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Lupus (S Manzi, Section Editor)

Prevention and Treatment of Bone Disease in Systemic Lupus Erythematosus

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Opinion statement

Systemic lupus erythematosus (SLE), an autoimmune chronic inflammatory disease, can be associated with significant morbidity and mortality of which bone disease such as osteoporosis is a contributor. Patients with SLE are at risk for low bone mineral density (BMD) due to a variety of reasons including inflammation, glucocorticoid use, vitamin D deficiency, premature ovarian failure, increased damage, and traditional risk factors such as age and gender. With better treatments for SLE, survival has improved; therefore, complications from morbidity including osteoporosis need better prevention and treatment strategies. In SLE patients with osteoporosis or those on glucocorticoids who meet guidelines for therapeutic intervention, we prefer bisphosphonates as first-line therapy for most patients. They have proven efficacy in increasing BMD and decreasing fracture risk, known safety profiles, and have a favorable cost-effectiveness profile. The newer agents, teriparatide and denosumab, have not only demonstrated improvement in BMD but also decreased risk of fracture. We typically recommend these medications for some high-risk populations, those who have failed bisphosphonate therapy or those who are intolerant of oral bisphosphonates. Estrogen-containing drugs are not recommended for first-line prevention and treatment of osteoporosis given the elevated risk of cardiovascular disease. Calcitonin has also been used in osteoporosis; however, the bisphosphonates and newer drugs have proven to be more efficacious. Supplementation with calcium and vitamin D is recommended in particular with those patients who are vitamin D deficient and those on glucocorticoids, although data documenting fracture prevention with this strategy is limited. Therapeutic strategies for premenopausal women of child-bearing

potential remain controversial because of limited data about safety in subsequent pregnancies. Decisions for these patients need to be made on a case by case basis weighing the risks and benefits to the individual patient. Future therapies targeting different mechanisms within bone resorption and formation are currently under investigation and will significantly add to our limited armamentarium.

Introduction

Systemic lupus erythematosus is an autoimmune disease that causes chronic inflammation affecting multiple organ systems [1, 2]. As patients with systemic lupus erythematosus (SLE) live longer, special attention to morbidity from disease complications is needed [3, 4]. Damage scores such as the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index evaluate morbidity in SLE by system, one of which is bone-related disease complications including osteoporosis with minimal trauma fracture, vertebral collapse, and avascular necrosis [5]. Glucocorticoid use contributes to these complications which place patients at risk for glucocorticoid-induced osteoporosis (GIOP) and avascular necrosis [6]. Osteoporosis has been associated with increased chronic pain affecting up to 85 % of patients with osteoporosis [7]. Patients with osteoporosis who suffer hip fractures are also at increased risk for death [8, 9]. Therefore, osteoporosis and fragility fractures are serious complications that can arise in the SLE population and require special attention.

Osteoporosis is a skeletal disorder characterized by low bone mass and deterioration of bone tissue microarchitecture causing bone fragility and elevated risk for fractures [1, 3, 10]. Osteoporosis is defined by a bone mineral density (BMD) T-score of less than 2.5 SD below the mean reference or fracture from minimal trauma, while osteopenia is BMD T-score less than 1 SD below the mean reference [3, 10]. Numerous studies have examined the prevalence of osteopenia and osteoporosis in SLE. In cross-sectional studies, osteopenia prevalence ranges from 11 to 62 % (lumbar) [11, 12] and 6 to 74 % (hip) [13, 14], while osteoporosis ranges from 4 to 42 % (lumbar) [14, 15] and 3 to 42 % (hip) [13, 14]. The wide range of prevalence between studies is likely due to ethnicity, age, sex, varying study designs, disease severity, glucocorticoid use, and disease duration [2, 3, 15, 16].

