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This complimentary e-newsletter from The North American Menopause Society (NAMS) presents clinical questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Michelle P. Warren, MD, the Editor of *Menopause e-Consult*, encourages your suggestions for topics to be addressed in future issues. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Warren. Previously published issues may be viewed on the NAMS Web site (www.menopause.org/econsult.html).

Question
How long should postmenopausal women continue to take bisphosphonate therapy for osteoporosis?

Commentary from:



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Bisphosphonates are biological analogues of naturally occurring pyrophosphates, by-products of adenosine metabolism, and were developed after the discovery that these nonmetabolized compounds have a high affinity for the calcium-phosphorus surface and can prevent both bone resorption or mineralization, depending on the type and dose of bisphosphonate.¹ The second-generation aminobisphosphonates (alendronate, risedronate, ibandronate, and zoledronate) have a ratio of inhibiting bone resorption to bone formation of greater than 1,000:1 and therefore do not inhibit mineralization or induce osteomalacia.

Bisphosphonates have a long retention time in bone and, while their affinity and detachment to

the denuded resorptive cavity differ among bisphosphonates in vitro and in vivo in animal models, it is unknown if there are differences in the so-called bone half-life in human beings.² Nevertheless, the bisphosphonates do get buried in bone and can remain there for years.

There have been several clinical and biochemical developments that have led clinicians to rethink how to use bisphosphonates in their postmenopausal population. These include:

1. The better understanding of bisphosphonate biology and pharmacokinetics.
2. The data on the effects of bisphosphonate discontinuation on bone mineral density (BMD), bone turnover markers (BTM), and incident fractures.
3. The concerns that have been raised from anecdotal data surrounding the potential for adverse skeletal effects of bisphosphonates, such as osteonecrosis of the jaw (ONJ) and specific femoral shaft fragility fractures with long-term alendronate use.

The advancements made in understanding bisphosphonate biology in the past decade have been enormous.³⁻⁴ The knowledge that bisphosphonates are recycled back into the circulation by two separate mechanisms (transcytosis, emanating through the osteoclast cell membrane; and detachment from bone during remodeling, retaining their molecular structure and biological activity) has given

bisphosphonates as a class pharmacokinetic properties that are nonexistent for any other drugs used in any disease management.⁵ After a bone “loading” period, it appears that the amount of bisphosphonate released back into the circulation can maintain BMD and BTM for a period of time, possibly years.⁶⁻⁷ There may be differences among bisphosphonates in the duration of this effect, and a finite period of administration may be needed (possibly 5 y) before this sustained benefit after discontinuation can be observed.⁸ Nevertheless, based on these data, there is a wider discussion evolving in medical practice concerning a “drug holiday” in postmenopausal women after 5 to 7 years of bisphosphonate administration, monitoring BMD and BTM on an annual basis to assess if the biological activity of sustaining the lower bone turnover is maintained. There are numerous opinions on which populations should be offered a drug holiday, and there is no standard of care for these approaches.⁹⁻¹⁰

The use of bisphosphonates in younger postmenopausal women increased following the publication of the Women’s Health Initiative (WHI), after which many women discontinued estrogen yet were concerned about their skeletal health. Women who were osteopenic were often prescribed bisphosphonates, at which time the metabolic bone community began to ask the question: “Is this use for life?” This question was not often asked when bisphosphonates were initiated in older patients. As data defined the sustained biological effect and persistence of effect of bisphosphonates after long term use, and the absolute fracture risk data from the World Health Organization (WHO) 10-year fracture risk assessment model (FRAX) clarified that these younger, untreated postmenopausal women were actually at fairly low 10-year fracture risk,¹¹ clinicians began to ask questions about duration of therapy. Whatever low risk these patients had before treatment was now even lower with treatment, and discussions surrounding drug holiday became more common. While there is no consensus on these approaches and management must be individualized, higher-risk patients (who had a previous low-trauma fracture, or were more

elderly [≥ 65 y] with BMD criteria for osteoporosis) are often not offered a drug holiday since their baseline risk is high.

