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Anti-resorptives in the management of osteoporosis

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Bone-active agents that decrease bone turnover (the anti-resorptive agents) have been, to date, the most thoroughly studied pharmacological agents for the management of osteoporosis in a variety of populations – postmenopausal, male, and glucocorticoid-induced osteoporosis – and have received both Food and Drug Administration (FDA) and Committee for Medicinal Products for Human Use (CHMP) as well as other worldwide registrations for the management of these conditions. While the mechanisms of action of 'anti-resorptives' as a class differ, their effect on increasing bone strength and reducing the risk of fragility fractures share common pathways: an increase in bone mineral content, and a reduction in bone turnover. Within the category of anti-resorptives: estrogen, selective estrogen receptor modulators, tibolone, calcitonin, bisphosphonates and denosumab all reduce vertebral fractures risk, but differ in their ability to reduce the risk of non-vertebral fractures in randomized clinical trials. This chapter will discuss the data on these effects for each class of anti-resorptive agent.

Key words: anti-resorptive; osteoporosis; bone mineral density; bone turnover; fragility fractures; vertebral fractures; non-vertebral fractures; estrogens; selective estrogen receptor modulators; tibolone; calcitonin; bisphosphonates; denosumab.

Bone remodeling is an ongoing process in human bone biology that is necessary to repair micro-damage and renew skeletal integrity and strength.[1,2] The process of bone remodeling in human beings replaces the entire human skeleton every decade. Bone resorption is intimately coupled to bone formation, and vice versa. This process is regulated by both systemic as well as local regulators of bone cell activity.[3–5] Systemic regulators of osteoblast differentiation and activity include endogenous parathyroid hormone (PTH), vitamin D metabolites, the interleukins, prostaglandins, phosphatonins, and the steroid hormones: both gonadal (estrogen and testosterone) and cortisol. Local regulators of bone remodeling that determine osteoclast differentiation and

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activity are the rank-ligand (RankL) and osteoprotogerin (OPG), peptides that emanate from osteoblasts. Osteoclast receptor rank and RankL binding leads to osteoclastogenesis. The decoy receptor to Rank (OPG), binding to RankL leads to an increase in osteoclast activity, since less RankL is available to down-regulate Rank. Inhibitors of RankL (such as anti-Rank ligand antibody) lead to a decrease in osteoclastogenesis and osteoclast activity, thus reducing bone resorption.[6] Regulation of bone remodeling also includes the dominant cell in bone, the osteocyte.[7,8] The osteocyte-derived phosphatonin, fibroblast growth factor 23 (FGF-23) and sclerostin also have direct and indirect effects on bone turnover.[9,10] Specifically, sclerostin down-regulates the critical osteoblast regulator, Wnt, and inhibition of sclerostin also leads to an increase in osteoblast genesis and activity, as does a group of peptides that may modify osteoblast activity independently of Wnt. These include DKK1.

Osteocytes also respond to mechanical signals which lead to alterations in periosteal bone formation and bone strength. Low-level mechanical signals are anabolic to bone via pathways that involve, in large part, the osteocyte mechanostat.[7]

Finally, there is a growing body of evidence that fat cells (adipocytes) may have a regulatory role in bone remodeling by affecting osteoblast differentiation via a number of pathways.[11,12]

Thus, while many local and systemic factors regulate osteoblast differentiation and activity, the final common pathway emanating from osteoblasts that regulate osteoclast activity is the RankL–osteoprotogerin competitive binding to osteoclast receptor, Rank. Since pharmacological 'anti-resorptive' agents alter bone resorption by altering osteoclast activity, this chapter will focus on how these agents affect bone turnover and bone strength, and reduce the risk for low-trauma fractures. While some of the anti-resorptive agents alter bone turnover by affecting the RankL system – estrogens, selective estrogen receptor modulators (SERMs), tibolone, denosumab – others have direct effects on osteoclasts (calcitonin, bisphosphonates).[13,14]

ESTROGENS

Estrogens are anti-resorptive agents that inhibit bone resorption, increase bone mineral density (BMD), and reduce the risk for both vertebral and hip fractures. While there are abundant data on the effect of estrogens on surrogate markers of bone strength (improvements in BMD and reduction in bone turnover markers), the best prospective fracture data come from the Women's Health Initiative (WHI).[15,16] Doses of hormonal replacement therapy (HRT) containing either 0.625 mg/day of conjugated equine estrogen plus 5 mg/day of methoxyprogesterone or 0.625 mg/day of estrogen alone significantly reduced the incidence of fractures at all skeletal sites as compared to placebo. One of the unique observations concerning the fracture data from the WHI is the reduction in fractures in a predominately non-osteoporotic (by World Health Organization BMD criteria). While the majority of patients randomized in the WHI population did not have BMD measurements, there is a reasonable amount of indirect data to suggest that, by WHO criteria, these patients were not osteoporotic.[17] While lower doses of estrogen have been shown to reduce bone turnover and increase BMD, prospective evidence showing a reduction in risk for fracture with-low dose estrogen is lacking.[18,19] There are plausible reasons to attempt to utilize lower doses of HRT for whatever indication, including a better safety profile at lower doses. Although HRT is no longer registered for the treatment of osteoporosis, there are concrete reasons to consider their application in early menopausal women, and prevention of the loss of BMD is an additional benefit.