The etiology for reduction in BMD in SLE is secondary to a variety of reasons and mechanisms. Traditional risk factors such as age, sex, and ethnicity play a role; however, it has been shown that the disease itself is associated with low BMD [2, 17]. Tang et al. [17] studied 30 Asian patients with SLE with a mean age of 46 on long-term glucocorticoids and 30 Asian patients with SLE not on glucocorticoids (defined as no steroids in the last 10 years prior to study entry or never taken steroids) compared to 60 healthy controls. They found that both groups of SLE patients had significantly decreased BMD compared to controls. No difference was seen between the SLE groups taking glucocorticoids and no glucocorticoids. Sun et al. [2] studied 119 untreated Chinese female SLE patients and measured BMD to determine risk factors associated with low bone density. They found an incidence of 31.1 % with osteopenia and 8.5 % with osteoporosis. Although the study did not have a control group, the patients were untreated, and therefore not on glucocorticoids, suggesting that SLE itself has an effect on low BMD. Increased damage as measured by the SLICC Damage Index has been correlated with low BMD as well [18].

Vitamin D deficiency has also been associated with low BMD in SLE. Jacobs et al. followed 126 SLE patients over 6 years and assessed variables associated with low BMD in SLE [19•]. They found that low baseline 25-hydroxyvitamin D levels were significantly associated with decreased spine BMD. Premature menopause has also been identified as a risk factor for fracture in the SLE population. One study found that patients with premature menopause had a higher Fracture Risk Assessment Tool (FRAX) [20] 10-year fracture risk compared to healthy age-matched controls [21•].

Glucocorticoid use is a well-known risk factor for osteoporosis in the general population with doses above 7.5 mg/day significantly associated with increased risk of non-vertebral and vertebral fractures compared to 2.5 mg/day [22]. In SLE, the results in studies evaluating the relationship between glucocorticoids and osteoporosis have been variable. Most studies have demonstrated an association with steroids and osteoporosis in SLE [6, 11–13, 19•], while others have failed to find similar

results [18, 23]. Although these findings suggest that glucocorticoids are not the only mechanism for low BMD in SLE patient, GIOP remains a serious problem for SLE patients. In 2010, the American College of Rheumatology (ACR) published guidelines for the prevention and treatment of GIOP, which are currently being updated [24]. Current treatment options for low BMD in SLE patients include calcium and vitamin D supplementation, calcitonin, bisphosphonates, denosumab, and teriparatide, which will be explored in this article.

Treatment

Diet and Lifestyle

- Certain lifestyle changes should be implemented in SLE patients to assist with bone health. Most of these are not specific to bone health in SLE patients but are applicable to patients at risk for low bone mass in general. Weight is viewed as a modifiable risk factor to maintain normal body mass index [25, 26]. Weight-bearing exercise has been shown to increase BMD in multiple studies as seen in a 2002 Cochrane review [27] as well as lower fracture risk in the healthy population [28]. While most studies on the effect of exercise on bone health have not been done in SLE, Kipen et al. [29] followed BMD over 3 years in 32 premenopausal SLE patients, and 21 of the study participants were exposed to glucocorticoids during the study. They found that among participants taking glucocorticoids, exercise was protective of femoral neck BMD loss.
- It is recommended by multiple guidelines including the ACR to reduce alcohol consumption and quit smoking [10, 24]. Smoking has been associated with higher fracture risk and lower BMD [30–32]. The data behind osteoporosis and alcohol use is not as strong with some studies, actually suggesting a positive correlation with BMD with low to moderate alcohol consumption [33, 34]. The EPIC study did not show a correlation between lifetime alcohol use and BMD; however, the group with heaviest alcohol use had lower BMD [35]. Alcohol consumption is also a variable in the World Health Organization's (WHO) FRAX to evaluate the fracture risk in patients [20]. Therefore, experts still recommend minimizing alcohol use.

