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Cost-Effectiveness of Therapeutic Drugs for the Prevention of Incident Vertebral Fracture in Patients with Postmenopausal Osteoporosis -Randomized Controlled Trial of 72 Week Follow-Up

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Abstract

Background: The importance of the treatment of osteoporosis is increasing in countries where the population age is rapidly advancing. A prospective study was planned for the purpose of determining the cost-effectiveness of various drugs for the prevention of incident vertebral fractures in patients with postmenopausal osteoporosis.

Method and findings: Two hundred and forty women aged 65 to 75 years old who started treatment with various therapeutic drugs for primary postmenopausal osteoporosis were included in this study. The bone mineral density (BMD) of the lumbar spine estimated by the percent value of the young adult mean (%YAM) was less than 60% and all subjects were diagnosed with severe osteoporosis. Eight therapeutic drugs for osteoporosis were estimated of cost-effectiveness to protect against incident vertebral fracture. The cost invested in our hospital to suppress one incident of vertebral fracture was 930,792 yen for daily parathyroid hormone (PTH), 872,004 yen for weekly PTH, 142,196 yen for denosumab, 195,4499 yen for monthly intravenous ibandronate, 192,234 yen for monthly minodronic acid hydrate,232,727 yen for monthly risedronate, 229,943 yen for weekly alendronate, and 352,639 yen for raloxifene. Denosumab was the most cost-effective drug, as seen from the suppression of incident vertebral fracture in severe osteoporotic patients with YAM value of less than 60% between 65 -75 years old.

Conclusion: Cost-effectiveness should be evaluated when choosing a therapeutic drug for patients with osteoporosis.

Keywords: Severe osteoporosis; Incident vertebral fracture; Cost-effectiveness; Denosumab; Elderly patient

Introduction

Osteoporotic vertebral fracture is the leading cause of disability and morbidity in elderly women [1-3]. The importance of the treatment of osteoporosis is increasing in countries where the population age is rapidly advancing. Most drugs for osteoporosis currently available are estimated to have a suppressive effect on vertebral fracture in postmenopausal osteoporotic patients [4-12], and the choice of therapeutic agents is largely due to the physician's discretion. Meanwhile, medical expenses have been steadily increasing and have a major impact on the national economy. However, little consideration has been given to the cost-effectiveness of drug therapy, which is an important treatment tool for osteoporosis patients. A prospective study on a single hospital was planned to determine the cost-effectiveness of various drugs for the prevention of incident vertebral fractures in patients with postmenopausal osteoporosis.

Materials and Methods

Two hundred and forty women 65 to 75 years old (mean age 69.7) with primary postmenopausal osteoporosis who visited our hospital during the 36 months from January 2012 to December 2014 and started treatment with various therapeutic drugs were included in this study. The bone mineral density (BMD) of the lumbar spine estimated by the percent value of the young adult mean (%YAM) was less than 60% and all subjects were diagnosed with severe osteoporosis [13,14]. Patients with previous osteoporotic fractures of the vertebral body, hip and upper extremities and patients already taking drugs for osteoporosis were excluded from this study. Patients with a burst fracture of the vertebral body due to a high-energy injury were also excluded. Eight therapeutic drugs, rh-paratyyroid hormone (PTH)1-34 (daily PTH), teriparatide acetate (weekly PTH), denosumab, monthly intravenous ibandronate, monthly minodronic acid hydrate, weekly oral alendronate, monthly oral risedronate and raloxifene were prescribed for the prevention of

incident vertebral fracture of the patients. Patients were divided into eight drug groups by randomized allocation with patients' agreement. If a patient dropped out during the follow-up period, additional cases were registered. Finally, 30 patients were collected for each drug. There was no bias in patient allocation in age or BMD between each group **(Tables 1 and 2)**.

Table 1: Age at the first visit of each drug group.

Drug	Subject (n)	Median BMD	95% confidence
Daily PTH	30	69.0	67.0-72.9
Weekly PTH	30	68.5	67.0-72.9
Denosumab	30	68.5	67.0-73.0
Ibandronate	30	70.0	66.1-74.0
Minodronic acid hydrate	30	71.0	67.0-73.0
Risedronate	30	69.0	67.0-73.0
Alendronate	30	69.0	66.1-72.0
Raloxifene	30	69.5	67.0-73.0

Table 2: Bone mineral density of each drug group.