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SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

The SERMs are molecules that share agonist and antagonistic mechanisms of action with the estrogen receptor.[20] While agonistic to bone, they are antagonistic to the estrogen receptor on breast and uterine endometrial tissue. Two SERMs are registered for management of postmenopausal osteoporosis (PMO), raloxifene and bazedoxifene, and there are additional SERMs in clinical trial developmental stages. The first SERM registered for the prevention and treatment of postmenopausal osteoporosis is raloxifene.[21] Bazedoxifene is registered for the prevention of postmenopausal bone loss and is under FDA consideration for a treatment indication after recently presented evidence for a significant reduction in vertebral fracture incidence in postmenopausal women with osteoporosis.[22] The pivotal raloxifene trial given the acronym MORE (Multiple Outcomes Raloxifene Evaluation) demonstrated that raloxifene (60 mg/day, the registered dose) reduced the incidence of new vertebral fractures in women with or without prevalent vertebral fractures yet who had baseline BMD standard deviation scores from the young normal premenopausal mean (T scores) of -2.0 or lower. There has been no evidence that raloxifene reduces the incident of non-vertebral or hip fractures. Raloxifene has also recently received registration for the reduction of invasive breast cancer.[23,24] For the management of skeletal health, raloxifene is perhaps most valuable for early and younger postmenopausal women with low BMD at the spine or with vertebral fractures but normal BMD at the hip, where the goal of treatment is to reduce the risk of vertebral fractures and the risk for non-vertebral fractures is lower. The same population could be selected for the use of bazedoxifene, which lowers the risk of incident vertebral fractures but, like raloxifene, had no evidence for the reduction of non-vertebral or hip fractures. Both of these SERMs may induce hot flushes and have a small but significant increase risk for thromboembolic events, such that their use should be avoided in women with a history of venous thrombosis. There are current clinical trials examining the potential ability of newer SERMs to cause fewer hot flush events, and combining bazedoxifene with low-dose estrogen to achieve fewer hot flushes while retaining the breast- and uterine-protective effects of SERMs. There are no head-to-head fracture comparisons between or among the SERMs.

TIBOLONE

Tibolone, an analogue of the progestin norethynodrel, is a drug with tissue-specific effects on receptors and enzymes that influences the synthesis and metabolism of endogenous estrogen, progesterone, and androgen.[25] This is achieved via the intestinal bioconversion of tibolone into metabolites that have tissue-specific agonistic and/or antagonistic estrogenic (3α- and 3β-hydroxytibolone) and progestogenic/androgenic (δ4 tibolone) properties. Tibolone is registered in Europe for the prevention and treatment of postmenopausal osteoporosis; it reduces hot flushes, and may improve sexual dysfunction.[26,27] In a head-to-head comparator trial the registered dose of tibolone (1.25 mg/day) increased spine and hip BMD to a greater amount than raloxifene, and recently tibolone has also been shown to reduce the incidence of vertebral compression fractures.[28] From surrogate marker data, tibolone increases BMD and reduces bone turnover, similar to the effect seen with estrogens. In the USA the pivotal prospective fracture trial was terminated early due to a greater risk of cerebrovascular accidents.

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CALCITONIN

Calcitonin, a peptide derived from the parafollicular cells of the thyroid, is an inhibitor of osteoclast activity.[29] In the management of PMO, most of the marketed forms of calcitonin are concentrated from the thyroid glands of salmon, although eel and human synthetic forms are also available.[30,31] Calcitonin is available in both injectable and nasal-spray formulations. The registered formulation and dose for PMO for nasal calcitonin is 200 IU/day, which is a single nasal-spray administration or 100 IU/day in the subcutaneous injectable formulation. In the pivotal clinical trial that led to the registration of nasal calcitonin, only the 200 IU/day dosage reduced the incidence of vertebral compression fractures, but the lower (100 IU/day) or higher (400 IU/day) doses did not.[32] Furthermore, there was no effect of any nasal-spray calcitonin dose on the incidence of non-vertebral or hip fractures. It has been suggested that calcitonin may improve bone strength through changes in bone micro-architecture, although this hypothesis has not been validated.[33] Calcitonin may have an analgesic effect on acute or chronic vertebral compression fractures, although the data are inconsistent for this potential benefit.[34] Side-effects with calcitonin are uncommon, but the injectable formulation may be associated with nausea. There have been rare reports of allergic reactions to the salmon preparation in the injectable form. Calcitonin use has been most popular in the elderly population who may not be able to follow the dosing instructions for oral bisphosphonates.

BISPHOSPHONATES

Bisphosphonates are biochemical analogues of naturally occurring pyrophosphate. Bisphosphonates have high affinity for bone, attaching to the denuded bone-resorptive cavity calcium–phosphorus surface by a physiochemical mechanism and reduces the depth of the resorption cavity.[35,36] Reducing both the number (remodeling space) and depth of the resorption cavity (stress risers) is a major mechanism whereby bisphosphonates increase bone mineral content and bone strength. Bisphosphonates also have a cellular effect on all three bone cell lines. Their best-studied and best-understood effect is on osteoclasts, where they are taken up by osteoclasts at the resorptive cavity site, altering their intracellular function and leading to a decrease in osteoclast activity and, perhaps, life span (apoptosis).[37,38] Bisphosphonates have unique pharmacokinetic properties, especially in that they are not metabolized, have a very long half-life in bone, are recycled – unchanged in molecular structure – back into the circulation where they can maintain a reduced bone-remodeling space and turnover even though they are not being provided to the patient. This recycling comes from both a detachment from the bone surface during bone resorption and by passing through the cell membrane of the osteoclast by a process termed transcytosis.[39] The bisphosphonate that is not in bone is excreted in the urine unchanged by either glomerular filtration or proximal tubular secretion. Approximately 50% of a given bisphosphonate dose is bound to bone, and 50% is excreted by the kidney. The effect of bisphosphonates on osteoblasts and osteocytes is becoming better clarified. In these cell lines they may be anti-apoptotic.[40,41]

