24 New Frontiers in Osteoporosis Management: Optimizing Sequential and Combination Therapy

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Introduction

The bone microstructure, composition, and volume are maintained by bone remodeling, a cellular activity carried out by bone multicellular units (BMUs). BMUs are focally transient teams of osteoclasts and osteoblasts that respectively resorb a volume of old bone and then deposit an equal volume of new bone at the same location. During young adulthood, bone remodeling is balanced; i.e., an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs [1]. Around midlife, bone formation by the osteoblasts of the basic multicellular units (BMUs) decreases, producing remodeling imbalance. At menopause time, the imbalance worsens with bone remodeling becoming rapid, with increase in the BMUs number, yet less bone is deposited than they resorb, resulting in bone loss, a reduction in bone volume, and consequent microstructural deterioration. This process occurs by each of the many BMUs initiated at the three (intracortical, endocortical, trabecular) components of the endosteal (inner) bone surface [2]. As a result, cortical bones become porous and thin, whereas trabeculae become thin, perforated, and disconnected, causing bone fragility. With advancing age, bone loss from the trabecular compartment lessens because trabeculae with their surfaces disappear (remodeling requires a surface to be initiated upon). Bone loss becomes predominantly cortical as intracortical surface area increases facilitating initiation of unbalanced intracortical remodeling [3, 4]. The microstructural deterioration produces bone fragility out of proportion to the bone loss producing it [5]. Anti-resorptive agents act by reducing the rate of bone remodeling so that fewer BMUs are available to remodel bone; hence, it reduces the fracture risk. However, bone fragility is not abolished by these drugs as the existing microstructural deterioration is not reversed. On the other hand, anabolic agents reduce fracture risk by stimulating new bone formation, which partly restores bone volume and microstructure [6]. This raises a question: Is anti-resorptive therapy the best treatment option for patients at highest risk for future fractures?

The burden of fragility fractures is increasing in absolute terms. One important factor that favors this notion is that patients' management is based mainly on DXA scan results. Patients identified as eligible for treatment are only those whose T-score lies in the osteoporosis range, whereas those whose T-score is not in the osteoporosis range do not receive any treatment. Women with osteopenia have been identified as the source of over 60% of all fragility fractures [7]. This may represent a real challenge. A fracture that occurs in people with low bone mass in

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the setting of minimal trauma – such as a fall from standing height – meets the criteria for the *clinical diagnosis of osteoporosis* and qualifies this particular individual for being at high risk of further fractures. This can be explained by the fact that bone weakness or fragility is related not only to quantitative aspects but also to structural and qualitative aspects that cannot be easily assessed in standard practice. Similarly, another cohort of patients who are at the highest risk of fracture are those with a silent vertebral fracture. Unfortunately, vertebral fractures are always missed as they are often asymptomatic and are reported as coincident findings in the X-ray report. Therefore, targeted screening and notification using spine imaging is, probably, as important as BMD testing.

As a chronic degenerative disease, osteoporosis requires long-term management. However, none of the currently available anti-osteoporotic agents has proven efficacy and safety beyond 10 years of treatment. Furthermore, long-term treatment with the most potent anti-resorptives, namely, bisphosphonates and denosumab, has been associated with rare, but severe adverse events, such as osteonecrosis of the jaw (ONJ) [8, 9] and atypical femoral fractures (AFF) [10, 11]. These adverse events appear to be time-related, leading expert panels of scientific societies and the US Food and Drug Administration (FDA) to recommend reevaluation of continuing therapy beyond 3 and 5 years on an individual basis [12, 13]. On the other hand, osteoanabolic agents can be administered only for a relatively short period, ranging from 1 year for romosozumab to 2 years for parathryroid hormone therapy. Therefore, transitioning from one therapy to another is quite common in clinical routine. Keeping in view the above facts, the real challenge to treat osteoporosis on a long-term basis is to set the optimal treatment strategy for each individual patient, e.g., how to use the available osteoanabolic and anti-resorptive agents, sequentially or in combination, in the most effective and safe way [14].

This chapter will review the unmet needs for prevention and management of bone fragility. It will then discuss the existing evidence regarding sequential and combination treatment for osteoporosis, classifying data under four studied scenarios: anti-resorptives after osteoanabolics, osteoanabolics after anti-resorptives, anti-resorptives after anti-resorptives, and finally combination of both anti-resorptive and anabolic therapy agents.

Unmet Needs in the Management of Bone Fragility

The word "osteoporosis" is often used synonymously with bone fragility, but women with osteopenia are not free of the risk of fracture [7, 15]. Indeed, most women and men sustaining fragility fractures have osteopenia and even some have "normal" BMD [16]. Women with osteopenia at risk for fracture can be identified by measuring microstructural deterioration [17, 18] but high-resolution imaging methods are not yet widely available. The use of clinical risk factor assessment tools such as FRAX has met with variable success [19, 20]. Challenges also arise in the uptake and adherence to therapy, in part, because of concerns regarding the serious but uncommon long-term adverse effects of therapy [21, 22].

Anti-resorptive agents are the first-line and most commonly used treatments for prevention and treatment of bone fragility [23]. Apart from denosumab, which virtually abolishes remodeling, most anti-resorptives slow unbalanced remodeling, so microstructural deterioration continues to occur albeit more slowly [24]. This lower rate of remodeling reduces fracture risk compared to untreated women in whom rapid remodeling continues to deteriorate the skeleton. This is a relative risk reduction. In absolute terms, fracture risk does not decrease during anti-resorptive therapy because microstructural deterioration present is not reversed and the slow continued unsuppressed and unbalanced remodeling continues to deteriorate bone. This, in part, may explain why fracture risk reduction with anti-resorptives is modest. Teriparatide increases bone matrix volume predominantly through remodeling-based bone formation [25]. It is likely that the anabolic effect of abaloparatide,

which acts via the same receptor as teriparatide, is also remodeling based like teriparatide, although rigorous assessment of its mechanism of action has not been undertaken [26]. Both reduce the risk of vertebral and non-vertebral fractures [27, 28] but no adequately designed trials have been done to determine whether hip fracture risk is reduced (Fig. 24.1).

Romosozumab has been recently licensed for the management of osteoporosis and fragility fracture prevention. Romosozumab is a dual acting agent that increases bone formation and also reduces bone resorption. It is administered once monthly for 1 year and produces marked increases in spine and hip BMD, almost certainly as a result of an early increase in bone modeling. The latest guidelines from the Endocrine Society, USA (2020), has suggested Romosozumab be considered as a first-line therapy in patients with multiple vertebral fractures or hip fracture and BMD in the osteoporotic range [29], in addition to being considered for individuals who have failed anti-resorptive treatments.

Two large phase 3 trials of romosozumab were conducted to test its efficacy in vertebral and non-vertebral fracture risk reduction [30–32]. Neither was powered to show an effect on hip fracture risk. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, 7180 postmenopausal women were treated with monthly injections of romosozumab or placebo. An analysis that compared romosozumab with placebo using a direct approach [3, 30] rather than a network approach [31] showed a 73% reduction in the risk of vertebral fractures (risk ratio [RR], 0.27; 95% confidence interval [CI], 0.16–0.47) but no significant effect on the risk of hip or nonvertebral fractures. Romosozumab and

