Combined and sequential therapies with anabolic and antiresorptive drugs in the management of patients with postmenopausal osteoporosis

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ABSTRACT

The aim of osteoporosis therapy is to reduce the increased fracture risk associated with osteoporosis-related bone fragility. Prevention of fragility fracture relies on balanced nutrition, weight-bearing and balance-improving physical exercises, and pharmacological therapies. Among the latter, the antiresorptive drugs are the most widely used. Bone formation stimulators (anabolics) are second line-therapy with reversible effects once discontinued. For patients at very high risk or imminent risk of fracture, the question arises of whether combining drugs with different modes of action, or using sequential regimens with these agents, could achieve early, higher-magnitude antifracture efficacy than is obtained with usual antiresorptives, and sustained antifracture efficacy. As regards combination therapies, until we have clear evidence that using drugs together provides greater fracture risk reduction than monotherapy, these therapies are not recommended. Anabolic treatments like teriparatide, the amino-terminal fragment of parathyroid hormone, abaloparatide, an analog of parathyroid hormone related protein, and romosozumab, the monoclonal antibody against sclerostin, decrease vertebral and non-vertebral fracture risk and are more efficacious in fracture risk reduction than antiresorptives, as shown in head-to-head trials. However, an anabolic agent should be followed by an antiresorptive drug to maintain and even further increase its antifracture efficacy, which is otherwise rapidly reversible. Because of their early, high-magnitude and sustained antifracture efficacy, such sequential regimens should become the standard of care for patients at very high or imminent risk of fracture.

KEYWORDS

Osteoporosis, fracture, treatment, bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab.

Introduction

The aim of osteoporosis therapy is to reduce the increased fracture risk associated with osteoporosis-related bone fragility. Prevention of fragility fracture relies on the triad of balanced nutrition, including calcium, protein and vitamin D; weight-bearing and balance-improving physical exercises; and pharmacological therapies. Anti-osteoporosis drugs are either antiresorptives or stimulators of bone formation, i.e., anabolics. The efficacy of the available anti-osteoporotic agents in increasing bone strength and reducing osteoporotic fracture risk has been demonstrated in well-conducted randomized, placebo-controlled trials with fracture risk as the primary outcome [1,2]. The antiresorptives are the most widely used category. Alendronate, basedoxifene, denosumab, ibandronate, raloxifene, risedronate, menopausal hormone therapy (MHT), and zoledronate decrease vertebral fracture risk. As for hip fracture, alendronate, denosumab, risedronate, and zoledronate reduce the risk in women with osteoporosis, MHT in postmenopausal women, and calcium and vitamin D in institutionalized patients [1,2]. Bone formation stimulators are second-line therapy with rapidly reversible effects once discontinued. In patients at very high or imminent risk of fracture [3], the question arises of whether combining drugs with different modes of action, or using sequential regimens with these agents, could achieve early, higher-magnitude antifracture efficacy than is obtained with antiresorptives, and sustained antifracture efficacy. In the present review, we briefly recall the antifracture efficacy of the various available agents, together with their major side effects, before describing the results of head-to-head trials of active agents. Therapies simultaneously combining an antiresorptive and teriparatide are reported before discussing how early, high-magnitude, and sustained fracture risk reduction can be achieved with sequential regimens including an anabolic followed by an antiresorptive.

Efficacy of anti-osteoporotic drugs in placebo-controlled trials: antiresorptives

Selective estrogen-receptor modulators

Selective estrogen-receptor modulators are non-steroidal agents that bind to the estrogen receptor and act as estrogen agonists or antagonists, depending on the target tissue. Raloxifene pre-

vents bone loss and reduces the risk of vertebral fractures by 30-50% in postmenopausal women with osteoporosis with or without prior vertebral fractures, as shown in the MORE trial [4]. There is no significant reduction of non-vertebral fractures, except in women with severe vertebral fractures at baseline [5]. The risk of invasive breast cancer is reduced by about 60% [6].

As regards adverse events, there is an increase of deep venous thromboembolism, of hot flashes, and of lower limb cramps. Raloxifene had no effect on cardiovascular death or on the incidence of coronary heart disease and stroke [7].

