Osteoporosis International (2019) 30:2401–2406
https://doi.org/10.1007/s00198-019-05147-8

CONCISE CLINICAL REVIEW

Lessons learned with Bone Health TeleECHO: making treatment decisions when guidelines conflict

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Received: 15 May 2019 / Accepted: 23 August 2019 / Published online: 31 August 2019

Abstract

Clinical practice guidelines provide helpful information for managing patients with metabolic bone disease. Good guidelines are based on the best available medical evidence; however, guidelines from different societies can conflict. Additionally, it is not possible for a guideline to anticipate the vast variability of circumstances, comorbidities, previous medical experiences, cultural differences, and preferences in real-world patients. Bone Health TeleECHO is a strategy for sharing knowledge on the care of patients with skeletal diseases through ongoing interactive videoconferences. We report three cases based on those presented at Bone Health TeleECHO, where, through discussion, treatment outside of commonly used guidelines was ultimately recommended. Guidelines developed by different organizations may provide "evidence-based" or "informed" recommendations which do not account for the variability of clinical circumstances encountered in the care of individual patients. This highlights the importance of Bone Health TeleECHO, where healthcare professionals can share knowledge, individualize treatment decisions, and improve patient care.

Learning objectives

At the end of this activity participants should be able to:

- *Distinguish between the onset and off of bisphosphonates versus other medications used in the prevention and treatment of osteoporosis and how this affects choice of a "drug holiday."*
- *Understand the limitations of clinical practices guidelines in the care of an individual patient and how interactive video conferencing can assist with decision making.*
- *Recognize that patients treated with glucocorticoids at high risk for fracture can benefit from more aggressive interventions for osteoporosis.*

Keywords Osteoporosis treatment · Guidelines · Telehealth · Telemedicine

The CME questions related to this article can be found at: https://cme.nof.org/default.aspx

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Introduction

Bone Health TeleECHO (Extension for Community Healthcare Outcomes) is a learning network for healthcare professionals to share knowledge about osteoporosis and metabolic bone diseases through ongoing interactive videoconferences [1–3]. Each videoconference consists of a brief didactic presentation and discussion of a topic of interest, followed by discussion on the management of real but de-identified patients with skeletal diseases. This recapitulates familiar learning methods from postgraduate medical education programs. The goal is to elevate the level of knowledge of all participants to provide better care for patients with skeletal diseases and reduce the osteoporosis treatment gap [4]. Bone Health TeleECHO has been shown to improve self-confidence of participants in 20 domains of osteoporosis care [5], providing

patients with an opportunity to receive better care, closer to home, and at lower cost than referral to an academic medical center that may be located far from the patient.

The ECHO model of learning was first developed at the University of New Mexico Health (UNM) Sciences Center to teach primary care providers in rural New Mexico to manage patients with chronic hepatitis C. The multidisciplinary team of specialists was located at UNM in Albuquerque, NM, USA. The learners consisted of teams of individuals located anywhere there was an Internet connection, often in remote communities far from UNM. A prospective cohort study showed that patients of ECHO participants eventually received hepatitis care that was as good as, or better than, the academic specialty center [6]. The ECHO model of learning has since expanded to include many disease states at universities and institutions worldwide [7].

Weekly Bone Health TeleECHO videoconferences have been held since October 2015, based at a videoconferencing center at UNM, with participants located throughout the USA and other countries. There is often little distinction between faculty and learners, with all participants gaining knowledge through the interactions of many medical disciplines (e.g., physicians of many specialties, advanced practice providers, physical therapists, dieticians, and clinical researchers). ECHO is neither telemedicine, where typically one physician cares for one patient at a distance, nor is it a webinar, which is usually a lecture online with limited opportunity for interaction. ECHO serves as a healthcare force multiplier by educating healthcare providers to manage many patients. In addition to the proof-of-concept Bone Health TeleECHO based in Albuquerque, others are now operational in Grand Blanc, MI, USA; Washington, DC, USA; Galway, Ireland; Moscow, Russia; and Chicago, IL, USA (listed in order of start-up dates). Additional Bone Health TeleECHO programs are expected to follow soon.

