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SECTION VII
Osteoporosis II (Therapeutics)

Section Editors:

CHAPTER 74 ■ OVERVIEW OF STRATEGIES FOR MANAGING OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Michael R. McClung, Ghada El Hajj Fuleihan, and E. Michael Lewiecki

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INTRODUCTION

Postmenopausal osteoporosis is a common condition characterized by both low bone mass and microarchitectural deterioration, resulting in impaired bone strength and increased risk of fracture (1). More than half of women aged 50 and older will develop osteoporosis or related fractures in their lifetime. In the United States, almost 2 million women aged 65 and older experienced a fracture in 2018, and that number is projected to increase by 68% by 2040 due the increasing number of older women (2). This is associated with an increase in the estimated annual US expenditure for all osteoporosis-related fractures from $57 billion in 2018 to over $95 billion in 2040. Similar projections have been made for Europe and Asia (3,4). The adverse effects of these fractures on health-related quality of life, physical and psychosocial quality of life and mortality, particularly in elderly patients, have been well documented (5).

Over the past 30 to 40 years, great strides have been taken in our understanding of the nature and regulation of bone metabolism and of the epidemiology and pathogenesis of postmenopausal osteoporosis (6). These advances provide scientific rather than empiric bases for developing effective management strategies. Approaches to the management of osteoporosis in men and premenopausal women and in patients with other disorders that contribute to impaired skeletal health are also covered in other sections of the *Primer*. Information in previous sections of this *Primer* emphasize that many determinants of postmenopausal osteoporosis, such as the acquisition of peak bone mass and the influence of many diseases on bone health, occur during childhood and adolescence and in premenopausal women. It is clear that promoting good general health across the lifespan results in healthier skeletons.

Chapters in this section highlight advances in both nonpharmacologic and pharmacologic approaches to management of postmenopausal women who have developed osteoporosis. Recommendations about general measures including good nutrition, regular physical activity, and avoiding harmful habits are applicable to all postmenopausal women, not just to those with or at risk for osteoporosis. We should help our patients appreciate that these nonpharmacologic approaches are important components of osteoporosis management, but that they are usually not sufficient to prevent postmenopausal bone loss nor treat postmenopausal osteoporosis. The importance of fall prevention and the special considerations in managing osteoporosis in very elderly patients are also included in our section. The remainder of the chapters in this section focus on the pharmacologic management of postmenopausal osteoporosis.

Bone loss after menopause and with advancing age is due to an imbalance in bone remodeling, with resorption outpacing formation. That appreciation led to the development of both antiresorptive agents and of teriparatide, the first osteoanabolic agent. These drugs were shown to improve bone strength and to reduce fracture risk in women with postmenopausal osteoporosis. Subsequent advances in the molecular biology of bone metabolism resulted in the development of very potent therapies that target specific regulators of bone metabolism such as RANK ligand and sclerostin. With these [AU4] advances, we have a full menu of treatment options with varied mechanisms of action (6). The antiresorptive drugs (more accurately called antiremodeling drugs), including bisphosphonates, estrogen agonists and denosumab, improve bone mineral density (BMD) and bone strength reduce fracture risk by slowing bone resorption. However, because they also decrease bone formation, they do not restore the deranged skeletal microarchitecture that characterizes osteoporosis. In contrast, bone-forming or osteoanabolic agents, by activating bone formation, improve trabecular and cortical microarchitecture in addition to increasing BMD. Current therapies also have different pharmacologic characteristics, different dosing regimens, and unique safety profiles. This plethora of choices presents clinical challenges in deciding which drug to choose for a specific patient, challenges made more difficult by the paucity of head-to-head comparisons and dearth of information about long-term effectiveness and safety.

Since the previous edition of the *Primer*, new insights and additional clinical experience have enhanced our understanding of and refined our approach to managing patients with postmenopausal osteoporosis. Several of those new insights are highlighted in this introductory overview chapter.

VERY HIGH OR IMMINENT FRACTURE RISK

For many years, we have known that the major risk factors for fracture in postmenopausal women are advanced age, low BMD, history of falls, and history of previous fractures. Several studies have now documented that a recent fracture in a postmenopausal woman is perhaps the most powerful predictor of subsequent fracture risk, and that risk is highest in the first couple of years after the incident fracture (7). The relative risk of experiencing a second fracture increases more than fivefold in the first 2 years after an incident fracture and then gradually decreases over the next few years to a stable value of about twofold above baseline. In absolute terms, the probability of a second vertebral fracture is almost 20% in the first year following the first vertebral fracture. Among American female Medicare recipients aged 65 years and older who experienced a fracture, 10% experienced a second fracture with 12 months of the first fracture and 18% within 24 months (7). Appreciating the importance of a recent fracture as an index of very high or imminent fracture risk, recently updated guidelines from several national and international societies have defined a category of "very high fracture risk" (8–11). These guidelines recommend that the choice of the initial osteoporosis treatment be based on the patient's current risk of fracture. For those patients at very high risk, more aggressive pharmacologic therapy beginning with an osteoanabolic agent is recommended. This recommendation is justified by the results of recent studies described below.

