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Drug Therapy Issues

Understanding and Communicating the Benefits and Risks of Denosumab, Raloxifene, and Teriparatide for the Treatment of Osteoporosis

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Abstract

The number needed to treat is a valuable metric to determine the benefit of therapy, but it must be viewed against the respective number needed to harm. Denosumab and teriparatide (TPTD) have proven antifracture efficacy at vertebral and nonvertebral sites, whereas raloxifene has proven antifracture efficacy at the spine only. Denosumab use has been associated with a small, yet statistically significant, increased incidence of eczema and serious cellulitis. Raloxifene use has been associated with statistically significant increases in the risk of venous thromboembolism and possibly deadly stroke, although not an increase in total strokes. No significant, nontransient adverse events have been reported with TPTD use. When used for the treatment of postmenopausal osteoporosis, denosumab, raloxifene, and TPTD all generally have favorable risk-to-benefit profiles, but therapy-specific contraindications necessitate thoughtful consideration of all available clinical information and individualization of treatment decisions.

Key Words: Benefit; fracture; osteoporosis; risk; treatment.

Introduction

Approved pharmacologic therapies reduce fracture risk in high-risk patients, with favorable benefit-to-risk ratios *(1)*. However, most high-risk patients are unidentified *(2)* and untreated *(3)*, and of those who receive treatment, many medicate incorrectly or for an insufficient duration *(4)*. Attribution (correctly or incorrectly) of undesirable symptoms to a drug and fear of side effects, are among the most common reasons for poor therapy adherence *(5)*.

Meaningful risk communication is achieved through physician-patient interaction, whereby the patient has all necessary information to weigh the intervention's benefits and risks, and the physician understands the patient's comorbidities, concerns, biases, and experiences.

This is a review of the use of denosumab, raloxifene, and teriparatide (TPTD) for osteoporosis with attention to understanding and communicating the balance of expected antifracture benefits to potential risks. A companion review of bisphosphonate therapy has recently been published *(6)*.

Understanding Risk

The benefits of osteoporosis treatment are often expressed as relative risk reduction—the percentage reductions in fracture risk in a group of clinical trial participants treated with an investigational agent compared with a matched group, usually receiving placebo. For example, if the treated group has a 5% risk of fracture and the placebo group a 10% risk over

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a studied time period, the relative risk reduction with treatment is 50% (0.05/0.10 × 100). The absolute risk reduction (ARR) is the difference between the fracture rates of the 2 groups; using the same example, the ARR is 5% ([0.10−0.05] × 100). The number needed to treat (NNT, 1/ARR) is the average number of patients treated to prevent 1 outcome of interest over a defined period. As an example, in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months (FREEDOM) trial *(7)*, 8.0% of the placebo group and 6.5% of the denosumab group experienced a nonvertebral fracture over 3 yr—a 1.5% ARR. Therefore, a total of 67 (1/1.5%) patients needed to be treated with denosumab for 3 yr to prevent 1 nonvertebral fracture. Conversely, the number needed to harm (NNH, 1/absolute risk increase) is the average number of patients treated to cause 1 additional adverse outcome over a defined period. Both NNT and NNH are influenced by baseline risk and the relative risk of harm or benefit with treatment. As an example, different clinical trials have different patient groups each with unique underlying risks for future fracture (e.g., differences in BMD and fragility fracture history). Identical therapies used in different cohorts will result in divergent NNT calculations. Thus, NNT or NNH results should not be directly compared among different cohorts.

Only head-to-head fracture data from a randomized controlled trial can be used to directly compare efficacy, and to date, these data are nonexistent. However, clinical trial data do provide a broad overview of the general benefits and risks of individual therapies in the population studied.

One of the intents of randomization is to determine whether there are statistically significant differences in adverse events or serious adverse events (SAEs) between groups of clinical trial participants, with the goal of assessing causality between the event and the investigational drug. Although common therapy-associated adverse events can be identified in registration trials and causality investigated, the trials are often inadequate in size and duration to capture rare events. Furthermore, ''real-world'' patients requiring treatment are often different than clinical trial participants to the extent that most would not qualify for inclusion in clinical trials for the drugs used to treat them *(8)*.

