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Review Article

RANKL-Targeted Therapies: The Next Frontier in the Treatment of Male Osteoporosis

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Male osteoporosis is an increasingly recognized problem in aging men. A common cause of male osteoporosis is hypogonadism. Thousands of men with prostate cancer are treated with androgen deprivation therapy, a treatment that dramatically reduces serum testosterone and causes severe hypogonadism. Men treated with androgen deprivation therapy experience a decline in bone mineral density and have an increased rate of fracture. This paper describes prostate cancer survivors as a model of hypogonadal osteoporosis and discusses the use of RANKL-targeted therapies in osteoporosis. Denosumab, the only RANKL-targeted therapy currently available, increases bone mineral density and decreases fracture rate in men with prostate cancer. Denosumab is also associated with delayed time to first skeletal-related event and an increase in bone metastasis-free survival in these men. It is reasonable to investigate the use of RANKL-targeted therapy in male osteoporosis in the general population.

1. Overview

Male osteoporosis is an important issue in men's health. More than 2 million American men have osteoporosis and approximately 7 million more at risk of developing the disease. It results in an increased risk of fracture due to a disrupted bone microenvironment with associated decreased bone mineral density (BMD) and increased bone fragility.

The impact of osteoporosis on otherwise healthy men is substantial. As men age, they generally lose BMD at a rate of 1% per year [1]. Fractures occur in one of eight men over 50 years old, with approximately 30% of all hip fractures occurring in men [2, 3]. Mortality one year after hip fracture for men has been estimated around 31–35%, a striking number when compared with 17–22% one-year mortality for women of the same age [4]. In-hospital mortality alone after a fraction is twice as high for men than for women [5, 6].

Osteoporosis has historically been classified as either primary or secondary. Primary osteoporosis is age-related or idiopathic osteoporosis that is not clearly due to another cause. Secondary osteoporosis results from various causes, the most common of which in men are glucocorticoid excess, heavy alcohol use, and hypogonadism. Although it can also result from other disorders, including hyperparathyroidism, hyperthyroidism, and malabsorptive disorders, more than 50% of male osteoporosis can be attributed to these three causes [7]. One of the more closely studied populations with secondary osteoporosis due to hypogonadism is prostate cancer survivors who have been treated with androgen deprivation therapy (ADT). This review will focus on this unique population as a model of hypogonadal osteoporosis to discuss the use of RANKL-targeted therapies in male osteoporosis.

2. Prostate Cancer

In the United States, prostate cancer is the most common malignancy in men and the second leading cause of cancer death. There were over 217,730 new diagnoses of prostate cancer in 2010, and this number continues to rise [8]. In 2010, it is estimated that there were approximately 32,050 deaths due to metastatic prostate cancer in the US [8]. Despite this, survival among all patients is 95% at 5 years, meaning a substantial portion of the prostate cancer population are survivors of their disease for lengthy periods of time [8].

3. Androgen Deprivation Therapy

Androgen deprivation therapy (ADT), by either bilateral orchiectomies or chronic administration of a gonadotropin releasing hormone (GnRH) agonist or antagonist, is the mainstay of therapy for metastatic prostate cancer. The intended therapeutic effect of ADT is severe hypogonadism. ADT decreases serum levels of total testosterone by more than 95% to below 20 ng/dL in most men.

ADT use has been associated with a survival advantage in several subgroups of prostate cancer patients. For men with high-risk locally advanced disease, the use of ADT in addition to definitive external beam radiation therapy results in improved disease-free and overall survival as compared to radiation therapy alone [10]. Additionally, there is evidence that the use of ADT after radical prostatectomy in men with positive lymph nodes likely improves overall survival [11]. ADT can be used alone or in combination with salvage radiation in men with a rising PSA after definitive radiation or prostatectomy although there is not yet sufficient evidence to prove a survival benefit [10].

