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Cost-Effectiveness of Zoledronic Acid to Prevent and Treat Postmenopausal Osteoporosis in Comparison with Routine Medical Treatment

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Abstract

Introduction: Fractures caused by osteoporosis are prevalent among elderly females, which reduce quality of life significantly. This study aimed at comparing cost-effectiveness of Zoledronic acid in preventing and treating post-menopause osteoporosis as compared with routine medical treatment.

Methods: This cost-effectiveness study was carried out retrospectively from the Ministry of Health and insurance organizations perspective. Costs were evaluated based on the cost estimation of a sample of patients. Outcomes were obtained from a systematic review. The Cost-Effectiveness Ratio (CER) and incremental cost-effectiveness ratio (ICER) for outcome of femoral neck Bone Mineral Density (BMD), hip trochanter BMD, total hip BMD and lumbar spine BMD and cost-benefit of consuming Zoledronic Acid were calculated for fracture outcome obtained from reviewing hospital records.

Results: The results and the ICER calculated for study outcomes indicated that one percent increase of BMD on femoral neck BMD requires further cost of $386. One percent increase of BMD on hip trochanter BMD requires further cost of $264. One percent increase of BMD on total hip BMD requires further cost of $388, one percent increase of BMD on lumbar spine BMD requires further cost of $347. The Cost Benefit Analysis (CBA) calculated for vertebral and hip fracture, non-vertebral fracture, any clinical fracture, and morphometric fracture for a 36-month period were about 0.82, 0.57, and 1.06, respectively. Vertebral and hip fractures, and non-vertebral fractures or any clinical fracture for a 12-month period were calculated as 1.14 and 0.64, respectively. In other words, Zoledronic acid consumption approach is a cheaper and better approach based on an economic assessment, and it can be considered as a dominant approach.

Conclusion: According to the cost-effectiveness of zoledronic acid in the prevention and treatment of osteoporosis in women, despite the costs, it is recommended that insurance coverage for the drug should be considered in the period after menopause and the benefits of this drug. This can reduce the costs imposed on the patients and also it can reduce the economic burden on the community, particularly as a result of the fracture.

Keywords: Cost-effectiveness, Cost-benefit, Zoledronic acid, Osteoporosis, Postmenopausal

1. Introduction

Postmenopausal osteoporosis is a major problem of public health that leads to increasing skeletal fragility and consequently, increased risk of fracture (1). There are about 200 million females diagnosed with osteoporosis across the world, and it caused 9 million fractures in 2000 (2). About 1.5 million fractures occur due to osteoporosis in the

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USA (3). Fractures caused by osteoporosis are the major causes of deaths in elderly females, which reduce quality of life significantly (4). The current direct medical costs related to osteoporosis in the USA are estimated to be 13.7-20.3 billion dollars (5). It is estimated that most females are diagnosed with osteoporosis in hips, lumbar spine, wrists, and femur over time and during postmenopausal period (6). As reported by Endocrines and Metabolism Research Center of University of Tehran, about 34 thousand years of the country's useful life is lost due to osteoporosis and it seems that its prevalence rate is increasing among females (7). The main goal in the treatment of those who are suffering from osteoporosis is preventing bone fractures. The drugs are approved to treat or prevent osteoporosis which can reduce bone fractures. Oral bisphosphonates have been the primary choice for treatment and prevention of osteoporotic fractures. However, the use of oral bisphosphonates, especially in the elderly, has been limited by their side effects and method of administration thus compromising their persistent use (8). Despite efficacy of bisphosphonates near 50% of patients within the first year discontinue using their prescribed drug or continue it inappropriately. Poor compliance is associated with negative outcomes, including increased fracture risk. Intravenous bisphosphonates avoids the gastrointestinal intolerance and the complex dosing instruction of the oral bisphosphonates ensuring full compliance which may provide improved efficacy (9). Zoledronic acid is a nitrogen-based bisphosphonate (10), and was approved for treating postmenopausal osteoporosis in females in August 2007 and osteoporosis in males in December 2008 (11). Every year, numerous new drugs are introduced into the pharmaceutical markets around the world. In general, the therapeutic efficiency of a drug is not satisfactorily defined at the time of its approval by the health authorities (12). Policy makers look for cost-effective treatments, pharmacoeconomy is an assessment tool that uses techniques such as CUA, CEA to evaluate the costs versus the consequences of the use of special medical treatments (13). Health centers and physicians have already prescribed Zoledronic acid for patients with osteoporosis. In Iran, the drug is consumed for treating postmenopausal osteoporosis; however, it has not been covered by the main health insurance companies of the country. Therefore, patients are often required to pay the total price of the drug. Furthermore, the high cost of the drug, especially the imported type, and weakness of public sector resources in Iran necessitate a comprehensive evaluation of the drug and its related diagnosis tests. However, without the implementation of such studies it was not clear whether health resources are properly spent or not. In fact, the results of the assessment of economic and social indicators, in other words, Health Technology Assessment (HTA) of the drug, can be used as one of the main inputs of evidence-based protocols to manage the disease. As no study has ever been conducted on cost-effectiveness of the drug in Iran, this study attempted to examine cost-effectiveness of Zoledronic acid in preventing and treating postmenopausal osteoporosis and compare its cost-effectiveness with routine medical treatment.