Pharmacologic Treatment

- Calcium and Vitamin D
  Calcium and vitamin D play a role in bone health, and most guidelines have recommended their supplementation [24]. Vitamin D deficiency (less than 20 ng/ml) is common in SLE with a prevalence between 4 and 54 % and insufficiency (less than 30 ng/ml) prevalence up to 96 % [36•, 37]. The cause is multifactorial including renal insufficiency; sun avoidance; diligent use of sunscreen; antivitamin D antibodies; and medications including antimalarials, antiepileptics, and glucocorticoids [36•, 37]. Studies on chronic steroid therapy that included SLE

patients have suggested that vitamin D and calcium supplementation may have a small effect on BMD both in prevention and increased BMD early in the disease process (see Table 1) [38, 39]. Also, as mentioned above, low vitamin D level is a risk factor for low BMD in SLE patients [19•]. In the ACR recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis, target vitamin D levels are to achieve "therapeutic" levels or supplementation with doses of 800–1000 IU/day [24]. Other expert reviews have set 25 hydroxyvitamin D levels to greater than or equal to 30 ng/ml as a target [36•, 37, 40]. In light of these recommendations, it is important to consider the u-shaped association between calcium intake and cardiovascular mortality found by Wang et al [41]. Compared to those with a daily dietary calcium intake of 800 mg/day, those with daily intakes of 500 mg/day or greater than 1200 mg/day were significantly associated with elevated risk of cardiovascular death. Additionally, a meta-analysis by Bolland et al. showed a 30 % increased incidence of myocardial infarction with calcium supplementation compared to placebo [42]. Of note, this meta-analysis did not include concomitant vitamin D supplementation nor patients taking glucocorticoids (which has an effect on calcium absorption in the intestines), and a few of the articles had self-reported cardiovascular outcomes. It is also important to note that calcium and vitamin D supplementation was used in clinical trials evaluating the efficacy of prescription medications. In conclusion, weighing the benefits of calcium intake with the risks, it would be best for the recommended calcium intake to be obtained from dietary sources if possible using supplementation when dietary calcium is inadequate.

- Hormonal Therapies

  Hormonal therapy such as estrogen, selective estrogen receptor modulators (SERMs), and dehydroepiandrosterone (DHEA) have been evaluated in studies for the treatment of low BMD. Bhattoa et al. [43] compared transdermal estrogen patch to placebo for BMD and bone turnover markers for postmenopausal SLE patients with osteopenia. They found an increase in lumbar BMD and decrease in bone turnover markers in the intervention group. However, the study had a high dropout rate; therefore, the authors concluded that only certain patients in a high-risk group would benefit. Another study examined hormone replacement therapy (HRT) compared to calcitriol in SLE patients with ovarian failure and again found an increase in lumbar spine BMD but no change at the hip or radius [44]. Neither study detected differences in SLE disease activity or flares. However, although these studies had favorable results using HRT on osteoporosis in SLE, HRT is associated with increased risk of cardiovascular disease (CVD) and stroke among healthy postmenopausal women as demonstrated in the Women's Health Initiative (WHI) trial [45]. Since patients with SLE are at increased risk of CVD, HRT is not recommended for prevention and treatment of low BMD as better options for the prevention and treatment of osteoporosis in lupus exist.

