Denosumab is really effective in the treatment of osteoporosis secondary to hypogonadism in prostate carcinoma patients? A prospective randomized multicenter international study

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Summary

Introduction. **Osteoporosis is a complication of androgen deprivation therapy (ADT) in men with prostate carcinoma. The best defense against osteoporosis in prostate cancer is to identify patients with a high risk for fracture during the first clinical visit, select an effective anti-osteoporosis agent, and advise the patient to change his lifestyle and diet to prevent further bone loss. New agents include denosumab, a human monoclonal antibody that inhibits the RANK ligand (RANKL). RANKL promotes the formation, activity, and survival of osteoclasts and, thus, supports the breakdown of bone.**
Purpose. **This is a multicenter, randomized, double-blind prospective study on use of denosumab *versus* alendronate in the therapy of secondary osteoporosis related to ADT in prostate cancer patients in three European countries (Italy, France, Switzerland).**
Patients and methods. **In this 24-month observation study we enrolled 234 patients with diagnosis of osteoporosis underwent ADT for prostate cancer. All patients aged ≥55 years and had a dual-energy X-ray absorptiometry (DEXA) T-score <-1.0 (hip or spine, measured within last 2 years) and ≥ 1 fragility fracture. Patients were randomly assigned 1:1 to receive denosumab 60 mg subcutaneously every 6 months or alendronate (70 mg weekly) for 2 years. All patient received supplemental vitamin D (600 IU per day) and supplemental calcium to maintain a calcium intake of 1200 mg per day. Effectiveness of therapy in both groups (denosumab group and alendronate group) was assessed by changes in bone turnover markers (BTMs), Bone Mineral Density (BMD), fracture incidence, Visual Analogue Scale (VAS) score for back pain, and Short Form-8 (SF-8TM) health survey score for health-related quality of life (HRQoL). Percent changes from baseline in BTMs and BMD were assessed using the paired t test; a P-value 0.05). Mean changes in BMD at final follow-up differed significantly between two groups. BMD changes at the lumbar spine at 24 months were 5.6% with denosumab *vs* -1.1% with alendronate (P<0.001). New vertebral fractures developed in fewer patients in the denosumab group than in the alendronate group during the 24-month period, although this difference was not significant (P=0.10). Back pain significantly (P<0.001) improved from baseline at all time points during the study in both study groups. SF-8 health survey scores significantly improved following treatment with both drugs. Incidence of adverse drug reactions were similar in both groups.**
Conclusion. **In our study denosumab and alendronate showed similar clinical efficacy in the therapy of ADT-related osteoporosis in men with prostate carcinoma; both drugs provided significant improvements in back pain and general health conditions. Denosumab showed significant increase of BTMs and BMD than alendronate with lower rate of new vertebral fractures.**

KEY WORDS: osteoporosis; prostate cancer; hypogonadism; denosumab; Bone Mineral Density.

Introduction

Despite some recent increased attention in men, osteoporosis is still considered a disorder of postmenopausal women. While some organizations have recommended screening older men for osteoporosis (1, 2). In the US, more than 2 million men have osteoporosis and another 12 million men are at risk (3). Men experience one-third of all hip fractures, and mortality rates after hip fractures are higher in men than women (4). The diagnosis of osteoporosis is based on bone mineral density (BMD), preferably measured in the hip and spine. Low BMD independently predicts fracture risk in men (5-8) and women (9). A Working Group of the WHO has defined osteopenia and osteoporosis in postmenopausal women based on their BMD compared to the mean values observed in young adults (10). Osteopenia is defined as BMD of between 1.0 and 2.5 SD below the mean for young adults (T score between -1.0 and -2.5). Osteoporosis is defined as BMD of more than 2.5 SD below the mean for young adults (T score less than -2.5). Fracture risk is doubled for every 1-SD decrease in BMD. Although the WHO definitions for osteoporosis were developed from data in women, these definitions are routinely applied to both men and women using gender-specific reference values. The fracture risk for men and women with osteoporosis is at least five-fold greater than for individuals with normal BMD. BMD can be measured by two non-invasive methods: dual-energy X-ray ab-

