Duration of Treatment in Postmenopausal Osteoporosis: How Long to Treat and What are the Consequences of Cessation of Treatment?

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There are few concerns about the consequences of long-term treatment of chronic disease except when the drugs being used accumulate within the body. Rheumatologists are well aware of the affinity of the choloroquines for the retina and its resulting ocular toxicity in select individuals. Bisphosphonates avidly bind to hydroxyapatite within bone and have limited biological degradation.[1–3] Although causality has not been definitively established, concern that bisphosphonate therapy could lead to specific bone toxicities such as osteonecrosis of the jaw (ONJ), and atypical fractures can be appreciated in this construct. Whether other potent antiresorptives such as denosumab, which do not bind to bone, have similar toxicities remains unanswered at this time.

In addition, there has been an appreciation that patients who have been treated with select bisphosphonates for several years could stop taking the drug without a rapid

decline in bone density or increase in markers of bone resorption. Some have taken this residual effect on bone density and bone turnover markers to imply continued fracture benefit even after drug cessation. However, studies demonstrating persistent fracture benefit are limited.

This review examines the different drug therapies currently approved by the Food and Drug Administration (FDA) for use in the management of postmenopausal osteoporosis, and evaluates the current data regarding effects of discontinuation on bone mineral density (BMD), bone turnover markers (BTM), and fracture risk reduction. The authors attempt to provide a general framework for clinicians to determine which patients are appropriate candidates for discontinuation of medical therapy, temporary suspension (drug holiday), and continued treatment. Two other excellent reviews on this topic with somewhat contrasting recommendations have appeared within the last 2 years, by Seeman[4] and Watts and Diab.[5]

There are other questions implicit in this discussion. What is the optimal duration of treatment with these agents in achieving fracture reduction and avoiding side effects related to cumulative exposure? What effect does a "holiday" have on the reduction of the risk of side effects? Does resumption of treatment after a holiday resume the risk? Does a change from an antiresorptive agent to an anabolic agent reset the cumulative risk of the antiresorptive agent back to baseline? Does a change in the mechanism of antiresorptive treatment (eg, bisphosphonate versus denosumab) change the cumulative risk? Unfortunately, there are currently few data to guide the answers to these important questions, yet clinicians are faced with these decisions daily.

DISCONTINUING OSTEOPOROSIS TREATMENT
The Effect on Bone Mineral Density and Bone Turnover Markers

Cessation of osteoporosis treatment has been shown to have a range of effects on BMD as well as BTM.

Bisphosphonates

Clinical trials demonstrate significant differences in the bisphosphonates regarding BMD and BTM following discontinuation of therapy. The effect of 1 year (1 dose) of zolendronate appears to persist for at least 3 years in women with osteopenia.[6] In patients with osteoporosis, alendronate for at least 5 years results in a greater persistence of effect than 2 to 3 years of therapy.[7–12] Discontinuation of risedronate following 3 years of treatment results in a more rapid loss of bone density and BTM than 2 years of alendronate or 3 years of zolendronate.[13,14]

Alendronate

When individuals were followed off of drug therapy following treatment with alendronate for 2 years or less, there were fewer robust effects on suppression of bone turnover and maintenance of BMD when compared with those for whom treatment with alendronate had been continued for 3 years or longer before discontinuation.[9–12]

Two cohorts of patients treated with alendronate for up to 10 years have been reported.[7,8] Both include an arm that saw placebo for 5 years following as many as 5 years of alendronate. In the Alendronate Phase III Osteoporosis Treatment Study Group, postmenopausal women with osteoporosis were randomized to alendronate 20 mg/d for 2 years followed by 5 mg/d for 1 year, 5 mg daily for 3 years, 10 mg daily for 3 years, or placebo.[15] Two 2-year extensions and then a 3-year extension were performed. The 5-mg and 10-mg daily arms continued on the same respective daily alendronate dose, whereas the placebo arm was discontinued after the first 2-year