Bisphosphonates have been registered for the prevention and treatment of osteoporosis in the postmenopausal population, as well as in men and in patients on chronic glucocorticoids.[42,43] Whereas the registration for PMO is based on 3 years of incident vertebral fracture risk reduction as compared to that in a placebo group, the registration for glucocorticoid and male osteoporosis is based on surrogate marker rather

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than fracture data. Likewise, all of the intermittent (weekly, intravenous quarterly, and monthly) bisphosphonate formulations have been approved on the basis of surrogate marker data.[44,45] For registration of these non-daily formulations, the scientific requirement was a non-inferiority end-point in BMD – that the intermittent formulations increased spine BMD by dual energy x-ray absorptiometry (DXA) equal to the fracture proven daily dose. The only intermittent bisphosphonate formulation that has direct prospective fracture data as compared to placebo is the annual intravenous zoledronic acid formulation. In the pivotal registration clinical trial for zoledronic acid, this bisphosphonate (5 mg/year for 3 years) reduced the risk of vertebral, non-vertebral, and hip fractures. These effects were seen even in the first year of administration.[46]

The ability of bisphosphonates to be given in less frequent dosing intervals is probably related to their affinity for and slow detachment from bone resorption cavities. While there are clear distinctions among the bisphosphonates in their physiochemical properties and effects on the osteoclast enzyme farnesyl pyrophosphate synthetase (FPPS), differences in their biology in vivo or in human beings is less clear. In addition, since there are no head-to-head comparative fracture data, any statements concerning fracture reduction benefits of one bisphosphonate over another are speculative. Since the bisphosphonates have been the most widely studied anti-resorptive agents, as well as the most widely prescribed agents for the management of osteoporosis, the following paragraphs will detail the clinical trial data and/or meta-analysis of each bisphosphonate in terms of its efficacy as well as safety.

Etidronate

Etidronate, a non-aminobisphosphonate and the first bisphosphonate to be developed and registered for osteoporosis, is registered for the treatment of PMO in most nations.[47] Registration in the United States was not obtained because the clinical registration trial did not achieve the required 3-year reduction in incident vertebral fracture as compared to placebo. The etidronate registration clinical trial was statistically powered for the primary end-point then required by the FDA for registration of treatment for PMO: i.e. a significant increase in spine BMD as compared to placebo. While this bisphosphonate trial was under way, the United States fluoride data were published, where 80 mg/day of sodium fluoride induced a linear increase in spine BMD yet no reduction in fractures and even a higher risk for non-vertebral fracture as compared to placebo.[48] With this new information and apparent disconnection between the increase in BMD and reduction in fracture risk, the FDA changed the primary end-point for registration from a BMD end-point to the 3-year reduction in fracture risk. Despite the fact that the cyclical etidronate pivotal clinical trial was not powered for fracture risk reduction, the data did show significant reduction in incident vertebral fractures through 2 years as compared to placebo, and reduction through 3 years in a post-hoc analysis of a subset of the initial randomized population. Nevertheless, USA registration was not obtained. Through many years of clinical practice, cyclical (400 mg QD for 14 days, repeated every 74 days) has been an effective intervention for the management of osteoporosis in many parts of the world. In addition, analysis from the UK General Practice Research Database (GPRD) has suggested that etidronate reduces the risk for hip fractures.[49] Despite this evidence, etidronate is less frequently used for the management of PMO due to the more compelling evidence for prospective fracture risk reduction by the aminobisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid).

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Etidronate is safe in prescribed doses even on quantitative bone histomorphometry.[50] While higher doses of etidronate have been associated with a mineralization defect and even frank osteomalacia, this defect in mineralization has not been seen with cyclical, intermittent use. While the aminobisphosphonates may be associated with upper gastrointestinal side-effects (UGI), UGI side-effects are uncommon with etidronate, while lower gastrointestinal side-effects are more common with etidronate.