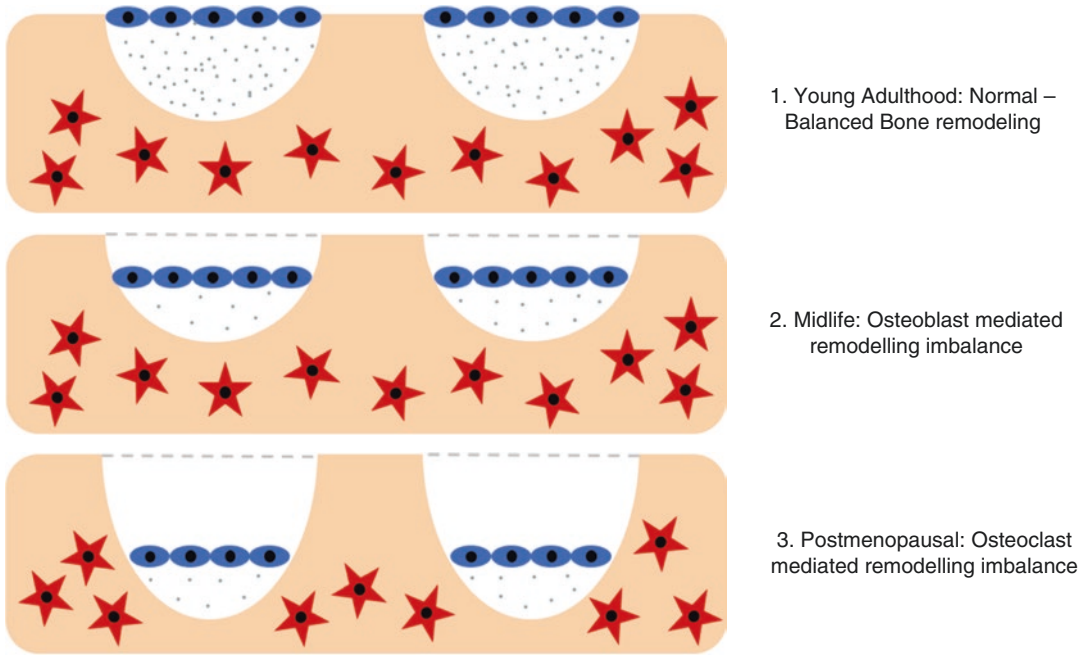

Fig. 24.1 Structural changes in bone with osteoporosis medications. The anti-resorptive medications (bisphosphonates and denosumab) and anabolic medications (teriparatide and likely abaloparatide) produce very different structural changes in bone. Although both classes increase trabecular bone, their effects on cortical bone are different. Bisphosphonates and denosumab do not expand periosteal bone but do decrease the endosteal diameter by an increase in endosteal bone volume. Anti-resorptives also reduce cortical porosity. Anabolic agents lead to an increase in periosteal bone with a simultaneous increase in endosteal bone resorption resulting in a bone without a large change in cortical thickness. At the same time, anabolic agents increase cortical porosity. Despite the increase in cortical porosity, the larger bone has increased strength. NC no change. (Quoted under open access scheme from Choksi et al. [212])

placebo treatments were followed by 12 months with the anti-resorptive agent denosumab to maintain/increase the gains in BMD. At 24 months, those treated with romosozumab followed by denosumab demonstrated a 75% lower risk for new vertebral fractures (RR, 0.25; 95% CI, 0.16–0.40). In the follow-up extension to the FRAME study, which investigated an additional year of denosumab treatment, similar significant reductions in relative risk and increases in spine and hip BMD with the initial therapy with romosozumab were sustained at 36 months [33].

In the trial, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) [32] (number of patients: 4093), 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 2 years of treatment with alendronate in postmenopausal women at high risk of fracture [5, 32]. The ARCH trial showed that romosozumab/alendronate as compared with alendronate/alendronate resulted in a 48% reduction in the risk of vertebral fractures at 24 months (RR, 0.52; 95% CI, 0.40–0.66), a 38% reduction in the risk of hip fractures at 24 months (hazard ratio [HR], 0.62; 95% CI, 0.42–0.92), and a 19% reduction in the risk of nonvertebral fractures at 24 months (HR, 0.81; 95% CI, 0.66–0.99) [32].

Clinical Vs Radiologic Osteoporosis

Osteoporotic fractures occur spontaneously or as a result of minimal trauma from day-to-day activities [34]. In 90% of all hip fractures, the leading mechanism of trauma is a simple fall [35–38], indicating bone fragility in these patients. Early detection of an impaired quality of bone is crucial in the prevention of osteoporotic fractures. Previous studies suggest broad under-diagnosis of osteoporosis [6, 39], and the opportunity to start bone modulating therapies before the occurrence of an osteoporotic fracture is missed in up to 84% of osteoporotic fracture cases [40].

The assessment of bone mineral density (BMD) as a surrogate marker of bone strength using non-invasive methods like dual-energy X-ray absorptiometry (DXA) is widely regarded as the gold-standard for diagnostic screening and as a guide prior to therapeutic decisions [41]. However, BMD accounts for only 60% of the variation in bone fragility [42], because it is unable to depict differences in bone material composition and structural design. Both characteristics influence bone strength to a large extent [43]. On the other hand, the occurrence of low trauma fracture would reflect the bone strength status and has been considered as a marker of clinical osteoporosis.

In vivo, bone experiences different loads from different directions and in different intensity and frequency over time. Bone has two main structural responses to changing loading patterns: altering structural density and increasing the degree of structural orientation along the acting force vectors, i.e., anisotropy [43–45].

These adaptive responses would not be possible without the existence of continuous bone remodeling. In bone remodeling, bone tissue is removed by osteoclastic resorption and new bone is formed by osteoblasts. In the early life span after skeletal maturity the amounts of bone removed and replaced with each cycle of bone remodeling are usually equal to each other, leaving the total volume of bone unchanged. With aging and in the setting of osteoporosis, the balance of bone resorption and formation becomes negative. The bone loss in aged and osteoporotic bone is a consequence of imbalanced and excessive bone remodeling [46]. The microstructural changes caused by this remodeling imbalance compromises bone strength disproportionately to the net bone loss leading to this deterioration [5, 47].

As bone remodeling occurs on osseous surfaces, osteoporotic bone loss is a function of surface available for bone remodeling. In individuals less than 65 years of age, the largest surface available for bone remodeling is the trabecular bone. In this population, trabecular bone – due to its lesser density when compared to cortical bone – provides only about 20% of the skeletal bone mass but it is responsible for most of the turnover [43, 48, 49]. Thus, the bone loss in early osteoporosis is mainly a trabecular bone loss.

With increasing age, the cortical bone becomes more and more porous and, therefore, its endocortical surface increases. As a consequence, the largest loss of absolute bone mass due to osteoporosis occurs in cortical bone by intracortical rather than endocortical or trabecular remodeling [46, 50, 51].

Such changes have important clinical implications. Women who attain high peak bone mass, as they pass to the postmenopausal period and start to lose bone, though they sustain microstructural deterioration, their BMD measurement decreases only to the osteopenia range or even remains in the low normal range. This may give a false impression that their fracture risk is low; hence, no treatment is suggested [52]. This may sound reasonable, supported by the finding that the fracture risk in osteopenic women is lower than that in those with osteoporosis; however, women with osteopenia are not immune from fractures. In fact, 60–70% of those women who sustain low trauma fractures have osteopenia (or even normal bone mineral density) [53]. This led to the conclusion that an important reason of bone fragility in women with osteopenia or even normal bone mineral density is microstructural deterioration [54, 55]. Another clinical implication is the finding that the transition from early trabecular to later cortical bone loss is consistent with the epidemiological data on osteoporotic fractures. Vertebral compression fractures, being "trabecular fractures," are more common in individuals aged less than 65 years. With increasing cortical bone loss after the age of 65 years, hip fractures, being rather "cortical fractures," become more frequent [56].

Pathophysiology: What Is and Is Not Achievable Using Different Osteoporosis Therapies?

All factors influencing bone's structural strength express their effects through a final common cellular machinery of bone remodeling. Bone remodeling, a sequential process of bone resorption and formation, occurs throughout life renewing the composition of the mineralized matrix volume [57]. During young adulthood, bone remodeling is balanced – an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs [1]. Around midlife, bone formation by the osteoblasts of the basic multicellular units (BMUs) decreases, producing remodeling imbalance [58]. In addition, as a consequence of the estrogen deficiency accompanying menopause, remodeling imbalance worsens and the rate of remodeling increases—less bone is deposited than was resorbed by each of the many BMUs initiated upon the three (intracortical, endocortical, trabecular) components of the endosteal (inner) bone surface [59] (Fig. 24.2).

It is useful to consider the mechanisms of bone loss in terms of the sequential changes at the single cross-sectional location as it travels perpendicular to the plane section. The resorption of bone volume and its replacement by osteoid tissue, followed by primary then secondary mineralization of the osteoid tissue, are not instantaneous events [60–62]. East step had a specific time course, such that the resorptive phase induced by the osteoclasts takes about 3 weeks; this is followed by a reversal phase, 1–3 weeks, which represents the time taken by the osteoblasts to differentiate and proliferate. The next step is the bone formation phase which takes up to 3 months [63]. During this phase, the osteoid tissue is deposited first and then endures fast primary mineralization within days of deposition to become bone. The last step of secondary mineralization takes 12–24 months to complete which represent the slower phase of bone mineralization. This phase is characterized by the enlargement of the calcium hydroxyapatite crystals which were deposited during the primary mineralization phase, with water displacement. This process gives the bone its resistance to bending, which is a vital character of bones that enables them to act as a lever [64].