extension. The 20 mg/d × 2-years, 5 mg/d × 1-year original arm received 5 mg/d in the first 2-year extension (alendronate × 5 years) and then saw placebo for 5 years. Tonino and colleagues[16] reported the results of the second 2-year extension at year 7. For the alendronate × 5-years placebo × 2-years arm, no significant decline in BMD at the lumbar spine or hip was seen, but significant declines in the forearm were noted. Urinary N-telopeptide increased during the first year off therapy but then remained stable well below baseline (year 5 level −73%, year 7 level −57.9%). The 10-year results of this study were reported by Bone and colleagues,[7] in which this same group had now been followed off therapy for 5 years. BMD was maintained in the spine. Declines in BMD were noted in the total hip after year 7 (off therapy for 2 years) but at year 10 were comparable to those on alendronate 5 mg daily for the entire 10 years. Urine N-telopeptide remained suppressed at more than 50% of baseline levels.

The second alendronate cohort comes from FLEX, the Fracture Intervention Trial (FIT) Long Term Extension. In FIT, all patients received alendronate 5 mg/d for 2 years followed by 10 mg/d. Average follow-up was 2.9 years in the vertebral fracture arm and 4.2 years in the clinical fracture arm. Patients were offered up to 1 year of alendronate 10 mg/d on completion of FIT. FLEX enrolled 1099 patients who were then rerandomized to placebo (n = 437), alendronate 5 mg/d (n = 329), or alendronate 10 mg/d (n = 333), and followed for an 5 additional years. Patients in the placebo arm saw a 1.52% increase in lumbar spine BMD, with declines of 1.48% in the femoral neck, 3.38% in the total hip, and 3.21% in the forearm. The decline in BMD of the total hip exceeded the baseline value at the start of FLEX by 0.16%. BTM gradually increased over 5 years compared with those who remained on alendronate. When compared with pretreatment levels in FIT 10 years earlier, serum C-terminal telopeptide of type 1 collagen was −7% and N-propeptide of type 1 collagen was −24% in those who had been randomized to the placebo arm.[8]

Risedronate

In the VERT-NA (Vertebral Efficacy with Risedronate Therapy—North America) trial,[17] 599 of the 818 who completed the study were enrolled in a 1-year extension in which risedronate and placebo patients stopped therapy. Lumbar spine BMD decreased 0.83% and femoral neck BMD dropped 1.23% in those who had stopped risedronate, although these values were still greater than the control group who had been on placebo in the VERT-NA trial. Urine N-telopeptide increased significantly from a median of 30.3 nmol bone collagen equivalents (BCE)/mmol creatinine at end of treatment to 50.9 nmol BCE/mmol creatinine after 1 year off risedronate. This increase in the BTM represented a complete resolution of effect when compared with the control group.[13]

Ibandronate

There are no published data on the cessation of ibandronate and subsequent effects on BMD and BTM.

Zolendronate

Zolendronate, 5 mg is approved for every 24-month dosing in patients with osteopenia. In a study of 50 postmenopausal women with osteopenia, the effect of a single intravenous dose of 5 mg zolendronate persisted for the duration of a 3-year trial when compared with placebo control.[6] BMD was higher in the zolendronate group by 6.8% at the lumbar spine and 4.0% at the total hip. Mean levels of serum C-telopeptide were 44% lower than the placebo group.

The HORIZON PFT (Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly Pivotal Fracture Trial) was a 3-year double-blind, placebo-controlled trial that enrolled 7736 postmenopausal women.[18] A 3-year extension of HORIZON PFT randomized 1233 women who had received intravenous zolendronate 5 mg yearly in the core trial to receive either 3 additional years of zolendronate[19] (Z6) or 3 years of placebo (Z3P3). The Z3P3 group saw declines of 2.03% in the lumbar spine, 1.2% in the total hip, and 1.04% in the femoral neck, values that were significant when compared with the Z6 group but still well above pretreatment levels. Markers of bone turnover "rose slightly" in the Z3P3 group but procollagen type 1 N-terminal pro-peptide remained "about 47% below" pretreatment values.[20]

Hormones

Estrogens have a waning effect on bone in postmenopausal women whether after short-term or long-term use. Short-term hormone therapy has been reported not to protect against bone loss after 1 or 2 years of discontinuation.[21–23] Long-term hormone therapy also failed to protect against bone loss. Evidence from the Framingham Study indicated that even after 7 years of estrogen therapy, there was little residual effect on bone density 10 to 20 years after estrogen withdrawal.[24,25]

