Tzu Chi Medical Journal 27 (2015) 159–163

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Original Article

Effects of denosumab on bone mineral density and renal function in postmenopausal women transitioning from raloxifene

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ARTICLE INFO

Article history:
Received 3 March 2015
Received in revised form
6 May 2015
Accepted 2 August 2015
Available online 28 September 2015

Keywords:
Adherence
Denosumab
Postmenopausal osteoporosis
Raloxifene
Transition

ABSTRACT

Objectives: Denosumab is a human recombinant monoclonal antibody that has been approved for the treatment of postmenopausal osteoporosis in women with a high risk of fracture. The antibody binds the receptor activator of nuclear factor κB ligand, which blocks the maturation, function, and survival of osteoclasts, and therefore reduces bone resorption. Many patients treated with denosumab for osteoporosis have previously received other antiresorptive therapy that may influence the antiosteoporotic effect. The aim of this study is to elucidate if transition from raloxifene to denosumab is beneficial in antiosteoporotic treatment.

Materials and methods: This retrospective study recruited postmenopausal women with bone mineral density (BMD) T-scores in the lumbar spine (LS) or femoral neck (FN) ≤ -2.5 who received regular treatment with raloxifene or/and denosumab. The patients were divided into three groups. The R group received oral raloxifene 60 mg daily for at least 24 months. The D group received subcutaneous denosumab 60 mg every 6 months for at least 24 months. The T group received raloxifene for at least 6 months, and then shifted to denosumab for at least 18 months. BMD and renal function were also evaluated in these patients.

Results: Approximately 60% of patients adhered to the raloxifene regimen and ~95% adhered to the denosumab regimen. Spine BMD increased less in the T group than in the D group at Month 24. BMD in the spine and hip increased more in the T group than the R group. There was no deterioration of renal function or adverse events in any of the three groups.

Conclusion: Patients who transitioned from raloxifene to denosumab showed good adherence with treatment and significant improvement in BMD in the spine and hip without a negative influence on renal function. Discussing the characteristics of both drugs and the best antiosteoporotic treatment with patients is critical for satisfactory results in the prevention of fractures.

1. Introduction

Osteoporosis is a chronic, progressive condition characterized by decreased bone mass and microarchitectural deterioration. It causes bone fragility and a significantly increased risk of fracture [1–3]. More than 75 million people throughout the world are affected by osteoporosis [4]. The goal of treatment is to alter the balance of bone remodeling to increase bone mass. Antiresorptive agents are the predominant therapy for the prevention and treatment of bone loss. Different medications are given orally, subcutaneously, or intravenously [5–7]. Several oral drugs used in the treatment of postmenopausal osteoporosis, which have all shown efficacy in reducing fracture risk, are greatly affected by adherence to treatment, a critical issue in the management of osteoporosis [8,9]. Many patients do not perceive the need for treatment of osteoporosis until they experience the first fracture [10].

Conflict of interest: none.

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http://dx.doi.org/10.1016/j.tcmj.2015.08.001

Denosumab reduces bone resorption with accompanying increases in bone mineral density (BMD) by inhibiting the receptor activator of nuclear factor κB ligand, which is essential for the formation, activity, and survival of osteoclasts [11–15]. In postmenopausal women with osteoporosis, denosumab 60 mg administered subcutaneously every 6 months significantly reduced bone turnover markers, increased BMD, and reduced new vertebral, hip, and nonvertebral fractures compared with placebo in a pivotal 36-month fracture trial [16]. In previous studies, denosumab treatment for up to 4 years significantly increased BMD in the lumbar spine (LS), total hip, distal third of the radius, and total body compared with placebo [17–20]. Patients who had never been treated, or had previously been treated with bisphosphonates, who then transitioned to denosumab treatment had better gains in BMD and decreased bone turnover markers compared with patients who received regular bisphosphonate medication only [21,22]. Raloxifene was first approved by the European Union and the United States Food and Drug Administration for treating and preventing osteoporosis in postmenopausal women. It is known as a benzothiophene selective estrogen receptor modulator, which partially mimics the effects of estrogens [23]. The beneficial effects of osteoporosis therapy in menopausal women are unclear, especially in those taking raloxifene or denosumab or transitioning between these medications.