4. Bone Loss and Fractures during ADT

In addition to causing numerous other metabolic side effects, ADT use is associated with a decline in BMD [12–16]. A reduction in BMD can be seen within six to nine months of initiating therapy, and BMD of the hip and spine continue to decrease by approximately 2-3% per year [5, 12–14].

The incidence of fractures in men receiving ADT is also elevated, approaching 20% after 5 years of therapy [15]. Several large population-based studies demonstrated a 21–45% relative increase in fracture risk among men being treated with ADT when compared to men without such treatment [15–17]. A recent analysis of SEER and Medicare data including over 50,000 men found a 19.4% rate of fracture in men receiving ADT as opposed to a rate of 12.6% in those who were not ($P < 0.001$) [15]. Similarly, an analysis of 3,887 Medicare records from men with nonmetastatic prostate cancer found ADT use associated with a relative risk of fracture of 1.21 when compared to men who were not on ADT (95% CI, 1.14–1.29, $P < 0.01$) [16].

The mechanism of ADT-related bone loss is likely partially due to increased bone turnover [14]. Markers of osteoclast and osteoblast activity, such as osteocalcin, are increased in men receiving ADT and tend to plateau around 6 months after initiating treatment [14]. There is also evidence that alterations in skeletal sensitivity to parathyroid hormone may cause increased bone turnover [18].

The effects of estrogen on bone also likely contribute to ADT-associated bone loss. ADT causes testosterone levels to plummet, which also results in low levels of serum estradiol due to the peripheral conversion of testosterone to estrogen. Estrogen signaling through estrogen receptors on osteoblasts and osteoclasts contributes to the regulation of bone remodeling in men [19]. Additionally, levels of estradiol in healthy older men correlate with spinal bone mineral density and are inversely associated with vertebral fracture risk [20–22].

Recently there has been interest in using RANKL-targeted therapy to reduce the incidence of osteoporosis and fracture in men with nonmetastatic prostate cancer receiving ADT. Like men in the general population with hypogonadal osteoporosis, the cause of osteoporosis in these men is low levels of testosterone. Because there is not yet primary data with RANKL-targeted therapy in men with osteoporosis in the general population, it is reasonable to consider extrapolating this data to men with other forms of hypogonadal osteoporosis for hypothesis generation and future investigation.

5. RANK-L Targeted Therapy

Bone exists in state of continuous remodeling, striking a delicate balance between osteoclast resorption and osteoblast formation of new bone. The receptor activator of nuclear factor-κB ligand (RANKL) system plays a critical role in this balance. RANKL is a member of the tumor necrosis factor (TNF) superfamily of proteins that is expressed by osteoclast precursors, marrow stromal cells, and activated T-cells, among others. It acts on its receptor, RANK, which is expressed by osteoclasts and their precursors, to stimulate osteoclast activation, differentiation, migration, and survival via downstream signaling through the nuclear factor kappa B (NFκB) signaling pathway [23]. This process ultimately results in increased osteoclast resorption of bone. A second TNF superfamily member, osteoprotegerin (OPG), functions as the brakes in the system by counteracting the resorptive effects of the RANKL/RANK interaction. OPG, which is produced by osteoblasts as well as many other tissues, is a soluble decoy receptor of RANKL, binding RANKL and inhibiting its interaction with RANK [23]. The quantity of OPG in relation to RANK-L is believed to be the mechanism by which bone achieves a balance between resorption and formation [24].

Manipulation of the RANKL system has been a target of pharmaceutical development, and denosumab is currently the only RANKL targeted therapy available. Denosumab is a fully human monoclonal antibody directed at RANKL. It has a half life of more than 30 days and does not accumulate in bone like bisphosphonates [25]. The drug works by mimicking the effects of OPG, binding RANKL, and resulting in a reduction in osteoclast formation and action.