Drug	Subject (n)	Median BMD	95% Confidence
Daily PTH	30	54	54.0-55.0
Weekly PTH	30	54.5	54.0-56.0
Denosumab	30	54.5	54.0-56.0
Ibandronate	30	54	54.0-55.0
Minodronic acid hydrate	30	54	54.0-56.0
Risedronate	30	55	54.0-56.0
Alendronate	30	55	54.0-56.0
Raloxifene	30	54.5	54.0-56.0
BMD=Bone mineral density, BMD shows by the value of young adult mean			

When an incident vertebral fracture occurred, the drug was changed to weekly PTH, and patients wore a brace following hospitalization for 2 weeks. The total of the presence or absence of incident vertebral fracture occurrence and the cost required for treatment was calculated during the observation period of 72 weeks, which is the use restriction period for weekly PTH injections. For the total expense, drug expenses, first visit/reassessment fee, injection technique fee, self-injection management guidance fee, trunk orthosis cost and 2-week hospitalization fee due to fracture occurrence were calculated. Costs related to imaging and bone metabolism markers were excluded from expenses because they were executed uniformly in the preceding example. This study was performed with the approval of patients and the ethics committee of our hospital.

Statistical analysis

The distribution of age and BMD (% YAM) between drug groups wastested using the nonparametric Kruskal-Wallis method [15].

Results

Incident vertebral fracture occurred during the observation period of 72 weeks in a total of 19 cases: 1 case with denosumab, 2 cases with monthly intravenous ibandronate, 2 cases with monthly minodronic acid hydrate, 4 cases with monthly risedronate, 4 cases with weekly alendronate and 6 cases with raloxifene. No incident vertebral fracture occurred in the groups of daily PTH and weekly PTH. The drug expense details for each group are summarized in **Table 3** and **Table 4**.

Table 3: Drug cost of eight groups for 72 weeks in patients without incident vertebral fracture.

Drug	Unit Price (yen)	Unit Needed	Cost of 72 weeks (yen)	No. of Completion	A (yen)
Daily PTH	43334	18	780012	30	23,400,360
Weekly PTH	10832	72	779904	30	23,397,120
Denosumab	29296	3	87888	29	2,548,752
Ibandronate	5059	17	86003	28	2,408,084
Minodronic acid hydrate	3476	18	62568	28	1,751,904
Risedronate	2771	17	47107	26	1,224,782
Alendronate	591	72	42552	26	1,106,352
Raloxifene	109	504	54936	24	1,318,464
A shows total drug cost of 72 weeks for patients without incident vertebral fracture.					

Out-patient treatment fee such as first visit/reassessment fee, injection technique fee, and self-injection management guidance fee was showed in **Table 5**. Additional cost due to incident vertebral fracture which includes cost of trunk orthosis and hospitalization was showed in **Table 6**.

According to the results, the cost-effectiveness ratio invested in our hospital to suppress one incident vertebral fracture was 930,742 yen for daily PTH, 872,004 yen for weekly PTH, 142,196 yen for denosumab, 195,449 yen for monthly intravenous ibandronate, 192,234 yen for monthly minodronic acid hydrate, 232,727 yen for monthly risedronate, 229,943 yen for weekly alendronate, and 352,639 yen for raloxifene. In this study, denosumab was the most cost-effective drug, as seen from the suppression of incident vertebral fracture in severe osteoporotic

patients 65-75 years old with a YAM value of less than 60% (**Table 7**).

Table 4: Drug cost of eight groups in patients with incident vertebral fracture.

Drug	Unit Price (yen)	Number of fractures	Units needed till fracture	Cost of drug (yen)	Units needed weekly PTH	Cost of additional PTH (yen)	B (yen)
Daily PTH	43,334	0	0	0	0	0	0
Weekly PTH	10,832	0	0	0	0	0	0
Denosumab	29,296	1	1	29,296	58	628,256	657,552
Ibandronate	5,059	2	7	35,413	110	1,191,520	1,226,933
Minodronic acid hydrate	3,476	2	10	34,760	103	1,115,696	1,150,456
Risedronate	2,771	4	20	55,420	200	2,166,400	2,221,820
Alendronate	591	4	76	44,916	207	2,242,224	2,287,140
Raloxifene	109	6	746	81,314	326	3,531,232	3,612,546

Unit needed till fracture means the sum of used drugs till incident vertebral fracture occurred; Cost of drug means the initial drug cost till incident vertebral fracture occurred; B is the sum of cost of drug and additional fee for weekly PTH.

Table 5: Cost of outpatient treatment.