Bazedoxifene reduces the risk of new vertebral fracture, with favorable effects on bone mineral density (BMD), bone turnover markers, and lipid profile [8,9]. In a subgroup of women at increased risk of fracture, bazedoxifene decreases non-vertebral fracture risk. As with raloxifene, venous thromboembolic events, deep vein thromboses, leg cramps, and hot flashes are reported adverse events [10]. Bazedoxifene is also combined with conjugated equine estrogen to create a tissue selective estrogen complex [11]. This association improves vasomotor symptoms while opposing breast and endometrial proliferation, preventing bone resorption, increasing BMD, and improving lipid profile.

Bisphosphonates

Bisphosphonates are stable analogs of pyrophosphate characterized by a P-C-P bond. Their potency depends on the length and structure of the side chains [12]. Bisphosphonates have a strong affinity for bone hydroxyapatite and are potent inhibitors of bone resorption. Amino-bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) inhibit the farnesyl pyrophosphate synthase step in the mevalonate pathway. Non-nitrogen-containing bisphosphonates (clodronate, etidronate, tiludronate) act as ATP competitors. *In vitro* potency of the various bisphosphonates can differ over a 10,000-fold range, so the doses used clinically also vary [12].

Oral bioavailability of bisphosphonates is around 1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. The oral formulation needs a 30- to 60-minute fast after ingestion and before any meal, without lying down, to ensure optimal intestinal absorption and prevent esophageal damage. Bisphosphonates are quickly cleared from plasma, about 50% being deposited in bone and the remainder excreted in urine. Their half-life in bone is very prolonged.

Alendronate

Oral alendronate lowers the incidence of vertebral, wrist, and hip fractures by approximately 50% in women with prevalent vertebral fracture [13]. In women without prevalent vertebral fracture, there is no significant decrease in clinical fractures in the overall population, but a reduction is seen in those patients with a baseline hip BMD T-Score lower than –2.5 SD [14]. In a case-control study performed in more than 90,000 men and women aged 80 years and older and with a prevalent fracture, alendronate use was found to be associated with a 34% decrease in hip fracture risk, and a 12% lower mortality risk, but with a 58% increase in the risk of mild upper gastrointestinal symptoms [15]. Pivotal trials have been conducted with a daily dose. Efficacy of the weekly 70 mg regimen has been shown

in bridging studies with BMD and bone turnover markers as outcomes [16]. An effervescent form that is easier to swallow could be of potential interest particularly in the oldest old [17].

Risedronate

Oral risedronate reduces the risk of vertebral and non-vertebral fractures by 40-50% and 30-36%, respectively, in women with prevalent vertebral fracture [18,19]. In a large population of elderly women, risedronate decreased the risk of hip fractures by 30%. This effect was present in osteoporotic women aged 70-79 years (–40%), but not significant in women over the age of 80 years without evidence of osteoporosis [20]. A delayed-release formulation of 35 mg risedronate weekly allows osteoporotic patients to take their risedronate dose immediately after breakfast, thereby allowing potentially improved adherence to treatment [17].

Ibandronate

Daily oral ibandronate reduces the risk of vertebral fractures by 50-60%, whereas a lower non-vertebral fracture risk was only demonstrated in a post-hoc analysis of women with a BMD T-Score below –3 SD [21,22]. In bridging studies, oral ibandronate 150 mg once monthly or intravenous ibandronate 3 mg every 3 months are equivalent or superior to a daily regimen in increasing BMD and decreasing biochemical markers of bone turnover [23,24]. In post-hoc analyses, ibandronate regimens with annual cumulative exposure superior to 10.8 g increase time-to-fracture for all clinical fractures versus placebo [25].

Zoledronic acid

In a large phase III trial comprising 7,700 postmenopausal osteoporotic patients, yearly infusion of zoledronate over three years reduced the incidence of vertebral and hip fractures by 70% and 40%, respectively [26]. Intravenous zoledronate decreases fracture risk and mortality when given shortly after a first hip fracture [27]. From an extension study to 6 [28] and 9 [29] years, it appears that prolonging treatment beyond 6 years does not provide additional benefits.

Bone pain, as well as joint and muscle pain, have frequently been reported with use of bisphosphonates, both oral and IV (about 5-10% of patients) [12]. Intravenous bisphosphonates are associated with transient flu-like symptoms (myalgia, arthralgia, headache, and fever), collectively called an acute phase reaction.