SUPERIORITY OF OSTEOANABOLIC THERAPIES OVER ANTIREMODELING DRUGS

While it is intuitive that a drug that restores disordered skeletal architecture would be a better treatment option than drugs that only prevent further deterioration in structure, evidence supporting that view has only recently become available. All three osteoanabolic agents induce larger increases in bone density than do either bisphosphonates or denosumab. Small studies demonstrated larger increases in BMD with teriparatide than with a bisphosphonate and hinted that nonvertebral fracture risk reduction was better with teriparatide (12). [AU5] Two large studies, described in detail in Chapters 82 and 83, clearly document the superiority of teriparatide and romosozumab over oral bisphosphonates for reducing fracture risk in women with postmenopausal osteoporosis at high risk of fracture (13,14). Similarly, a post hoc analysis demonstrated superior fracture risk reduction with abaloparatide versus alendronate (15).

TREATMENT-RELATED BMD RESPONSES AND FRACTURE RISK

The strong relationship between BMD and fracture risk was described many years ago (16). Analyses from early clinical trials with bisphosphonates and teriparatide suggested that treatment-related increases in BMD explained only a small proportion of fracture risk reduction (17–19). Larger doses of alendronate, risedronate, and teriparatide resulted in larger BMD increases but no differences in vertebral fracture risk. Meta-analyses correlating changes in BMD and nonvertebral fracture risk were inconclusive. Recently, however, a meta-regression analysis of most of the large placebo-controlled fracture endpoint studies demonstrated that the drugs inducing the largest increases in BMD relative to placebo were associated with the largest reductions in fracture risk (20). When individual patient data from those studies were analyzed, patients with larger increases in BMD had lower fracture rates, irrespective of the drug they received (21). These results were complemented by studies showing that higher total hip T-scores achieved on alendronate, denosumab, or romosozumab were associated with lower risk of nonvertebral fracture in the subsequent year (22,23). These results suggest that treatment-related BMD effects could be adopted as a surrogate for fracture risk reduction in future registration trials (21).

GOAL-DIRECTED THERAPY

The demonstration that on-treatment BMD is predictive of a patient's current risk of fracture, coupled with the recent availability of drugs and sequences of therapy that produce large increases in BMD, raises the possibility of goal-directed therapy where the objective of treatment would be achieving a specific total hip BMD on therapy (24,25). Decisions about an initial therapy and any subsequent therapy would be made based on the probability that the treatment would achieve the BMD target. As expected, drugs and sequences that induce the largest gains in BMD increase the probability of a patient reaching a treatment target (26). If more data supporting this approach are produced, goal-directed therapy may be incorporated into the next iteration of treatment guidelines.

SEQUENTIAL THERAPY

With most osteoporosis drugs, efficacy plateaus or even wanes with long-term therapy, while rare but important adverse events are associated with long-term bisphosphonate therapy. Moreover, the skeletal benefits of all osteoporosis drugs dissipate, at varying rates, upon discontinuation of therapy. Thus, there is no short-term solution to osteoporosis management. Rather, optimal osteoporosis treatment requires long term if not lifelong management and involves the use of different drugs in different sequences or perhaps combinations (27,28). Most studies evaluating the combination of drugs with different mechanisms of action have not shown meaningful benefit. The exception is the combination of denosumab and teriparatide that resulted in modestly larger BMD increases during the first 12 months of therapy than with either drug alone (29). Studies using romosozumab with an antiremodeling drug have not yet been reported.