In addition to improvement in bone density, the renal effects of antiosteoporotic agents are also a critical issue. As both osteoporosis and renal insufficiency become more prevalent with age, it is important for doctors to understand the effect of medical therapies in osteoporotic patients with different levels of renal function. Although a previous study revealed that denosumab seemed to be safe for patients in all stages of chronic kidney disease [15] and raloxifene may have a renoprotection effect [23], the renal effect of transition therapy is still seldom studied.

The current study was conducted in postmenopausal women previously treated with raloxifene to evaluate the safety, BMD, and renal function in those transitioning to denosumab in comparison with those continuing raloxifene therapies.

2. Materials and methods

We performed a retrospective analysis of 2000 female patients who received regular raloxifene or/and denosumab in the Orthopedic Outpatient Department of Hualien Tzu Chi Hospital, Haulien, Taiwan from January 2009 to September 2014. Patient data were reviewed from medical records by an orthopedic surgeon. The patients were divided into three groups. The R group received oral raloxifene 60 mg per day for at least 24 months, the D group received subcutaneous injections of denosumab 60 mg every 6 months for at least 24 months, and the T group received raloxifene for at least 6 months and then transitioned to denosumab for at least 18 months. The inclusion criteria were as follows: ambulatory postmenopausal women at least 55 years of age with BMD measurements in the LS or femoral neck (FN) corresponding to a T-score of < -2.5, who received regular subcutaneous injections of denosumab 60 mg every 6 months or oral raloxifene 60 mg per day for at least 6 months. The exclusion criteria were: (1) male patients, (2) younger than 55 years, (3) postmenopausal period < 5 years, or (4) previous treatment with other osteoporotic medications, such as bisphosphonates and teriparatide. Adherence to medication therapy was defined in terms of the ratio of total number of days of drug administration therapy (based on dispensed prescriptions) between the accurate prescription date and date of the first follow-up survey to the total number of calendar days between these dates. We collected the BMD in the LS and FN by dual energy X-ray absorptiometry and the estimated glomerular filtration rate (eGFR) at baseline and 24 months after treatment in the R and D groups. In the T group we collected the BMD data at transition and 24 months after beginning denosumab treatment. The fracture risk assessment (FRAX) of these patients was calculated from the site: http://www.shef.ac.uk/FRAX/tool.jsp?lang=cht based on Taiwan population data. We used the BMD percentage change (BMD-PC) as an indicator of improvement in bone density, which was calculated as follows: (posttherapy absolute BMD − pretherapy absolute BMD)/pre-therapy absolute BMD. We also collected the T scores of the patients, which are the values of their BMD compared with the ideal or peak BMD of healthy 30-year-old adults. The differences in the worst total spine T score pre/post therapy were also collected and divided into three stages: ≤ 0, 0–0.5, >0.5.The data were used for analyses. The eGFR was calculated following the formula: 186*Serum creatinine$^{-1.154}$* Age $^{-0.203}$ (* 0.742 if female).We collected body mass index (BMI data and divided the patients into four groups: underweight (BMI < 18.5), normal ($18.5 \leq$ BMI < 24), overweight ($24 \leq$ BMI < 27), and obese ($27 \leq$ BMI). Fractures after 48 months of treatment were reported as adverse events. The percentage of adherence to the medication regimen was assessed by prescription records.