Table 1. RCTs in GIOP on BMD change

Study	Number	Mean cumulative prednisone dose (mg/day)	Intervention	Control	Change in lumbar spine BMD		Patients with new vertebral fractures		Patients with non-vertebral fractures	
					Treatment	Control	Treatment	Control	Treatment	Control
Lambrinoudaki et al. (2000) [39]	81	28 (mean cumulative dose in grams)	Calcitriol/calcium or calcium/placebo calcitriol	Placebo	+2.1 % calcitriol/ calcium[a]	+0.3	NA	NA	NA	NA
Mok et al. (2011) [47]	114	6.7	Raloxifene/calcium/ calcitriol	Calcium/ calcitriol	+1.3 %	−-0.9 %	0 (0 %)	3 (5 %)	NA	NA
Saag et al. (1998) [52]	477	10	Alendronate 5 or 10 mg per day	Calcium/ vitamin D	+2.1 % (5 mg), +2.9 % (10 mg)	−0.4 %	6 (2.3 %)	5 (3.7 %)	4.4 %	4.4 %
Reid et al. (2000) [60]	290	15	Risedronate 2.5 or 5 mg per day	Calcium/ vitamin D	+2.9 %[b]	+0.4 %	3 (5 %)[b]	9 (15 %)[b]	6 (6 %)[b]	8 (9 %)[b]
Reid et al. (2009) [62]	771	10	Zoledronic acid	Risedronate	+4.06 %	+2.71 %	5 (1 %)	3 (<1 %)	NA	NA
Ringe et al. (2003) [64]	105	11	Ibandronate	Alfacalcidiol	+11.9 %	32.2 %	5 (9.6 %)	10 (19.2 %)	9 (17.3 %)	11 (21.2 %)
Sambrook et al. (1993) [98]	103	25	Calcitriol/calcitonin/ calcium	Calcium	−0.2 %	−4.3 %	2 (6.8 %)	2 (6.8 %)	0 (0 %)	1 (3.4 %)
			Calcitriol/calcium/ placebo		−1.3 %		1 (2.9 %)		1 (2.9 %)	
Saag et al. (2007) [76]	428	7.5	Teriparatide	Alendronate	+7.2 %	+3.4 %	1 (0.6 %)	10 (6.1 %)	12 (5.6 %)	8 (3.7 %)
Cummings et al. (2009) [79][c]	7868	NA	Denosumab	Calcium	+9.2 % (compared to placebo)	0 %	86 (2.3 %)	264 (7.2 %)	238 (6.5 %)	293 (8.0 %)
Glüer et al. (2013) [99][d]	92	8.8	Teriparatide	Risedronate	+6.94 %	+3.33 %	0 (0 %)	0 (0 %)	0 (0 %)	5 (10.6 %)
Hakala et al. (2012) [100]	140	6.71	Ibandronate	Calcium/ Vitamin D	+3.2 %	−0.1 %	0 (0 %)	0 (0 %)	1 (1.4 %)	3 (4.3 %)

BMD bone mineral density
[a] $p < 0.05$ for comparison to baseline, no difference compared to calcium or placebo groups
[b] Risedronate 5 mg/day
[c] Study did not include chronic glucocorticoid use
[d] Study participants men only

Raloxifene is a SERM which has been studied by Mok et al. for its prevention of bone loss in patients with SLE [46, 47]. In 2005, they compared raloxifene plus calcium to calcium alone and found preservation of spine and hip BMD in the raloxifene group with no significant increase in flares. In 2011, Mok et al. looked at efficacy in lupus patients on glucocorticoids comparing raloxifene to placebo with both groups also receiving calcium and vitamin D. Lumbar spine BMD was significantly increased in the raloxifene group compared to baseline. Raloxifene is associated with an increased risk of thromboembolism, which is a concern in a lupus population. In the 2010 ACR recommendations for GIOP, it was not one of the recommended therapeutic interventions.

DHEA is an androgen that may play a role in bone metabolism. Several studies have examined the use of DHEA (prasterone) at a dose of 200 mg/day in SLE patients. One trial demonstrated that prasterone provided mild protection against bone loss in female SLE patients on chronic steroids [48]. However, in the premenopausal population, other trials have shown no effect on BMD and even potentially worsening of lipid profile with decreased HDL levels [49, 50].

- Bisphosphonates

  Bisphosphonates are a class of antiresorptive agents that remain a first-line therapy for prevention and treatment of osteoporosis (see Fig. 1). A meta-analysis conducted by Feng et al. [51•] examined bisphosphonate efficacy in fracture prevention and bone mass preservation in rheumatic patients. They found that bisphosphonates preserve BMD and decrease vertebral fractures for this population with increased efficacy when used for prevention and treatment. Of the bisphosphonates, alendronate, risedronate, and zoledronic acid have been approved by the ACR for use in GIOP [24].