The sequence of these four phases creates a state of normal delay, producing a transient state of focal deficit in the bone matrix and its mineral content [60]. This temporary state is reversible fully without any consequent permanent microstructural decline. In young adults, at any specific

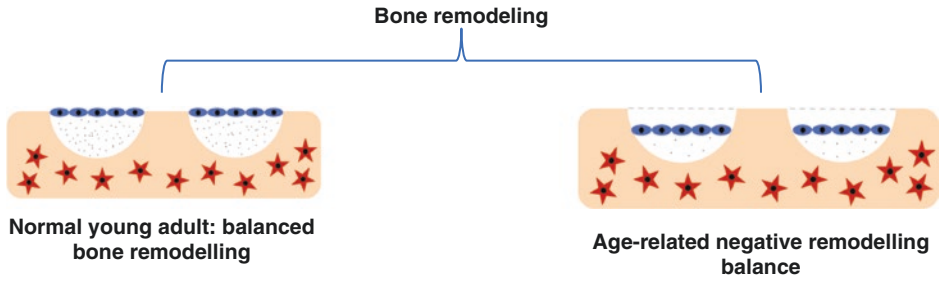

Fig. 24.2 Reversible and irreversible deficits in bone volume is based on the cellular mechanisms of remodeling: (1) Normal-depth resorption cavity, completely refilled with new mineralized bone (mineralization occurs in 2 phases: primary (dotted) and secondary (yellow). In your adulthood, the deficit is reversible as the cavities are completely refilled with matrix, which undergoes slow secondary mineralization. (2) Resorption cavity of normal depth that is incompletely refilled by a subnormal amount of new bone. The lost bone is represented by the clear area between the original bone surface (dotted line) and the new surface location. Remodeling imbalance occurs when the excavated cavities are not being filled and the osteoid tissue gets mineralized, thereby causing bone loss and microstructural deterioration of the reduced bone volume. (3) Exacerbation of the irreversible deficit by menopause related estrogen deficiency, which increases the life span of the osteoclasts (causing resorption cavity of excessive depth) and reduces the lifespan of the osteoblasts (leading to deposition of less bone in the larger cavity), which further aggravates remodeling imbalance and focal microstructural deterioration

time, there are several cavities excavated by BMU at different stages of their remodeling cycle. Considering that in average there are 10% of bone volume undergoing remodeling per year, there is a state of reversible deficit mainly in the mineral content (bearing in mind that secondary mineralization takes 1–2 years to complete). Consequently, the new osteons of cortical bones and hemiosteons of trabecular bones are completely reconstructed months before they become fully mineralized [60].

At midlife (45–50 years old) in both sexes, the process of aging is associated with an increase in the rate of bone remodeling in both cancellous and cortical bone. The remodeling that occur around mid-life is characterized by reduction in the volume of the resorbed bone by each BMU, associated with an even bigger reduction in the volume of the bone deposited by the BMU at the same location, resulting in a negative remodeling balance. Morphologically, this remodeling imbalance leads to irreversible bone loss, deterioration of the bone microstructure, and consequently increased bone fragility. This process is replicated each time bone is remodeled trying to repair matrix damage. As the deposited bone is less than reabsorbed one, this leads to the development of permanent microstructural changes [65–67], namely, increased cortical porosity, cortical thinning, complete loss of trabeculae connections, and disconnection of the trabeculae with each other and the cortex [64].

By menopause, with associated estrogen deficiency (which lead to increase in the osteoclast life span and concurrent reduction in the osteoblast life span), there is an exacerbation of this irreversible bone loss state as a result of deposition of less bone in the larger cavity. This aggravates the remodeling imbalance, leading to excavation of larger cavities and focal microstructural decline [68].

Therapeutic Implications

Anti-resorptive Therapy

Bisphosphonates Bisphosphonates (alendronate, risedronate and zoledronic acid) are currently first-line treatment and the most common anti-resorptive therapy used. The anti-resorptive efficacy of bisphosphonates depend on inhibition of farnesyl pyrophosphate (FPP) synthase, required for osteoclast resorptive function, as well as their affinity for mineral which influences uptake, distribution, and retention in the

bone [69–71]. Bisphosphonates slow but do not abolish remodeling. Consequently, these drugs reduce the number of BMUs turning over in the skeleton [23, 72, 73]. The bisphosphonates, similar to all other anti-resorptive agents, do not reduce the irreversible component of the deficit in the matrix and its mineral content (which developed as a results of the remodeling imbalance). However, the acute reduction in the number of resorption cavities excavated slows the decline in bone volume [23, 72]. Also, the fewer resorption cavities result in fewer stress concentrators [74]. Thirdly, most of the resorption cavities are partly refilled, reducing focal stress by distributing the load more widely. Lastly, the newly deposited matrix undergoes rapid primary mineralization, while matrix deposited several months earlier (before starting the bisphosphonate therapy) undergoes slower state of secondary mineralization [75].

However, high affinity binding agents, like alendronate, have a reduced ability to penetrate and distribute widely in deeper cortical matrix (bisphosphonates bind mainly to the superficial matrix beneath the endosteal surface and do not distribute into deeper volumes of cortical bone as widely as they distribute in the thin trabecular plates), so that when osteoclasts remodel deeper layers of the cortical bone they encounter matrix free of bisphosphonates and continue to resorb bone. Therefore, unbalanced remodeling continues in deeper cortical bone despite bisphosphonate therapy.

The net result of bisphosphonate therapy is an increase in the mineral content of diminishing total bone volume, features that might increase bone fragility and the risk of fracture [76].

Denosumab Remodeling suppression with denosumab is greater than that achieved with any other anti-resorptive agent [77]. Denosumab is widely distributed throughout both the cortical and trabecular bone, thus more completely suppression of the new BMUs in both cortical and trabecular bone (in comparison to bisphosphonates) [23, 72, 73]. Similar to bisphosphonates, the mineral content of the total bone matrix volume increases, but the total bone matrix volume might not be less, or might decrease less, than that achieved during bisphosphonate therapy as little remodeling takes place [73].

Changes in BMD During the first 6–12 months of anti-resorptive therapy, there is an early rapid increase in the BMD. This increase is not attributed to increase or restoration in the bone mass or bone volume (i.e., the increase does not represent an anabolic effect). In contrast to anabolic therapy which adds bone upon the periosteal and endosteal surfaces, anti-resorptive medications slow the removal of bone. This is achieved though the reduction of the number of excavation cavities, and primary mineralization of the already excavated cavities shortly developed before the initiation of bisphosphonate therapy. As far as the cavities developed several months before treatment, secondary mineralization of the matrix occurs.

Beyond the first year of anti-resorptive therapy, the slow continued increase in BMD is mostly a result of secondary mineralization, the slowest component of the formation phase of bone remodeling cycle and thereby, the last to reach completion [60–62]. However, in patients receiving bisphosphonate medication, the increase in the matrix mineral density and BMD cease to occur, as secondary mineralization is complete after 3–5 years of bisphosphonate therapy [23, 72]. On the other hand, denosumab treatment is associated with a continued increase in BMD during 8–10 years of therapy [78].

Selective Estrogen Receptor Modulators (SERM) The stability of BMD or slow continued increase in BMD during 3–10 years reported with powerful remodeling suppressors (e.g., bisphosphonates and denosumab) is not observed with weak remodeling suppressants such as calcium or SERM, which slow the remodeling rate by only 20–30% of the pre-treatment rate [79, 80]. Therefore, the bone continues to be remodeled to a greater extent than with bisphosphonates or denosumab.

Similar to bisphosphonates as well as denosumab, at the onset of therapy, SERM inhibit remodeling with a result of incomplete refill of the excavated cavities which occur in the first 6–12 months of treatment, but in contrast, during the same period (6–12 months of therapy), most (70–80%) of the pre-treatment BMU continue to remodel bone and thus only a modest early net increase in BMD of a fewer percentage points occurs [6].

Beyond a 12 month of therapy with these weaker anti-resorptive medications, the remodeling rate stabilizes at 70–80% of the pre-treatment rate. The 20–30% fewer cavities excavated during the first 6–12 months incompletely refill, but similar number of BMUs, or even more, excavate new cavities, producing a net decrease in BMD. The decrease in BMD is detectable because there is little, if any, concurrent increase in matrix mineral density obscuring the decrease in bone volume (as occurs with powerful remodeling agents). Most of the matrix is still rapidly renewed and replaced with young bone. Continued unbalanced remodeling decreases total bone matrix volume and produces microstructure deterioration, features that probably account for the lack of evidence of non-vertebral or hip fracture risk reduction reported with these weaker drugs [81, 82].