Even though the Fracture Intervention Trial Long-term Extension (FLEX) data did not show an increase in hip, nonvertebral, or morphometric vertebral fractures in those subsets of patients randomized from the original Fracture Intervention Trials (FIT) taking alendronate for 5 years following 5 years without treatment, there was a statistically significant increase in clinical vertebral fractures in those patients off of alendronate for 5 years.⁶ Hence, despite the limitations of the FLEX data (selection bias and cofounders due to selection of some but not all of the original FIT population), it still remains unclear if bone strength is maintained at all skeletal sites during a drug holiday. There are observational data that a lower hip fracture risk off of alendronate may not be certain if the initial duration of use of alendronate is under 2 years.⁸ Hence, if a drug holiday is considered in lower-risk, younger women, a minimum duration of 5 years of alendronate use seems reasonable. As mentioned, there may be differences among the bisphosphonates in duration of effect, though there are not head-to-head data defining these durations or offset period. There are preliminary data that the reduction in bone turnover after a single injection of zoledronic acid (4-5 mg) may be sustained beyond a year¹² even though the standard of care is to follow the registered labeling from the Food and Drug Administration (FDA) for zoledronic acid (5 mg/y \times 3 y) following the reduction in all fractures in the pivotal zoledronic acid clinical trial.¹³ Monitoring BMD and BTM is, at the present time, the only means to judge sustained biological efficacy.¹⁴⁻¹⁵

Another less scientifically sound reason for considering a drug holiday is the anecdotal observational data on the risk of either ONJ or diaphyseal (femur) fractures in very small numbers of patients on bisphosphonates. In contrast to the greater risk (1%-10%) for ONJ seen in the oncology population who have received high doses of intravenous pamidronate

or zoledronic acid in combination with chemotherapy for metastatic (to bone) carcinomas or multiple myeloma, there have been fewer than 100 adjudicated cases of ONJ validated in the osteoporosis population who receive the far lower doses of bisphosphonates.¹⁶ Yet, the perception in the general dental and lay public is that ONJ is common, which has often led to unnecessary discontinuation of bisphosphonates. Such a decision in high-risk patients could possibly render them at far greater risk for fracture than the calculated attributable risk of ONJ in the postmenopausal population (<0.7 cases/100,000 patient/y exposure). Withholding bisphosphonates or temporarily discontinuing them before dental surgery (specifically extractions or implants) is suggested by expert opinion. Yet, there are no data that these management alterations in bisphosphonate use change any risk for this very low-risk dental condition. Nevertheless, discussions concerning drug holidays from bisphosphonates often arise out of concerns for ONJ.

Finally, there have been several anecdotal reports of the development of spontaneous, often bilateral diaphyseal femoral shaft fractures with long-term (≥ 5 y) use of alendronate.¹⁷ The mechanism associated with these fractures is unknown. It is also unknown if these types of fractures are seen in people not exposed to bisphosphonates because the reporting of such cases has not been systematic. Once large Medicare databases are carefully studied, we may know if these unusual fractures are confined to the bisphosphonate-exposed population. To date, all of these cases have been associated with long-term alendronate use. It is unknown if this is a class effect or not, since alendronate was the first FDA-approved bisphosphonate for osteoporosis management and has the largest exposed population. Therefore, only time and careful reporting will tell if these fractures are specific to alendronate, or if they might also be seen with other bisphosphonates or in nonbisphosphonate-treated populations. Nevertheless, due to the intense media exposure and the unique litigation climate that pervades US medicine, patients and

our colleagues are starting to question drug holidays for this potential fracture risk concern as well. There is no science to guide us here, and patient management must be individualized. Like the broader issue of a drug holiday in any patient, the potential risks and benefits of discontinuation need to be discussed.

Bisphosphonates will continue to be used to benefit patients with a variety of diseases including postmenopausal osteoporosis. The vast majority of treated patients have reduced fracture burden and costs, along with an exceptional safety record. It is the responsibility of practitioners to examine the issue of drug holidays, given the strong science that has evolved in bisphosphonate pharmacokinetics, and be open-minded about potential safety issues that demand good science to clarify. In the meantime, consideration of bisphosphonate drug holidays continues to be based on opinion, without a standard of care, and individualized for each patient.

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Case

A 56-year old woman presented with hair shedding and thinning over the vertex scalp for the last few years, particularly since reaching spontaneous menopause at the age of 51. She stopped taking her hormone therapy (HT) 1 year ago after the news reports of the risks associated with this medication. She has a positive family history for pattern hair loss (PHL) and has not tried any treatments. What is needed for workup and what are her treatment options?

Management Issues by:



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Onset of hair loss during the menopausal transition and in postmenopausal women may be due to a variety of conditions. Female pattern hair loss (FPHL; androgenetic alopecia) and telogen effluvium are the most common causes. FPHL is more common after menopause; the altered estrogen-to-androgen ratio may play a role in pathogenesis in some women. Another form of hair loss, frontal fibrosing alopecia—a lichen planopilaris variant—also occurs in postmenopause. Other causes of hair loss (including thyroid disease, cicatricial alopecias, trichotillomania, and alopecia areata) are less common, but should not be excluded.