An increased risk of atrial fibrillation reported as a severe adverse event was observed in the pivotal HORIZON study with zoledronic acid. Post-hoc analyses of other bisphosphonate trials and several large population-based studies have not confirmed this suspicion. A decrease in myocardial infarction has even been associated with bisphosphonate use in patients with rheumatoid arthritis [30].

Osteonecrosis of the jaw, defined as exposed bone in the maxillofacial region that shows negligible healing over a period of 8 weeks, is mostly reported in cancer patients receiving high-dose IV bisphosphonates [31]. Atypical subtrochanteric, low-trauma, femur fractures have been reported in bisphosphonate-treated patients, some with prodromal thigh pain in the preceding period. Although there is an association with dura-

tion of bisphosphonate use, atypical fractures can also be observed in untreated patients [32].

Denosumab

Receptor activator of nuclear factor NFkB (RANK), its ligand RANKL, a member of the tumor necrosis factor superfamily, and osteoprotegerin, which acts as a decoy receptor for RANKL, are critical molecules for the differentiation and action of osteoclasts, and hence for bone resorption [33]. The fully human antibody against RANKL, denosumab, prevents the interaction of RANKL with the receptor RANK.

In the pivotal FREEDOM placebo-controlled trial, half of 7,762 postmenopausal women received 60 mg denosumab subcutaneously every 6 months over 3 years. There was a 68% reduction in the incidence of new vertebral fractures. Non-vertebral fracture risk was reduced by 20%, and hip fracture risk by 40% [34]. In an extension study, women from the denosumab group had 7 more years of treatment (long-term group) and those in the placebo group received 7 years of denosumab (cross-over group) [35]. The yearly incidence of new vertebral fractures remained low during the extension, whereas non-vertebral fractures further decreased beyond the first 3 years of the trial to reach a stable level. Discontinuation of denosumab is associated with a rapid increase in bone turnover, even above pretreatment levels, a BMD decrease, and a marked increase in vertebral fracture rate [36]. Multiple vertebral fracture risk is even higher than in the placebo group [36]. A bisphosphonate could be considered when discontinuing denosumab to retard or blunt the turnover rebound [37].

Regarding adverse events, in the FREEDOM trial, 7 cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the cross-over group [36]. In a meta-analysis of four trials, a non-statistically significant relative risk of serious adverse events for the denosumab group compared with the placebo group was 1.33, of serious adverse events related to infection 2.10, of neoplasm 1.11, of study discontinuation due

to adverse events 1.10, and of death 0.78 [38]. Denosumab is not excreted by the kidney and could therefore be used in patients with impaired renal function. However, the administration of such a potent bone resorption inhibitor in patients with terminal renal failure and possibly adynamic bone disease may further inhibit bone turnover.

Menopausal hormone therapy (MHT)

Estrogens decrease the risk of vertebral and non-vertebral fractures (including hip fracture) by about 30%, regardless of baseline BMD [39,40]. In a recent re-assessment of the long-term outcomes of Women Health Initiative (WHI) trials, MHT with conjugated estrogen and medroxyprogesterone acetate for a median of 5.6 years, or with conjugated estrogen alone for a median of 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years [41].

Efficacy of anti-osteoporotic drugs in placebo-controlled trials: anabolics (Table I)

Teriparatide

Whilst a continuous increase in endogenous production of parathyroid hormone (PTH) is deleterious for the skeleton, intermittent administration of PTH leads to an increase in bone mass, an improvement in skeletal microstructure at both cancellous and cortical skeletal sites, and higher bone strength [42].

In the Fracture Prevention Trial, a daily subcutaneous dose of 20 μg of the 1-34 N-terminal PTH fragment teriparatide reduced the risk of vertebral fractures by 65% and of non-vertebral fractures by 35% [43]. Treatment with teriparatide is registered for 18 to 24 months; beneficial effects on non-vertebral fracture risk with teriparatide persist for up to 30 months after stopping the drug, likely in relation to the administration of bisphosphonates [44]. In a post-hoc analysis of data from the

Table I Vertebral and non-vertebral fracture relative risk reduction in postmenopausal women with osteoporosis.