Anabolic Therapy

Reconstruction of the bones ("cure" of the bone thinning and fragility) requires anabolic therapy. Anabolic skeletal effects can be achieved through changes in bone remodeling, bone modeling, or a combination of both. Two anabolic medications are available for clinical use in patients with severe bone loss and microstructural declining who are expected to benefit from restoration of the lost bone: Teriparatide (PTH 1–34) and abaloparatide. Teriparatide is formed of the first 34-amino acids of the parathyroid hormone (PTH) [83], the hormone product of the parathyroid hormone. Abaloparatide is formed of 34-amino acids peptide; the first 21-amino acids are identical to those of the parathyroid hormone–related protein (PTHrP), with substitutions up to amino acid 36. PTHrP acts as an autocrine and paracrine regulator in many tissues [84–87]. In bone PTHrP is produced by the cells of the osteoblast lineage.

Circulating PTH and PTHrP use a common G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R), to activate target cells. The biological activity achieved by both PTH and PTHrP is included within the amino-terminal 36-residues [84]. Both teriparatide and abaloparatide are administered by daily subcut injections as the pharmacokinetics require a brief peak circulating level of PTH activity returning to baseline within 3 h to achieve the anabolic effect [85].

In iliac crest bone, intermittent administration of teriparatide stimulates modeling-based bone formation on cancellous, endosteal, and periosteal surfaces, an effect that is most evident in the early stages of treatment [88]. However, the majority of the anabolic effect in cancellous bone is achieved through remodeling with overfilling of remodeling units (Fig. 24.2). In cortical bone, the effects vary according to site; increased total bone area, increased cortical porosity, and the formation of hypomineralized new bone can occur in the early stages of treatment, which results in little change or a decrease in BMD at sites such as the hip and radius [89].

However, increased bone strength has been reported with longer-term treatment in the hip, and cortical thickness mapping has shown localized increases at sites that are subjected to mechanical loading [90–93]. The effects of abaloparatide have not been reported in full detail; however, in postmenopausal women treated for 12–18 months with abaloparatide, bone remodeling indices in cancellous iliac crest bone were generally similar to those in a placebo group, and to those treated with teriparatide [26, 94]. Table 24.1 shows the main characteristics of both teriparatide and abalopratide.

Romosozumab

Sclerostin is an osteocyte-derived inhibitor of bone formation [114]. The anabolic effects of sclerostin inhibition are mediated through an early and transient increase in bone formation

Table 24.1 The main characteristics of both teriparatide and abaloparatide agents

	Teriparatide	Abaloparatide
Structure	The first 34-amino acids of the parathyroid hormone.	34-amino acid peptide, of which the first 21-amino acids are identical with those of the parathyroid hormone–related protein.
Function	Hormone released by parathyroid gland.	Autocrine and paracrine regulator in many tissues. In the bone it is produced by cells of the osteoblast lineage.
Receptor to activate target cells	G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R).	G protein-coupled receptor (GPCR), PTH1 receptor (PTH1R).
Anabolic effect	70% remodeling-dependent (mediated through PTH1R) 30% modeling-dependent (increased modelling-based bone formation upon the periosteal surface; increased remodeling as well as modeling-based bone formation upon the endocortical and trabecular surfaces).	Mainly remodeling-based rather than modeling-based (not yet fully studied, remains an open question). There are claims of an anabolic effect with relatively less bone resorptive effect of abaloparatide, based on the measurements of biomarkers [102–104].
Effects on bone cells	1. Early phase: osteocyts and osteoblast precursors: promote RANKL production which enhances osteoclast formation and bone resorption. 2. Second phase: production of local factors from osteoclasts and resorbed matrix which initiate bone formation by BMUs [95–98].	Physiological regulator of bone formation by promoting the differentiation of committed osteoblast precursors and by inhibiting apoptosis of mature osteoblasts and osteocytes [99–101].
Impact on BMU	Act on existing BMUs in different stages: Reversal phase: promote osteoblast lineage differentiation into mature osteoid producing cells. Formation phase: inhibit osteoblast apoptosis which lead to increased matrix production [84, 96].	Exact effect on BMU and bone remodeling has been fully reported. In postmenopausal women treated for 12–18 months with abaloparatide, bone remodeling indices in cancellous iliac crease bone were generally similar to those treated with teriparatide [26, 94].
Bone morphology	Early phase: the initial increased new BMU formation leads to increases in the excavated cavities numbers (mainly upon intracortical canal, endocortical, and trabecular surfaces [95, 98]. This leads to increased porosity mainly in the cortex adjacent to the medullary canal (unlikely to increase bone fragility at this location [98]). Formation phase: deposition of incompletely mineralized bone leads to increase in bone matrix per unit volume. Crosslinks: the remodeling-based bone formation replaces matrix collagen crosslink by advanced glycation end products with new and less glycosylated bone [26, 105]	There are claims of an anabolic effect with relatively less bone resorptive effect of abaloparatide, based on measurements of biomarkers [102–104].
Time of onset	The anabolic effect of teriparatide is rapid and demonstrable within 3 months.	Not reported. There were reports showing that abaloparatide have sequences susceptible to proteolysis [108]. Inactivation after subcut injection might reduce the amount of agonist presented to target cells, making abaloparatide weaker in vivo agonists of PTH1R than teriparatide [109–113]
Stopping therapy	Stopping teriparatide therapy is consistently followed by bone loss, therefore, it is recommended to administer anti-resorptive therapy at the time of stopping teriparatide therapy [106, 107].	

combined with a sustained decrease in bone resorption. In iliac crest biopsy samples obtained from postmenopausal women in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) [115], large increases in bone formation were seen in cancellous and endocortical bone after 2 months of treatment with romosozumab (a monoclonal antibody that binds and inhibits sclerostin), although the effect was no longer evident after 12 months of treatment. The eroded surface was significantly reduced at both timepoints, and trabecular bone volume, microarchitecture, and cortical thickness were significantly improved at 12 months.

Modeling-based periosteal and endocortical bone formation thickens the cortex and increases its total cross-sectional area. Modeling-based bone formation lead to thickening of the trabeculae and might improve connections between trabeculae. Whether modeling occurs upon intracortical surfaces is not clear [6]. Thus, the anabolic effect of romosozumab shows that it produces an absolute increase in the total mineralized matrix volume which increases BMD by modifying bone structure [95–98].

As with teriparatide, anti-sclerostin therapy needs to be followed by anti-resorptive agents [6].

Does the Sequence Matter?

The availability of different osteoporosis therapy options, with two main different mechanisms of action, whether anabolic or potent raised the question which treatment modality is the best for the patient and which medication to start treatment with. Both anabolic and anti-resorptive agents (bisphosphonates, denosumab) have been shown to improve bone mineral density (BMD) and reduce the risk of fracture in patients who have not been on prior osteoporosis treatments [116–122]. One clue came from studies which revealed that effects of most osteoporosis medications differ in patients who have already been pre-treated with other potent osteoporosis medications [123–128]. Studies on patients treated with de novo parathyroid hormone therapy (PTH), namely, teriparatide, revealed that BMD responses to initial PTH followed by potent anti-resorptive therapy are substantial in both spine and hip sites as a result of the effects of both components of the treatment sequence. In contrast, several studies have indicated that hip BMD responses to PTH treatment are lower in patients who have already been pre-treated with potent anti-resorptive therapies and consistently decline transiently for the first year or even longer [129–133]. Although there are no fracture endpoint trials in these anti-resorptive pre-treated patients, the substantial differences in BMD outcome, particularly for the hip region, suggest that PTH effects against fracture could also differ in these pre-treated patients. More than 50% of PTH prescriptions are written for this group of patients, so these observations have important clinical significance [134–136].

Further insight was gained from the studies carried out using the newly approved anabolic medication romosozumab. In the trial, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) (n = 4093), 1 year of treatment with romosozumab followed by 1 year of alendronate was compared with 2 years of treatment with alendronate in postmenopausal women at high risk of fracture [32]. The ARCH trial showed that romosozumab/alendronate as compared with alendronate/alendronate resulted in a 48% reduction in the risk of vertebral fractures at 24 months (RR, 0.52; 95% CI, 0.40–0.66), a 38% reduction in the risk of hip fractures at 24 months (hazard ratio [HR], 0.62; 95% CI, 0.42–0.92), and a 19% reduction in the risk of nonvertebral fractures at 24 months (HR, 0.81; 95% CI, 0.66–0.99).