Hormones influence hair growth¹ and both estrogen and androgen receptors have been found on hair follicles.^{2,3} The exact mechanism of action of estrogen on hair follicles is unknown; however, estrogen is believed to protect against hair loss, with the estrogen-receptor pathway involved with telogen-anagen follicle cycling.^{1,4} This is illustrated by women's increased hair density during pregnancy from prolongation of anagen and the postpartum telogen effluvium that accompanies the fall in maternal estrogen levels. Androgens,

importantly dihydrotestosterone, which is converted from testosterone by 5-alpha reductase at the hair follicle level, act via the androgen receptor.³ Androgens have differential effects on hair follicles depending on their body site, and on the scalp cause progressive miniaturization of susceptible hair follicles and shortening of anagen.^{3,5,6} This androgen effect occurs in genetically susceptible individuals to cause hair loss, although in FPHL the role of androgens is less clear than in male PHL.⁷

In postmenopausal women, estrogen production and levels fall to low levels and there are alterations in androgen production.^{8,9} Testosterone levels are minimally lower than premenopausal levels, but androstenedione levels are significantly lower.⁹ A total of 50% of testosterone production in the postmenopausal woman is believed to originate from the ovary, with peripheral conversion also contributing to circulating testosterone levels.⁷ There is also an age-related decrease in adrenal gland production of dehydroepiandrosterone sulfate (DHEAS).⁹ Therefore, during postmenopause, estrogen levels are low and testosterone levels usually normal or only slightly decreased,⁹ leading to a hypoestrogenemic and relative hyperandrogenic state,^{1,9} causing an increase in the androgen-to-estrogen ratio that may lead to PHL in susceptible individuals.¹⁰ Interestingly, in a group of premenopausal women with FPHL, the ratio of estrogen to androgen was also found to be significantly lower compared to the control group and was suggested as the hair loss trigger.¹¹ Other factors may be involved in FPHL, such as the aromatase enzyme, alterations in the androgen receptor, or androgen and estrogen metabolism in the hair follicle.¹⁰

In this clinical scenario, FPHL is the most likely diagnosis. History, examination, and laboratory investigations should confirm your diagnosis and exclude other disorders. Most treatments for PHL are antiandrogens directed at lowering the amount of androgens available to the hair follicle. Topical estrogen preparations, aimed at increasing local estrogen concentrations at the hair follicle, are available in Europe. Topical minoxidil and nutritional support are an

essential part of treatment, as are patient education and support.

Clinical history and examination. A thorough clinical history is required, including the duration, pattern, and percentage of hair loss. A detailed female history is needed, including menstrual history, number of pregnancies, age at menopause and menopausal symptoms, HT use, and associated symptoms of androgen excess such as acne, seborrhea, and hirsutism. A family history is needed, focusing on PHL, autoimmune conditions, thyroid disorders, and malignancies. Further hair loss triggers should be sought, including medication history, severe illness, surgery, or weight loss. A detailed dietary and hair care history should be obtained. Past medical history and systems review should also be performed. Clinical examination should confirm the distinctive pattern of loss over the crown with widening of the central part and retention of the frontal hairline seen in FPHL⁷ and exclude other types of hair loss including a cicatricial alopecia such as frontal fibrosing alopecia with loss of visible follicular openings. Females can also show a male-type pattern of alopecia with vertex balding and bitemporal recession.⁷ Other signs of hyperandrogenism should be screened including acne, clitorromegaly, and hirsutism. The scalp is usually normal and hair pull tests may be positive early in FPHL.

Laboratory investigations. In any woman presenting with hair loss, additional causes should be excluded. A complete blood count, comprehensive metabolic panel, thyroid function tests (TSH, T4 level), iron, ferritin, and a zinc level will exclude systemic disease, thyroid disease, and nutritional deficiency. In women with FPHL and/or other signs of androgen excess, an androgen screen is required to exclude an androgen-secreting tumor or other endocrinopathy.⁷ A total and/or free testosterone level and levels of sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS) can identify high androgen levels. Further investigation and referral to an endocrinologist may be required. A small study suggested that some postmenopausal women

with FPHL do not have statistically significant differences in their levels of testosterone, estradiol, or SHBG compared to matched controls without FPHL.¹² Levels of testosterone and DHEAS greater than 200 ng/dL and 700 ug/dL, respectively, are suggestive of an ovarian or adrenal tumor.¹³ Estradiol and FSH levels can demonstrate postmenopausal hormone levels.⁹ Histology, if needed, can confirm the diagnosis of FPHL with miniaturization of terminal hair follicles into vellus hairs, leading to a diagnostic ratio of terminal to vellus hairs of less than 4:1.¹⁴

