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Editor

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Only doubt is certain and disbelief worth believing.
Without this courage there can be no learning.
Believe nothing.
*Anonymous**

"The quarterly journal *Progress in Osteoporosis* began in October 1993 as *Advances in Osteoporosis*. Its purpose was to provide readers without easy access to the literature with summaries of the most important literature. We now inhabit a virtual world. Information is instantaneously accessible to all at the tap of a keyboard; understanding is not. In the spirit captured by the anonymous author*, the purpose of this publication is to provide critical evaluation of the most important literature and so to provoke discussion. It is our intention to promote dialogue which examines the quality of information published and so its credibility. The opinions expressed are my own and do not necessarily reflect those of the International Osteoporosis Foundation."

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In this Issue

Advances have taken place in existing therapies and new therapies. These treatments are important contributions in a field in need for more effective ways of identifying persons at risk for fracture, in enabling the uptake and adherence with therapy, and in finding ways to monitor treatment.

Antiresorptive Agents

Zoledronic acid

Zoledronic acid has a fascinatingly long duration of action. Are we using it wisely? The reduction in clinical fractures was ~30% in women receiving one dose compared to those receiving three doses (1). Reid et al reported a single dose of 2.5 or 5 mg zoledronic acid resulted in similar increases in BMD at 2 years but greater at 5 years in the 5 mg group (2). The question is whether fracture risk reduction is achievable with lower doses given less often (3).

'Osteoporosis' is used synonymously with 'fragility', but women with osteopenia are not free of the risk for fracture. On the contrary, most of the burden of fragility fractures arises from women with osteopenia (4). Randomized placebo controlled trials are done in women with osteoporosis because the absolute risk for fracture is higher than in women with osteopenia, so detecting antifracture efficacy requires fewer participants. Of the trials done in women with osteoporosis, few demonstrate nonvertebral fracture risk reduction; and when a benefit is detected, there is only a 20-30% risk reduction. This is not satisfactory because 80% of all fractures are nonvertebral. Moreover, most of these arise among women with osteopenia.

Reid I, Horne A, Mihov B, Stewart A, Garratt L, Bolland M, Bastin S, Gamble G. Zoledronate every 18 months for 6 years in osteopenic postmenopausal women reduces non-vertebral fractures and height loss. Calcif Tissue Int 2018;102:S22 (abstract P068).

Reid et al tackled both unmet needs in a placebo controlled 6-year trial including 2000 women with osteopenia, zoledronic acid 5 mg every 18 months for 4 doses resulted in a 34% reduction in nonvertebral fractures (HR 0.66, 95%CI 0.51-0.85). An important contribution to the field.

Denosumab

Denosumab is a fully human monoclonal antibody directed against RANK ligand, a major regulator of osteoclast development which inhibits osteoclast recruitment, activity and survival. The osteoclast precursors are prevented from differentiating and may reside in bone marrow niches ready to differentiate if the opportunity arises. treatment for 3 years results in a 68% reduction in vertebral fractures, 40% reduction in hip fracture and 20% reduction in nonvertebral fractures (5).

Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, Roux C, Torring O, Valter I, Wang AT, Brown JP. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res 2018;33:190-8.

Cessation of denosumab causes a rapid reinitiation of unbalanced bone remodeling with each resorption cavity excavating more bone than is subsequently deposited. There is a decline in BMD within 12 months and progression of existing microstructural deterioration (which was never restored by treatment). Microstructural deterioration progresses and there is now evidence of an increased risk in multiple vertebral fractures. Of 1001 participants discontinuing denosumab, vertebral fracture rate increased from 1.2 to 7.1 per 100 participant-years, similar to 470 women discontinuing placebo (8.5 per100 participant-years). Among those with ≥1 off-treatment vertebral fracture, the proportion with multiple vertebral fractures was 60.7% compared with placebo (38.7%; p=0.049), corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively; odds ratio for multiple vertebral fractures after stopping was 3.9 times higher in women with vertebral fractures before or during treatment than those without fractures. Nonvertebral fracture rates were not increased. Patients discontinuing denosumab should transition to an alternative treatment either before or shortly after stopping denosumab.

When any antiresorptive is stopped, there is an increase in the number of remodeling units excavating bone. The question is, does this occur disproportionately when denosumab is stopped? There are at least two reasons why this might be so. Firstly, denosumab is not retained in bone and then released and readsorbed into bone after stopping, as occurs with bisphosphonates. When a bisphosphonate is stopped, increased numbers of osteoclasts remove bisphosphonate bound matrix and release the bisphosphonate which is readsorbed into bone, aborting the osteoclast activity and so attenuating the loss of bone. This does not occur when stopping denosumab. Osteoclasts are not prevented from resorbing bone. Secondly, if the osteoclast precursors originally prevented from differentiating, now do so, this might produce large numbers of differentiating osteoclast precursors; increased resorption cavities upon trabeculae create stress concentrators which predispose to microcrack propagation and vertebral fracture risk. Whether this overshoot in remodeling markers is a surrogate of disproportionate bone loss still remains to be proven. BMD returns to baseline, not to the level observed in placebo; the latter should occur if bone loss is disproportionate and greater than the accelerated loss found after stopping any remodeling suppressant.

Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY, Roux C, Malouf J, Bradley MN, Daizadeh NS, Wang A, Dakin P, Pannacciulli N, Dempster DW, Papapoulos S. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 2017;5:513-23.

In this study, women were treated with denosumab for 3 years then another 7 years but without a placebo controlled arm. Ten years of therapy was associated with continued suppression of bone remodeling, increases in BMD and 'low' fracture rates attributed to denosumab therapy. This may be so, but as ~50% of the inception cohort was lost and there was no control group shown to have continued fractures, the 'low' fracture rates could be the result of healthy user bias.

Stopping treatment results in increased remodeling, microstructural deterioration and increased fracture risk. Nevertheless, to assume antifracture efficacy in the absence of a control group shown to be continuing to suffer fractures is not evidence based. Indeed, attributing the 'low' fracture rates as causally related to treatment implies that we no longer need randomized trials to establish causation.

Antiresorptives are not anabolic, they do not reassemble the skeleton. Microstructural deterioration present at the time of starting treatment cannot be reversed beyond reduction in the reversal deficit in mineralized bone matrix volume produced by reducing the rate of remodeling. Most antiresorptives, apart from denosumab, do not abolish remodeling; so microstructural deterioration continues, albeit more slowly, because residual unbalanced remodeling continues to erode the skeleton. With denosumab, remodeling is virtually eliminated, so microstructural deterioration present at baseline may not worsen. However, the total bone matrix volume remains reduced and microstructure remains deteriorated. With continued remodeling suppression, the bone matrix may become more completely and homogenously mineralized, may accumulate advanced glycation end products, features that reduce matrix ductility.

Ominsky MS, Libanati C, Niu QT, Boyce RW, Kostenuik PJ, Wagman RB, Baron R, Dempster DW. Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. J Bone Miner Res 2015;30:1280-9.

In the FREEDOM trial, BMD increased by 21.7% in the spine and 9.0% in the femoral neck at 10 years. This is partly due to secondary mineralization, but increases in BMD produced by secondary mineralization should become asymptotic as more and more of the matrix becomes completely mineralized. This was not observed. Continued rise in BMD was observed during 8-10 years in human subjects. This may be due to a permissive effect of remodeling suppression on age-related *modelling*-based bone formation which now is detected as it is no longer being removed by rapid *remodeling* because this remodeling is suppressed by denosumab. This modeling-based bone formation is observed during remodeling suppression in cynomolgus monkeys as reported by Ominsky et al. The question is does modeling occur in human subjects and does this contribute to bone strength in a beneficial way. We don't know.

Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, Miller PD, Rao SD, Kendler DL, Lindsay R, Krege JH, Alam J, Taylor KA, Melby TE, Ruff VA. Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA Study. J Bone Miner Res 2018;33:298-306.

There is evidence to suggest the presence of age-related trabecular *modeling* occurs in human subjects and becomes detectable when denosumab suppresses rapid *remodeling*. Postmenopausal women with osteoporosis received 20 µg/d teriparatide (n=33) or 60 mg/6 months denosumab (n=36) for 6 months. Teriparatide increased remodeling-based and modeling-based formation upon cancellous and endocortical envelopes and modeling-based periosteal bone formation ($p<0.001$). Denosumab suppressed the surface extent of remodeling due to reduced birth rate of new BMUs, but cancellous modeling-based bone formation increased 2.5-fold ($p=0.048$). This effect was modest and seen at 3 months. The relevance of this finding to restoring bone strength is not known.

Anabolic Agents

Abaloparatide

Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C, ACTIVE Study Investigators. Effect of abaloparatide vs. placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 2016;316:722-33.

There is a new anabolic agent available for patient care. Abaloparatide shares amino acid sequences with parathyroid hormone-related protein (PTHrP) and PTH and acts via the PTHR1 receptor. Like PTH, the anabolic effect is likely to be predominantly remodeling-based and less so modeling-based. Miller et al randomized 2463 postmenopausal women to 18 months of 80 µg abaloparatide daily, placebo or open-label 20µg teriparatide daily. New morphometric vertebral fractures occurred in 0.58% of the abaloparatide group, 4.22% of the placebo group (RR 0.14),

and 0.84% of the teriparatide group. The event rate for nonvertebral fracture was 2.7% for abaloparatide, 4.7% for placebo (HR 0.57, 95%CI 0.321.00), and 3.3% for teriparatide (nonsignificant compared to placebo and abaloparatide). Major osteoporotic fractures were said to be reduced with abaloparatide relative to placebo (6.2%) and teriparatide (3.1%).