The rate of bone loss from studies after estrogen withdrawal is still controversial. Some studies have reported identical bone loss rates compared with placebo, whereas others have reported accelerated bone loss versus placebo.[23] Some of the controversy is due to differences in study population (healthy or osteoporotic), duration of treatment and discontinuation periods, method of measuring bone mass changes, different treatment regimens, age of study population, and menopausal status.[23,26]

Raloxifene

The benefit of raloxifene for bone appears to be short lived after cessation of treatment. Naylor and colleagues[27] showed that the bone turnover response was lost 6 months after treatment cessation despite nearly 2 years of therapy. In addition, bone loss that was greater than in the control group, suggesting accelerated bone loss. Hip BMD was 2% less than baseline 192 weeks after treatment. Neele and colleagues[23] showed that 5 years of treatment with raloxifene did not protect against bone loss 1 year after withdrawal of therapy, and that the rate of bone loss was not significantly different from that of placebo-treated women.

Denosumab

Denosumab treatment has reversible characteristics that have been demonstrated in several clinical trials. In a study of osteopenic postmenopausal women, after treatment with denosumab (60 mg every 6 months × 4), cessation of therapy resulted in a return to baseline in serum C-telopeptide within 9 months followed by a compensatory overshoot at 12 months and return to baseline by 30 months after stopping denosumab.[28] BMD returned to baseline within 18 months of stopping the drug but remained above the BMD of the placebo treatment cohort.[12,28]

Teriparatide

BMD data were collected over an 18-month period after the conclusion of the Teriparatide Fracture Prevention trial. The BMD at the total hip and lumbar spine was maintained during this time, although it was somewhat confounded by the use of some osteoporosis medications such as bisphosphonates in 47% of those followed. The use of bisphosphonates for 12 months or more was associated with a greater maintenance of BMD gains than for those who did not use osteoporosis drugs.[29,30]

Similar results were seen in the lumbar spine BMD of men 30 months after stopping teriparatide.[31]

DISCONTINUATION OF OSTEOPOROSIS TREATMENT AND SUBSEQUENT FRACTURE RISK
Bisphosphonates

Studies suggest that a minimum of 2 to 3 years of bisphosphonate therapy with good compliance is needed to demonstrate fracture benefit. Furthermore, treatment with bisphosphonates for 3 to 5 years and subsequent discontinuation for 3 to 5 years is not associated with an increased risk of hip fracture (alendronate; zolendronate), but when compared to those who continued on bisphosphonate, is associated with increased risk of vertebral fractures (alendronate; zolendronate), and an increased risk of nonvertebral fractures in women without prevalent vertebral fractures and BMD T-scores of −2.5 or less (alendronate).

Information regarding the effects of discontinuation of bisphosphonates on fracture risk is limited, and drawing conclusions based on this is problematic. There are two sources of information that can be accessed: administrative databases and clinical trial extensions.

Gallagher and colleagues[32] studied 36,164 women in the General Practice Research Database (GPRD) in the United Kingdom who received a new prescription for alendronate (74.1%) or risedronate (25.9%). There was no evidence of residual effect on fracture risk after stopping bisphosphonate when the mean follow-up was 2.39 years, and few used bisphosphonates for 5 years of longer. Patients who recently stopped bisphosphonates had a similar fracture risk to those who had discontinued further in the past and to patients who had just started therapy.

New users of alendronate (77%) and risedronate (23%) were also the subject of a study by Curtis and colleagues.[33] In addition, they evaluated for the effect of compliance as measured by the medication possession ratio (MPR). A cohort of 9063 women who were members of "a large US healthcare organization" and compliant with drug therapy for at least 2 years were examined. Women who discontinued drug therapy had lower hip fracture rates than nonadherent women, if they had previously taken bisphosphonates for 2 or more years and had been compliant with drug therapy (MPR of 66%–100%). However, when time since discontinuation was examined, there was a twofold to threefold increased hazard ratio for hip fracture in women who had stopped more than 9 months ago. Women who discontinued drug therapy and who had higher degrees of compliance (MPR 88%–100%) and those previously having received bisphosphonates for 3 or more years had numerically lower rates of hip fracture than those who were less compliant or on shorter duration of drug therapy. Nevertheless, the fracture rates were still higher than those who remained on bisphosphonates.