The experience of Bone Health TeleECHO is that patients seen in clinical practice are often complex, with circumstances that may not always be addressed in randomized clinical trials or reflected in clinical practice guidelines. Clinical management can be confounded by competing guidelines with differing recommendations directed to different medical specialties. This report describes three patients for whom consideration of treatment outside of commonly used guidelines is appropriate.

Patient #1: What to do after stopping estrogen therapy

A 59-year-old woman presents after a bone density test with dual-energy X-ray absorptiometry (DXA) reveals a T score of − 2.3 in the femoral neck, consistent with the diagnosis of osteopenia. She has a strong family history of osteoporosis with maternal hip fracture, but no personal history of fracture. She had been taking transdermal estradiol with progesterone since menopause at 51 years, but recently stopped due to concerns about possible adverse effects with long-term use. She is otherwise healthy and active. Basic screening labs are normal with adequate serum 25-OH vitamin D. Should she be started on pharmacological therapy for skeletal health?

National Osteoporosis Foundation guide

This patient's calculated risk via FRAX in the next 10 years is 17% for major osteoporotic fracture and 1.4% for hip fracture. The National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis [8] suggests pharmacologic treatment for women with T scores between − 1.0 and − 2.5 when the FRAX 10-year probability of major osteoporotic fracture is 20% or greater or the 10-year probability of hip fracture is 3% or greater. According to her current risk of fracture, the only treatment recommended would be non-pharmacologic, with adequate intake of calcium and vitamin D, regular weight-bearing and muscle-strengthening physical activity, avoidance of smoking and excess alcohol, and fall prevention.

What was recommended and why

This patient's current risk of fracture is low according to the FRAX calculator; however, stopping estrogen must be taken into account when thinking about her long-term plan for bone health. Estrogen is an effective treatment for menopausal symptoms and provides skeletal protection as well [9, 10]. The main mechanism for the skeletal effects of estrogen is suppression of osteoclast action with decreased bone turnover. The benefits of estrogen are not expected to continue after cessation of medication. Studies looking at bone mineral density (BMD) and bone turnover markers confirm a rapid return to high bone turnover marker levels, a different profile than observed after stopping long-term bisphosphonate therapy, where a slow rise of bone turnover markers can be expected [11, 12]. Many studies show hip and vertebral fracture rates to return to baseline or even increase after withdrawing menopausal hormone therapy [13–15]; although, follow-up of a subgroup of women from the Women Health Initiative showed sustained hip fracture protection [16, 17]. The latest Endocrine Society guidelines for postmenopausal osteoporosis suggests alternative treatments be started when estrogen is stopped in women with osteoporosis [18], but this does not cover lower risk women, such as this patient. Her risk could be further assessed with bone turnover markers after estrogen is stopped or perhaps with other imaging to rule out occult vertebral fractures. Options of watchful waiting with aggressive non-pharmacological management as well as consideration of a selective estrogen receptor modulator (SERM) were discussed. Given that bisphosphonates can benefit postmenopausal women with osteopenia [19, 20] and this patient's

concerns based on family history, it was suggested she consider a bisphosphonate for 1–3 years to mitigate the bone loss likely to occur with the withdrawal of estrogen, rather than wait for her BMD to decrease and fracture risk become higher.

Clinical tips

- Estrogen has benefits for menopausal symptoms and bone health, but these effects do not last after cessation of therapy.
- The US Food and Drug Administrations has approved bisphosphonates for prevention of postmenopausal osteoporosis; although, this is not an indication for treatment according to the NOF guide.
- Understanding the rapidity of offset of osteoporosis treatment effects is important; all currently available medications, except for bisphosphonates, have a rapid offset of effect with discontinuation.

Patient #2: How long to treat with denosumab

A 73-year-old woman comes for an annual visit. Her medical history is significant for hypertension, type 2 diabetes mellitus complicated by diabetic nephropathy with chronic kidney disease stage 3b (estimated glomerular filtration rate 30 mL/min/1.73 m^2), and gastroesophageal reflux with Barrett's esophagus treated for many years with omeprazole. She was diagnosed with osteoporosis 5 years ago, based on a DXA T score of − 3.2 at the lumbar spine (L1–L4). Because of mild kyphosis, a thoraco-lumbar spine X-ray was done, showing an age-indeterminate T11 vertebral compression fracture. She was started on denosumab 60 mg subcutaneously every 6 months. A recent follow-up DXA on the same instrument showed the lowest T score of − 2.6 at the left total hip and statistically significant bone density increases in both the hip and spine. How long should she stay on denosumab therapy?