sorptiometry (DXA) and quantitative CT. DXA is the favored method to measure BMD in most cases, and can easily and precisely measure BMD at several skeletal sites with nominal radiation exposure. The hip is the preferred skeletal site to screen men for osteoporosis using DXA. Average BMD of the posterior-anterior axis of the lumbar spine, as measured by DXA, increases in men over 55 years of age due to development of osteoarthritis in the posterior spinous elements (11, 12). Accordingly, DXA might overestimate real BMD of the spine in older men. Quantitative CT is a more sensitive but less precise method than DXA to detect osteoporosis in men, and it is not widely available. Quantitative CT of the spine evaluates trabecular BMD in the central region of the vertebral bodies, thereby avoiding the potential problems related to osteoarthritis (13). Alcohol abuse, chronic glucocorticoid therapy, and hypogonadism are the major causes of acquired osteoporosis in men (14, 15). These three causes account for approximately half of all cases of male osteoporosis (16). Surprisingly, men get osteoporosis the same way women do: by losing estrogen. More specifically, they lose estradiol, a metabolite of testosterone that is released through aromatization and carries out the same bone-related activities seen in women. A second major testosterone metabolite -dihydrotestosterone (DHT)-also plays a role in bone health. This role is not yet entirely clear, although preliminary studies suggest that it promotes periosteal apposition and modulates the activity of several bone growth factors, including insulin-like growth factor I (17). With the continued production of testosterone and aromatase being virtually ubiquitous, the average 50-year-old man can produce about twice as much estradiol as a menopausal woman of the same age. Consequently, the effects of aging leading to osteoporosis are usually not seen in men until about 15 years after they appear in women. Unlike women, however, men are more likely to develop osteoporosis secondary to an underlying condition or as an adverse effect of pharmacotherapy, i.e., his diagnosis is more likely to be secondary osteoporosis (18). A key contributor to osteoporosis in men is androgen deprivation therapy (ADT), a common approached to advanced cases of prostate carcinoma. In men until about 15 years after they appear in women (19, 20). Hormone therapy for prostate cancer is a major cause of male hypogonadism. Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of treatment for metastatic prostate cancer and a routine part of management for many men with locally advanced or recurrent nonmetastatic prostate cancer. Prostate carcinoma is the most common type of cancer in the United States. It is diagnosed in more than 230,000 men each year (21) which means that, potentially, 230,000 cases of osteoporosis go undetected every year. ADT is the mainstay of treatment for metastatic prostate carcinoma. Options for androgen deprivation therapy include bilateral orchiectomy, administration of a gonadotropin-releasing hormone (GnRH) agonist, or combination therapy with a GnRH agonist and an anti-androgen (22, 23). The large amount of patients prefer GnRH therapy than orchiectomy for psychological implications; GnRH agonists decrease serum concentrations of testosterone by greater than 95% and estrogen by approximately 80% (24, 25). Different retrospective studies reported that ADT increases fracture risk in men with prostate carcinoma (26-29). The best defense against osteoporosis in prostate cancer is to identify patients with a high risk for fracture during the first clinical visit, select an effective anti- osteoporosis agent, and advise the patient to change his lifestyle and diet to prevent further bone loss. The only reliable pharmaco-therapeutic option currently available for osteoporosis in males is the bisphosphonate (alendronate, risedronate) but has not been studied in men receiving ADT. Two intravenous bisphosphonates have been suggested as alternatives for patients who cannot tolerate the oral formulation: pamidronate (Aredia) and zoledronate (Zometa). Pamidronate appears to slow the rate of bone loss in patients with prostate cancer, but does not seem to increase bone mass. Moreover, its tolerability is poor because of a prolonged perfusion period. It has virtually been replaced by zoledronate, which has a considerably shorter infusion time (4 h *vs* 30 min) and builds bone in men with prostate cancer (30). Bisphosphonates are adequate during the earliest stages of the disease, when the options are watchful waiting and a radical prostatectomy, radiation therapy, or both. All efforts must be made to preserve bone strength because of the risk for metastasis to bone. Unfortunately, bone-building drug choices are slim to none at this point. Alendronate may be a valid choice in advanced cancer. If that doesn't work, we could try low-dose oestrogen-but we'd have to monitor the patient for thromboembolic events (31, 32). Several new therapeutic approaches to hormone-refractory prostate cancer are currently under investigation. New agents include denosumab, a human monoclonal antibody that inhibits the RANK ligand (RANKL). RANKL promotes the formation, activity, and survival of osteoclasts and, thus, supports the breakdown of bone. Denosumab blocks its effects by inhibiting osteoclast activity and enhancing osteoblast activity to build bone mass. Interim data from two phase 2 studies suggest that denosumab rapidly suppresses bone turnover after the cancer has metastasized to bone, whether the patient is receiving IV bisphosphonate therapy or not (33). The purpose of this paper is to present the results of our experience using denosumab versus alendronate in the treatment of this kind of secondary osteoporosis in patients with prostate cancer.