Drug	First visit/reassessment fee (yen)	Injection technique fee (yen)	self-injection guidance fee (yen)	C (yen)
Daily PTH	473,400	0	40,50,000	4,523,400
Weekly PTH	1,639,800	1,123,200	0	2,763,000
Denosumab	216,620	226,200	0	442,820
Ibandronate	586,920	302,640	0	889,560
Minodronic acid hydrate	581,960	0	0	581,960
Risedronate	683,080	0	0	683,080
Alendronate	686,800	0	0	686,800
Raloxifene	685,000	0	0	685,000

C is the sum of cost of first visit/reassessment fee and injection technique/self-injection guidance fee.

Discussion

Medical care is not business. However, considering the current national finances of Japan, it is impossible to ignore the increase in medical expenses. Even drugs that are extremely effective at suppressing incident vertebral fractures do not necessarily have an appropriate medical price. Recently, cost-effectiveness analysis has been used to compare and examine the therapies for various disease [16,17]. Evaluation of the cost-effectiveness of drugs for patients with osteoporosis is essential for national finance. Cost-effectiveness has generally been estimated by the analysis of the number needed to treat (NNT) [18,19] or the expense per quality-adjusted life year (QALY) [20,21]. However, these studies require a large-scale collection of cases, and this is impossible for a single center to perform. We designed a prospective study on a single hospital to evaluate the cost efficacy of drugs for osteoporosis by calculating the cost-effectiveness ratio. This study was performed to determine a real-world cost efficacy of drugs for osteoporosis.

The risk of subsequent vertebral fracture in patients with an incident fracture is increasing by the domino effect [22]. It is very important to prevent incident vertebral fracture in patients with osteoporosis. The authors of the current study subjected the patients without any osteoporotic fracture who showed severe osteoporosis. The data give us valuable information for clinician who treats osteoporotic patients without osteoporotic fracture.

In our current study, daily PTH and weekly PTH were most effective to suppress incident vertebral fracture for patients with severe osteoporosis. However, both drugs are very expensive, incurring a high cost to suppress one incident vertebral fracture. Denosumab was the most cost-effective out of eight drugs for osteoporosis to suppress incident vertebral fracture. However, there are no patients with incident vertebral fracture occurrence who are treated with daily and weekly PTH. If both drugs were

less expensive, PTH would become the most cost-effective one for the prevention of incident vertebral fracture.

Table 6: Cost of trunk orthosis and hospitalization.

Drug	Number of case	Cost of trunk orthosis (yen)	Hospitalization Fee	D (yen)
Daily PTH	0	0	0	0
Weekly PTH	0	0	0	0
Denosumab	1	64,556	410,000	474,556
Ibandronate	2	129,112	820,000	949,112
Minodronic acid hydrate	2	129,112	820,000	949,112
Risedronate	4	258,224	1,640,000	1,898,224
Alendronate	4	258,224	1,640,000	1,898,224
Raloxifene	6	387,336	2,460,000	2,847,336
D is the sum of cost of trunk orthosis and hospitalization fee.				

Table 7: Cost-effectiveness ratio on the eight drug groups.

Drug	A+B+C+D (yen)	Number of case with goal (n)	Cost-effectiveness ratio
Daily PTH	27,923,760	30	930,792
Weekly PTH	26,160,120	30	872,004
Denosumab	4,123,680	29	142,196
Ibandronate	5,473,689	28	195,449
Minodronic acid hydrate	5,382,544	28	192,234
Risedronate	6,050,906	26	232,727
Alendronate	5,978,516	26	229,943
Raloxifene	8,463,346	24	352,639
Cost-effectiveness ratio means A+B+C+D/n			

The limitation of the current study is the number of subjects. We need a large-scale collection of cases to determine where denosumab is the most cost-effective drug to suppress incident vertebral fractures in patients with postmenopausal osteoporosis. Mori et al. [23] recently reported the cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan using a Markov microstimulation model [24]. They concluded that denosumab is superior to alendronate from the viewpoint of cost-effectiveness. However, their study was performed not in a real-world but among hypothetical community-dwelling cohorts. We prospectively calculated the costs for each drug to suppress incident vertebral fracture in 30 elderly patients with severe osteoporosis in the real-world. The expenses for each case included additional therapeutic fee for incident vertebral fracture. Clinician should consider the total cost of treatment including the drug fee and additional medical fee following vertebral fracture. The follow-up period after prescribing drugs was only 72 weeks in this study because of limitation of the weekly use of PTH. Patients in this study might encounter incident vertebral fracture after 72 weeks. A longer follow-up survey is necessary to determine the true cost-effectiveness of the drugs evaluated in this study.

Competing Interests

The authors declare that there are no conflicts of interest on this study.

Approval code issued by the IRB: No 86 of Ethical institution of Imakiire General Hospital

Authors' Contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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