American College of Physicians guidelines

This is a postmenopausal female over 65 diagnosed with osteoporosis based on World Health Organization criteria. Bone density improved after 5 years of denosumab therapy, consistent with a beneficial effect of treatment. Guidelines of the American College of Physicians recommend that clinicians treat osteoporotic women with pharmacologic therapy for 5 years [21], suggesting there is no value in longer treatment.

What was recommended for this patient and why

This patient's current risk of fracture remains high considering her chronic kidney disease stage 3b [22], diabetes mellitus [23], and ongoing therapy with proton pump inhibitors [24]. Increasing age is an independent risk factor for fracture as well, with bone microarchitecture quality decreasing each decade after age 50, even when BMD is stable [25]. She was successfully treated with denosumab for 5 years, as she was not a candidate for oral or IV bisphosphonates due to her history of Barrett's esophagus and decreased renal function. Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, increasing BMD, and reducing vertebral and non-vertebral fracture risks [26]. It is a potent and rapid suppressor of bone turnover. After stopping treatment, levels of bone turnover markers rapidly return to baseline and subsequently rise above the initial baseline. This has been associated with loss of BMD [27], return of vertebral fracture risk to baseline, and possible increase in the risk of multiple vertebral fractures [28]. Stopping denosumab in this patient, without initiating another treatment, could put her at increased risk for vertebral compression fractures [28]. In contrast to the ACP guidelines, the newly published Endocrine Society Guidelines [18] recommend not to interrupt or stop denosumab therapy without administering another therapy to prevent the risks of rebound rapid bone turnover as noted above. Additionally, long-term denosumab treatment appears safe and effective with ongoing low fracture incidence and continued increase in BMD without a plateau for up to 10 years [29, 30]. One atypical femoral fracture occurred in each group during the 7-year extension and 7 cases of osteonecrosis of the jaw were reported in the long-term group and 6 cases in the crossover group. These data support continuing denosumab as a reasonable recommendation for this patient.

An alternative option could be to switch to anabolic therapy (e.g., teriparatide, abaloparatide, romosozumab); however, one clinical trial showed a decrease in hip BMD in the 12 months after switching from denosumab to teriparatide [31]. When teriparatide was used as an active comparator for abaloparatide, a significantly greater proportion of patients treated with abaloparatide experienced increases in BMD [32] and decreased risk for major osteoporotic fractures [33] than did those treated with teriparatide; however, there are no reported data yet with regard to treatment with abaloparatide or romosozumab following denosumab and similar concerns may exist. There are no contraindications to continue denosumab for at least another 5 years, which is what was recommended for this patient.

Clinical tips

- Osteoporosis is a lifelong disease that warrants lifelong attention.
- Denosumab 60 mg subcutaneously every 6 months for 10 years is generally safe, decreases fragility fracture risk, and continues to increase bone density without a plateau.
- The effects of denosumab are not sustained when treatment is discontinued. There is no "drug holiday" with denosumab.

Patient #3: Treatment of glucocorticoid-induced osteoporosis

A 62-year-old man with sarcoidosis has been on chronic glucocorticoid therapy for 2 years, currently taking prednisone 30 mg daily. He presented with back pain and was found to have a T9 compression fracture with 50% vertebral height loss. Subsequent DXA testing showed T scores of − 1.6 in the lumbar spine and − 1.4 in the femoral neck. Biochemical assessment was unremarkable. How should his osteoporosis be treated?

American College of Rheumatology guidelines

In August 2017, revised American College of Rheumatology guidelines for the prevention and treatment of glucocorticoid induced osteoporosis were published [34]. Consistent with these guidelines, this patient would be considered to be at "high risk of future fracture." Initiating treatment with an oral bisphosphonate is favored over intravenous bisphosphonates, denosumab, and teriparatide based on safety, cost, and "lack of superior anti-fracture benefits" from other medications. This recommendation would hold despite his recent vertebral compression fracture.

What was recommended for this patient and why?