A population-based, nested case-control study of women 68 years or older from Ontario, Canada recently looked at the incidence of subtrochanteric fracture in those on an oral bisphosphonate between 2002 and 2008. During this 6-year interval, short-term use of bisphosphonate (100 days to 3 years) did not reduce fracture risk, but use for 3 or more years did reduce fracture risk.[34]

Alendronate Clinical Extension Studies

The Alendronate Phase III Osteoporosis Treatment Study Group obtained lateral radiographs of the spine at the end of each extension. Morphometric vertebral fractures and clinical fractures were reported as safety end points. At 10 years, there

was no evidence of an increased rate of morphometric vertebral fractures in the ALN5P5 discontinuation group (6.6%) as compared with the ALN10 (10 mg/d × 10 years) group (5.0%). During years 8 to 10, 12.0% of the ALN5P5 group sustained a first nonvertebral fracture compared with 8.1% in the ALN10 (10 mg) group and 11.5% in the ALN10 (5 mg) group.[7]

In the FLEX cohort, 437 patients who took alendronate 5 mg/d for 2 years then 10 mg/d for up to 3 years were randomized to placebo for 5 years. When compared with patients on 10 years of alendronate, clinical vertebral fractures were more common in the placebo group despite a slight increase in bone density in the spine over 5 years: placebo, 23 of 437 (5.3%) versus alendronate, 16 of 662 (2.4%) (95% confidence interval [CI] 0.24–0.85). A nonsignificant increase in morphometric fractures was also noted, but there was no difference in hip or nonvertebral fractures.[8]

A post hoc analysis of FLEX reported by Schwartz and colleagues[35] looked at those women without prevalent vertebral fractures at FLEX baseline, and found a greater risk of nonvertebral fractures in those who stopped alendronate after 5 years if their femoral neck T-score was −2.5 or less at FLEX baseline.

Risedronate Clinical Extension Studies

In the extension of VERT-NA, despite seeing significant declines in BMD and increases in BTM in the 1 year off risedronate, the incidence of new morphometric vertebral fractures was decreased by 46% compared with the placebo group (relative risk 0.54, 95% CI 0.34–0.86, $P = .009$). New vertebral fractures occurred in 26 of 398 (6.5%) patients who had previously taken risedronate and in 42 of 361 (11.6%) patients on placebo. By contrast, there was no significant difference in nonvertebral fractures, with 19 of 398 (4.8%) in the risedronate group and 18 of 361 (5.0%) in the placebo group (although these were collected as adverse events and radiologic confirmation was not required).[13] This result suggests a residual protective effect of risedronate on morphometric fractures but, because there was not a comparator group that continued on risedronate, questions as to diminished fracture benefit associated with drug holiday cannot be addressed.

Zolendronate Clinical Extension Studies

In the 3-year extension of the HORIZON PFT trial, with more modest declines in BMD and slight increases in BTM, new morphometric vertebral fractures occurred more frequently in the Z3P3 group compared with those who continued on zolendronate (Z6). There were 30 fractures in 486 patients (6.2%) in the Z3P3 group and 14 fractures in 469 patients (3.0%) in the Z6 group (hazard ratio 2.07, $P = .04$). However, there were no reported differences in the rate of clinical vertebral, hip, and nonvertebral fractures between the Z3P3 and Z6 groups.[20]

Hormone Therapy

Case-control studies have suggested a minimum of 5 years of estrogen treatment to reduce fracture risk.[26] The Women's Health Initiative (WHI) noted a 33% reduction in hip fractures in healthy postmenopausal women (not just women with osteoporosis) who had been treated with estrogen therapy for an average of 5.6 years.[36] However, estrogens have been relegated to short-term use at the lowest possible dose to alleviate menopause symptoms, not for the prevention of chronic disease.[37,38] Studies of fracture risk after cessation of estrogen have noted a loss in fracture risk protection.[36,38–40] The FDA no longer recommends estrogen therapy for the treatment of osteoporosis.