Alendronate

Alendronate was the first registered aminobisphosphonate for the management of PMO. The pivotal registration clinical trial that led to the registration of alendronate, the fracture intervention (FIT) trial, randomized postmenopausal women with (FIT-1) or without (FIT-2) prevalent vertebral compression fractures, and used 5 mg/day for the first 2 years and 10 mg/day for the third year.[51,52] This trial demonstrated a significant reduction in incident vertebral fractures in both populations. Reduction of non-vertebral fractures was not observed in either population (except wrist fracture reduction in FIT-1) fractures. Hip-fracture reduction was observed in FIT-1 but not FIT-2, except in a post-hoc analysis of the population randomized using the hip reference population database (National Health and Nutrition Examination Survey III {NHANES-III}) with T scores of −2.5 or lower. Nevertheless, based on these data, alendronate is registered for the reduction of vertebral and hip fractures, but not non-vertebral fractures, at a dose of 10 mg/day. Interestingly, most of the fracture risk reduction in the alendronate trials was seen with the 5-mg/day dose used for the first 2 years of the 3-year registration trial. In a separate, non-registration trial, 70 mg/week of alendronate was effective in reducing the risk of non-vertebral fractures as compared to control.[53] Although the 35-mg/week formulation is registered for the prevention of early postmenopausal bone loss, and might be considered off-label for treatment (e.g. gastrointestinal tolerability at higher doses) of PMO, in most countries the price of the 35 mg/week versus the 70 mg/week is comparable. Hence, the recommendation is to use the 70 mg/week formulation, if the intermittent dosing formulation is used.

While there are no head-to-head fracture comparative trials between or among the bisphosphonates, there has been a prospective and randomized 2-year trial comparing alendronate (70 mg/week) to risedronate (35 mg/week), with the end-points being changes in BMD and bone turnover markers (BTMs) between these two aminobisphosphonates. This trial, given the acronym 'FACT' (fosamax actonel comparator trial) did show that weekly alendronate significantly increased BMD and reduced BTMs greater than changes in similar surrogate markers than risedronate.[54] However, this trial was not designed as a fracture comparative trial, so there cannot be any firm conclusions about differences between these bisphosphonates and improvements in bone strength. In general, bisphosphonates increase bone strength through multiple mechanisms, and the relationship between changes in BMD mediated by bisphosphonates and changes in bone strength is neither linear nor proportional.[45,55–59] Hence, although greater improvements in BMD are associated with greater improvements in bone strength, both in individual trial analysis as well as meta-analysis of bisphosphonates, because the relationship is not linear, differences in bone strength mediated between or among bisphosphonates as a function of changes in DXA-derived BMD remain speculative.[60,61] This non-linear relationship is related to the data that bisphosphonates improve bone strength through multiple mechanisms, and these non-BMD factors (e.g. bone quality) cannot be measured in clinical practice at this time.[62–67]

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One additional alendronate dataset should be discussed here: the 'FLEX' trial (Fosamax Long Term Extension).[68] FLEX followed a subset of the original FIT trials for 10 years, and to keep the analysis practical, fundamentally, patients were followed for either 10 years on continuous alendronate, or were on alendronate for 5 years and then off therapy for the following 5 years. Patients on 10 years had a slight continual rise in spine and hip BMD and reduction in BTMs, while those on 5 years and then off for 5 years had also had a suppression of BTMs; although the resorption markers for this group of patients began to rise during the 'off' period, they never approached the baseline, pre-treatment level. The BMD response during the off period was heterogeneous: the spine BMD remained stable, while the total hip BMD returned to baseline. The real question is: what happened to bone strength during the 'off period'? This is where the data become less certain, since the number of fractures in the continuously treated group versus the discontinued group are small in number, and since the follow-up period was not randomized, there may be selection biases. Nevertheless, FLEX represents the longest-term follow-up data off bisphosphonates. During the 5-year follow-up, there were no differences in hip, morphometric or non-vertebral fractures between the continuously treated as compared to the discontinuously treated groups. There was a significantly greater number of clinical vertebral fractures in the discontinuous group (5% in 437 patients) as compared to the continuously treated group (2% in 662 patients; $P < 0.05$). Given the limitations of these data, they still represents the longest data available off bisphosphonates after long-term use. The data do provide clinicians with some scientific grounds for suggesting a 'drug holiday' from bisphosphonates. How long alendronate should be administered before considering a bisphosphonate break is another question that has recently been raised by Curtis and colleagues.[69] These investigators conducted a post-hoc analysis of a large US health-care database and observed that patients given a 'drug holiday' from alendronate who had been on this bisphosphonate for 2 years or less had a greater risk for hip fractures than those patients on alendronate for more than 2 years. These data might suggest that a certain amount of skeletal loading could be necessary to see a protective effect after discontinuation. In a separate short-term follow-up risedronate study, Watts and colleagues did not see an increase in fracture risk in a subset of risedronate patients.[70]

Why would a drug holiday even be considered? When bisphosphonates were first registered for PMO, younger postmenopausal women were infrequently counseled on bisphosphonate use to protect their skeletal health. This paradigm changed after the publication of the Women's Health Initiative where data suggested that HRT increased the risk of cardiovascular disease in women started on HRT. Women who were concerned about osteoporosis increasingly sought counsel and BMD testing, and many were begun on bisphosphonates in their early postmenopausal years. At that time physicians increasingly began to ask questions about the duration of bisphosphonate use. Based on the science unraveling the long bone retention and then the recycling of biologically active bisphosphonates, the consideration of a 'drug holiday' became a real consideration. Since the true half-life among bisphosphonates is unknown in head-to-head comparative studies in human beings, it remains unknown whether the bisphosphonate-off period could differ among bisphosphonates. Only opinion exists in providing recommendations of the duration of any 'drug holiday' among the different bisphosphonates. The pragmatic approach is to measure annual BMD and BTM in such patients and make clinical decisions according to the changes in these surrogate markers.