2.1. Statistical analysis

The data were expressed as frequencies, proportions, or mean ± standard deviations, depending on the characteristics of each item. The Chi-square test was used to evaluate the association between two categorical variables. One-way analysis of variance (1-way ANOVA) was used to compare the differences in means between different groups. The Bonferroni correction was adopted to perform multiple comparisons of group means whenever there was a significant F test result in ANOVA. Statistically significant differences were defined as $p < 0.05$. All of the statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Among 2,000 cases reviewed, 1615 women enrolled in the study: 1000 in the R group, 477 in the D group, and 138 in the T group. The percentages of adherence to the medication regimen were 65 ± 16%, 98 ± 22%, and 96 ± 32% in these groups, respectively (Table 1). The adherence in the R group was significantly less than in the D and T groups ($p < 0.001$).

Of the 1615 women, 134 (8.3%) had complete data for the BMD and pretherapy and posttherapy eGFR (Table 2), 67 in the R group, 33 in the T group, and 34 in the D group. The mean age in the R group was lower than that in the T and D groups ($p < 0.001$). More women in the D and T groups had hypertension and a history of vertebroplasty for vertebral compression fracture than in the R group ($p < 0.05$). According to the FRAX values, there were significant differences in the risks of main and hip fractures between groups with the highest values in the T group, followed by the D group, with the lowest rate in the R group ($p < 0.001$).

BMD-PCs in the spine and bilateral hips were significantly greater in the T group than the R group ($p < 0.001$; Table 3). BMD-PCs in the spine in the D group were significantly higher than those in T group ($p < 0.001$). A *post hoc* test revealed that BMD-PCs in the spine and bilateral hips were significantly higher in the T and D groups than the R group. There was no difference between the T and D groups for BMD-PC of the bilateral hips. There were no significant changes in the three T score stages between these three groups.

The pretherapy mean eGFRs were not significantly different in the three groups (Table 4). The posttherapy mean eGFR in the R

Table 1
Adherence of the three groups.

	R group	D group	T group	*p*	*Post hoc*[b]
N	1000	477	138		
Adherence	0.65 ± 0.16	0.98 ± 0.22	0.96 ± 0.32	<0.001[a]	E group << T group/P group

Data are presented as mean ± standard deviation.
[a] $p < 0.05$ was considered statistically significant after analysis of variance.
[b] Bonferroni correction was adopted while performing *post hoc* test.

Table 2
Demographic data.

	T group	D group	R group	*p*
N	67	33	34	
Age (y)[a]	73.2 ± 11.0	69.1 ± 8.6	62.8 ± 8.4	<0.001[c]
BMI group (kg/m^2)[b]	—	—	—	0.057
Normal	33 (49.3)	9 (27.3)	16 (47.1)	
Underweight	6 (9.0)	2(6.1)	0 (0.0)	
Overweight	11 (16.4)	11 (33.3)	12 (35.3)	
Obese	17 (25.4)	11 (33.3)	6 (17.6)	
Previous vertebroplasty[b]	9 (13.4)	2 (6.1)	0 (0.0)	0.037[c]
Steroid user[b]	1 (1.5)	1 (3.0)	0 (0.0)	0.744
RA[b]	2 (3.0)	1 (3.0)	4 (11.8)	0.179
Hypertension[b]	43 (64.2)	22 (66.7)	12 (35.3)	0.011[c]
Psychologic disease[b]	16 (23.9)	5 (15.2)	2 (5.9)	0.062
Heart disease[b]	22 (32.8)	8 (24.2)	6 (17.6)	0.266
DM[b]	18 (26.9)	11 (33.3)	6 (17.6)	0.334
Dialysis[b]	2 (3.0)	1 (3.0)	0 (0.0)	0.617
Other autoimmune disease[b]	4 (6.0)	1 (3.0)	0 (0.0)	0.439
FRAX(W/O BMD)[a]	11.7 ± 9.7	6.7 ± 5.3	4.5 ± 3.3	<0.001[c]
FRAX(W/I BMD)[a]	23.8 ± 11.6	18.1 ± 8.6	14.4 ± 6.7	<0.001[c]

Data are presented as *n* (%) or mean ± standard deviation.
BMD = bone mineral density; BMI = body mass index; DM = diabetes mellitus; FRAX = the fracture risk assessment (being calculated from the site: http://www.shef.ac.uk/FRAX/tool.jsp?lang=cht based on Taiwan population data.); RA = rheumatoid arthritis.
[a] The *p* value was computed from analysis of variance.
[b] The *p* value was computed from Chi-square test.
[c] The *p* value < 0.05 was considered statistically significant after test.

group was significantly higher than that in the T and D groups ($p = 0.003$). The posttherapy mean eGFRs in the T and D groups showed mild but insignificant decreases compared with the pretherapy mean eGFRs.