Raloxifene

Raloxifene has been shown to be effective in preventing postmenopausal bone loss and vertebral fractures over a 3-year period in the randomized double-blind MORE trial (Multiple Outcomes of Raloxifene Evaluation) and the 3-year continuation with the CORE trial (Continuing Outcomes Relevant to Evista). This trial ultimately produced 8 years of safety data with raloxifene use and no significant change in fracture data, including no significant reduction in hip fracture risk compared with placebo.[27,41,42] There is no limit on duration of treatment with raloxifene. Significant declines in bone density occur shortly after cessation of raloxifene therapy.[43] However, there are no data on the change in fracture risk after discontinuing raloxifene.

Denosumab

Denosumab, given subcutaneously twice yearly for 3 years, was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis.[44] Six years of continuous treatment was associated with continued BMD accrual.[45] The original pivotal fracture trial will be expanded through a 7-year extension, which will provide 10 years of data regarding long-term efficacy and safety. There is currently no recommended limit on duration of denosumab therapy.

There have not been sufficiently large studies to clarify fracture rates after stopping denosumab treatment in comparison with placebo. However, in the BTM and BMD study previously noted, there were no fracture rate differences in the 2-year period after 2 years of treatment compared with placebo: 3% nonvertebral fractures in each group and no clinical vertebral fractures were reported.[28]

Teriparatide

In the Fracture Prevention Trial (FPT), treatment with once-daily teriparatide significantly reduced the risk of vertebral and nonvertebral fractures over a median duration of observation of 21 months.[46] Lindsay and colleagues[19] concluded that increased duration of teriparatide therapy resulted in a progressive decrease in the rate of nonvertebral fragility fractures and back pain, and adverse events occurred early in the treatment and not later, thus suggesting that patients may achieve improved outcomes by persisting on teriparatide therapy.

Expert review of the finding of osteosarcoma in teriparatide-treated Fischer 344 rats indicated that this finding was unlikely to predict an increased risk of osteosarcoma in human patients receiving teriparatide treatment for up to 2 years. Therefore in the United States, approval by the FDA was for 2 years of treatment.[30] Further efficacy and safety was found in glucocorticoid-treated subjects considered at high risk of fracture when treated with 3 years of teriparatide therapy; nevertheless, the FDA has not altered the recommended treatment interval of 2 years.[47]

There were 18 months of follow-up after the cessation of teriparatide in the FPT. Although there was confounding with bisphosphonate use, there was a continued significant fracture reduction effect that continued during this period, independent of bisphosphonate use, according to a logistic regression analysis.[29,30] Again this was similar to the continued vertebral fracture efficacy in males up to 30 months after cessation of teriparatide treatment.[31]

DECIDING WHAT TO DO WITH PATIENTS; WHAT TO MAKE OF REPORTS OF ATYPICAL FRACTURES IN PATIENTS ON LONG-TERM BISPHOSPHONATES?

Among the drugs approved for treatment of postmenopausal osteoporosis, only the bisphosphonates have demonstrated suppression of BTM and maintenance of

BMD for more than 12 to 18 months after a drug is withdrawn. This finding is consistent with their unique mechanism of action in binding to hydroxyapatite in bone. Moreover, the presence of atypical fractures has to date only been linked to patients treated with bisphosphonates. Therefore, at present the concept of drug holiday, whereby one might maintain fracture risk reduction while minimizing adverse events, is really only applicable to bisphosphonates.

Among the bisphosphonates, there are no current studies that demonstrate comparable across-the-board fracture benefit for those who discontinue the drug as opposed to those who continue on treatment, for whom length of therapy is at least 3 to 5 years before cessation. Therefore, for those at sufficiently high risk for fracture, a decision as to whether to continue drug therapy is based on the perception of risk of drug side effects.

Of the side effects reported to be associated with long-term bisphosphonate use, namely ONJ and atypical subtrochanteric femoral shaft fractures (SFSF), ONJ appears to occur less frequently in the postmenopausal population, with a prevalence of 1 in 10,000 to 1 in 100,000.