Risk Communication

Risk communication is ''one-to-one communication in which the intervention includes a stimulus to patients to weigh the risks and benefits of a treatment choice or behavioral (risk reducing) change'' *(9)*. Effective risk communication can improve patients' awareness of health risks and promote risk-reducing behavior. ''Decision aids'' (e.g., handouts, videos) can potentially improve physician-patient communication and facilitate better clinical decisions *(10)*.

The physician must explain the balance between the expected antifracture benefit of treatment and the potential risks. Often, the patient's *perception* of risk carries more weight in decision making than the probability of harm, even if the balance of risk-to-benefit is clearly favoring benefit *(11)*. With osteoporosis treatment, the fear of rare nonfatal occurrences, such as osteonecrosis of the jaw (ONJ), may overwhelm the fear of a more probable, potentially fatal, fracture.

Shared Decision Making

Shared decision making combines patient and physician perspectives of the expected benefits and potential risks of therapy to reach a mutually acceptable treatment plan *(10)*. The physician should translate complex information into nontechnical language, encouraging the patient to respond, using decision aids when appropriate *(12)*. It should be made clear that the goal of therapy is fracture risk reduction. When communicating therapy efficacy, clinical trial data should be scrutinized for patient applicability *(8)*. The treatment decision should be medically reasonable from the physician's perspective and acceptable to the patient.

Efficacy of Osteoporosis Therapy

Denosumab, raloxifene, and TPTD are useful for the management of osteoporosis by significantly decreasing the risk of vertebral, nonvertebral, and/or hip fractures (Table 1).

Denosumab

Potential Benefits of Denosumab Therapy

In the FREEDOM trial, denosumab (Prolia; Amgen Inc, Thousand Oaks, CA), 60 mg, injected subcutaneously every 6 mo significantly reduced the incidence of morphometric vertebral, nonvertebral, and hip fractures over 3 yr compared with placebo *(7)*. In the extension studies of FREEDOM to 5 yr *(13)*, global fracture risk reduction was maintained without new safety concerns. Denosumab is also beneficial for the treatment of osteoporosis in men *(14)*.

Denosumab inhibits the differentiation, activity, and survival of osteoclasts and does not reside in the skeleton. Biopsy data indicate that denosumab induces rapid, marked but fully reversible bone remodeling inhibition *(15,16)*. Bone turnover inhibition wanes by 6 mo after denosumab injection, necessitating reinjection biannually *(15)*. Denosumab's parenteral administration ensures compliance for 6 mo, avoids gastrointestinal side effects, and allows for patients with impaired absorption or low renal function to receive effective therapy.

Potential Adverse Events With Denosumab Therapy

The exposure of denosumab to clinical populations has been limited because of its recent market introduction (June 2010). However, some potential safety concerns were identified from clinical trials. In the FREEDOM trial *(7)*, the incidence of SAEs classified as cellulitis was significantly higher in the denosumab group as compared with the placebo group (0.3% vs $<0.1\%$, respectively; $p = 0.002$); however, this difference was not observed in the extension study *(13)*. The incidence of eczema was low in the FREEDOM trial yet significantly higher in the denosumab group than the placebo

Table 1
Antifracture Benefits of Common Osteoporosis Therapies for the Treatment of Postmenopausal Osteoporosis

		Absolute risk reduction			Relative risk reduction			Number needed to treat to prevent 1 fracture		
Medication (registration trial)	Yr	Vert fx (%)	Non-vert fx (%)	Hip fx (%)	Vert fx (%)	Non-vert fx (%)	Hip fx (%)	Vert fx	Non-vert fx	Hip fx
Denosumab[a] (FREEDOM; *(7)*)	3	4.8	1.5	0.5	67.5	18.8	41.7	21	67	200
Raloxifene (MORE; *(20)*)	3	3.5	0.8	NA	35.0	8.6[b]	NA	28	126	NA
Teriparatide *(31)*	1.7	9.3	3.5	NA	65.3	52.9	NA	11	28	NA

Note: Widely ranging populations with regards to bone mineral density, age, and previous fracture status make direct comparison of therapies impossible. These data are provided as a broad overview of the general benefits of the therapies. For more information regarding the particular populations studied for each therapy, please refer to the references publication.