Sequential therapy includes considering a switch from a bisphosphonate to either denosumab or to an osteoanabolic agent if a patient remains at high fracture risk after 3 to 5 years of therapy because continuing therapy provides no incremental BMD or fracture risk benefit while exposing patients to an increasing risk of atypical femoral fracture. Following denosumab with a potent bisphosphonate for perhaps 2 years, with careful monitoring of markers of bone resorption, is required to at least blunt the rapid loss of BMD and fracture protection. Because the anabolic effects of all osteoanabolic therapies wane with continued administration, their use is generally limited to 12 to 24 months, after which, transition to an antiremodeling drug is required to maintain the skeletal benefits. Importantly, the fracture protection benefit of osteoanabolic therapy persists for at least 2 years after transition to either alendronate or denosumab (14,30,31). (Note that the switch from teriparatide, and probably abaloparatide, to denosumab is not recommended.) The opposite transition, from an antiremodeling drug to an osteoanabolic

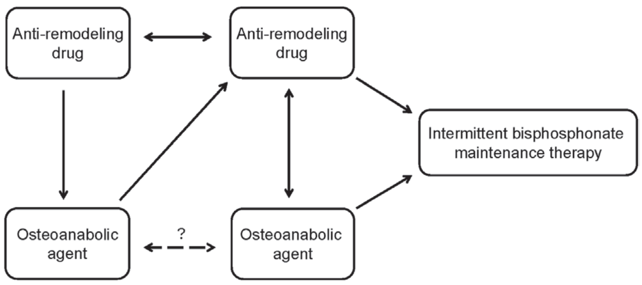

Figure 74.1: Sequence options for the use of drugs with different mechanisms of action.

agent, is associated with smaller BMD gains than observed in treatment-naive patients (32). The sequence of an osteoanabolic agent followed by a potent antiremodeling drug provides the best chance of improving hip BMD, the potential target of therapy (32). Of all the sequences thus far studied, romosozumab for 12 months followed by denosumab induces the largest and fastest increments in bone density (26).

More experience with various sequences over longer intervals of time is needed, including the use of multiple courses of the same or different osteoanabolic drugs and the optimal therapy between those courses (Fig. 74.1). The initial aim of therapy should be to optimize bone mass, structure, and strength with an anabolic agent and then to maintain that improved strength with an antiremodeling drug, perhaps repeating that sequence until the patient reaches a treatment goal and a level of modest fracture risk (24). Upon achieving that objective, a more simple strategy of intermittent bisphosphonate maintenance therapy could be employed to preserve that improved skeletal status.

CURRENT STATUS OF OSTEOPOROSIS CARE

Despite these impressive advances in assessment and management, osteoporosis remains woefully underdiagnosed and undertreated. Too few women are screened or treated, and in those who begin therapy, few remain on treatment beyond 12 months. In the United States, about one-third of women [AU6] aged 65 to 80 have had a DXA exam in the past 3 years, and the rates are even lower in younger and older postmenopausal women (33). The proportion of women treated following a hip fracture declined from a poor 9.8% in 2004 to a pitiful 3.3% in 2014 (34). In more recent data of American adults aged 50 and older who had a fracture between from May 2017 and March 2019 until March 2020, 88.6% remained untreated at any time after the incident fracture, and only 8.6% had BMD testing in the year following the fracture (35). Subsequent fractures occurred in 13.6% with higher rates among the older patients. Among patients followed for at least 12 months, the average duration of treatment with different drugs ranged from 7 to 13 months and persistence varied between 20% and 45%. Age-adjusted hip fracture rates, which had fallen between 1995 and 2008, have plateaued or even increased, attributed, at least in part, to the declining screening and treatment rates (36).

It is apparent that we are missing important opportunities to reduce fracture risk by not recognizing and then treating patients at high fracture risk. Postmenopausal women who have a fracture should be thought of as having had a "bone attack," and all such patients deserve fracture risk assessment. Multiple explanations exist for this poor overall performance including limited knowledge among many physicians, incorrect information possessed by patients, inadequate supply of clinicians experienced in the care of patients with osteoporosis, conflicting or confusing clinical guidelines, and reimbursement policies that stifle the use of drugs other than bisphosphonates. Implementation of health policies that encourage appropriate screening and then treatment of at-risk patients would not only improve the lives of millions of patients but provide substantial cost savings to the overall health systems (2,5).

THOUGHTS FOR THE FUTURE

The osteoporosis community must strive to overcome the inertia or outright reluctance to treat women with postmenopausal osteoporosis. This will not be solved with new drugs, especially in the near future, since there are no new molecules in Phase 2 or 3 clinical development specifically for osteoporosis treatment. While many candidate osteoporosis therapies have been identified in preclinical studies, it will be many years [AU7] before any will come to market. Adopting treatment-related BMD effects as a surrogate endpoint in registration trials for new drugs might spur more active development. Perhaps drugs being developed to prevent, delay or even reverse aging could have an important effect on osteoporosis risk and management (37).