General treatment. Nutritional deficiencies should be corrected, and biotin and multivitamin supplements given to support hair regrowth. Topical minoxidil 2% or 5% is beneficial for hair regrowth,¹⁵ but is a nonspecific hair promoter.⁷ For FPHL, only the 2% solution is approved by the Food and Drug Administration (FDA) but the 5% solution is more effective. Facial hypertrichosis can be a side effect.^{7,15} No randomized placebo-controlled trials (RCTs) using the combination of minoxidil and an antiandrogen for FPHL exist; however, this therapeutic combination is commonly used in patients with FPHL. Where appropriate, creative hair styles, hairpieces, or hair transplant can be helpful as adjunctive treatments.⁷

Specific hormonal treatments. Antiandrogens compete with circulating androgens for the high-affinity androgen receptor and are helpful for FPHL.^{7,16} The aim of treatment is to prevent progression of the hair loss, rather than hair regrowth. It is still unclear, however, whether women with FPHL and measurable levels of androgen excess respond differently to antiandrogen therapy compared to women with FPHL and normal androgen levels.⁷ There are no large RCTs investigating antiandrogens in peri- or postmenopausal women with FPHL.

Spironolactone competitively blocks the androgen receptor and suppresses ovarian androgen synthesis.¹⁶ It has been used in doses of 50 mg to 200 mg daily as an antiandrogen for FPHL.^{7,16,17,18} Hyperkalemia is a risk so baseline and continued monitoring of serum potassium is

needed.¹⁹ Other adverse effects include fatigue, postural hypotension, and liver abnormalities.^{7,16,19} Spironolactone was found to be tumorigenic in animal studies, although the significance to humans is unknown.¹⁹ Therapies such as antiandrogens that alter the hormonal milieu should be avoided in women with a personal or family history of estrogen-dependent cancers such as breast, uterine, or ovarian cancer.

The antiandrogen cyproterone acetate is also used for the treatment of FPHL in postmenopausal women (not available in the United States). Cyproterone acetate competitively inhibits the androgen receptor and inhibits luteinizing hormone release.^{7,17,20} It can be used continuously in postmenopausal women at 50 mg daily, alone or in combination with an estrogen-based hormone replacement.^{7,16} Side effects include nausea, weight gain, depression, breast tenderness, and decreased libido.¹⁶

Finasteride, a type 2 5-alpha reductase inhibitor, prevents conversion of testosterone to the more potent dihydrotestosterone.²¹ Finasteride is used for MPHL, but has been found ineffective in postmenopausal women with FPHL at oral doses of 1 mg daily.²¹ Higher doses of 2.5 mg to 5.0 mg daily of finasteride may be effective in some women with FPHL.²² Finasteride has also been tried in postmenopausal women with frontal fibrosing alopecia without success.²³ Dutasteride inhibits both type 1 and type 2 5-alpha reductase enzymes and is effective, but not FDA approved, for MPHL.²⁴ No cases are reported of dutasteride treatment for FPHL in postmenopausal women.

Flutamide is a potent antiandrogen, but is associated with significant risk of hepatotoxicity and is not used for treatment of FPHL.¹⁷ Topical estrogen preparations are not available for FPHL treatment in the United States.¹⁰

HT and hair loss. Given that estrogen is believed to be protective for hair, cessation of HT can precipitate hair shedding and unmask FPHL. In the senior author's experience, HT, if appropriate to continue, can support hair growth

as it supports other skin structures. The decision to continue HT should be directed by the patient's gynecologic care provider, depending on risk factors, menopausal symptoms, and the patient.

Editor's note: The hypothesis that FPHL is a relative high-androgen state has led to the use of antiandrogens or androgen suppressors. However, the use of these agents and their efficacy are still questionable. All of the agents discussed for the treatment of FPHL are off label. Also of concern is that studies of these treatments were small and not double-blinded or placebo-controlled. Patients with hair loss who have testosterone measurements are sometimes found to have very low levels, and using antiandrogens in this clinical scenario is questionable. The use of these agents in patients without overt hyperandrogenism has not specifically shown to be effective.—Michelle P. Warren, MD

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