Abbr: Hip fx, hip fracture; MORE, Multiple Outcomes of Raloxifene Evaluation; NA, not assessed; Non-vert fx, nonvertebral fracture; Vert fx, vertebral fracture; Yr, average years of follow-up.

[a]Vertebral fracture incidence rate estimated from proportional hazards models.

[b]Not statistically significant.

group (3.0% vs 1.7%, respectively; $p < 0.001$). A recent in-depth analysis of the infectious events in the FREEDOM trial concluded that there were no relationships between SAEs and the timing or duration of denosumab administration *(17)*. To reflect the potential for increased risk of infection, the package insert states ''Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections.''

Although no cases of ONJ were reported in the FREEDOM trial *(7)*, there were 2 cases in 2207 crossover patients (3 yr of placebo followed by denosumab) in the first 2 yr of the FREEDOM extension study *(13)*. Oncology trials of denosumab administering higher and more frequent doses of denosumab (120 mg/mo) reported ONJ incidence similar to that reported with oncologic dosing of bisphosphonates *(18)*, suggesting that the magnitude of suppression of bone turnover may be causally related to ONJ.

Case reports of primarily mild and transient hypocalcemia have been described with denosumab therapy, stressing the importance of adequate vitamin D and calcium replacement. There were no incidences of hypocalcemia in the denosumab arm of the FREEDOM trial, whereas 3 events occurred in the placebo group *(7)*. Denosumab is safe in renally compromised patients supplemented with sufficient calcium and vitamin D and does not require dosing adjustment for glomerular filtration rate *(19)*.

Table 2 highlights the reported rate and the respective NNH for SAEs reported with administration of denosumab, raloxifene, and TPTD for osteoporosis treatment.

Raloxifene

Raloxifene (Evista; Eli Lilly and Company, Indianapolis, IN) is a selective estrogen receptor modulator that confers estrogen agonistic effects on bones, lipids, vascular endothelium, and the central nervous system and antagonistic effects on the breasts and genitourinary tract.

Benefits of Raloxifene Therapy

Raloxifene is used in younger postmenopausal women with osteoporosis who are at modest risk of fracture and has proven antifracture efficacy at the spine only *(20)*. As raloxifene is not bound to bone, its antifracture effect is lost rapidly after discontinuation *(21)*.

Raloxifene has important extraskeletal benefits. Raloxifene reduces the rate of invasive breast cancer over 4 yr (72% reduction; *(22)*) and 8 yr (66% reduction; *(23)*) of therapy, particularly for invasive estrogen receptor−positive breast cancer *(24)*. In a high-risk subset of women with increased cardiovascular risk (n = 1035), there were significant reductions in the risk of cardiovascular events with raloxifene use *(22)*; however, this benefit was not confirmed in a larger randomized placebo-controlled trial specifically designed to assess cardiovascular outcomes *(25)*.

Potential Adverse Events With Raloxifene Therapy

Raloxifene can potentially affect numerous estrogen-sensitive tissues negatively. In the Raloxifene Use for the Heart trial, raloxifene was associated with a 49% increased risk of fatal stroke (59 vs 39 events; hazard ratio, 1.49; 95% confidence interval, 1.00−2.24; absolute risk increase, 0.7 per 1000 woman-years; *(25)*). It should be noted that the fatal stroke risk was observed in an older population at high baseline risk for cardiovascular disease, that the overall risk of stroke was similar, and that this may be less of a concern in healthier, younger women. In contrast, a recent large observational analysis concluded that the risk of stroke or fatal stroke was not elevated in women who initiated therapy with raloxifene *(26)*. Until further evidence supports its use, patients at high stroke risk should avoid raloxifene therapy.