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Risedronate

Risedronate is the second aminobisphosphonate registered worldwide for the management of PMO. While it is another aminobisphosphonate, it differs chemically from alendronate in that the nitrogen atom is incorporated into a pyridinoline ring. This chemical difference is hypothesized to potentially make risedronate less irritating to the upper gastrointestinal mucosa, although evidence for this potential difference is based on weak data. However, the pivotal trials documenting the benefit of risedronate to reduce fracture risk are compelling. As with all other bisphosphonate fracture data, the registration trials showing a fracture reduction benefit are based on the daily (5 mg/day) formulation as compared to placebo.[71,72] In this regard, risedronate is effective in reducing the incidence of vertebral fractures, and has the longest placebo-controlled data showing risk reduction through 5 years as compared to placebo.[73] In addition, the risedronate data are the only data showing a prospective reduction in non-vertebral fracture risk with an oral bisphosphonate.[71] The risedronate clinical trials were designed such that vertebral x-rays were performed at baseline and the first year after initiating risedronate. In this manner, the daily risedronate dose was shown to reduce the incidence of vertebral fractures in 1 year. This may be an important observation, since in the placebo group those patients with a radiographic vertebral fracture within the first year of these risedronate clinical trials had a very high risk for another vertebral fracture within the following 12 months. Other clinical trials with oral bisphosphonates either did not examine incident vertebral fractures at year 1 or, if they did, did not demonstrate or report the data.[74,75] While the hypothesis of 'speed-of-onset' has been suggested from this early risk reduction seen with risedronate, it remains a speculative finding due to the absence of head-to-head fracture data. Post-hoc data of the risedronate datasets, as well as prescription/hospital-based records, suggest an earlier onset of effect for non-vertebral as well as hip fractures with risedronate as compared to aledronate, these data are biased by selection and confounder.[76] Risedronate does have the largest prospective hip fracture trial of all Bisphosphonates.[77] There was a significant reduction in hip fractures in those patients randomized with a femoral neck T score ≤ -2.5. Although a robust finding, risedronate did not gain registration for hip fracture reduction due to the registration agency requirements that the primary end-point must be achieved first, and the hip fracture reduction in those randomized with WHO osteoporosis at the hip was a secondary end-point. Recently, the monthly formulation (150 mg/month) of risedronate was registered.[78] It is hoped that these intermittent – as opposed to the daily – formulations will lead to better compliance with bisphosphonates that might translate into better risk reduction and overall costs of osteoporosis.[79]

Ibandronate

Ibandronate was registered for the treatment of PMO (2.5 mg/day) on the basis of the registration trial.[75] The monthly formulation (150 mg/month) was subsequently approved, as the other less frequent dosing schedules for oral bisphosphonates, on the basis of a non-inferiority end-point: that the increase in spine BMD with monthly ibandronate was equivalent to the fracture proven daily dosage.[80] Ibandronate was also the first intravenous bisphosphonate registered for the treatment of PMO (3 mg intravenous injection every 3 months) also on the basis of a non-inferiority

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end-point.[81,82] The fracture proven daily dose did not show evidence of reduction in non-vertebral or hip fractures in prospective data, but did show a reduction in non-vertebral fractures in a post-hoc analysis in a subset of the initial randomized population in whom femoral neck T scores were ≤ -3.0. As previously stated, non-vertebral or hip fracture data are not as robust as primary end-point vertebral fracture data.[83,84] It is interesting to also be cognizant of a post-hoc analysis examining the relationship between the calculated cumulative dose of ibandronate (termed the annual cumulative exposure, ACE) and the reduction in non-vertebral fracture (and hip fracture) events.[85,86] In these two analyses, the higher ACE obtained with the higher doses of ibandronate (150 mg/month or 3 mg intravenously every 3 months) was associated with significant reductions in non-vertebral as well as hip fractures as compared to the registration dose (2.5 mg/day) or other lower doses of ibandronate. These data lead to interesting speculation that the higher blood levels that might be obtained might lead to greater risk reduction than can be achieved with lower doses. Finally, in a head-to-head non-inferiority trial comparing monthly ibandronate to weekly alendronate, both formulations were equal in their increases in BMD and without differences in safety profiles.[87]

Zoledronic acid

Intravenous (5 mg in a 15-minute infusion) of zoledronic acid, given for three annual infusions, was the first intermittent bisphosphonate formulation to have randomized, prospective data to show a reduction in the incidence of vertebral and non-vertebral (including hip) fractures in a postmenopausal population as compared to placebo.[46] In addition, this bisphosphonate reduced the fracture risk in randomized patients who were treatment-naive (labeled 'stratum I') as well as in a smaller sample size of the original randomized population who were on and continued for the first year of the 3-year trial who were receiving a different anti-resorptive agent (calcitonin or raloxifene). There are ongoing analyses (extension studies) of this population that should answer many long-term management questions. One of these questions is: are three annual infusions of zoledronic acid all that is required to have long-term maintenance of bone turnover and risk reduction? This discussion emanates from the known high affinity for the crystal surface of zoledronic acid, the long-term suppression of bone turnover markers (12+ months) seen after a single 4-mg infusion of zoledronic acid in the dose-ranging study, and the alendronate FLEX data previously mentioned where there may be sustained effects on bone biology after the skeleton has been loaded with bisphosphonate.[88] It is possible that, after three annual infusions, there is enough zoledronic acid in the bone to be re-cycled, allowing maintenance of BMD and BTM and risk reduction.[89] The extensions studies of the pivotal zoledronic acid registration trials for PMO will help answer some of the questions concerning duration of use, possible drug holidays, or the need to continue therapy beyond 3 years. Most of the extension-study data will, by virtue of selection biases and use of surrogate markers for fracture, be suggestive of long-term outcomes rather than definitive scientific answers. This latter comment is a simple fact from the nature of studies (including FACT) that do not retain all of the initial randomized study population. Nevertheless, the long-term extension studies of the zoledronic acid registration trial will provide valuable data to guide physicians on the long-term use of zoledronic acid for PMO.

