates would have a big impact. With denosumab, BMD continues to increase after 3 years, and fracture rates remain low, despite an aging population [11▪]. A modeled twin placebo study corroborated the apparent reduction in fractures with long-term denosumab treatment [35]. However, with both denosumab and bisphosphonates, there are safety concerns (atypical femur fractures, osteonecrosis of the jaw; [36,37]) that appear to increase in frequency with longer duration of use (more clear with bisphosphonates than with denosumab).

In contrast to the antiresorptive agents, anabolic therapies, which stimulate bone formation (teriparatide, abaloparatide and romosozumab), produce rapid reductions in risk of fracture, within 12–19 months for both vertebral and nonvertebral skeletal sites. Furthermore, the magnitude of the nonvertebral fracture risk reduction with these anabolic therapies is 40–50%. With teriparatide, vertebral fracture risk is reduced by 65% and nonvertebral fragility fracture by 53% within a median treatment period of 19 months [38]. Over 18 months with abaloparatide treatment, vertebral fracture risk is reduced by 86% and nonvertebral fracture by 43% [39]. With romosozumab, vertebral fracture risk is reduced by 73% and nonvertebral fracture reduced by 42% (rest of the world population) [40], with just 12 months of treatment.

There are also several powerful head-to-head comparator studies indicating that anabolic agents are superior to antiresorptive agents against fracture over 1–2 years. In glucocorticoid-induced osteoporosis, teriparatide reduced vertebral fractures by 90% compared to alendronate over 18 months [41]. In patients with acute painful vertebral fractures, teriparatide reduced vertebral fractures by 50% compared to risedronate over 1 year [42]. In patients with prevalent vertebral fracture, teriparatide significantly reduced vertebral fractures and produced a nearly significant reduction in nonvertebral fractures compared to risedronate over 2 years [43▪]. Most recently, romosozumab was compared with alendronate in patients with prevalent fracture (mostly prevalent vertebral fracture). Romosozumab resulted in a significant reduction in the incidence of vertebral, nonvertebral and hip fractures compared with alendronate over 2 years [44▪].

Although patients who present with very low BMD in the absence of a prior fracture may not be at high imminent risk for fracture, remaining lifetime fracture probability is very high. Sequential therapy with anabolic followed by antiresorptive agents provides the greatest gain in BMD and will likely produce the greatest protection from long-term fracture risk. In contrast, switching from bisphosphonate or denosumab to teriparatide results in a decline in hip BMD for at least a year, most prominently for women previously on denosumab [45▪,46,47]. Therefore, when possible, anabolic therapy should be initiated first. We do not know how recently bisphosphonates have to be administered to observe the decline in hip BMD upon starting teriparatide; however, it is likely that the effect will wear off within a few years. In the subgroup analysis of the trial comparing teriparatide with risedronate, there was no apparent effect of recent bisphosphonate use (yes or no) on the fracture effect of teriparatide, which was reassuring; however, recent use was liberally defined as 6 months within the preceding 3 years [48]. For patients who are currently on a bisphosphonate or denosumab who need teriparatide or abaloparatide because of a fracture or declining BMD, it might be best to continue an antiresorptive (perhaps the most potent) and add the anabolic medication. This recommendation is based on extrapolation from data where teriparatide was added to ongoing alendronate [49,50] and data where teriparatide and denosumab were combined *de novo* in patients who were primarily treatment naive [51].

When a course of anabolic therapy is followed by antiresorptive treatment, continued fracture protection is seen in patients originally randomized to anabolic therapy during the subsequent antiresorptive period where all patients receive active therapy. For example in the ACTIVE Extension trial, patients randomized to either abaloparatide or placebo for 18 months were then transitioned to alendronate for 2 subsequent years. The cumulative incidence of vertebral and nonvertebral fractures remained lower in the group originally treated with abaloparatide after 6 months of alendronate [52] and throughout the 2-year alendronate treatment period [53]. Similarly, in patients randomized to treatment with romosozumab compared with placebo for 1 year, followed by 2 years of denosumab treatment in all, fracture risk reductions were maintained over 2 years [40] and over a full 3 years of therapy in the group that originally received romosozumab, despite the fact that all patients received active denosumab for 2 years of the 3-year study [54].

For patients at very high risk of imminent fracture or long-term risk of fracture, who cannot or will

not accept anabolic therapy, denosumab would be the next best option. There may be no stopping point, especially for women with multiple fractures. For other patients, after a course of denosumab, transition to bisphosphonate may be warranted once evidence suggesting the best transition regimen is available.

MAINTENANCE OF EFFECT

Intermittent administration of intravenous zoledronic acid and/or oral bisphosphonates might be a desirable strategy to help maintain BMD and bone strength after sequential monotherapy with any of the other agents above. There is little evidence to guide decision making here. It is clear that the effects of bisphosphonates do resolve over time, though the rate of resolution is much slower with bisphosphonates than with nonbisphosphonate agents, and no rebound increase in bone remodeling rates above pretreatment baseline is seen [55]. The slow resolution of effect is particularly prominent for bisphosphonates with greater affinity to hydroxyapatite (zoledronic acid and alendronate). A regimen using an infusion of zoledronic acid or 1–2 years of oral bisphosphonate treatment every 3–5 years might be an effective maintenance regimen with very low risk of adverse events.

CONCLUSION

In early menopausal patients with low BMD, estrogens and SERMs prevent further skeletal deterioration and bridge the gap to older age when fracture risk increases. For patients with moderate osteoporosis (BMD without fractures) in their late 60s and beyond (or younger women who cannot take estrogens/SERMS), bisphosphonates for 3–4 years will improve and/or maintain BMD and reduce risk of fracture throughout the skeleton. Although denosumab is not anabolic, it does result in continued long-term BMD accrual. However, it needs to be continued indefinitely or if stopped, replaced with a different osteoporosis agent. Use of intravenous zoledronic acid and/or oral bisphosphonates might allow denosumab withdrawal, though optimal timing and dosing to maintain full skeletal integrity are not yet known.

Anabolic agents have capability to fundamentally change skeletal integrity with improved skeletal mass and structure, but evidence shows that the best effects are attained when these agents are used as first-line treatment rather than after other therapies. Therefore, when possible, anabolic therapies should be considered first line for fracture patients, especially in those with recent fracture and those with multiple fractures. Anabolic agents reduce fracture risk quickly and to a greater extent than antiresorptive medications and provide the bone mass and architectural foundation for greater long-term strengthening of the skeleton. Anabolic agents should be followed by denosumab, for greatest continued BMD gain and fracture risk reduction, or bisphosphonates for those who appear to be already at minimized risk after a course of anabolic treatment or in whom denosumab is contraindicated or not tolerated.

Bisphosphonates can be used at the end of a treatment sequence to maintain skeletal benefits. It might be necessary to repeat a course of anabolic therapy in the future if a fracture occurs or if BMD falls substantially. Alternatively, if BMD starts to fall or bone turnover markers start to increase, another 1–2 years of bisphosphonate treatment might be enough to maintain skeletal integrity.

Optimal sequential monotherapy, following a goal-directed approach, should be able to minimize exposure to pharmacology while maximizing benefits on bone strength and reducing risk of fracture.

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