2. Material and Methods

2.1. Research design

This study, considered as economic assessment and assessment of health technology, is a synthetic research. The perspective of this study to estimate the cost-effectiveness of the zoledronic acid, was assumed the perspective of the ministry of health and insurance organizations, which is based on cost data from the Ministry of Health as the main aspect responsible for the health system and insurance organizations. Zoledronic acid was considered as an intervention and placebo was considered as the alternative that the intervention is compared with. The time frame of the study was considered 12 and 36 months.

2.2. Method to Collect Cost Data

Direct costs (appointments, hospitalizations, drugs, and diagnosis tests) were considered in costs evaluation. Costs collection strategy through bottom-up estimation method was utilized for costs evaluation based on cost evaluation of a sample of patients. The strategy employed for calculating drug cost was based on the dose consumed by a patient during the relevant period and cost of any dose. Cost evaluation was estimated for the costs related to disease not the patient, as it is difficult to divide the problems related to a patient and the problems caused by a disease. The costs calculated here include direct medical costs, which are as follows:

2.2.1. Medical records of the patients with osteoporosis referred to offices of rheumatology specialists in Qazvin were used for obtaining the data required on the direct medical costs including costs for outpatient appointments, hospitalizations, drugs, diagnostic tests, tests, and bone densitometry.

2.2.2. Zoledronic acid consumption rate was obtained through drugstores distributing it in Qazvin by reviewing resources, clinical guide, and drug cost in Iran. As Zoledronic acid is injected annually, drug cost should be multiplied by one for calculating its cost for 12 month for the intervention group (those consumed Zoledronic acid), and it should be multiplied by 3 for calculating its cost for 36 months. Drug cost of the control group (the group receiving placebo) was considered zero.

2.2.3. A 6-hour hospitalization is needed for injection of Zoledronic acid. The hospitalization cost obtained from one of hospitals in Qazvin was multiplied by one for calculating cost of 12 months and it was multiplied by 3 for calculating cost of 36 months. Hospitalization cost was also considered zero for the group receiving placebo.
2.2.4. Outpatient appointment cost was obtained with respect to the annual visits of the patients by a specialist physician. The cost of each appointment was multiplied by one for 12 months and it was multiplied by 3 for 36 months.
2.2.5. Test cost obtained through a diagnostic test for both 12 and 36 months was multiplied by one to calculate cost of tests including calcium test, which is performed once before starting treatment. To calculate cost of bone density test for 12 months that is performed for these patients in Iran once every two years, the test cost obtained from one of the centers in Qazvin that performs the test was multiplied by 0.5. Then it should be multiplied by 1.5 for 36 months.
2.2.6. The cost to see the test results was calculated as a period of each test explained above.
2.2.7. Finally, total cost for 12- and 36-month consumption of Zoledronic Acid was calculated by adding all the above items.