There were no records of atypical fracture events or jaw osteonecrosis in these 1615 cases after 48 months of antiosteoporotic treatment.

4. Discussion

This is a retrospective study comparing BMD-PC and renal function tests in postmenopausal women with osteoporosis between those who received regular administration of raloxifene or denosumab or transitioned from raloxifene to denosumab.

In general, BMD is an important predictor of bone strength and the prevention of bone loss is an important mechanism in fracture prevention. In this study, the BMD of the T group significantly increased compared with the R group in the spine and hip. The critical factors appeared to be poorer adherence and the younger age of those in the R group. Consistent with a previous study, we found that patients treated with raloxifene were younger, were less likely to receive a diagnosis of osteoporosis and have BMD screening, and had lower rates of pretherapy fracture than those treated with other antiosteoporotic agents [24]. We found that denosumab can effectively increase BMD, whether it is used initially or after transition from raloxifene. Previous studies revealed good improvement in BMD after transition from bisphosphonates to denosumab, and prior bisphosphonate use may decrease the improvement effect of denosumab [25]. Our study had similar results in that raloxifene seemed to have some effects on the antiosteoporotic activity of denosumab.

In our study, renal function remained good after raloxifene or denosumab use. The R group had better renal function, possibly because these patients were younger and had fewer comorbid conditions such as vertebral fracture or hypertension before therapy than those in the other groups. A previous study revealed that participants on raloxifene had a slower yearly rate of increase in creatinine and a significantly slower yearly rate of decrease in the eGFR compared with those in the placebo group over 3 years of follow-up [22]. Raloxifene was associated with significantly fewer kidney-related adverse events compared with placebo and seemed to be safe and renoprotective [26]. Previous study of denosumab revealed that no adjustment is required in patients with renal impairment because its metabolisation is via the reticuloendothelial system and not through the kidneys [27]. Patients on both medications showed no impairment in renal function after long-term use. This result implies that these drugs may benefit those patients who have concomitant osteoporosis and chronic kidney disease and those who have chronic illnesses, which are significant risk factors for chronic renal failure, such as uncontrolled diabetes mellitus or hypertension.

Table 3
Absolute bone mineral density percentage change comparison between different groups.

Result	T group	D group	R group	*p*	*Post hoc*
N	67	33	34		
BMD-PC(Spine)[a]	8.1 ± 5.8	12.1 ± 6.5	−1.2 ± 5.8	<0.001[c]	E group<T group<P group
BMD-PC(Left Hip)[a]	9.6 ± 6.4	10.0 ± 7.7	1.2 ± 9.2	<0.001[c]	E group<T group/P group
BMD-PC(Right Hip)[a]	8.0 ± 6.5	10.4 ± 8.0	2.0 ± 11.1	<0.001[c]	E group<T group/P group
TTS[b] (Posttherapy−Pretherapy)	—	—	—	0.587	
<=0	19 (28.4)	6 (18.2)	12 (35.3)		
0–0.5	16 (23.9)	10 (30.3)	9 (26.5)		
>0.5	32 (47.8)	17 (51.5)	13 (38.2)		

Data are presented as *n* (%) or mean ± standard deviation.
BMD-PC = percentage change of bone mineral density; TTS = total spine T score.
[a] The *p* value was computed from analysis of variance and Bonferroni correction was adopted while performing *post hoc* test.
[b] The *p* value was computed from Chi-square test.
[c] The $p < 0.05$ was considered statistically significant after test.