An update FRAX tool that will include other risk factors [AU8] such as the recency of fracture, history of falls and type 2 diabetes is anticipated, based on meta-analyses of more and larger databases, hopefully improving fracture risk prediction (38). The impact of artificial intelligence (AI) on managing osteoporosis is just beginning to be appreciated. It is already being used to interpret skeletal radiographs and bone density tests and to predict fracture risk (39–41). Perhaps, by using genetic and biochemical markers, AI might guide precision therapy, based on probability of salutary responses to different treatments. These and other technical advances will surely enhance our future treatment capabilities.

In the meantime, while we await new developments, we must make optimal use of our current diagnostic and therapeutic tools. There are several strategies and research priorities that our field should consider, including the following:

- Provide accessible, accurate, evidence-based information for patients about the risk factors and consequences of fractures and both the risks and benefits of osteoporosis therapies.
- Support the importance of general measures of good nutrition and exercise for skeletal as well as general health while dispelling the perception that those measures or unproven supplements are adequate treatment for women with osteoporosis.
- Endorse and provide multifaceted fall prevention programs for older adults.
- Encourage risk-based case finding with risk assessment and BMD testing not only for women aged 65 and older but for all postmenopausal women after a fracture or who have risk factors for osteoporosis.
- Collate the competing American guidelines into a single, practical set of recommendations and strategies, based on evidence of best practice when available, to identify and treat the appropriate patients with the optimal sequence(s) of therapy.

- Increase educational opportunities for experienced clinicians about the implementation of these best practice recommendations.
- Motivate and incentivize physicians to specialize in the management of bone health.
- Support the development of secondary fracture prevention programs. Such programs, employed successfully and cost effectively in many parts of the world, would be an obvious first step in closing the large treatment gap. Many of those programs are embedded in orthopedic or specialty medical practices where care of the patients is provided by nurse practitioners or physicians assistants.
- Develop a curriculum and training platform for these advanced practice providers–and physicians–who wish to become proficient in the management of patients after a fracture or at high fracture risk.
- Take advantage of "big data" to conduct more real-world studies comparing efficacy of different drugs and different sequences of therapies.
- Evaluate the long-term cost-effectiveness of various treatment sequences, recognizing that the skeletal benefits of osteoanabolic therapy persist for several years after transition to less expensive antiremodeling drugs.
- Advocate for health policies at both national and local levels that are based on evidence of best outcomes and cost-effectiveness.

Preventing osteoporosis

Tangential to the focus of this section on treating postmenopausal osteoporosis is the possibility and strategy of preventing osteoporosis. During the menopause transition, bone loss is relatively rapid and is associated with significant deterioration in bone microarchitecture and strength (42,43). Women who come to menopause with low bone mass (T-score <–1.0) are at very high risk for developing osteoporosis by age 70 without estrogen or other pharmacologic prevention therapy. Estrogen preparations with or without progestins or bazedoxifene, raloxifene and low-dose bisphosphonates are government approved to prevent postmenopausal osteoporosis. Estrogen therapy and bisphosphonates are effective in maintaining bone density in young postmenopausal women as long as treatment is given (44,45). In women even at low fracture risk, estrogen therapy substantially reduces the risk of vertebral and hip fracture (46). The benefit: risk profile of menopausal hormone therapy is excellent when begun at or soon after menopause in women without important risk factors for breast cancer (47). If estrogen is discontinued, skeletal benefits are quickly lost (48,49). Transitioning to a bisphosphonate for 2 years, followed by intermittent bisphosphonate maintenance therapy, could then maintain bone density and bone structure indefinitely (50). Most guidelines focus on identifying postmenopausal women at high risk of fracture for whom treatment would be indicated. The North American Menopause Society (now The Menopause Society) recommends that therapy to prevent bone loss be considered in women coming to menopause with low bone density (9). Women at high risk of osteoporosis (but not yet at high risk of fracture) can be easily identified at the time of menopause. By not offering therapy to prevent the loss of bone density and structure in early menopause, we are missing an important opportunity to preserve bone health and to optimize outcomes in later life.

SUMMARY

Postmenopausal osteoporosis is a very common disorder, and all clinicians who care for postmenopausal women should be comfortable in assessing and treating those women. We have excellent tools for diagnosis and risk assessment and a wide range of treatment options of drugs with varied and complementary mechanisms of action. Long-term management is required, and optimal therapy entails the use of different drugs in various sequences. The chapters of this section of the *Primer* will provide the reader with valuable information and guidance for the management of women with postmenopausal osteoporosis. No algorithm for treatment is provided for there is no single therapeutic approach that is appropriate for each patient. Treatment is individualized, depending on the patient's risk of fracture, coexisting medical issues, and her perspectives and objectives. Instead of thinking about treating osteoporosis, we should focus on treating patients who have osteoporosis.

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