Finally, zoledronic acid was shown in a separate trial to reduce the incidence of a second clinical fracture in elderly patients with a recent hip fracture.[90] An interesting

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and unexplained observation in this trial by Lyles et al is that the overall mortality rate was also lower in the patients that received zoledronic acid than placebo.

DENOSUMAB

The first monoclonal antibody to RankL (denosumab) will offer another choice for the management of PMO.[91,92] The phase-II clinical dose-ranging data, now extended for 4 years, shows that the planned registered dose (60 mg subcutaneously every 6 months) has a rapid onset of inhibition of bone turnover to a greater extent than with alendronate (70 mg/week), and that this reduction of bone turnover dissipates rapidly after discontinuation of denosumab, while reintroduction of denosumab results in a return of responsiveness when re-started.[93] Furthermore, the return of denosumab's responsiveness after 1 year of discontinuation mimics (slope of the decline in BTM) that seen with treatment-naive patients. Hence, it would appear that there is no blunting of the BTM effects of denosumab after prior denosumab exposure. A very interesting observation for the long-term phase-II denosumab data is that early on in the off-set phase after 1 year of prior treatment is that both the serum CTX as well as BSAP not only return to baseline but go above baseline ('over-shoot'), yet nevertheless return to baseline the following year even though additional therapy has been applied. The basic bone biology leading to the overshoot and return to baseline is unknown. There are theories that bone tissue is responding as a mechanostat in these scenarios, and readjusting its level of turnover as a function of the mechanostat regulation of bone.[94] This theory is supported by the BMD responses after continual discontinuation of denosumab. During the first year after discontinuation, BMD of the spine and hip all decline to baseline. However, during the second year of discontinuation, where there has been no denosumab in the bone for at least 1 year, the BMD at all skeletal sites increases again to baseline. These returns (decreases) in BTM and increases in BMD, despite denosumab being no longer available, are suggestive of a mechanostat homeostasis adjustment in remodeling. Since the pharmacokinetics of denosumab differs from those of bisphosphonates in many ways, including the absence of bone retention for denosumab, it is entirely plausible that the readjustment in bone turnover and density seen after densoumab exposure followed by discontinuation is unrelated to the drug. A mechanostat hypothesis highly likely to provide at least some of the answers.

In the three phase-II denosumab publications, an increase in forearm BMD was observed with denosumab administration, while the forearm BMD declined in the placebo as well as the alendronate groups. Forearm BMD also either remained unchanged or declined in the other registered bisphosphonate clinical trials, as well as in the 1–34 and 1–84 parathyroid hormone (PTH) trials. This unique property of denosumab is intriguing, and there is speculation that this increase in forearm BMD may suggest differential effects of denosumab on cortical bone and perhaps on cortical bone strength. Preliminary data do show an increase in forearm and spine quantitative computerized tomography (QcT) at both QcT-measured cancellous and cortical bone forearm sites.[95] This denosumab effect on cortical bone, combined with the observations that denosumab increases the two-dimensional cross-sectional area (CSA) of the hip femoral neck and femoral shaft as measured by hip structural analysis (HSA), provides evidence that denosumab may increase cortical bone strength and reduce non-vertebral and hip fractures. These questions will be answered shortly when the phase-III prospective global denosumab fracture registration data are presented in September 2008. If the results on fracture outcomes in the

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phase-III fracture trial are anticipated to be as positive as expected from the surrogate marker changes of bone strength, then it is likely that denosumab will become another anti-resorptive agent for the management of postmenopausal osteoporosis. The exciting and unique biological property of this fully human monoclonal antibody is that it will not reside in bone or be retained in bone, factors which have led to some of the exciting and yet consternating biological properties of bisphosphonates. While there may be merit in a substance that has a long bone $T_{½}$, and once recycled maintains bone turnover, there could be a downside to this unique pharmacokinetic property as well. Denosumab is not retained in bone, and its duration of effect is short and reversible once discontinued. This pharmacokinetic property may have its benefits as well as its downside. The increase in bone turnover and reduction in BMD seen within 1 year of discontinuation of denosumab could, theoretically, translate into impaired bone strength. This important question may be answered by the planned extension studies of the phase-III denosumab registration studies. Discontinuation of estrogen also leads to an increase in bone turnover, although an increase in fracture risk has not been observed in estrogen withdrawal data; however, the data are not robust. In the NORA (national osteoporosis risk assessment) study there was a higher 1-year risk of hip fracture in those women discontinuing estrogen, but in this specific aspect of the NORA population there was a substantial selection bias and low power to make definitive conclusions concerning bone strength associated with estrogen-withdrawal-related increase in bone turnover.[96] While in basic bone biology, high bone turnover is generally associated with a reduction in bone strength, it is unknown whether the increase in bone turnover following withdrawal of the effects of anti-resorptive agents is also associated with an impairment in bone strength. Altering the remodeling space in treatment-naive subjects may not have the same consequences on bone strength as in pharmacologically treated patients. It has yet to be determined whether the rebound in bone remodeling observed after the bone is exposed and then unexposed to pharmacological agents differs from that seen in bone not previously treated. Certainly the availability of denosumab for the management of PMO will offer a new option for physicians to consider in their armamentarium of pharmacological agents for osteoporosis, and one with an easy and infrequent parenteral route of administration.