This is a contribution because reconstructing the skeleton is an important goal in therapy. However, the claim that abaloparatide produced an earlier and more efficacious fracture risk reduction than teriparatide requires cautious interpretation. There was an increase in number of women having fractures in the first weeks in the placebo and teriparatide groups that is unlikely to be associated with allotment to placebo or drug. This was not found in the abaloparatide group. Differences in fracture rates in the second and third 6 months of the 18-month trial in the two treatment arms were minimal. The claim that the anabolic effect is accompanied by less bone resorption with abaloparatide than teriparatide and that this accounts for the 1-2% difference in BMD are also interpretations that are difficult to accept for a range of reasons (6,7).

Romosozumab: Modeling-based anabolic therapy

Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532-43.

Two studies support the antifracture efficacy of this anabolic agent. Cosman et al enrolled 7180 postmenopausal women with osteoporosis to romosozumab (210 mg) or placebo monthly for 12 months, followed by denosumab (60 mg 6 monthly) for 12 months. At 12 months, risk reductions were reported for vertebral fractures by 73% (P<0.001), for clinical fractures by 36% (P=0.008), and nonvertebral fractures by 24% (P=0.10). At 24 months, vertebral fracture risk was reduced by 75% (P<0.001).

Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27.

Saag et al assigned 4093 postmenopausal women with osteoporosis and a fragility fracture to romosozumab (210 mg) or weekly alendronate (70 mg) for 12 months then open-label alendronate in both groups. At 24 months, romosozumab/alendronate reduced vertebral fracture risk by 48% (P<0.001), clinical fractures by 27% (P<0.001), nonvertebral fracture by 19% (P = 0.04), hip fractures by 38% (P = 0.02). At 12 months, romosozumab/alendronate reduced vertebral fractures (RR 0.63; 95%CI 0.47-0.85), clinical fractures (HR 0.72; 95%CI 0.54-0.96). The nonvertebral fracture risk reduction of 26% was not significant (P=0.06). During year one, more cardiovascular adverse events observed with romosozumab than alendronate (2.5% vs. 1.9%).

Holdsworth G, Greenslade K, Jose J, Stencel Z, Kirby H, Moore A, Ke HZ, Robinson MK. Dampening of the bone formation response following repeat dosing with sclerostin antibody in mice is associated with up-regulation of Wnt antagonists. Bone 2018;107:93-103

Antibodies to sclerostin (Scl-Ab) increases bone mass, BMD and bone strength by increasing bone formation and decreasing bone resorption. The increase in bone formation markers is attenuated upon repeat dosing with Scl-Ab. The authors reported that attenuation in bone formation was associated with expression of antagonists of Wnt signalling. Female Balb/c mice treated with Scl-Ab had a large increase in serum P1NP following the first dose which attenuated with multiple doses. Expression of SOST, SOST-DC1, DKK1, DKK2, SFRP1, SFRP2, FRZB, SFRP4 and WIF1 transcripts increased 1.5-4.2 fold following a single dose of Scl-Ab. With the exception of SFRP1, these changes were maintained or increased following six doses of Scl-Ab and the abundance of SFRP5 also increased. Wnt antagonists may exert a negative feedback to increased Wnt signalling induced by Scl-Ab self-regulating bone formation. After an antibody-free period of four weeks, the P1NP responsiveness returned and a second phase of treatment with Scl-Ab elicited additional gains in BMD, suggesting a treatment-free period may restore full bone formation responsiveness to Scl-Ab.

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

McClung et al reported loss of benefit of romosozumab soon after cessation of therapy. 364 postmenopausal women with low bone mass were treated with romosozumab for 24 months and then randomized to either denosumab or placebo for a further 12 months. Treatment with romosozumab led to a continued increase in BMD over 2 years with further accrual in those that transitioned to denosumab, whereas BMD returned toward pretreatment levels in those that

transitioned to placebo.

Dkk1: Another target for anabolic therapy

McDonald MM, Morse A, Schindeler A, Mikulec K, Peacock L, Cheng T, Bobyn J, Lee L, Baldock PA, Croucher PI, Tam PPL, Little DG. Homozygous Dkk1 knockout mice exhibit high bone mass phenotype due to increased bone formation. Calcif Tissue Int 2018;102:105-16.

Like sclerostin, a product of the SOST gene, the Wnt antagonist Dkk1 is a negative regulator of bone formation. Homozygous Dkk1 (-/-) mice heterozygous for Wnt3 loss of function mutation show a high bone mass phenotype with 3-fold increases in trabecular bone volume. Cortical bone was increased in the tibiae and vertebrae, which correlated with increased strength. Dynamic histomorphometry identified increased bone formation with no changes in bone resorption. Targeting Dkk1 has therapeutic potential.