Patients and methods

This is a multicenter, randomized, double-blind prospective study on use of denosumab *versus* alendronate in the therapy of secondary osteoporosis related to ADT in prostate cancer patients in three European countries (Italy, France, Switzerland); the study protocol was approved by local ethics board as required by the individual study sites. The study was conducted in accordance with the principles of the Declaration of Helsinki (34). All patients signed informed consent at the commencement of the study before any procedures were performed. In this 24-month observation study we enrolled 234 patients with diagnosis of osteoporosis underwent ADT for prostate cancer. This study was conducted between June 30, 2011 and June 27, 2014 using a central registration method. All patients aged ≥ 55 years and had a dual-energy X-ray absorptiometry (DEXA) T-score < -1.0 (hip or spine, measured within last 2 years) and ≥ 1 fragility fracture. Prevalent fractures were based on self report, spinal radiography or other diagnostics. This study was conducted at 5 clinical centers located in Europe (Sassari-Italy; Santorso-Italy; Turin-Italy; Nice-France; Fribourg-Switzerland). Patients were randomly assigned 1:1 to receive denosumab 60 mg subcutaneously every 6 months or alendronate (70 mg weekly) for 2 years. All patient received supplemental vitamin D (600 IU per day) and supplemental calcium to maintain a calcium intake of 1200 mg per day.

Effectiveness of therapy in both groups (denosumab group and alendronate group) was assessed by changes in bone turnover markers (BTMs), BMD, fracture incidence, Visual Analogue Scale (VAS) score for back pain, and Short Form-8 (SF-8™) health survey score for health-related quality of life (HRQoL).

Serum concentration of two bone formation markers (bone-specific alkaline phosphatase [BSAP] and carboxy-terminal extension peptide of procollagen type I [PICP]) and urinary concentration of two bone resorption markers (free deoxypyridinoline [DPD]) and

N-terminal telopeptide [NTX]) were assessed in each group at baseline and at 6, 12, 18 and 24 months after study initiation. Blood and urine specimens were collected in the morning at baseline. Specimens were stored at -20°C at the study site for 2 to 4 weeks and sent to a central laboratory for processing (Fribourg Laboratories, Switzerland).

In both groups of therapy patients had lumbar spine BMD measurements at baseline and at 24 months. BMD was assessed by DEXA using Hologic (Hologic Corp., Bedford, MA, USA), Norland (Norland Corp., Ft Atkinson, WI, USA) and GE-Lunar equipment (Lunar Corp., Madison, WI, USA). To monitor the response to therapy some adjustments for precision errors must be made because BMD measured by DEXA is not perfectly reproducible (35). Precision estimates can be used to calculate the smallest change in BMD that is considered to be statistically significant (36).

To eliminate differences attributable to manufacturer, spine and femoral neck BMD values were converted to standardized units (expressed in milligrams per square centimeter) (37, 38).

The number of new clinical fractures was counted at 6-monthly intervals. Incident vertebral clinical fractures were defined as new fragility fractures that were reported at any post-baseline visit and were subsequently confirmed by radiographs at study sites. Patients rated the severity of their back pain at baseline, at 6, 12, 18 and 24 months using the VAS score for pain, where a score 0 indicates no back pain and a score 100 indicates worst possible back pain. Patients rated their HRQoL at the same observation time points as back pain using the SF-8 health survey (39).

Statistical analysis

Frequency and incidence were calculated for binary variables. Mean and standard deviation (SD) were calculated for continuous variables, except for percent changes from baseline in BTMs (where first [Q1], second [median], and third [Q3] quartiles were also calculated) and BMD (where mean and 95% confidence interval [CI] were calculated). Percent changes from baseline in BTMs and BMD were assessed using the paired *t* test; a *P*-value <0.05 was considered statistically significant. Fracture rate was assessed using the Kaplan-Meier Method. All statistical analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC, USA).

Table 1 - Baseline demographics, disease characteristics and comorbidities.