Clinical trials with denosumab have demonstrated efficacy in fracture prevention and increased BMD in postmenopausal women [26, 27]. A fracture prevention trial included 7868 postmenopausal women with osteoporosis who were randomized to receive placebo or twice yearly denosumab. The denosumab group had significantly fewer new vertebral fractures, nonvertebral fractures, and hip fractures than the placebo group during the 36-month study (relative decreased risk of vertebral fractures 68%, of nonvertebral fractures 20%, and of hip fractures 40%) [28]. Based on this study, denosumab has been approved by the Food and Drug Administration to treat postmenopausal women with osteoporosis.

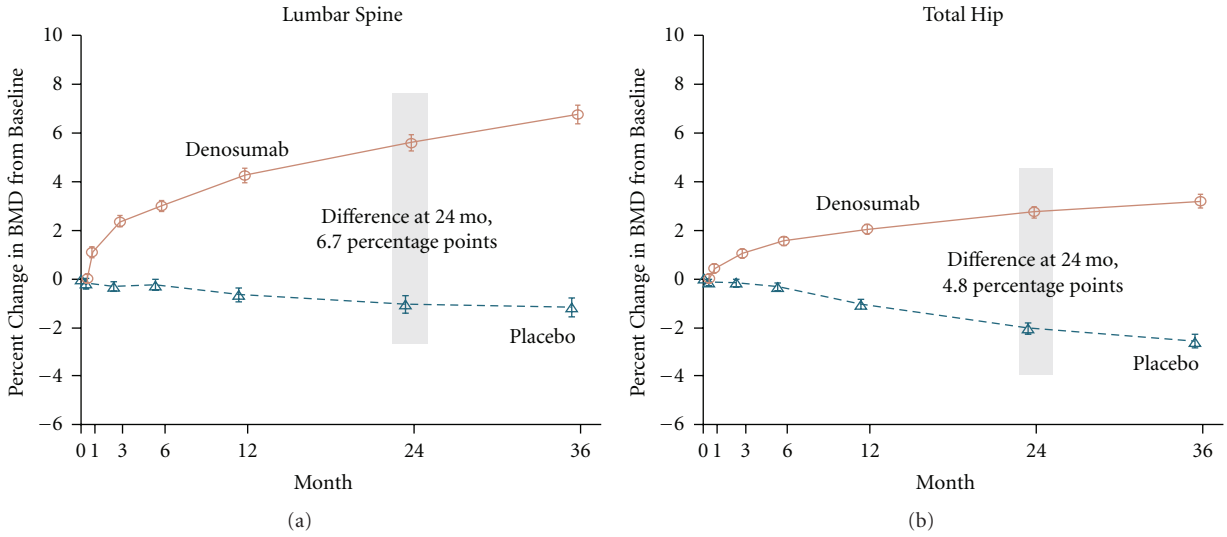

Figure 1: Mean BMD percent changes from baseline in lumbar spine and total hip sites. Results are reported as least-square means of BMD at the lumbar spine and total hip. All values are significantly greater in the denosumab group than the placebo group ($P \leq 0.001$) [9].

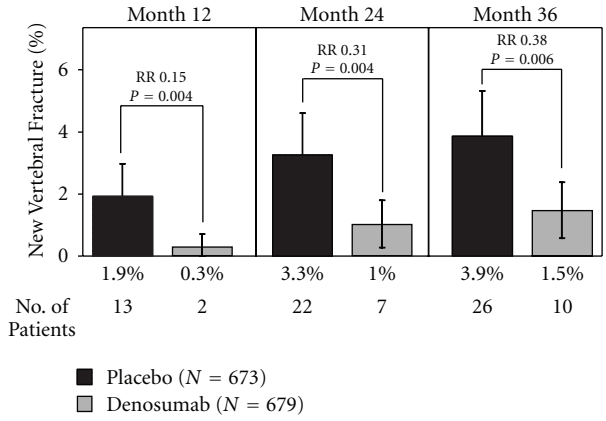

Figure 2: Incidence of new vertebral fractures during study period in denosumab and placebo groups. Relative risk calculated for vertebral fracture in 679 patients in the denosumab group versus 673 patients in the placebo group were 0.15 (12 months), 0.31 (24 months), and 0.38 (36 months) [9].