There is an increase in the rate of venous thromboembolic events (VTE) with raloxifene use, particularly in the initial year of therapy. In the Multiple Outcomes of Raloxifene

Table 2
Denosumab, Raloxifene, and Teriparatide Serious Adverse Events, Reported Rates, and Respective Numbers Needed to Harm When Used as an Osteoporosis Therapy (Source Reference in Parentheses)

Therapy	Adverse event	Population	Reported rate	Estimated NNH
Denosumab	Serious cellulitis	P3 CT PM O *(7)*	T: 0.3%, P: <0.1% over 3 yr	353
	Eczema	P3 CT PM O *(7)*	T: 3.0%, P: 1.7% over 3 yr	73
Raloxifene	Fatal stroke	P3 CT PM CHD *(25)*	T: 0.22%, P: 0.15% over 5.6 yr	250
	Venous thromboembolic events/disease	P3 CT PM O *(27)*	T: 1.1%, P: 0.5% over 4 yr	158
		P3 extension CT PM O *(23)*	T: 1.72%; P: 1.01% over 8 yr	140
		P3 CT PM CHD *(25)*	T: 0.39%, P: 0.27% over 5.6 yr	156
	Leg cramps	P3 CT PM O *(28)*	T: 9.2%, P: 6.0% over 4 yr	31
		P3 extension CT PM O *(23)*	T: 14.94%; P: 11.82% over 8 yr	32
	Hot flashes (flushes)	P3 CT PM O *(28)*	T: 10.6%, P: 7.1% over 4 yr	28
		P3 extension CT PM O *(23)*	T: 12.55%, P: 6.92% over 8 yr	17
Teriparatide	Dizziness	P3 CT PM O *(31)*	T: 9%, P: 6% over 21 mo	33
	Leg cramps	P3 CT PM O *(31)*	T: 3%, P: 1% over 21 mo	49
	Mild hypercalcemia	P3 CT PM O *(31)*	T: 11%, P: 2% over 21 mo	11

Note: Many of these studies are presented as the known worst-case scenarios and involve patients with risk factors for these events. Furthermore, many trials that did not show a difference, as discussed in the text, are not included in this table as their NNH is infinite. All doses used for calculations were of dose most commonly used for treatment of osteoporosis.

Abbr: CHD, with CHD or multiple risk factors for CHD; CT, clinical trial; O, osteoporosis; P, placebo arm; P3, phase 3; PM, postmenopausal; T, therapeutic arm.

Evaluation (MORE, 4 yr) trial, there were 1.44 and 3.32 events per 1000 woman-years for placebo and raloxifene, 60 mg/d, respectively *(27)*, and in the Continuing Outcomes Relevant to Evista (CORE, 4-yr extension of MORE) trial, there were 1.3 and 2.9 events per 1000 woman-years for placebo and raloxifene, 60 mg/d, respectively *(23)*. In the Raloxifene Use for the Heart trial, the rate of VTE was 44% higher in the raloxifene group as compared with the placebo group (hazard ratio, 1.44; 95% confidence interval, 1.06−1.95; absolute risk increase, 1.2 per 1000 woman-years; *(25)*). Women with risk factors for VTE should not be prescribed raloxifene. Furthermore, if patients are expecting to be immobilized for a prolonged period, treatment with raloxifene could be stopped a few days prior and restarted after the limited mobility period has passed.

Raloxifene use may increase the rate of leg cramps, with 9.2% of women given raloxifene, 60 mg/d, in the MORE trial reporting leg cramps as compared with 6.0% of the women provided placebo ($p < 0.001$; *(28)*). In the CORE trial, 3.6% of the raloxifene-treated patients reported leg cramps compared with 3.1% of placebo patients ($p = 0.52$; *(23)*).

Lastly, raloxifene increases the incidence of hot flashes in a minority of women, more so in younger women than older women *(28,29)*. In the MORE trial, 7.1% of the placebo group reported vasodilatation, whereas 10.6% reported this in the 60 mg/d raloxifene group ($p < 0.001$; *(28)*). However, in CORE, flushing occurred in only 0.86% of the placebo group and 1.10% of the raloxifene group ($p = 0.61$; *(23)*).

Teriparatide

Two forms of recombinant human parathyroid hormone (rhPTH) are effective anabolic therapies for osteoporosis when given by daily subcutaneous injection: the synthetic biologically active amino terminal fragment of rhPTH (PTH 1−34)—TPTD (Forteo; Eli Lilly and Company) and rhPTH (PTH 1−84, Preos; NPS Pharmaceuticals, Bedminster, NJ). This section will focus on TPTD.

Benefits of TPTD Therapy

TPTD decreases the risk of vertebral and nonvertebral fractures in women with at least 1 prior osteoporotic fracture *(30,31)*. TPTD acts directly and indirectly on the cells responsible for bone turnover and has no skeletal residency. After 24 mo of TPTD therapy (maximum duration), switching to an antiresorptive agent prevents or blunts bone loss *(32)*.