A second clue came from the variation of response to therapy according to the site. Studies revealed that the effects of treatment sequence at the hip are more dramatic than those found for the spine. In the spine, the effects of PTH therapy after bisphosphonates and denosumab remain positive, although slightly blunted [129–133]. Furthermore, even after transition from denosumab to PTH, the resultant spine BMD level was the same 2 years after the transition as it was when the sequence began with PTH followed by denosumab [133]. The findings are very different

for the hip region. In treatment-naïve postmenopausal women, for over 19–24 months with teriparatide therapy, resulted in an average gain of about 3% in the total hip and neck of the femur [133, 134]. After teriparatide, transition to a bisphosphonate led to further increase of about 2% in both sites (total hip and femoral neck) after 1 year [137, 138]. After transition from teriparatide to sequential denosumab, BMD increments in the total hip and femoral neck FN are even higher (about 6% in both sites after 1 year of denosumab) [133].

When individuals established on potent antiresorptive therapies are switched to parathyroid hormone therapy, changes in the hip BMD are below baseline for the first 12 months, remaining unchanged from baseline at 18 months and slightly above baseline at 24 months [23, 25–27, 29, 129–131]. The findings differ somewhat after switching from bisphosphonates compared to switching from denosumab. At 18 months, hip BMD is slightly above baseline after switching from bisphosphonates but still below baseline after switching from denosumab. Furthermore, after 24 months of parathyroid hormone therapy, hip BMD is increased by 2–3% after a switch from bisphosphonates but still below baseline after a switch from denosumab [133, 139].

The impact on BMD of a 48-month treatment sequence was studied formally by Leder and colleagues [133]. This study allows direct comparison of a 4-year sequence of teriparatide for 2 years, followed by denosumab for 2 years, compared with the opposite sequence, denosumab for 2 years followed by PTH for 2 years. Over 4 years, in the group that transitioned from teriparatide therapy to denosumab, mean total hip and femoral neck BMD increased 6.6% and 8.3%, respectively. In contrast, in those who switched from denosumab to teriparatide, BMD at both the total hip and femoral neck declined precipitously for the entire first year and levels were still below the end of denosumab treatment baseline for the total hip and just above that baseline for the neck of the femur. The entire 48-month sequence when denosumab is administered first, followed by PTH, resulted in mean total hip and neck of the femur increments of 2.8% and 4.9% (approximately 50% lower hip BMD gains compared with the sequence of teriparatide followed by denosumab, all significantly different versus the former sequence). Furthermore, after transition from 24 months of denosumab to 24 months of teriparatide, progressive bone loss at the radius was also found, in contrast to a slight increase in radius BMD when teriparatide was given followed by denosumab.

Optimizing Osteoporosis Therapy: Combination and Sequential Therapies

As osteoporosis therapy options have expanded, and clinical guidelines have begun to embrace the concept of limited treatment courses and "drug holidays," the choices that physicians must make when initiating, electing to continue, or switching therapies have become more complex. Combining or sequencing treatments with anabolic and resorptive agents have been studied for some time, in an effort to achieve synergism by capitalizing on distinct modes of action of different agents. Different scenarios have been suggested for such form of management. These include the following.

Sequential Therapy

Anti-resorptives After Anabolic Agents for the Treatment of Osteoporosis

When teriparatide therapy is commenced and maintained, biomarkers (both urine as well as serum) of bone remodeling return to their pretreatment baseline measures before the end of the 24-month course while BMD continues to increase over the entire period of management. This apparent discrepancy may be clarified by histomorphometric analysis which revealed the ability of teriparatide to continue stimulating modeling-based bone formation even while remodeling rates revert to baseline [140]. However, when teriparatide therapy is stopped, BMD decreases quickly (though faster in postmenopausal women compared to eugonadal

men) [141]. However, while early study suggested that some antifracture efficacy may be maintained for up to 18 months after the drug has been stopped [142], it is likely that most of the teriparatide beneficial effects do eventually disappear.

Numerous studies have investigated strategies to maintain teriparatide-induced gains in bone mass after the drug is discontinued. Some studies even showed that the teriparatide-induced BMD gains are maintained or even further increased with sequential anti-resorptive treatment [137, 143]. In a 30-month observational follow-up study which included 1262 patients after stopping their teriparatide therapy, total hip and femoral neck BMD returned to baseline among patients receiving no further treatment, while in the 60% of women who started another anti-resorptive therapy, mainly bisphosphonates, BMD remained stable or was further increased [138].

The EUROFORS study documented the stabilizing and/or beneficial effect of a sequential anti-resorptive agent. In this study, postmenopausal women with severe osteoporosis, treated with teriparatide for 1 year, were randomized to raloxifene, no treatment, or continue taking teriparatide; raloxifene prevented bone loss, as measured by BMD, at the lumbar spine in contrast to those patients who did not receive active treatment, while inducing further increases in the total hip BMD [144]. Furthermore, the risk of new vertebral fractures was reduced by 41% among patients who started anti-resoprtives within 6 months after stopping teriparatide treatment [142].

In the DATA-Switch study, 2 years of teriparatide therapy followed by 2 years of denosumab resulted in further increases in the BMD (100). Results of the study showed that when denosumab is given for 2 years after 2 years of teriparatide, there was an additional increase in the spine BMD by 9.4% (18.3% total 4-year increase) and increased total hip BMD an additional 4.8% (6.6% total 4-year increase), gains that appear to be significantly greater than what can be achieved with bisphosphonates therapy after teriparatide [133, 145]. Moreover, denosumab was also able to further increase BMD in patients who previously received 2 years of combined teriparatide/denosumab therapy [133].

In other publications of the abaloparatide trial by Bone et al. [146], alendronate was administered after abaloparatide (given for 18 months), which maintained the fracture risk reduction relative to placebo. Unfortunately, the design of this study does not address the question of whether stopping abaloparatide produces loss of benefits as found with teriparatide, which requires an arm with abaloparatide given placebo. However, the likelihood is that stopping abaloparatide will result in loss of benefits.

The extension of FRAME study investigated the efficacy of 1-year treatment with romosozumab followed by 2 years of denosumab [33]. In specific, BMD increased further after switching romosozumab to denosumab; at the end of the 36-month period, the subjects who received romosozumab followed by denosumab achieved significantly higher BMD increases from baseline compared to the placebo-to- denosumab group (LS: 10.6; TH: 5.2%; FN: 4.8%) [33].

Additionally, although all subjects received active treatment during the last 2 years of the study, patients who received romosozumab during the first year exhibited significantly higher fracture risk reductions compared with those who received placebo (66%, 27%, and 21% for vertebral, clinical, and nonvertebral fractures, respectively). In contrast, in the extension of the ARCH study, postmenopausal women transitioning to ALN after 1 year of romosozumab maintained the BMD gains at lumbar spine, total hip, and femoral neck BMD, which were initially achieved with romosozumab without further increases [32]. However, over a total period of 24 months of treatment with romosozumab followed by alendronate resulted in a higher fracture risk reduction of 48% for vertebral fractures, 27% for clinical fractures, 19% for non-vertebral fractures, and 38% for TH fractures compared with alendronate alone [32].

Anabolics After Anti-resorptive Agents for the Treatment of Osteoporosis

Several studies reported on using anabolic agents after anti-resorptive therapy. The commonest

focused on the bisphosphonates to teriparatide sequence. On the other hand, limited data are available for the sequence of raloxifene or denosumab to teriparatide or other sequences. So far, there are not studies available, to the best of our knowledge, regarding the sequence of anti-resorptive abaloparatide therapy. The assessment of biomarkers in the bisphosphonates to teriparatide sequence revealed that both bone formation and resorption markers increase consistently after switching from anti-resorptives to teriparatide.