  Alendronate has been studied in multiple trials that included SLE patients with all demonstrating its efficacy. Saag et al. conducted a randomized controlled trial (RCT) of alendronate (2.5 vs 5 vs 10 mg/

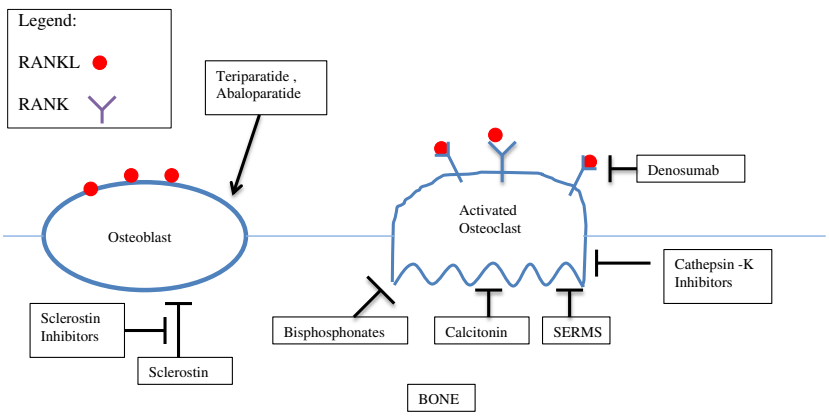

Fig. 1. Drug mechanism of action.

day) vs placebo use in patients on long-term glucocorticoid therapy (SLE 10 % of cohort) [52]. They found that 5 and 10 mg of alendronate significantly increased BMD of the lumbar spine, trochanter, and femoral neck compared to placebo. Although fracture was not a primary outcome, the number of new vertebral fractures was less in the treatment group compared to placebo, but this did not meet statistical significance. A 2-year follow-up study by Adachi et al. demonstrated continued efficacy on prevention and treatment of GIOP with alendronate [53]. Similar results have been seen with alendronate in premenopausal SLE women on glucocorticoids [54, 55]. Studies have also shown superiority of alendronate compared to calcium and vitamin D [56–58]. The cost for 70-mg weekly generic can be as low as $78/year [59].

Risedronate has also been shown to improve BMD in GIOP. Two RCTs with study populations including SLE compared risedronate to placebo in high-dose glucocorticoid therapy. Reid et al. found that 5 mg/day risedronate increased BMD at the lumbar spine, trochanter, and femoral neck (SLE 7.6 % of cohort) [60]. Additionally, a reduction in the incidence of vertebral fracture was observed, although this result did not meet statistical significance. Mok et al. examined risedronate plus calcium vs placebo plus calcium and found improvement in lumbar spine BMD, but a decrease in hip BMD (SLE 52 % of cohort) [61]. Cost for generic risedronate 35 mg a week is $1200/year [59].

Zoledronic acid is an intravenous bisphosphonate administered once a year. Reid et al. conducted a randomized controlled non-inferiority study that examined zoledronic acid vs daily risedronate in 833 patients on glucocorticoids of whom 13 % had SLE [62]. The study found that zoledronic acid was non-inferior and superior to risedronate at lumbar spine, femoral neck, trochanter, and total hip BMD for both prevention and treatment of GIOP. No difference was found between the two groups for frequency of new vertebral fractures. A recent study by Sambrook et al. compared zoledronic acid and risedronate in GIOP for men only and similarly found that zoledronic acid was superior to risedronate with increased lumbar spine and total hip BMD for both prevention and treatment, although no difference was observed at the femoral neck [63]. Estimated cost of zoledronic acid 5 mg is $1000/year, which does not take into account intravenous administration fees [59].

Ibandronate is a bisphosphonate that comes in both oral and intravenous (IV) formulations. Ringe et al. compared daily oral alfacalcidol to every 3-month IV ibandronate in treatment of GIOP, which demonstrated increased lumbar spine and femoral neck BMD [64]. The ibandronate arm had a 50 % reduction in new vertebral fractures compared to the alfacaldiol arm, although this was not significant. At the time of the manuscript preparation, ibandronate 150 mg monthly was as low as $564/year [59].

The use of bisphosphonates in premenopausal women is controversial given the long half-life of the drug and its potential harm to a fetus.