Characteristics	Patients (n. 234)
Age	
Mean (SD) years	68.6
Median (min. max) years	69 (54, 81)
55 to 65 years n. (%)	109 (46.6)
65 to 75 years n. (%)	57 (24.3)
75 to 85 years n. (%)	68 (29.1)
Height mean (SD), cm	168.0 (7.8)
Weight mean (SD), kg	77.3 (8.9)
Current smoker n. (%)	112 (47.8)
Alcohol consumption (>3 U/d). n. (%)	17 (7.2)
Vertebral fracture	
1	159 (67.9)
2	51 (21.8)
≥3	24 (10.3)
BMD,% of YAM, n. (%)	
≥80%	42 (17.9)
70 to <80%	73 (31.2)
<70%	119 (50.9)

Abbreviations: BMD, bone mineral density; min, minimum; max, maximum; n, number; SD, standard deviation; YAM, young adult mean

Table 2 - Adverse drug reactions in patients treated with denosumab and alendronate.

Adverse drug reaction	Denosumab Group n (%)	Alendronate Group n (%)
Hypocalcemia	3 (9.7)	0
Eczema	1 (3.2)	2 (6.4)
Urticaria	1 (3.2)	4 (12.9)
Rash	2 (6.4)	3 (9.7)
Abdominal discomfort	3 (9.7)	1 (3.2)
Nausea	1 (3.2)	1 (3.2)
Decreased appetite	3 (9.7)	1 (3.2)
Headache	1 (3.2)	4 (12.9)

Results

A total of 234 patients was enrolled in the study and 227 were included in the effectiveness analysis. 7 patients were excluded because they did not attend periodic visits of follow-up. All patients were treated by ADT for non metastatic prostate cancer. Mean (SD) age was 62.7 (9.1) years. All patients experienced one or more vertebral fractures before registering in the study (Table 1).

A total of 31 adverse drug reactions was reported in both groups (Table 2).

In the denosumab study group level of BTMs for bone formation (BSAP and PICP) were significantly increased from baseline at all time points during the study. The median (Q1, Q3) percent change from baseline at the last observation at 24 month follow-up visit was 247.8% (91.0, 434.6) for PICP and 62.4% (16.3, 98.6) for BSAP (*P*<0.001). The levels BTMS for bone resorption (DPD and NTX) were significantly decreased from baseline at all time points during the study; the median (Q1, Q3) percent changes at the last follow-up visit was 231.4% (134.3, 347.8) for DPD and 29.4% (4.7, 58.1) for NTX (*P*<0.001). In the alendronate study group level of BTMs for bone formation (BSAP and PICP) were increased from baseline at all time points during the study. The median (Q1, Q3) percent change from baseline at the last observation at 24 month follow-up visit was 172.3% (86.0, 294.1) for PICP and 38.95% (17.1, 67.4) for BSAP (*P*>0.05). The levels BTMS for bone resorption (DPD and NTX) were decreased from baseline at all time points during the study; the median (Q1, Q3) percent changes at the last follow-up visit was 274.1% (135.7, 386.2) for DPD and 48.2% (8.1, 74.3) for NTX (*P*>0.05).

Mean changes in BMD at final follow-up differed significantly between two groups. BMD changes at the lumbar spine at 24 months were 5.6% with denosumab *vs* -1.1% with alendronate (*P*<0.001). Mean changes in trabecular BMD of lumbar spine also differed significantly between groups (*P*=0.02).

New vertebral fractures developed in fewer patients in the denosumab group than in the alendronate group during the 24-month period, although this difference was not significant (18 [15.38%] *vs* 24 [20.51%], respectively) (*P*=0.10).

Back pain significantly (P<0.001) improved from baseline at all time points during the study in both study groups. The mean (SD) back pain VAS score at baseline was 41.8 in denosumab study group and 42.3 in alendronate study group. In the denosumab study group the mean (95% CI) change from baseline in back pain VAS sco-