As far changes in the BMD, after switching from bisphosphonates to teriparatide, an increase in the lumbar spine BMD has been observed in all studies. Overall, the mean increase in BMD was in the range of 4.1–10.2% after 12–24 months on teriparatide. Interestingly, on switching from denosumab to teriparatide, there was an initial transient decrease in the lumbar spine BMD, with quick recovery and final increase observed [133]. The increase in the lumbar spine BMD has been reported to be higher after switching to teriparatide than continuing the same anti-resorptive treatment [147]. However, the increases in BMD at both the lumbar spine and total hip were observed to be lower than those achieved when teriparatide is administered in osteoporosis therapy naïve patients [148] (although similar increases have been reported in another everyday practice study including a small number of patients) [149]. Notably, when teriparatide was administered in patients with poor response to previous anti-resorptive treatment, a similar increase in BMD was observed compared to those patients who showed sufficient response to previous treatment [27]. Furthermore, higher increase in BMD was observed when teriparatide was administered following raloxifene in comparison to alendronate [150, 151]. Limited data from head-to-head comparative studies with bisphosphonates showed a superior lumbar spine BMD response to teriparatide when previously treated with etidronate over risedronate and alendronate [129], or risedronate over alendronate [135].

On the contrary, there has been initial decline in both the total hip and femoral neck BMD below baseline after switching from risedronate, alendronate, or denosumab to teriparatide which lasts for 6–12 months [129, 133, 135, 148, 150–153]. Although there is no head-to-head comparative study, this total hip BMD loss may be more prominent and prolonged with denosumab than bisphosphonates [16, 133]. Upon continuing teriparatide therapy, this decrease in the total hip and femoral neck BMD is reversed, reaching to a final increase of small magnitude at the end of most, but not all, studies [14]. In contrast, this decline in the BMD at both total hip and femoral neck was not observed after switching raloxifene to teriparatide [29, 30]: BMD at the total hip as well as femoral neck remained essentially unaffected for 6 months and then increased up to the end of the relevant studies [150, 151]. This data suggests that the more potent the anti-resorptive previously used, the lower and slower the response in the BMD at both the total hip and femoral neck to teriparatide.

On another front, considering another anabolic agent, romosozumab, the decrease in the total hip and femoral neck BMD has not been observed when alendronate was switched to romosozumab, which led to a progressive increase in BMD at both sites (total hip and femoral neck) similar to lumbar spine [153]. On the contrary, following denosumab, a second romosozumab course in a small number of patients (n = 16) led to an increase in the lumbar spine BMD (2.3%), whereas the total hip BMD was maintained. However, these patients had received an initial 2-year treatment with romosozumab before denosumab, which may have distorted the net effect of romosozumab after denosumab [14].

Considering the distal forearm, limited data revealed a decrease in radius BMD after switching from denosumab or other anti-resorptives to teriparatide [133, 147]. Contrary to the total hip and femoral neck BMD, radius BMD does not seem to recover after 24 months of teriparatide therapy following denosumab [133].

Regarding the effect of teriparatide on bone quality after switching from anti-resorptives to anabolic therapy, earlier studies revealed that teriparatide therapy increased both cortical turnover and cortical bone formation similarly in patients previously treated with alendronate and treatment naïve individuals, although the former

initially have lower bone turnover than the latter cohort [154, 155]. Teriparatide was reported to reduce the accumulation of microdamage in the iliac crest of patients previously treated with alendronate [156]. Previous bisphosphonate administration may have null or minimal impact on the favorable effects of teriparatide on bone mineral and organic matrix properties, including initial mineralization, mineral maturity/crystallinity, and collagen maturity [157, 158]. Limited data showed a potential superiority of teriparatide on the bone biomechanical properties when switching from risedronate over alendronate [159], or raloxifene over alendronate [130]; however, there are insufficient comparative data for valid conclusions. Importantly, in the unique to-date, head-to-head comparative study, the estimated hip strength was increased when alendronate was switched to romosozumab, whereas decreased at six months when switched to teriparatide, findings which are largely in line with BMD results [153].

Regarding fracture efficacy, there is no anti-resorptive to osteoanabolic study with fractures as primary endpoint. Unfortunately, small sample sizes and numbers of fractures in the abovementioned studies do not allow the drawing of secure conclusions. Although it can be assumed that the increase in the lumbar spine BMD may imply higher anti-fracture efficacy, it remains unknown whether the initial decline in the total hip/femoral neck BMD may increase fracture risk when bisphosphonates or denosumab treatment switches to teriparatide [160]. Although switching to teriparatide is a common practice in patients who did not respond to anti-resorptives or those having completed the maximum duration of anti-resorptive therapy, this is probably not the optimal sequence, at least in high-risk patients, as it could lead to transient loss of the total hip/femoral neck BMD and strength. In this regard, starting treatment with bisphosphonate or denosumab rather than anabolic agent should be carefully considered, especially in high-risk patients. A more secure sequence would more likely be teriparatide following raloxifene, as it does not seem to negatively impact on the total hip/femoral neck BMD in contrast to bisphosphonates or denosumab. Alternatively, romosozumab, where available, instead of teriparatide may be used after anti-resorptives; however, more comparative data are still needed [14, 160].

Anti-resorptives Sequential to Anti-resorptives for the Treatment of Osteoporosis (Anastasia)

Transitioning from one anti-resorptive to another is probably the most common treatment sequence in standard clinical practice. However, a logic query can be raised: Is it meaningful to switch to another, alleged to be more potent, anti-resorptive? It is possible that ensuring better compliance such as that expected with parenteral osteoporosis therapy, e.g., with zoledronate infusion or denosumab injection, along with possibly higher efficacy could improve bone status in patients having a high fracture risk, despite treatment with oral anti-resorptives.

In patients who received alendronate therapy for a mean of 4 years, a single zoledronate infusion maintained their lumbar BMD for the next 12 months. Assessing the bone turnover biomarkers, they decreased during the first 3-months, while returned to baseline levels at 6 months and increased thereafter [161]. One study revealed that zoledronate infusion therapy was preferred by the majority of patients over alendronate [161]. Similarly, in the DAPS study, patients expressed preference for denosumab over weekly alendronate and showed better compliance/persistence to treatment with denosumab compared to alendronate [126]. Furthermore, in postmenopausal women previously treated with oral bisphosphonates, denosumab significantly increased BMD at all skeletal sites [162] and was more efficacious in terms of BMD accrual and bone turnover markers suppression compared to all available bisphosphonates [125, 127, 128, 163]. However, it is worth noting that, in patients previously treated with bisphosphonates, the BMD increases attained with denosumab were more modest compared to treatment-naïve patients treated with denosumab; however, they were still significant [127, 128, 164]. On the other hand, denosumab administration resulted in similarly suppressed bone turnover markers,

despite the lower baseline levels in patients pretreated with bisphosphonates compared to treatment-naïve patients [164, 165]. Up to date, there are no anti-fracture efficacy data in patients transitioning from bisphosphonates to denosumab or generally from one anti-resorptive to another.

Finally, transition to an anti-resorptive, particularly a potent oral or intravenous BP, is mandatory to maintain BMD gains and avoid the rebound increase in fracture risk in patients discontinuing denosumab [166, 167]. Alendronate administered for 1 year following 1 year of denosumab treatment-maintained BMD at the lumbar spine as well as both the total hip and femoral neck [126, 168]. On the contrary, several case series of limited power suggested that both zoledronate and risedronate resulted in retaining of only part of the BMD gains achieved with denosumab [169–171]. In the DATA follow-up study, BMD increases achieved after 2–4 years of denosumab therapy were maintained only in patients that continued denosumab or were promptly switched to bisphosphonates [172]. In the only randomized controlled trial (RCT) published on the topic up to date, a single zoledronate infusion given 6 months after the last denosumab injection prevented bone loss for the following 2 years [173].

Combination Therapy

Combination therapies have been investigated for efficacy and safety in severe osteoporosis conditions. Combination therapy refers to coadministration of an osteoanabolic agent (most studies referring to teriparatide) with a variety of anti-resorptive agents, or HRT with other anti-resorptives [174]. Most studies evaluated differences between combination and monotherapy in terms of areal BMD. Few studies evaluated the volumetric BMD using quantitative computed tomography (QCT). However, none of the studies has evaluated or been designed or adequately powered to assess differences in fracture incidence between the combination therapy and monotherapy [175]. Therefore, combining anti-resorptive and anabolic therapy can be considered as a missed opportunity for two reasons [176]. First, no studies have been done demonstrating greater antifracture efficacy than achieved by either treatment alone. This is a valid reason for a cautionary approach to the uptake of this regimen. The second reason is the widely held belief that anti-resorptive therapy, "blunts," (suppresses) remodeling-based bone formation by teriparatide therapy. The notion of blunting was based on the assumption that a higher BMD or higher P1NP mean more bone formation and a lack of response means less bone formation [177–179].