Schilcher and Aspenberg[48] noted an SFSF incident density of 1 per 1000 patient-years in a defined health care registry in Sweden, with a mean duration of exposure of 5.8 years (range 3.5–8.5 years). Dell and colleagues[49,50] noted an SFSF incidence of 0.02 per 1000 patient-years for the first 2 years and 0.78 per 1000 patient-years for 8 years of bisphosphonate therapy in a study of patients seen in the Kaiser Permanente health care system in California. In both of these studies, radiographs were individually reviewed for features of atypia. By contrast, Park-Wyllie relied on ICD-9 codes for the diagnosis of subtrochanteric and femoral shaft fractures, and identified an increased risk of 1.35 per 1000 patients in those on bisphosphonates for 6 years and 2.22 per 1000 patients for those on treatment for 7 years.[34] Using the population of women studied in FIT, the risk for osteoporotic fracture is 10-to 23-fold greater than for SFSF for women with a prior vertebral fracture, and 7- to 10-fold greater in those without a prevalent vertebral fracture.[49,51]

Two recent studies have looked at larger populations to attempt to overcome issues related to the small number of cases of SFSF. Schilcher and colleagues[52] reviewed all 1234 radiographs of femoral subtrochanteric or shaft fractures reported in the 2008 National Swedish Patient Register, and linked this to patient history and medication use. The age-adjusted relative risk of atypical fracture with any use of bisphosphonate was 47.3 (95% CI 25.6–87.3) with a number needed to harm of 1 case per 2000 patients per year of bisphosphonate use. Wang and Bhattacharyya[53] used the Nationwide Inpatient Sample (NIS) to examine 90 million hospital discharge records in men and women older than 65 years between 1996 and 2007, and the Medical Expenditure Panel Survey to estimate rates of medication use. In the setting of an increase in bisphosphonate use in women from 3.5% to 16.6%, there was a decline in hospitalization for typical osteoporotic hip fractures of greater than 30,000, with a small but significant increase of 2500 subtrochanteric fractures. Using age-adjusted rates, the investigators estimated that for every 100 typical osteoporotic hip fractures prevented by bisphosphonate use, there was an increase of 1 atypical subtrochanteric fracture.

Thus all recent studies demonstrate that the risk-benefit ratio favors drug therapy in those postmenopausal women at risk for osteoporotic fracture. However, effectively communicating this to patients is hampered by several factors. Numeracy—the ability to understand numbers—is remarkably limited.[54] In one study 16% of highly educated people incorrectly answered simple questions about risk magnitude, such as which represents the larger risk: 1%, 5%, or 10%? Presenting absolute risk (eg, among users of bisphosphonates, 1 patient out of 1000 will have an atypical fracture) increases

comprehension over relative risk (eg, 46% greater likelihood of an atypical fracture in bisphosphonate users vs nonusers).[54] Numerous other factors also influence risk perception. Newly discovered risk (eg, recent news reports of spontaneous femoral fractures) may be perceived as a greater risk than those that are well established. A dreaded risk (eg, spontaneously fracturing your femur while walking down the hall) is also overestimated.[54,55]

An Alternative Form of Drug Holiday: Switching from Bisphosphonate to Teriparatide

Theoretically, the switch from a bisphosphonate to an anabolic drug such as teriparatide might undo the suppressive effects of bisphosphonates on bone and lower the risk of SFSF. In a small study of 38 postmenopausal women who had been on bisphosphonates for a mean duration of approximately 5 years, 24 months of teriparatide (20 μg/d) reduced microdamage accumulation seen on iliac crest biopsies compared with a placebo group that had not previously seen a bisphosphonate.[56] In postmenopausal women with osteoporosis based on BMD, 2 years of teriparatide increased bone formation (based on biopsy and biochemical markers) to a comparable level in both treatment-naïve patients and individuals previously treated with alendronate for a mean of slightly longer than 5 years.[57] In addition, 1 year of teriparatide following at least 2 years of alendronate or risedronate therapy demonstrated an increase in heterogeneity in BMD distribution, as measured on paired iliac crest bone biopsies obtained before and after teriparatide therapy.[58]

An Algorithm for Patients Already on Drug Therapy

Given the limitations with available data, an approach when discussing "how long to treat" with individual patients is to first categorize their fracture risk (low, intermediate, high). This gradation can be based on a clinical assessment that includes but is not limited to fracture history, age, BMD (spine and hip; changes over time), FRAX, and frailty including frequency of falls. There are no universally accepted criteria to stratify according to risk, and a variety of approaches exist.[4,5,59,60]

Five years can be a decision point, because most case reports of SFSF were on bisphosphonates for at least that long, and the limited number of extension studies saw bisphosphonates for 3 to 5 years before going on to placebo.