res at 6, 12, 18 and 24 months were -10.0 (-12.0 to -8.0), -12.8 (-15.4 to 10.3), -13.7 (-16.5 to -11.2) and -13.4 (-15.2 to 11.7) respectively. In the alendronate study group the mean (95% CI) change from baseline in back pain VAS scores at 6, 12, 18 and 24 months were -10.4 (-12.3 to -8.2), -12.5 (-15.1 to 9.7), -13.4 (-16.2 to -11.0) and -13.6 (-15.4 to 11.5) respectively.
SF-8 health survey scores significantly improved following treatment with both drugs. The mean (SD) SF-8 scores at baseline in denosumab group study ranged from 38.26 (9.34) for the physical component summary score to 46.34 (8.23) for the mental health domain. The mean (95% CI) change from baseline to the last follow-up in SF-8 scores ranged from 2.43 (1.71-3.03) for the mental component summary score to 4.48 (3.71-5.25) for the role physical domain. The mean (SD) SF-8 scores at baseline in alendronate group study ranged from 37.93 (9.23) for the physical component summary score to 46.51 (8.26) for the mental health domain. The mean (95% CI) change from baseline to the last follow-up in SF-8 scores ranged from 2.52 (1.75-3.07) for the mental component summary score to 4.53 (3.74-5.19) for the role physical domain.

Discussion

Some men develop osteoporosis during ADT because it accelerates bone loss and increases fracture risk. Several prescription options are also available for the treatment of osteoporosis in men. Actually therapies approved by the US Food and Drug Administration (FDA) include bisphosphonates (alendronate, risedronate, and zoledronic acid), teriparatide, and denosumab. Bisphosphonates are anti-resorptive medications typically used as first-line therapy. Alendronate is administered orally, usually in a daily or weekly regimen and it is effective at increasing BMD in the spine and femoral neck and reducing the incidence of vertebral fractures (40-42).
Intravenous bisphosphonates, such as zoledronic acid, present an alternative option to oral bisphosphonates, avoiding gastrointestinal adverse effects and offering regimens with less frequent dosing and thus improving adherence to therapy. In one randomized trial, zoledronic acid at an annual dose of 5 mg reduced overall clinical fractures (35% relative risk reduction) and mortality (43). A recent comparative study of once-yearly zoledronic acid 5 mg and once-weekly alendronate demonstrated noninferiority of zoledronic acid with regards to changes in BMD and bone turnover markers in men with osteoporosis (44). The most recently published multicentre double-blind, placebo-controlled trial of 1199 men reported fewer incident vertebral fractures with zoledronic acid (1.6% *versus* 4.9%, p=0.002), along with significant increases in BMD and decreases in bone turnover markers (45). Zoledronic acid use also has limitations and inconveniences: need for intravenous access and administration; monitoring of renal function, with dose adjustments and withholding to prevent renal injury in patients who develop renal impairment during treatment. Renal issues can be particularly important in elderly patients with prostate cancer who frequently have renal dysfunction caused by urinary tract obstruction. These limitations do not apply to denosumab, which is given subcutaneously, has no effect on renal function and no need for renal monitoring.
Anabolic agents, such as teriparatide, may remedy an underlying defect in osteoblast function, which has been implicated in men with idiopathic osteoporosis but is not permitted in oncologic patients (46, 47).
Denosumab is approved by the FDA to increase bone mass in men with osteoporosis at high risk for fracture. It is the only medication in its class, is a novel biologic, and has an unique mechanism of action. Denosumab is effective in increasing BMD at the lumbar spine in men with osteoporosis, and significantly reduces urinary BTMs levels for bone resorption. We noted that patients treated with denosumab had significantly greater suppression of NTX and DPD, paralleling the reduction in new vertebral fractures. Many studies indicate that denosumab is effective and safe, and has superior adherence and patient satisfaction rates, in part because of twice-yearly in-office administration (48). Denosumab may be an appropriate therapy in men with intolerance or contraindications to bisphosphonates (gastrointestinal complications, hypersensitivity, inability to stand or sit upright). Denosumab, which is given subcutaneously, has no effect on renal function and no need for renal monitoring (49). Hypocalcaemia is a side-effect of denosumab manageable with appropriate supplementation with a combination of oral vitamin D and calcium to maintain intake of 1200-1500 mg per day.
Although long-term data and further research on fracture reduction rates in men should be explored, at this time denosumab is an appropriate first-line option for men with osteoporosis secondary to hypogonadism in prostate cancer patients.

Ethical considerations

This study was performed with informed consent of patients and following all the guidelines for experimental investigation with human subjects in accordance with the ethical standards of the institutional and/or national research committees and the Helsinki Declaration of 1975 and the 1983 revision of the same.

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