SAFETY OF ANTI-RESORPTIVES

The generally well-tolerated and safety profiles of all of the anti-resorptive agents used in the doses for management of PMO, male and glucocorticoid-induced osteoporosis is well established. However, a number of important although infrequent side-effect/toxicity issues for each agent merits consideration.

Estrogen and SERMs

Estrogens as a class have the potential to increase the risk of breast cancer, cerebrovascular accidents (CVAs), and deep-vein thrombosis. These events attributable to HRT are rare, and certainly the benefits far outweigh the risk. According to the population defined, all of these risks are small, but nevertheless should be discussed with individual patients, and in individuals with a greater risk (e.g. high circulating levels of clotting factors that may predispose to CVAs) then HRT should be avoided. The same statements should apply to the SERMs where the risk of CVA mimics that of HRT.[15,18,19,23,24] From this point on, there are differences in the risk/benefit profile

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of HRT versus SERMs. HRT increases and SERMs decrease the risk of breast cancer and endometrial cancer. HRT reduces and SERMs increase the risk of hot flushes. Hence, here again, choice of agents becomes an individual patient management decision based on the risk/benefit profile.

Calcitonin

Calcitonin has been an extremely safe therapy for PMO. There may be nasal irritation with the nasal formulation, and local skin (very rarely systemic allergic) reactions to the injectable formulation. It is advised in the registration label that patients that may have an allergy to salmon undergo a skin allergy test before initiating injectable calcitonin. The commonest side-effect of calcitonin is nausea, more common in the injectable than the nasal-spray formulations.

Bisphosphonates

'Oversuppression of bone turnover'

Due to their effect on mineralization and their long bone retention time, bisphosphonates have been studied extensively with regard to the effect of these properties on various tissues and organs (bone) with long-term exposure. While with etidronate the ratio of impairment in bone mineralization to inhibition of bone resorption is 1:1, leading to the potential of a mineralization defect when used at high doses for prolonged periods of time (osteomalacia), this is different from the effect of the newer aminobisphosphonates on mineralization. The newer bisphosphonates do not induce osteomalacia, but due to their ability to induce long periods of secondary mineralization, they alter the mineralization density of the human skeleton. The ideal mineralization density of the human skeleton remains unknown, and it is possible that in vary rare cases of long-term bisphosphonate exposure, over-mineralization may occur leading to unusual mid-shaft femoral fractures. This rare event, to date reported in $<$50 uncontrolled case series, is often bilateral and at times becomes displaced, necessitating orthopedic surgical repair.[97] Since most of these patients, on quantitative bone histomorphometry, have very few or no single tetracycline labels, it has been proposed that this rare bisphosphonate femur fragility is due to 'over-suppression' of bone turnover resulting in the accumulation of micro-damage.[98,99] Although it is possible that there may be a subset of patients that might develop these fractures with long-term bisphosphonates use, the data are uncontrolled and anecdotal and need scientific confirmation by a controlled and randomized study. However, it is currently felt that these cortical shaft fractures are not observed in the general population, and that they are somehow associated with bisphosphonates. In addition, to date, these fractures have only been seen with long-term alendronate use and not with the other bisphosphonates. This latter observation could be a selection bias, since alendronate has been the most widely prescribed bisphosphonate for PMO. Finally, to date, in the case series reported there does not appear to be a way to predict who may develop these fractures, and this observation is also driving consideration for a bisphosphonate 'drug holiday' after 5 years of use in lower-risk patients. Certainly much more scientific data are needed before bisphosphonates can be proven to be the cause of any bisphosphonate-associated femoral shaft fractures. To date the quantitative bone histomorphometry data performed in the bisphosphonate clinical trials (up to 10 years with alendronate) has never documented 'frozen bone.'

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Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw was rarely reported before the advent of bisphosphonates, and previously was seen in patients who had received radiation therapy to the jaw. Hence, the increasing prevalence of ONJ seems to be associated with bisphosphonates, although nearly all validated cases have been reported in the oncology population who receive high-dose monthly intravenous bisphosphonates and simultaneous chemotherapy for metastatic cancer to bone or multiple myeloma.[100] There has been a consensus in the medical and dental communities regarding the definition of ONJ: an area of exposed bone in the mandible or maxilla that persists for at least 8 weeks despite conservative management.[101,102] Most of these cases have followed a tooth extraction or dental implant, with fewer cases following jaw trauma or in patients with underlying severe periodontal disease. There have been fewer than 60 adjudicated cases in the world in patients on the osteoporosis doses of bisphosphonates, although the perception in the dental community is that the link between bisphosphonates is far greater than the scientific data would support. This perception has led to many patients inappropriately being taken off bisphosphonates, or dentists refusing to do dental procedures in patients on bisphosphonates. This is where a healthy communication between physicians, dentists and patients needs improvement. Since the pathophysiology of ONJ is unknown, management is opinion-based. Until we have a better understanding of how bisphosphonates are linked to ONJ, there has been an opinion-based recommendation expressed by many professional societies to withhold or discontinue bisphosphonate for 3 months prior to major dental procedures in lower-risk but not high-risk (those with a prior fragility fracture) patients, and restart the bisphosphonate after the dental tissue has healed.[101,102] There is no evidence that this bisphosphonate-withholding advice has any effect on the natural history of ONJ, but is based on a fundamental concept that if an average bone-remodeling cycle last for ~90 days, then a 3-month withholding period may allow previously suppressed remodeling sites to recover under the untested hypothesis that ONJ is related to suppression of remodeling. There is also anecdotal advice from certain experts in the USA dental community that a serum resorption marker (preferably serum CTX) be measured as a guide to the degree of suppression of remodeling by bisphosphonates in the jaw-bone regions. The advice is not to do dental surgery if the serum CTX is $<$150 pg/mL. There is no scientific basis for such a recommendation.