Denosumab has also been shown to increase BMD in women with breast cancer who are being treated with aromatase inhibitors [29]. Aromatase inhibitors stop estrogen production in peripheral tissues and cause a decline in BMD in women using them. A recent study of women being treated for breast cancer with aromatase inhibitors has demonstrated that denosumab significantly increased BMD as compared to placebo at the lumbar spine (BMD increased by 5.5% and 7.6% at 12 and 24 months, respectively ($P < 0.0001$ at both time points)).

6. Denosumab to Prevent Fractures during ADT for Prostate Cancer

A phase 3, multicenter, double-blind, randomized controlled trial evaluated the effect of denosumab on osteoporosis and fracture rate in men treated with ADT [9]. The trial included men with nonmetastatic, hormone-sensitive prostate cancer who were being treated with GnRH agonists. They were randomized to receive denosumab or placebo once every 6 months with an evaluation of bone mineral density at 24 and 36 months. Similarly to prior studies with bisphosphonates and SERMs, the primary endpoint was the change in lumbar spine BMD. However, this trial also reported the incidence of new vertebral fractures and the incidence of fractures at any site as more clinically meaningful secondary endpoints.

The trial demonstrated that denosumab improved BMD and decreased the rate of clinical fractures in men who were treated with ADT [9] (Figures 1 and 2). At 24 months, patients who were randomized to denosumab had an increase in BMD of the lumbar spine of 5.6% as compared with a decrease in BMD of 1.0% in the placebo group (<0.001). Significant differences in BMD were evident in some patients as soon as one month after treatment. At 36 months, there was a significant difference in the incidence of vertebral fractures, with an incidence of 3.9% in the placebo group versus 1.5% in the denosumab group (relative risk 0.38, $P = 0.006$).

Subgroup analyses found an improvement in BMD with denosumab at all skeletal sites and in all subgroups assessed (Figure 3) [30]. The most pronounced improvement in BMD occurred in men with the highest markers of bone turnover (serum C-telopeptide and tartrate-resistant alkaline phosphatase). Adverse events were not significantly different between the two groups.

Denosumab has been recently approved in Europe for the treatment of men receiving ADT for fracture prevention based on this study. Approval of the drug in the United States for men with nonmetastatic prostate cancer is pending.