			RRR VS PLACEBO IN PIVOTAL TRIALS (%)					RRR VS CONTROLS[b] IN SEQUENTIAL TREATMENTS (%)				
			RRR		RRR				RRR	RRR		
TRIAL	ANABOLIC AGENT	DURATION (months)	VERTEBRAL (%)	P	NON-VERTEBRAL (%)	P	ANTI-RESORPTIVE AGENT	TOTAL DURATION (months)[a]	VERTEBRAL (%)	P	NON-VERTEBRAL (%)	P
PFT [43]	Teriparatide	19	65	0.001	35	0.04	NA					
ACTIVE [51]	Teriparatide	18	80	0.001	28	0.22	NA					
ACTIVE [51]	Abaloparatide	18	86	0.001	43	0.049	Alendronate	24 [52]	87	0.001	52	0.02
								42 [53]	84	0.001	39	0.038
FRAME [57]	Romosozumab	12	73	0.001	25	0.10	Denosumab	24 [57]	75	0.001	25	0.06
								36 [58]	66	0.001	21	0.04

RRR: relative risk reduction. **teriparatide**: 20 μg/day, SC; **abaloparatide**: 80 μg/day SC; **romosozumab**: 210 mg/month SC; **alendronate**: 70 mg/week orally; **denosumab**: 600 mg/6 months SC
[a]: sequential treatment with anabolic agent followed by an antiresorptive; [b]: in the antiresorptive phase, all patients (previously in the treated or placebo groups) received the antiresorptive

Fracture Prevention Trial, the relative hazard for non-vertebral fragility fractures decreased by around 7% for each additional month of teriparatide treatment [45].

However, the beneficial effects of teriparatide on femoral neck and hip BMD are reversible following its discontinuation. Such declines in BMD can be prevented by administration of a bisphosphonate after teriparatide treatment. An increase in P1NP and osteocalcin (bone formation markers) is observed in the first six months of treatment, then there is a slight decrease over time. CTX also increases over six months and then decreases almost back to baseline by 18 months [46].

Adverse events with teriparatide are nausea, pain in the limbs, headache, and dizziness. Slight and transient elevations of serum calcium concentrations have been observed following injection of teriparatide [47]. The use of peptides belonging to the PTH family is contraindicated in conditions such as hypercalcemia, metabolic bone diseases other than osteoporosis, Paget's disease, prior radiation therapy to the skeleton, malignancies or bone metastasis, or severe renal impairment. In rats, very high doses of teriparatide since weaning increase the risk of osteosarcoma [48]. There is no confirmation of these findings in humans. Indeed, a post-marketing surveillance study showed that the incidence of osteosarcoma associated with teriparatide use during the 15-year surveillance period was not different from that which would be expected based on the background incidence rate of osteosarcoma [49].

Abaloparatide

Abaloparatide is a 34-amino-acid peptide with 76% homology to parathyroid-related protein (PTHrP) (1-34) and 41% homology to PTH (1-34) [50]. Abaloparatide is a potent and selective activator of the PTH receptor type 1 signaling pathway.

In the ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) trial, abaloparatide treatment at a daily dose of 80 µg subcutaneously for 18 months reduced new morphometric vertebral fractures by 86% and non-vertebral fractures by 43% in comparison with placebo, in women with postmenopausal osteoporosis [51]. There was rapid separation in non-vertebral fracture risk between the abaloparatide and placebo groups. In the ACTIVExtend trial, 18 months of daily subcutaneous abaloparatide compared with placebo (the ACTIVE trial) was followed by oral, open-label alendronate 70 mg weekly up to 24 months [52]. Reductions, of 52%, 58%, and 45%, in non-vertebral, major osteoporotic, and clinical fractures, respectively, were observed in the abaloparatide followed by alendronate group vs the placebo followed by alendronate group [52]. With extension of the alendronate period up to a total follow-up of 43 months, vertebral fracture risk was 87% lower in the abaloparatide-alendronate compared with the placebo-alendronate group [53].

Regarding P1NP and CTX, the profiles of changes differ between abaloparatide and teriparatide. Indeed, a steep increase in the first 3 months followed by a slow decline to baseline is observed with abaloparatide, compared with a slower rise reaching a peak at 6-12 months with teriparatide. This observation indicates rapid stimulation of bone formation [54], with a possible more rapid onset of action for the PTHrP analog [55].

Adverse events are nausea, dizziness, headaches, and palpitations, all of which are generally mild to moderate in severity [47,51].