This is a chronically ill man, with a systemic inflammatory disease on high-dose glucocorticoids with severe osteoporosis as demonstrated by low trauma fracture. Glucocorticoid treatment is a well-known cause of osteoporosis, leading to vertebral and non-vertebral fractures with dose-dependent effects [35]. The etiology of glucocorticoid-induced osteoporosis is multifactorial—causing reduced osteoblast function and osteocyte apoptosis as well as increased osteoclast number and activity [35]. Additionally, impaired gut calcium absorption may lead to urinary calcium wasting and secondary hyperparathyroidism [36]. Many patients treated with glucocorticoids develop hypogonadism and steroid-related myopathy, further compromising bone health [35]. As glucocorticoids negatively affect bone quality, the T score may underestimate fracture risk, as patients on glucocorticoids are known to fracture at higher bone densities [36]. This patient's "imminent fracture risk" [37] is very high, with a recent vertebral fracture greatly increasing the risk of future fractures, especially in the following 1–2 years. Therefore, aggressive osteoporosis treatment should be considered.

In 2007, Saag et al. reported greater lumbar spine BMD increases for glucocorticoid-treated patients taking teriparatide than the comparator, alendronate [38]. In a study comparing teriparatide versus alendronate with fractures as a secondary endpoint, teriparatide users were found to have greater increases in BMD and fewer new vertebral fractures than subjects treated with alendronate [39]. Importantly, Neer et al., in 2001, documented the efficacy of teriparatide for reducing fracture risk in a pivotal study where most patients were "treatment naïve [40]." Other studies suggest that there may be a blunting of the effect of anabolic therapy when antiresorptive therapy is used previously [31, 41]. Therefore, the preferred sequence of therapy for high-risk patients is an anabolic agent first, followed by an antiresorptive drug [42]. In contrast to the ACR guidelines, Adami and Saag summarize 6 international guidelines on glucocorticoid-induced osteoporosis [43] and indicate consideration of teriparatide for high-risk groups. The 2016 Italian guidelines would support the use of first-line teriparatide in glucocorticoid-induced osteoporosis in the presence of hip or vertebral fracture, such as in our patient [44]. With consideration of his high fracture risk associated with long-term glucocorticoid use and documented vertebral fracture, it was recommended that he be treated with teriparatide as a first line treatment. After 18–24 months, it should be followed up with antiresorptive therapy [45].

Clinical tips

- Glucocorticoid bone loss is rapid and sustained and there remains no safe dose, so vigilance in clinical care to address the bone health needs of patients on long-term glucocorticoids is indicated.
- While bisphosphonates are appropriate choices for many patients on glucocorticoids, there is an evidence-based rationale for the use of teriparatide as first-line treatment, especially the highest risk patients.
- Glucocorticoid effects on bone quality are not fully recognized with DXA testing; therefore, DXA results may be falsely reassuring.

Summary

The patient cases presented here illustrate scenarios for which recommendations fall outside guidelines that are commonly used in clinical practice. Guidelines may conflict and this illustrates the importance of individualizing treatment decisions and highlights the benefits of participation in Bone Health TeleECHO, where healthcare professionals can share knowledge to improve patient care. Clinical practice guidelines cannot account for the variability of circumstances encountered in the care of individual patients.

Compliance with ethical standards

Conflict of interest MSR has nothing to disclose.

TPO is a consultant and serves on a speakers' bureau for Amgen and Radius.

IS has received no direct income from potentially conflicting entities. Her employer Panorama Orthopedics and Spine Center receives research grants from Alexion, Amgen, Radius Health, and Regeneron. She serves on a speakers' bureau for Radius Health.

KK is a speaker and consultant to Radius and has a retirement pension from Eli Lilly.

EML has received no direct income from potentially conflicting entities. His employer, New Mexico Clinical Research & Osteoporosis Center, has received research grants from Radius, Amgen, Mereo, Bindex; income for service on scientific advisory boards or consulting for Amgen, Radius, Alexion, Sandoz, Samsung Bioepis; service on speakers' bureaus for Radius, Alexion; project development for the University of New Mexico; and royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis. He is a board member of the National Osteoporosis Foundation, International Society for Clinical Densitometry, and Osteoporosis Foundation of New Mexico.

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