Table 4
Pretherapy/posttherapy estimated glomerular filtration rate of the three groups.

	T group	D group	R group	*p*	*Post hoc*
N	67	33	34		
Pre-eGFR(mL/min/1.73 m^2)[a]	63.7 ± 27.3	66.4 ± 30.5	63.6 ± 13.9	0.861	
Post-eGFR(mL/min/1.73 m^2)[a]	58.2 ± 26.7	65.4 ± 23.4	76.3 ± 20.2	0.003[b]	E group << T group/P group

Data are presented as mean ± standard deviation.
eGFR = estimated glomerular filtration rate.
[a] The *p* value was computed from analysis of variance and Bonferroni correction was adopted while performing *post hoc* test.
[b] The *p* value < 0.05 was considered statistically significant after test.

Adherence to an antiosteoporotic medication regimen is a critical factor in the successful treatment of osteoporosis. A practical advantage of denosumab over current therapies is its convenient biannual administration, leading to better long-term adherence. Although it has a disadvantage in terms of rapid BMD reduction and putative fracture risk increase after discontinuation, rendering a drug holiday prohibitive, good adherence and few complications seem to make up for this deficit in the treatment of osteoporosis [28]. In this study we had satisfactory percentages of adherence in the T and D groups, similar to the results of the BMD-PC. Raloxifene has been considered an excellent drug for the treatment of osteoporosis and prevention of estrogen receptor-positive breast cancer because it guarantees an excellent safety profile on the endometrium and is good for those who have concomitant dyslipidemia. Although it has resulted in less improvement in the BMD-PC and turnover rate of bone-specific biomarkers, raloxifene appears to prevent spine fracture [29]. However, weaker adherence can be a problem in oral administration of raloxifene for elderly osteoporotic women because of combination with many drugs for other chronic diseases and poor memory about taking medications. In our study, the R group, although younger, had significantly poorer adherence than the D and T groups. The selection of patients for adequate osteoporotic treatment according to needs and characteristics is an important issue for orthopedic surgeons.

The application of FRAX is practical as it is calculated by collecting clinical risk factors to estimate the 10-year probability of the risk of main and hip fractures. The estimate can be used alone or with BMD to strengthen fracture risk prediction. In this study, the FRAX value was significantly lower in the T group, and the main reason was the younger mean age in this group. FRAX uses data derived from nine cohorts from all over the world, including centers in North America, Europe, Asia, and Australia. It has been validated in 11 independent cohort studies with comparable environmental factors [30]. The larger the sample applied in the examination of the general relationship of each risk factor by age, sex, duration of follow-up, and continuous variables (BMI and BMD), the lower the relationship of risk related with the variable itself. So the risk of publication bias is also eliminated by the use of primary data. The validity of the clinical risk factors identified is supported by the expected relationships between fracture risks and BMD [31].

Limitations of this study include the small amount of data that could be traced from a review of charts and the lack of analysis of bone specific biomarker levels. The relatively small case numbers in the transition group and denosumab group may have critical influence on medical adherence. Compared with the other groups, patients in the R group were younger and had less comorbidity, such as hypertension and spinal vertebral body compression fracture, which is indicative of vertebroplasty. These factors may also contribute to sequential BMD and eGFR changes. Future work such as regression risk factor analysis on a greater number of patients can show their influence on changes in bone density and renal function. Prospective study of those who intend to transition from raloxifene to denosumab is also needed and more data related to serum biomarkers of bone turnover rates should be collected from those who receive regular treatment with raloxifene or denosumab.

In conclusion, patients who transitioned from raloxifene to denosumab showed good adherence to treatment and significant improvements in the BMD of the spine and hip without a negative influence on renal function. There were still some effects from the previous use of raloxifene on increases in the BMD in the spine, but more comprehensive study is needed to investigate this point. Discussing the best antiosteoporotic treatment and the characteristics of both drugs with patients is important for satisfactory results in the prevention of fractures.

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