Then, gauge the patient's "risk profile": are they more concerned about risk of drug side effects or the risk of fracture? This usually becomes apparent in a discussion about ONJ and SFSF in the setting of bisphosphonate use.

This algorithm would not be applicable to patients with poor compliance on oral bisphosphonates, or those who have had clear evidence of a significant decline in bone density while on bisphosphonate therapy. It is assumed that these patients are not seeing the suppressive effects on bone turnover that may lead to SFSF.

For Patients at Very Low Risk for Fracture

This category is based on FRAX and clinical assessment (no evidence of accelerated bone loss; without frequent falls). This category would include many patients originally started on drug therapy for "prevention," for example.

- Bisphosphonates can be stopped until fracture risk is increased
- Evista can be continued for at least 5 to 10 years[61] to prevent bone loss and lower risk of invasive breast cancer
- Hormone therapy: use lowest possible dose for shortest possible time.

For Patients at Intermediate Risk for Fracture

Individuals no prior fragility fractures as an adult, are osteopenic on BMD, but whose FRAX 10-year risk for fracture meets National Osteoporosis Foundation (NOF) guidelines for treatment.

- Bisphosphonates
  - Assess patient's risk tolerance:
    - Concerned about drug side effects > risk for fragility fracture
      - Bisphosphonates can be used for 5 years with periodic check of oral health and thigh pain
        - Then stop for drug holiday of several years
        - Monitor bone density every 2 years and BTM yearly
        - Resume therapy if significant declines in BMD, significant increase in BTM, or new interval fractures
    - Concerned about risk for fracture > drug side effects
      - Continue on drug therapy monitoring oral health and thigh pain
- Raloxifene: can be continued for at least 5 to 10 years[61] to prevent bone loss and lower risk of invasive breast cancer
- Hormone therapy: not recommended long term.

For Patients at High Risk for Fracture

Individuals with prior fragility fractures, FRAX 10-year risk for fracture that exceeds NOF guidelines for treatment; or very low BMD (−3.0 or <) without prior fracture.

- Bisphosphonates can be used for at least 10 years with periodic check for oral health and thigh pain
  - If no prior teriparatide therapy or contraindications, consider switching to 2 years of teriparatide for drug holiday from bisphosphonates
  - If opposed then:
    - Assess patient's risk averseness
      - Concerned about drug side effects > risk for fracture
        - Stop for drug holiday of several years
        - Monitor bone density every 2 years and BTM yearly
        - Resume therapy if significant declines in BMD or greater than 40% increase in BTM
      - Concerned about risk for fracture > drug side effects
        - Continue on drug therapy monitoring oral health and thigh pain
- Denosumab: monitor for ONJ and SFSF
- Teriparatide for 2 years followed by yearly intravenous bisphosphonate or denosumab.

Patients with Documented Atypical Subtrochanteric Fracture on Bisphosphonate

- Stop bisphosphonate
- Evaluate for stress reaction on contralateral femur
- Consider teriparatide for 2 years; subsequent intravenous zolendronate perhaps less often than yearly, or denosumab.

SUMMARY

In providing recommendations to patients regarding drug therapy, the health care provider must balance drug efficacy with side effects against drug therapy. Thus the FDA defines "safe" as meaning that the benefit outweighs the risk. For the

postmenopausal woman with low bone mass, the question is one of relative risk: is the risk of fragility fracture greater than the risk of drug side effect?

There are no current studies that demonstrate comparable across-the-board fracture benefit for those who discontinue a drug as opposed to those who continue on treatment, for whom length of therapy is 3 to 5 years before cessation. The residual effect on BMD and BTM during the "holiday" after cessation of bisphosphonate treatment implies ongoing fracture risk reduction, but such a benefit has not been definitively established. Therefore, for those at sufficiently high risk for fracture, a decision as to whether to continue on drug therapy is based on the perception of the risk of drug side effects.

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