Potential Adverse Events of TPTD Therapy

The incidence of SAEs was similar in TPTD and placebo patients in the initial clinical trials *(31,33)*, and no new concerns have arisen since its clinical availability.

The phase III TPTD osteoporosis trial was stopped prematurely (mean treatment duration 19 mo) because carcinogenicity studies demonstrated a dose-dependent increased risk of osteogenic sarcoma in rats treated with high doses of TPTD (more than clinical dose) for most of their life span *(34)*. Rats are postulated to have a higher risk of bone tumors in response to PTH as compared with humans because of their exuberant response to PTH and their lifelong skeletal growth

Table 3
Comparing the Number Needed to Treat to Prevent Fracture to the Number Needed to Harm for Selected Adverse Events

Therapy	Adverse event	NNH	NNT vert	NNT non-vert	NNT hip
Denosumab	Serious cellulitis	353	21	67	200
	Eczema	73			
Raloxifene	Fatal stroke	250	28	126	NA
	Venous thromboembolic events/disease	140−158			
	Leg cramps	31−32			
	Hot flashes (flushes)	17−28			
Teriparatide	Dizziness	33	11	28	NA
	Leg cramps	49			
	Mild hypercalcemia	11			

Note: NNH and NNT values for divergent treatment periods—for treatment period specifications, see Tables 1 and 2.
Abbr: Hip fx, hip fracture; NA, not assessed; NNH, number needed to harm; NNT, number needed to treat; Non-vert fx, nonvertebral fracture; Vert fx, vertebral fracture.

(34). Accordingly, patients at increased risk for osteosarcoma should not be prescribed TPTD, such as patients with Paget's disease of bone, prior radiotherapy, previous bone tumors, and children/adolescents experiencing skeletal growth. Two cases of osteosarcoma have been reported in patients who received TPTD *(35,36)*, within the expected 1:250,000 incidence in the untreated older adult population. The results of the initial 7 yr of a preplanned 15-yr postmarketing surveillance study of osteosarcoma and TPTD found that none of 1448 osteosarcoma patients identified between 2004 and 2011 had a history of TPTD treatment *(37)*.

From what is known of the physiological actions of PTH, increased serum calcium and uric acid levels may be expected with TPTD, but serious clinical problems have not arisen. Serum calcium rises within the first 6−8 h after injection, usually within the normal range, and almost always returning to baseline within 20−24 h. Testing of serum calcium after TPTD initiation should be done at least 16 h after TPTD injection. Increased serum or urine calcium in the clinical trials was usually managed by reducing calcium intake during the initial weeks of treatment. In the postmenopausal osteoporosis and male TPTD registration trials, the average increase from baseline in urinary calcium excretion was 32 mg/d; there was not, however, an increase in frequency of renal stones formation as compared with placebo *(38)*. In prior renal stone formers, management decisions should first be directed at assessing and correcting the cause of stone formation, then using TPTD, and assessing urinary calcium post-treatment initiation accordingly *(39)*. After this period, the recommendations for calcium and vitamin D for all patients are as standard.

Although uric acid levels rose above the normal range in a small minority of patients, attacks of gout were not reported in the pivotal clinical trial *(31)*; 1 case was reported in the trial of TPTD in prevention/treatment of glucocorticoid-induced osteoporosis *(40)*.

Nausea, headache, dizziness, arthralgia, and leg cramps after TPTD injection occur in 5%−15% of patients but are unrelated to changes in serum calcium and are usually transient *(31,41)*.

Weighing the Benefits and Risks

Treatment decisions to optimize skeletal health require an assessment of fracture risk, consideration of all factors contributing to skeletal fragility, and effective communication of the expected benefit and potential risks of treatment options. For most patients at high risk for fracture, and in selected individuals, the benefit of reduction of fracture risk with approved non-bisphosphonate therapies far outweighs the possibility of harm (Table 3 summarizes NNH and NNT for denosumab, raloxifene, and TPTD). Adherence to therapy and achievement of the desired clinical outcomes may be enhanced by a full understanding of possible adverse drug effects and individualizing treatment decisions according to the circumstances of each patient.

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