There is agreement that in clinical practice patients should be counseled about their oral dental care and oral hygiene, and the ONJ risk should be put into proper context. There is also agreement that if a true case of ONJ is discovered in a non-oncology patient on a bisphosphonate, that interventional dental surgery should be avoided and the bisphosphonate discontinued. Management of high-risk patients that require discontinuation of a bisphosphonate should entail use of a different bone-active agent to reduce the fracture risk.

Atrial fibrillation

Atrial fibrillation (AF) was observed in a subset of the pivotal registration trial of zoledronic acid.[46] The terminology 'serious' AF has been introduced, not only in the registration trial but subsequently in reports of AF seen or not seen in post-hoc analysis of the bisphosphonate clinical trial data, and in case-controlled population data.[103,104] However, this wording is incorrect since the AF in the zoledronic acid registration trial for PMO was seen in the subset of the study population with serious

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adverse events: those patients in the clinical trial who needed hospital admission for any reason not necessarily connected to a cardiac event. Even though the difference between the treated versus placebo groups that developed AF was significant, there was no adverse clinical outcome in these patients. In addition, no plausible pathophysiological mechanism explains these events. To date the FDA has not considered these AF events seen in hospitalized patients as necessarily being directly related to intravenous zoledronic acid, but is requiring all companies that produce bisphosphonates to conduct ongoing post-marketing data. In a post-hoc analysis of the small number of AF events seen in the zoledronic acid registration trials, the one risk factor for AF that trumped all others was a prior history of cardiac arrhythmias. It remains to be determined if history of prior cardiac arrhythmia should be a precaution observed in considering bisphosphonate use.

Renal effects

Bisphosphonates are excreted by the kidney both by glomerular filtration and by proximal tubular secretion. The registration labels for the USA as well as Europe advises that bisphosphonates not be administered in patients with glomerular filtration rates (GFR) $<$30–35 mL/min. Most of these data are based on bisphosphonate renal toxicity studies in rats and the observed renal effects of high doses of intravenous bisphosphonates seen in the oncology population. In addition, since the majority of clinical trials leading to the approval of bisphosphonates randomized patients with serum creatinine concentrations $>$2.0 mg/dL, there are few data on the effect or safety of bisphosphonates in patients with GFR $<$30 mL/min (stage 4–5 chronic kidney disease, CKD).[105] Nevertheless, there are many scenarios where bisphosphonate use is a worthy consideration in high-risk patients with stage 4–5 CKD, and recent post-hoc analysis of risedronate as well as alendronate datasets suggest efficacy and safety for 2–3 years of use in patients randomized in the clinical trials with estimated GFR (eGFR) down to 15 mL/min.[106,107] Patients with stage 5 CKD are best managed by first evaluating the bone histomorphometry to exclude other forms of renal osteodystrophy that may mimic osteoporosis before use of any bisphosphonate.[108,109]

The recent zoledronic acid data showed that a 15-minute infusion of 5 mg is safe in the populations studied for registration, even in patients with preexisting diabetes and hypertension or on non-steroidal anti-inflammatory drugs (NSAIDs). In a short-term renal safety study (9–11 days post zoledronic acid infusion) there were a few – yet statistically significant – rises in serum creatinine after the second infusion that did return to baseline before the next annual infusion.[110] The potential renal damage that can be seen with rapid infusions of zoledronic acid are rare with longer ($\geq$15 minutes) infusion rates. Intravenous ibandronate injections have not been associated with renal failure in the populations studied[111], although any potential differences in renal safety between these two intravenous bisphosphonates has not been tested in head-to-head studies.

CONCLUSIONS

Anti-resorptive agents have been the best-studied agents for the management of osteoporosis, and have been highly effective in reducing the risk for fractures in multiple prospective placebo-controlled clinical trials.[112–114] There are several different

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pharmacological agents to choose from that have specific advantages or disadvantages in specific clinical circumstances. From the aspect of global fracture risk reduction, the bisphosphonates have the best evidence of reducing the risk of vertebral, non-vertebral, and hip fracture risk, although there are now many questions being raised concerning their long-term use and safety that require ongoing investigation. Newer anti-resorptives are under investigation that may offer different modalities to improve bone strength and reduce fracture risk that will broaden the choices of anti-resorptive agents for physicians and patients alike.

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