Bisphosphonates have a half-life of years; therefore, women of childbearing age who have used bisphosphonates still risk exposure of the drug to the fetus even if the drug was discontinued years ago [65•]. Bisphosphonates are pregnancy class C and may be teratogenic. Animal studies in pregnant rats who were exposed to large doses of bisphosphonates (more than human doses) showed protracted deliveries thought to be caused by hypocalcemia and fetal bone growth retardation [66, 67]. Bisphosphonates should be used with caution in premenopausal women given the lack of data regarding safety in pregnancy; if they are used, a risk benefit discussion with the patient is advised.

Safety issues of bisphosphonates include osteonecrosis of the jaw, atypical hip fractures, gastrointestinal side effects, and concern for esophageal cancer. It is important to note though that although physicians and patients should be aware of these potential side effects, the incidence is small and the data suggests that the benefit of bisphosphonates outweighs the risks. For example, one study found the typical hip fracture incidence in patients on bisphosphonates to be 463/100,000 person-years, whereas the incidence for atypical femur fracture was 1.78/100,000 person-years [68]. The incidence of bisphosphonate-related osteonecrosis of the jaw is less well known but has been estimated between 0.028 and 4.3 % [69]. Ideal duration of bisphosphonate therapy is unknown and debated. The idea of a "drug holiday" after 3 to 5 years of therapy has arisen with results from the FLEX trial and extension of HORIZON trial, both suggesting that discontinuation of bisphosphonate therapy does not increase the risk of fracture [70, 71]. However, this may not apply to high-risk SLE patients with osteoporosis, previous fracture, and on chronic glucocorticoids [72].

- Calcitonin

  Calcitonin is a naturally occurring peptide hormone with antiresorptive properties that has been used in osteoporosis. Although trials have not been done specifically examining SLE and calcitonin, multiple studies have looked at GIOP and calcitonin. A Cochrane review assessing the efficacy of calcitonin for treatment and prevention of GIOP demonstrated preservation in lumbar BMD at 12 months, but not at 24 months compared to placebo [73]. One study found that alendronate was significantly better than intranasal calcitonin at increasing BMD and decreasing bone turnover [74]. There is also a concern for increased risk of malignancy such as basal cell carcinoma and prostate cancer, although the data is not strong for a causal relationship [75]. For these reasons and with the development of more efficacious drugs, calcitonin is not considered as first-line therapy for the treatment of osteoporosis. Intranasal calcitonin costs about $540/year [59].
- Teriparatide

  Teriparatide is an anabolic agent comprised of recombinant human parathyroid hormone. Its use is primarily in high-risk postmenopausal women and men over age 50 with a 10-year risk of a major

osteoporotic fracture greater than or equal to 20 % [24, 25]. Teriparatide has been shown to significantly increase BMD and decrease number of vertebral fractures in GIOP. A RCT by Saag et al. (SLE 11 % of cohort) compared alendronate to teriparatide and found increased lumbar spine and total hip BMD ($p < 0.001$ for both) as well as significantly fewer vertebral fractures than alendronate [76, 77]. Teriparatide should not be prescribed to patients at increased risk of osteosarcoma as there has been a dose- and duration-dependent elevated risk for development of osteosarcoma with this medication in animal models [78]. Main side effects include transient hypercalcemia, GI upset, and weakness. Dosage is 20 μg subcutaneous (SQ)/daily for no longer than 2 years. Cost is $24,240/year with some financial assistance programs available for those who qualify [59].

- Denosumab
  Denosumab is a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) and is a newer agent for osteoporosis treatment. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial, denosumab was shown to reduce the risk of fracture (vertebral, non-vertebral, and hip) and increase lumbar and hip BMD [79]. Denosumab has also been shown to increase BMD significantly when compared to alendronate; however, a meta-analysis comparing fracture risk between denosumab and alendronate showed no difference [80, 81]. Efficacy of denosumab on GIOP and SLE populations has not specifically been studied. This would be interesting given the association with increased expression of RANKL with steroid use [82]. Side effects include hypocalcemia, osteonecrosis of the jaw, and atypical femur fractures [83••, 84••]. Concern for increased risk of infection has been raised, and given that RANK and RANKL are used in T cell proliferation and inhibition of RANKL may impair the immune response [85]. Overall incidence of infection was not increased in the denosumab arm in the FREEDOM trial; however, severe cellulitis was significantly increased compared to placebo [79]. Therefore, it would be prudent to exercise caution should the medication be used in immunosuppressed patients. Dosage is 60 mg SQ every 6 months and can be used in renal insufficiency [86]. Two injections per year cost about $1800 [59].