Combination Therapies with Anabolics and Anti-resorptive Agents

Several combinations of anabolics and anti-resorptive agents have been evaluated over the past years. The combination of teriparatide and raloxifene has been assessed in both previously treated osteoporotic and drug-naïve postmenopausal women. In patients previously treated with raloxifene for at least 1 year, the addition of teriparatide has induced greater increases in both the lumbar spine and total hip BMD compared to raloxifene monotherapy [180]. In this study, however, superiority of the combination therapy versus teriparatide monotherapy could not be demonstrated since a treatment arm with teriparatide alone was not included. In subsequent studies, the combination of teriparatide/raloxifene was directly compared to teriparatide monotherapy in both drug-naïve and previously treated patients. In osteoporotic women previously treated with raloxifene, 18 months of teriparatide/raloxifene combination did not achieve greater BMD increases compared to teriparatide monotherapy at any skeletal site measured [131, 181]. In contrast, the addition of raloxifene in postmenopausal women already on teriparatide for 9 months resulted in greater increases in lumbar spine BMD with no difference in total hip BMD compared to teriparatide monotherapy [61, 182]. The above findings imply that the net effect of teriparatide/raloxifene combination on BMD may be affected by the nature of the previous anti-resorptive or anabolic therapy. On the other hand, in a 6-month trial in drug-naïve patients,

teriparatide/raloxifene achieved greater increase in total hip BMD, but not lumbar spine BMD or femoral neck BMD compared to teriparatide monotherapy [183].

The combination of teriparatide with a bisphosphonate has demonstrated inconsistent results. The outcomes were attributed to the type of bisphosphonate used, the route of administration (oral alendronate/ibandronate or parenteral zoledronate), and the history of previous treatment. Three studies have evaluated the teriparatide/bisphosphonate combination in drug-naïve osteoporotic women, two with alendronate, and one with zoledronate. In previously treatment-naïve women, coadministration of teriparatide/alendronate following a 6-month alendronate monotherapy achieved smaller BMD gains at both the lumbar spine and total hip compared to teriparatide monotherapy [184]. In contrast, another study reported the superiority of the teriparatide/alendronate combination in total hip and femoral neck BMD compared to teriparatide monotherapy; however, in the latter study, the dose of teriparatide was 40 μg/day, which is double the approved dose.

The combination of teriparatide and zoledronate was compared with both teriparatide and zoledronate monotherapy for the treatment of naïve postmenopausal osteoporosis women [185]. At 12 months of treatment, the combination achieved greater increases in both the total hip and femoral neck BMD compared to teriparatide monotherapy, with no difference in lumbar spine BMD, implying an additive effect of the teriparatide/zoledronate combination in the hip region compared with teriparatide monotherapy at least in the early treatment period. It has been noted that the combination of teriparatide/zoledronate was not superior than zoledronate monotherapy in hip BMD. Clinical fractures were less in the combination group compared to both zoledronate and teriparatide monotherapy but reached statistical significance only compared with zoldredonate monotherapy [185].

In long-term alendronate-treated postmenopausal women, the addition of teriparatide therapy resulted in greater increases in lumbar spine and total hip BMD compared to alendronate monotherapy [65, 186] and teriparatide monotherapy [131]. In addition, hip BMD did not decline in the teriparatide/alendronate combination group, in contrast to what has been reported in studies with parathyroid hormone or teriparatide monotherapy after the withdrawal of antiresorptives [181].

Similar results were obtained when alendronate was added in postmenopausal women previously treated with teriparatide for 9 months. Both areal and volumetric lumbar spine and total hip BMD increases were greater with the teriparatide/alendronate combination compared to teriparatide monotherapy [182].

The combination of ibandronate with parathyroid hormone 1–84 was also studied in 44 postmenopausal women diagnosed to have osteoporosis. The patients were randomized to receive 3 months of parathyroid hormone 1–84 followed by 9 months of oral ibandronate 150 mg/month (repeated in two cycles) or 6 months of combined parathyroid hormone/ibandronate followed by 18 months of ibandronate alone [187]. Increases in both areal and volumetric BMD were similar between treatment groups at all skeletal sites measured. Risedronate has been evaluated as a combination treatment with TPTD in male osteoporosis [188]. This was a randomized, double-blinded study of risedronate (35 mg weekly plus placebo injection), teriparatide (20 μg subcutaneously daily plus placebo tablet), or both risedronate plus teriparatide (combination) for 18 months in 29 men with low BMD. The primary endpoint was percentage change in lumbar spine BMD at 18 months. Secondary outcomes included changes in bone markers and BMD at other sites and interim time-points. All therapies increased lumbar spine BMD as compared with baseline ($p < 0.05$), but there were no between-group differences at 18 months. Total hip BMD increased to a greater extent in the combination group (mean ± SEM, 3.86 ± 1.1%) versus teriparatide (0.29 ± 0.95%) or risedronate (0.82 ± 0.95%; $p < 0.05$ for both). Femoral neck BMD also increased more in the combination group (8.45 ± 1.8%) versus risedronate (0.50 ± 1.7%; $p = 0.002$) but was not different from teriparatide alone. In the combination

group, P1NP and CTX increased rapidly, mirroring the teriparatide-alone arm. There were no between-group differences in adverse events. The combination of teriparatide and risedronate increased BMD at the lumbar, total hips, and the femoral neck and provided greater BMD increases at the total hip than monotherapy. The results suggest the combination of risedronate and teriparatide therapy holds promise as a treatment for osteoporosis [188].

Among all combination treatments published so far, the studies of teriparatide and denosumab co-administration demonstrated the best and most promising results. In the DATA trial, which included a cohort of largely treatment-naïve postmenopausal women, the teriparatide/ denosumab combination treatment induced greater increases in all the three sites: lumbar spine, total hip, and femoral neck as well as radius BMD compared to either agent alone after 12 [189] and 24 months of therapy [190]. BMD changes with the teriparatide/denosumab combination in this study were similar to those seen with the teriparatide/zoledronate combination in the first 6 months [185], although the magnitude does not refer to direct comparison. However, in contrast to the terparatide/zoledronate combination, BMD levels continued to increase with the teriparatide/ denosumab combination after the first 6 months, when the waning effect of zoledronate on bone resorption is seen. In the DATA-HD trial, the combination of denosumab with higher teriparatide dose (40 μg) increased lumbar spine as well as total hip BMD more than the standard teriparatide 20 μg/denosumab combination therapy [191, 192], further supporting the rationale of using this combination in severe osteoporosis.

Regarding the other two currently commercially available osteoanabolic agents, abaloparatide and romosozumab, there are no studies published so far on the coadministration of either drug with an anti-resorptive agent.

Combination Treatment with Hormone Replacement Therapy

Hormone replacement therapy (HRT) has been tested as a combination treatment with oral bisphosphonates, such as alendronate, risedronate, and cyclic etidronate, as well as with calcitonin and parathyroid hormone analogues.

Earlier studies published assessing the combination of HRT with another anti-resorptive agent revealed significantly greater increases in both lumbar spine and total hip BMD compared to monotherapy with either HRT or the anti-resorptive medication [193–198]. This beneficial effect was sustained up to 4 years in the combination with bisphosphonates [194], but only up to the first year of therapy with calcitonin [197].

Various parathyroid hormone analogues have also demonstrated beneficial effects in BMD gains when added to HRT in postmenopausal women with osteoporosis [199–201]. Limitations of these studies include the lack of a teriparatide monotherapy arm and of fracture risk assessment. It should also be highlighted that all studies preceded the publication of the teriparatide Fracture Prevention Trial [120] and the approval of teriparatide 20 μg/day for the treatment of osteoporosis used teriparatide doses higher than the currently approved teriparatide doses. In these studies, the teriparatide/HRT combination increased BMD more than HRT alone, but these increases were comparable to teriparatide monotherapy.

Challenges with the Outcomes of Sequential and Combined Osteoporosis Therapy

Most of the comparator studies use changes in BMD and bone remodeling markers as the outcome variable. By themselves, they can be considered problematic endpoints. Remodeling-based anabolic therapy increases bone matrix volume by replacing more fully mineralized bone with young less fully mineralized bone. Modeling-based anabolic therapy adds young less fully mineralized bone to existing older bone. Imaging using radiation transmission often results in a net reduction in BMD because young less mineralized bone transmits rather than attenuates photons, leading to the inference that bone "loss" and fragility have occurred. Anti-resorptives slow remodeling. Matrix no longer

"turned over" undergoes more complete mineralization increasing BMD leading to the inference that bone "volume" or "mass" has increased, and that bone strength has increased even though the matrix becomes less ductile. These challenges were discussed in the article written by Ramchand and Seeman [202].