Anabolic vs. Antiresorptive Agents

Teriparatide vs. risedronate

Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2018;391: 230-40.

There is now evidence that PTH1-34 reduces vertebral and clinical fracture risk more effectively than risedronate. Kendler et al compared antifracture efficacy of 20 µg of teriparatide once daily vs. 35 mg of oral risedronate in postmenopausal women with severe osteoporosis in a double-blind trial. During 24 months, new vertebral fractures occurred in 28/680 (5·4%) of patients in the teriparatide group and 64/680 (12·0%) patients in the risedronate group (RR 0·44, 95%CI 0·29-0·68; p<0·0001). Clinical fractures occurred in 4·8% in the teriparatide group and 9·8% in the risedronate group (HR 0·48, 95%CI 0·32-0·74; p=0·0009). Nonvertebral fragility fractures occurred in 4·0% patients in the teriparatide group and 6·1% in the risedronate group (HR 0·66; 95%CI 0·39-1·10; p=0·10).

Teriparatide vs. romosozumab

Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet 2017;390:1585-94.

In an unblinded study comparing romosozumab 120 mg monthly vs. teriparatide 20 µg daily in postmenopausal women previously treated with bisphosphonates, total hip BMD increased with romosozumab by 2.6% and decreased by 0.6% with teriparatide. Both drugs increased spine BMD (romosozumab 9.8% vs. teriparatide 5.4%). At the hip, romosozumab increased cortical vBMD, while teriparatide decreased it. Trabecular vBMD was similarly increased with both drugs. What are we to infer about such studies? BMD may decrease when a large volume of under mineralized bone is deposited, but what happens to bone strength? This cannot be inferred. Some insight may result in assessment of microstructure; but even then, when radiation transmission is used to quantify structure, inferences regarding bone strength are difficult to make because matrix volume can increase but this will not be 'seen' by radiation transmission if the matrix is undermineralized. Errors are likely to occur when microstructure measured incorrectly because changes in microstructure alter bone strength exponentially (8).

Combining Anabolic & Antiresorptive Agents

Tsai JN, Nishiyama KK, Lin D, Yuan A, Lee H, Bouxsein ML, Leder BZ. Effects of denosumab and teriparatide transitions on bone microarchitecture and estimated strength: the DATA-Switch HR-pQCT study. J Bone Miner Res 2017;32:2001-9.

To assess the effects of transitions from teriparatide to denosumab and the reverse, HR-pQCT at the distal tibia and radius in postmenopausal osteoporotic women was used in patients who received 24 months of teriparatide 20 µg daily followed by 24 months of denosumab 60 mg every 6 months, 24 months of denosumab followed by 24 months of teriparatide, or 24 months of both medications followed by 24 months of denosumab. 77 women completed at least one post-switch

visit are included. Tibial cortical vBMD increased in the teriparatide-to-denosumab (net 48-month change -0.8±2.4%) and combination-to-denosumab groups +2.4±4.1%) but decreased in the denosumab-to-teriparatide group -3.4±3.2%, p<0.001). Changes in total vBMD, cortical thickness, and estimated stiffness followed a similar pattern, as did changes at the radius. Conversely, tibial cortical porosity remained stable in the teriparatide-to-denosumab and combination-to-denosumab groups (net 48-month changes +7.2±14.8% and -3.4±12.1%, respectively) but increased in the denosumab-to-teriparatide group (net +16.2±11.5%, p<0.05 vs. other groups). Trabecular vBMD changes did not differ among groups. The use of teriparatide after denosumab should be avoided. The use of combined teriparatide/denosumab followed by denosumab alone may be useful.

References

1. Reid IR, Black DM, Eastell R, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. J Clin Endocrinol Metab 2013;98:557-63.

2. Grey A, Bolland MJ, Horne A, et al. Duration of antiresorptive activity of zoledronate in postmenopausal women with osteopenia: a randomized, controlled multidose trial. CMAJ 2017;189:E1130-E6.

3. Grey A, Bolland M, Mihov B, et al. Duration of antiresorptive effects of low-dose zoledronate in osteopenic postmenopausal women: a randomized, placebo-controlled trial. J Bone Miner Res 2014;29:166-72.

4. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med 2004;164:1108-12.

5. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-65.

6. Martin TJ, Seeman E. Abaloparatide is an anabolic, but does it spare resorption? J Bone Miner Res 2017;32:11-6.

7. Seeman E, Nguyen TV. Bone remodeling markers: so easy to measure, so difficult to interpret. Osteoporos Int 2016;27:33-5.

8. Schaffler MB, Burr DB. Stiffness of compact bone: effects of porosity and density. J Biomech 1988;21:13-6.

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