Emerging Therapies

- Abaloparatide is a PTHrP analog similar to teriparatide which has shown promising results for increased BMD and reduction of fractures. In the phase II study by Leder et al. with 222 healthy postmenopausal women with osteoporosis [87], 80 μg SQ/day abaloparatide showed greater increase in lumbar spine and femoral neck BMD when compared to teriparatide and placebo. The recent phase III study evaluating fracture prevention compared to placebo and to teriparatide

demonstrated reduced new vertebral fractures, non-vertebral, and clinical fractures compared to placebo. Abaloparatide also had a significantly lower incidence of hypercalcemia compared to teriparatide [88••].

- Odanacatib is a cathepsin K inhibitor that is an anticatabolic agent. Cathepsin K is a protease found primarily in lysosomes of osteoclasts that breaks down type I collagen (major component of bone matrix) in acidic environments [89, 90]. Inhibition of cathepsin K blocks the collagenolytic action, thus not only stopping bone resorption but preserving bone formation [88••, 89, 90]. Prior cathepsin K inhibitors under development were discontinued because of side effects. Odanacatib underwent a phase III fracture study (LOFT) [91•], in which all primary end points (radiographically detected vertebral, clinical hip, and clinical non-vertebral fractures) were met early. A significant relative risk reduction of new and worsening vertebral fractures, hip fractures, and clinical non-vertebral and vertebral fractures was seen with odanacatib compared to placebo. Additionally, BMD was increased in lumbar spine and total hip.
- Romosozumab, blosozumab, and BPS804 are sclerostin inhibitors which serve to block sclerostin resulting in increased osteoblast activity and decreased osteoclastogenesis [88••]. Phase II studies have been completed for all three drugs. Romosozumab and blosozumab had increased BMD at the lumbar spine, total hip, and femoral neck excluding distal radius [92•, 93]. BPS804 phase II results have not yet been released. Phase III trial assessing efficacy for fracture reduction for romosozumab is underway.

Pediatric Considerations

Guidelines for prevention and treatment of low BMD in the pediatric population are lacking especially for GIOP, given the limited treatment options and lack of studies in this population. In general, vitamin D and calcium supplementation is advised, although daily supplementation in the absence of deficiency has not shown a benefit in trials for other chronic inflammatory diseases [94]. Other preventative strategies include physical activity and weight-bearing exercise. One study surveyed pediatric rheumatologists across North America and found that most respondents prescribed calcium and vitamin D supplementation. However, in patients with osteoporosis (based on BMD), only at most half prescribed a bisphosphonate [95]. There have been some studies demonstrating the utility of bisphosphonates for children with osteoporosis. Bianchi et al. [96] included 38 children with low bone mass treated with alendronate compared to 38 children with the same diffuse connective tissue diseases (SLE 31 % of cohort) as the study group but in a less severe form. They found a significant increase in lumbar spine BMD compared to controls. A recent Cochrane review [97] assessing bisphosphonate treatment for children with secondary osteoporosis concluded that there was not enough evidence for bisphosphonate use as standard therapy. Further studies are required for prevention and treatment guidelines in the pediatric population at risk for osteoporosis and fractures.

Compliance with Ethical Standards

Conflict of Interest

Tracy Lin declares that she has no conflicts of interest. Jennifer Grossman reports that she has received support in the form of grants from Bristol Myers Squibb, Human Genome Science, Astra Zeneca, and UCB and has been on an advisory board for Genetech, outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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