Romosozumab

Romosozumab is an anti-sclerostin humanized monoclonal antibody that binds and inhibits sclerostin, with a completely different mechanism of action from PTH or PTHrP analogs. It transiently stimulates bone formation and more persistently inhibits bone resorption [56].

The FRAME trial is a one-year placebo-controlled study, followed by one year of denosumab 60 mg 6-monthly in both groups. It enrolled 7,180 postmenopausal women between the ages of 55 and 90 years with osteoporosis defined by a T-Score ≤–2.5 at the spine, hip, or femoral neck [57]. Romosozumab was given subcutaneously at a dose of 210 mg monthly for 12 months. It reduced vertebral fracture risk by 73%, and clinical fracture risk by 36%, whilst the 25% decrease observed for non-vertebral fracture was not statistically significant. At 24 months, following the transition to denosumab in both groups, the rate of vertebral fractures was 75% lower in the former romosozumab group than in the former placebo group.

In the FRAME extension study, one year of romosozumab followed by 2 years of denosumab (compared with 1 year of placebo followed by 2 years of denosumab) led to a 66%, 27%, and 21% reduction in the risk of new vertebral, clinical, and non-vertebral fractures, respectively [58]. In the group that received romosozumab followed by 2 years of denosumab, at 36 months, the proportion of participants with a T-Score in the osteoporosis range was found to have decreased from 63% at baseline to 20% at the spine and from 53% to 14% at the total hip. The BMD gains were of large magnitude in the romosozumab/denosumab treatment sequence since at 2 years they were similar to the BMD gains observed with 7 years of denosumab alone in the Freedom/Freedom Extension study [35,59].

The beneficial effects of romosozumab are rapidly reversible upon discontinuation of therapy. Indeed, women receiving romosozumab who transitioned to denosumab continue to accrue BMD, whereas BMD returns toward pretreatment levels with placebo [60]. After a second course of romosozumab, administration of an antiresorptive such as intravenous zoledronate maintains the BMD gains observed with romosozumab [61].

These results with teriparatide, or abaloparatide, or romosozumab preceding an antiresorptive open the way for sequential regimens for the treatment of osteoporotic patients. However, to support this sequence, it needs to be established whether an anabolic is superior to an antiresorptive in terms of early and high magnitude fracture risk reduction [62].

Face-to-face trials

Teriparatide vs risedronate or alendronate

The VERO study was a double-blind, double-dummy trial in postmenopausal women with at least two moderate or one severe vertebral fracture and a BMD T-Score ≤–1.5. Participants were randomized to 20 µg teriparatide once daily plus oral weekly placebo or 35 mg oral risedronate once weekly plus daily injections of placebo for 24 months, with 680 patients in each group [63]. At 24 months, new vertebral fractures were reduced by 56% in the patients in the teriparatide group as compared with those in the risedronate group. Clinical frac-

tures were also reduced by 52% whilst there was no significant difference in non-vertebral fragility fractures. This trial thus showed the superiority of the anabolic over the antiresorptive agent in preventing fragility fractures. However, there exist few studies testing a longer treatment duration. In one study of teriparatide versus alendronate in glucocorticoid-induced osteoporosis, an increase in lumbar spine and hip BMD was observed over a 36-month period, with fewer new vertebral fractures in the teriparatide group than in patients treated with alendronate [46].

Teriparatide vs raloxifene

In the prospective randomized controlled EUROFORS study, which had a two-year duration, the effects on BMD of three follow-up treatments, i.e., teriparatide, raloxifene (an antiresorptive), or no treatment, were compared after 1 year of teriparatide. Over the 2-year teriparatide therapy, lumbar spine BMD increased by 10.7%. Patients receiving raloxifene in year 2 showed maintenance of BMD, whereas patients receiving no active follow-up treatment had a 2.5% BMD decrease in year 2 [64].

Teriparatide vs abaloparatide

In the ACTIVE trial, abaloparatide was also compared with teriparatide. The results of a NNT analysis are usually largely dependent on the fracture risk in the placebo group. In the ACTIVE trial, the placebo group was the control for both anabolics, thereby allowing some comparison of the NNT [65]. In order to prevent one new vertebral fracture, 28 women should be treated with abaloparatide and 30 with teriparatide, whilst to prevent one non-vertebral fracture, 55 women should be treated with abaloparatide and 92 with teriparatide. The BMD changes were slightly greater with abaloparatide than with teriparatide at the total hip, femoral neck and lumbar spine.