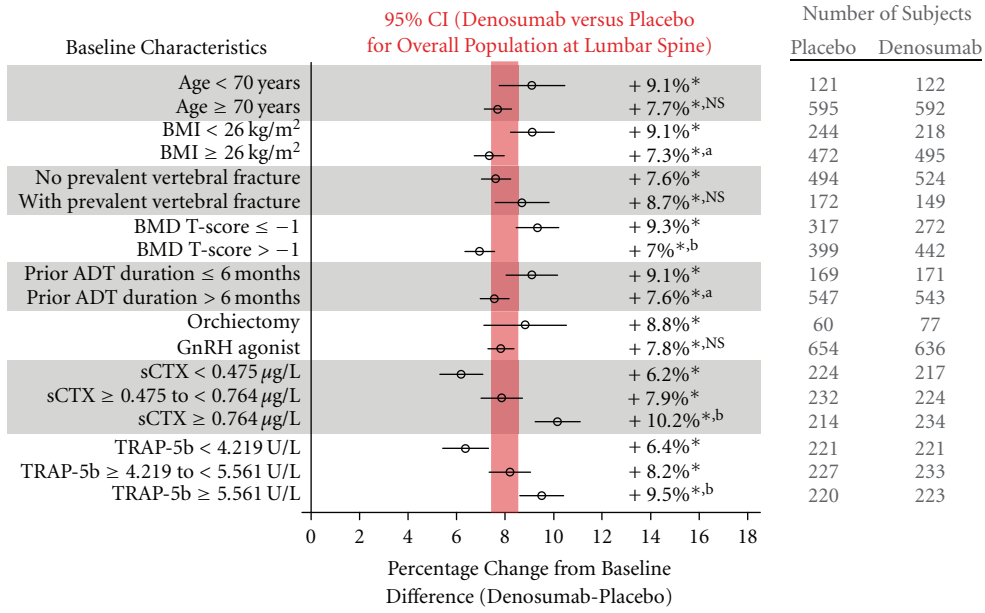

Figure 3: Forest plot of percentage change in BMD from baseline of denosumab versus placebo at lumbar spine. Vertical bar outlines the percentage difference in BMD between denosumab and placebo at lumbar spine at 36 months [30].

7. Denosumab to Prevent Skeletal Related Events in Metastatic Prostate Cancer

Men with prostate cancer commonly develop complications of disease related to bony metastases. Because these complications are not infrequent, and because they have a drastic impact on patients' quality of life, trials of bone-targeted therapies frequently include them as study endpoints. These bone-related complications are referred to as skeletal related events (SREs) and are specifically defined as pathologic fracture, need for radiation therapy or surgery to bone, or spinal cord compression.

Denosumab was evaluated for fracture prevention in men with metastatic castration-resistant prostate cancer (CRPC) in a phase III study with time to first SRE as the primary endpoint. CRPC is an advanced disease state marked with progression despite treatment with GnRH agonists and castrate levels of serum testosterone. This population frequently has multiple sites of metastatic prostate cancer involvement in the bone, and fracture is a common adverse event.

This study randomized 1,904 men with at least one site of bony metastasis to receive monthly zoledronic acid or denosumab [31]. The primary endpoint was time to first skeletal related event, and the primary objective was the demonstration of noninferiority of denosumab when compared to zoledronic acid. Denosumab significantly delayed the time to first SRE when compared with zoledronic acid (time to first SRE 20.7 months with denosumab versus 17.1 months with zoledronic acid; HR 0.82; $P = 0.008$ for superiority) [31]. Adverse events, including incidence of osteonecrosis of the jaw, were not significantly different between the two groups.

As of early 2011, denosumab has been FDA approved to prevent SREs in patients with solid tumors and bone metastases, including men with prostate cancer.

8. Denosumab to Prevent Bone Metastases

Almost all men with fatal prostate cancer eventually develop metastatic disease to bone [32]. Impairing signaling in the bone microenvironment through RANKL-targeted therapies has not previously been explored for metastasis prevention in prostate cancer. A recently completed phase III trial evaluated the efficacy of denosumab in the prevention of bone metastases in men with nonmetastatic CRPC [33]. The study randomized 1432 men who were at high risk to develop bony metastases to receive denosumab (120 mg monthly) or placebo. The primary endpoint was bone metastasis-free survival, and secondary endpoints included time to first bone metastasis and overall survival.

Denosumab significantly increased bone metastasis-free survival (time to first occurrence of bone metastasis or on-study death from any cause) when compared to placebo (median bone metastasis-free survival 29.5 months and 25.2 months for denosumab and placebo, resp.) [33]. This was a 15% decrease in risk of developing a bone metastasis for patients treated with denosumab. Although there was no significant difference in overall survival between the groups, denosumab increased the time to first bone metastasis (median time to first bone metastasis 33.2 months with denosumab versus 29.5 months with placebo).

9. Conclusions

Osteoporosis in men is a common and important health problem. Men with prostate cancer are at particular risk for

osteoporosis and fractures based on older age and androgen deprivation therapy. ADT decreases bone mineral density and increases fracture risk. In men receiving ADT for prostate cancer, denosumab (60 mg every 6 months) significantly increases bone mineral density and decreases incidence of vertebral fractures. In men with castration-resistant prostate cancer and bone metastases, denosumab (120 mg monthly) is superior to zoledronic acid to prevent skeletal related events. Denosumab in the same dose and schedule also significantly increases bone metastasis-free survival in men with castration-resistant nonmetastatic prostate cancer.

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