As an example, even if an increase or lack of an increase in BMD is accepted on face value, the results of Black et al. study [176] do not support the notion of blunting. Relative to parathyroid hormone therapy alone, combined therapy (1) did not produce a smaller increment in spine or femoral neck BMD, (2) did produce a greater increase in total hip BMD, (3) did reduce the decline in distal radius BMD, and (4) did prevent the reduction in total hip and femoral neck vBMD produced by parathyroid hormone alone. Curiously, the increase in total hip and femoral neck cortical volume by PTH, a modeling effect, was prevented by combined therapy. Moreover, combined therapy increased trabecular vBMD less than parathyroid hormone alone but this may be a benefit, not blunting. The anti-resorptive might prevent a PTH-mediated increase in intracortical remodeling, cortical porosity, and the increase in cortical fragments that look like "trabeculae" [203]. Blunting of the rise in P1NP and CTX is likely to be the result of suppressed remodeling, not a reduction in the net volumes of bone deposited or resorbed, respectively [204]. If blunting of the BMD response was due to fewer BMUs, then blunting should be more severe with the coadministration of PTH with zolendronate, denosumab, or osteoprotegerin (OPG, an endogenous inhibitor of RANKL) than with alendronate. The opposite is reported, and many studies report additive effects [205, 206].

The difficulties in using BMD are also present using high-resolution peripheral computed tomography. Tsai et al. [207] report that combined PTH 1–34 and denosumab increased cortical vBMD, yet PTH 1–34 reduced it and denosumab had no effect. Combined therapy increased cortical matrix mineral density, yet PTH 1–34 decreased it and denosumab had no effect. Combined therapy had no effect on porosity, yet PTH 1–34 increased it while denosumab had no effect. These findings do not add up, probably because there are methodological challenges in segmenting (separating) the cortical and trabecular compartments and quantifying porosity and trabecular density because low image resolution and changes in matrix mineral density influence the quantification of microstructure [208–210].

The Way Forward

In the long-term management of osteoporosis, transitioning from one treatment agent to another is quite common in standard practice and in several cases is probably a necessity. Setting the optimal long-term management plan tailored to the individual patient's needs, preferences as well as comorbidities are vital to ensure best compliance and adherence to therapy yet is a challenge to the treating physician.

A major challenge in standard practice is the protocol of patients' management adopted. The standard protocols recommend starting with the generic bisphosphonates and keep the anabolics until the last step of management; consequently, anabolic agents are restricted for patients with severe osteoporosis. On the other hand, the treat–to-target approach recommend setting up the treatment protocol subject to the patient's BMD measurement and risk of fracture. Another challenge is the duration of therapy. While osteoanabolics increases BMD and reduces fracture risk, they are administered for a maximum of 12 months (romosozumab) and up to 24 months (teriparatide, abaloparatide). Third challenge is the cost, as generic anti-resorptives are cost-effective, while osteoanabolics are of high cost. Fourthly, loss of BMD gains has been reported after some anti-resorptives (e.g., denosumab) as well as most of the anabolics known so far. Therefore, sequential treatment with an anti-resorptive agent is strongly recommended for these patients. Lastly, osteoporosis therapeutic

agents vary in their effect on the bones. Among anti-resorptives, denosumab has the best performance, at least in terms of BMD accrual. Similarly, all osteoanabolics induce a state of positive remodeling balance.

Transitioning from an anti-resorptive to an osteoanabolic agent is less effective than the opposite, as the BMD increase is more modest and delayed, probably because the chronically suppressed bone turnover needs more time to be enhanced than in treatment-naïve individuals receiving an osteoanabolic as the initial therapeutic approach. Changes in remodeling activity, leading to changes in cortical porosity, may also be responsible for part of the BMD changes observed in this setting. It seems that the more potent the anti-resorptive previously used, the lower and slower the responses of bone turnover markers and BMD to the osteoanabolic agent. The sequences that have been studied are mainly bisphosphonates and raloxifene followed by teriparatide and romosozumab. The anti-resorptive osteoanabolic treatment sequence could be considered in patients with severe disease who do not improve or exhibit treatment failure under an anti-resorptive agent, e.g., fractures while on treatment and/or significant bone loss despite several years of treatment administration.

Transitioning from an anti-resorptive to another anti-resorptive given at larger intervals is the more likely scenario in the standard practice. Anti-resorptives given intravenously or subcutaneously could also improve patients' compliance. Transitioning from a bisphosphonate to another bisphosphonate is expected to maintain BMD values whereas transitioning from a bisphosphonate to denosumab may probably induce a further increase of the BMD values. Zoledronate or alendronate are recommended to follow denosumab treatment to maintain most of the BMD gains achieved and prevent the increase of fracture risk, especially that of multiple vertebral fractures. The sequential use of an osteoanabolic after another osteoanabolic agent has not been investigated up to date. Concerns regarding safety issues exist. Furthermore, cumulative use is not recommended to exceed 2 years during a patient's lifetime, at least for teriparatide and abaloparatide [14, 211].

Combinations of parathyroid hormone analogues, mainly teriparatide, with various anti-resorptives have been tested in patients with severe osteoporosis. Among them, only the combination of teriparatide with denosumab has shown clear, long-term advantage over teriparatide monotherapy, especially in the hip, while the combination of teriparatide with zoledronate has a similar effect but of a potentially shorter term. The other two currently available osteoanabolic agents, namely, abaloparatide and romosozumab, have not been tested in combination with an anti-resorptive up to date. Notably, the majority of healthcare systems do not regularly fund or endorse osteoporosis combination therapy; this has been attributed to the considerable higher cost and the lack of fracture data supporting its superiority against monotherapy. However, in most healthcare systems and in cases of a well-documented severe disease, the off-label coadministration could be applied [14].

In conclusion, the increase in BMD produced by anti-resorptive agents is mostly the result of remodeling suppression, which enables more complete secondary mineralization of the slowly diminishing bone volume (in the case of bisphosphonate) or stable bone volume (in the case of denosumab, which effectively abolishes remodeling). The differences in morphological changes in structure, composition, and its impact on bone strength raised the question of the validity and significance of comparing the increase in BMD produced by anabolic versus anti-resorptive therapies, also calling into question the value of adopting new policies of management such as sequential or combined therapy. In the long-term osteoporosis management, transitioning from one treatment agent to another is quite common in standard practice and in many cases is a necessity. Given that in all the published studies investigating sequential or combination treatment fracture data are scarce, outcomes are based

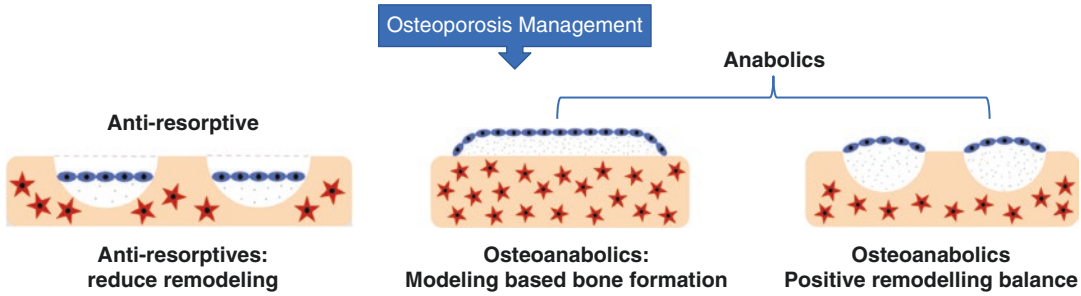

Fig. 24.3 Osteoporosis management: Effects of anti-resorptive and osteoanabolic medications on the bone remodeling and modeling process. During young adulthood, bone remodeling is balanced – an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs. Age-related bone loss is associated with an increase in remodeling and a negative remodeling balance in individual bone remodeling units. Anti-resorptive agents act predominantly by reducing the remodeling rate. Anabolic agents produce their effects by increasing bone modeling as well as remodeling, leading to a positive remodeling balance

mostly on BMD, as a surrogate marker of bone strength, and as an endpoint to draw conclusions regarding the efficacy of each sequential or combination modality (Fig. 24.3).

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