Abaloparatide vs alendronate

No direct comparison of the efficacy of abaloparatide and antiresorptive therapies is available. In a post-hoc analysis, the antifracture efficacy of abaloparatide in ACTIVE during 18 months was compared with that of alendronate in ACTIVExtend, also during 18 months [66]. The vertebral fracture rate was 71% lower during abaloparatide treatment in ACTIVE than during alendronate treatment in ACTIVExtend. The rates of non-vertebral fractures and clinical fractures were not significantly different. Thus, treatment with abaloparatide may result in greater vertebral fracture reduction compared with alendronate in postmenopausal women with osteoporosis.

Romosozumab vs alendronate

In the ARCH trial, romosozumab (210 mg once monthly SC) was compared with weekly oral 70 mg alendronate in a double-blind fashion during 1 year and then both groups received the bisphosphonate for a median treatment period of 2.7 years [67]. Four thousand forty-three women, with an age range of 55 to 90, and with prevalent osteoporotic fracture were enrolled. By 2 years, vertebral, non-vertebral, and hip fracture risk were decreased by 48, 19, and 38%, respectively. By year 2, gains in BMD in patients who received romosozumab were very similar to those seen in FRAME and higher compared with alendro-

nate in year 1. BMD increased further after the transition to alendronate. However, the BMD gains at 36 months were not as high as those seen in FRAME with a transition from romosozumab to denosumab [67]. Regarding bone turnover markers, a rise in P1NP has been observed followed by a return to baseline within the first 6 months of treatment, alongside a decrease in CTX on treatment beginning, returning to baseline at 3 to 6 months, with both markers remaining below baseline at month 12. This suggests that romosozumab is a mild bone remodeling inhibitor, rather than a potent bone forming agent by 1 year of administration [60]. In the ARCH trial, a higher number of adjudicated severe cardiovascular events was recorded in the romozosumab-treated patients (2.5 vs 1.9%). In post-hoc analyses of the composite outcome of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, heart failure and non-coronary heart disease, the incidence was 2.0% in the romosozumab group and 1.1% in the alendronate group, with a hazard ratio of 1.7 (95% CI 1.1–2.6) [47]. Post-marketing surveillance studies are ongoing to further address this issue.

Romosozumab vs teriparatide

In a randomized, open-label, active-controlled trial, 436 women (aged 55 to 90 years) with postmenopausal osteoporosis who had received an oral bisphosphonate for at least 3 to 4 years were randomly randomized to subcutaneous romosozumab (210 mg once monthly) or subcutaneous teriparatide (20 μg once daily) for 12 months (STRUCTURE study) [68]. At that time, the mean percentage change from baseline in total hip areal BMD was 2.6% in the romosozumab group and –0.6% in the teriparatide group. Thus, in patients transitioning from a bisphosphonate to an anabolic, romosozumab leads to gains in hip BMD not observed with teriparatide. In a substudy of a phase II trial, vertebral strength as assessed by finite element analysis increased more with romosozumab than with teriparatide (27.3% versus 18.5%; p = 0.005). With the former agent, both the cortical and trabecular bone compartments are influenced [69,70].

Combination therapies

Since nearly all pharmacological therapies are recommended in vitamin D and calcium replete patients, all treatments are thus in fact combination therapies, i.e., pharmacological agents combined with calcium-vitamin D. However, there is no demonstrated benefit of combining two antiresorptive therapies together to obtain a higher fracture risk reduction [71]. Furthermore, the added costs and side effects of combination therapies should be considered.

Combination of PTH analogues and bisphosphonates

To attenuate the secondary stimulation of bone resorption associated with an anabolic like PTH or teriparatide, combinations of PTH analogs with oral or intravenous bisphosphonates have been investigated in a few trials [72-75]. None of these studies were powered to evaluate the effect on fracture risk. In the PaTH study, the combination of PTH (1–84) and alendronate

did not increase BMD more than either monotherapy over 12 months. Alendronate even seemed to reduce the bone-forming effect of teriparatide [76]. Another study evaluated the effect of zoledronate (a single infusion) in combination with teriparatide (administered daily) in comparison with either agent alone for one year [75]. BMD increased in all three groups. However, the relative changes differed according to the skeletal site assessed. At the lumbar spine, the increases were similar for zoledronate combined with teriparatide and teriparatide alone, and superior to what was observed with zoledronate. In contrast, at the hip level, zoledronate combined with teriparatide had the same effect as zoledronate, which was higher than that of teriparatide.

Thus, studies combining teriparatide and bisphosphonates have not reported any significant benefit over teriparatide alone. The same is true for experimental designs in which teriparatide was either discontinued or added to alendronate at 6 months.

Combination of teriparatide and denosumab

The DATA trial combined teriparatide and denosumab for 24 months. Increases in BMD obtained with combined treatments were greater than those obtained with either agent alone [77]. Then, after switching from teriparatide to denosumab, BMD continued to increase, whereas switching from denosumab to teriparatide resulted in bone loss [78].

A recent meta-analysis included a variety of trials with participant numbers as low as 13 per group, some evaluating the not registered teriparatide dose of 40 µg daily or the non-available PTH (1–84) [79]. Alendronate, zoledronate, ibandronate, risedronate, denosumab, MHT, and raloxifene were the antiresorptive treatments studied. Combining an anabolic with antiresorptives increases lumbar spine and total hip BMD more than monotherapy. Compared to all anabolic and antiresorptive regimens together, combination therapies reduced fracture risk by 36%, whilst the difference when compared with either anabolics or antiresorptives was not statistically significant.

Thus, the current evidence does not support the widespread use of combination therapy in the treatment of patients with osteoporosis.

Cost-effectiveness

Monotherapies for anti-osteoporosis are generally cost-effective, and even cost-saving in the oldest old [80]. In the field of osteoporosis, the availability of newer and more expensive anti-osteoporosis therapies has highlighted the importance of cost-effectiveness analysis.

A 2021 updated systematic review of the cost-effectiveness analyses of drugs for osteoporosis addressed the cost-effectiveness of sequential therapy in the form of an anabolic agent followed by an antiresorptive [81]. In this review, two studies showed that abaloparatide followed by alendronate is superior than teriparatide followed by alendronate. Abaloparatide followed by alendronate, when compared with a placebo or no treatment, is cost-saving or cost-effective depending on the treated population [82]. Conversely, abaloparatide and teriparatide followed by alendronate are not cost-effective when compared with a placebo followed by alendronate. The high

costs of abaloparatide and teriparatide largely affect incremental cost-effectiveness ratios. By limiting the studied population to women with severe osteoporosis (BMD T Score ≤−3.5 and without prevalent fracture, or with a T-Score between −2.5 and −3.5 with a prevalent osteoporotic fracture), sequential abaloparatide followed by alendronate is cost-effective compared to generic alendronate monotherapy [83]. In a Swedish population of patients aged 74 years and over with a recent major osteoporotic fracture, romosozumab for 12 months followed by alendronate for up to 48 months was compared with alendronate alone for a maximum duration of 60 months [84]. The cost of sequential romosozumab-to-alendronate treatment is lower than a Swedish reference willingness-to-pay per QALY of €60,000. Thus, evidence emerges that a sequential treatment in osteoporosis, with bone-forming agents followed by antiresorptive agents is cost-effective compared with antiresorptive agents alone [83]. This mostly concerns patients at very high risk of fracture. However, the fracture probability at which a sequential treatment regimen becomes cost-effective should still be more precisely determined.

Conclusions

The risk of osteoporotic fractures is a major healthcare concern, particularly in patients at very high risk or imminent risk of fracture. The costs borne by society are also significant, in terms of both immediate care and rehabilitation, and, in the longer term, dependence. There is now sufficient evidence of the short-term high-magnitude benefits of treatment and of the long-term safety profile of anti-osteoporosis treatments. Head-to-head studies demonstrate greater rapidity of action and magnitude of effect of anabolic compared with antiresorptive therapies in fracture risk reduction. In patients at very high or imminent fracture risk, the use of an anabolic agent as the initial treatment, followed by maintenance of the effect with an antiresorptive agent, offers a more effective strategy than first-line antiresorptive therapy for fracture risk reduction in these very vulnerable patients (Table I). These regimens in very high-risk patients are cost-effective. With the limitation of country-specific drug registration and reimbursement policies, such sequential regimens should become the standard of care for patients at very high or imminent risk of fracture.

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