2.3. Calculations

For calculating mean of cost for a fracture, 50 hospitalization records of patients with different fractures including hands, legs, hips, femurs etc., hospitalized in Shahid Rajaei Hospital and Zakaria Razi hospitals in Qazvin were selected randomly, studied, and mean of cost of one fracture was obtained. Estimation of efficiency, which was made by calculating cost-effectiveness and cost-benefit, cost of imported drug in U.S. dollar in 2013 and based on Cost effectiveness Ratio (CER) and Incremental Cost effectiveness Ratio (ICER), is as follows:
2.3.1. For calculation of CER as per cost / outcome formula, we need to estimate costs and outcomes in the intervention and control groups. The Method of costs calculation was explained above. The outcomes were obtained by systematic review of resources including femoral neck BMD, hip trochanter BMD, total hip BMD and lumbar spine BMD. It should be noted that the costs were calculated both for 12 months and 36 months, as the outcomes were reported based on 12 months in some studies and 36 months in other studies, used for reviewing resources. CER was once calculated by considering the numerical difference of outcomes and once by considering the percentage difference of outcomes.
2.3.2. ICER was calculated by the numerical difference of outcomes and percentage difference of outcomes between the intervention and control groups as the following formula: ICER = Difference of costs in intervention and control group / Difference of outcomes in intervention and control group. Cost-benefit of Zoledronic acid consumption can be calculated by fracture outcome report as 12-month and 36-month forms in studies for 12 and 36 months as follows: CBA of Cost Benefit = Cost of the drug under study - Cost of placebo / Cost of fracture in intervention group-Cost of fracture in placebo group. Fracture percentage in intervention group (the patients consuming Zoledronic acid) and control group (the group receiving placebo) was obtained from a systematic review of resources. Mean cost of a fracture can be calculated as stated earlier by reviewing the patients' records. Total cost of fracture in the intervention group was obtained by multiplying the fracture percentage in the intervention group by mean cost of a fracture. Likewise, total cost of fracture in the control group can be obtained by multiplying fracture percentage in the control group by mean cost of a fracture. In the next stage, the cost of the drug under study (Zoledronic acid) including the cost of Zoledronic acid, the cost of 6-hour hospitalization for its injection, and the cost of placebo (zero) were calculated. Then the difference of fracture cost in both groups should be calculated. Finally, the cost-benefit of Zoledronic acid consumption was obtained by dividing these two values as per the above-mentioned formula.

3. Results

3.1. Calculation of CER with respect to numerical and percentage differences of outcomes

On femoral neck BMD, CERs were calculated as $3,764 and $322 with respect to the numerical difference of outcomes in the intervention group and in the control group (placebo), respectively. These results showed that the mean of cost in the intervention group (Zoledronic acid) was higher. On hip trochanter BMD, total hip BMD and lumbar spine BMD, mean of cost in the intervention group (Zoledronic acid), as shown by the Table 1, was higher. On femoral neck BMD, CERs were calculated as $517 and $189 with respect to the percentage difference of outcomes in the intervention group and in the control group (placebo), respectively. This implies that the mean of cost in the intervention group (Zoledronic acid) is higher. On hip trochanter BMD, total hip BMD and lumbar spine BMD, mean of cost in the intervention group (Zoledronic acid), is higher as shown by the calculations of Table 2.

Table 1. Calculation of CER with Respect to Numerical Difference of Outcomes

Variables	Intervention group (ZOL)			Control group (placebo)		
	Cost	Outcome (Numerical)	CER	Cost	Outcome (Numerical)	CER
Femoral neck BMD	2144	0.5695	3764.64	174.1	0.5395	322.79
Hip trochanter BMD	2144	0.196	10938.59	174.1	0.176	989.45
Total hip BMD	2144	0.705	3041.08	174.1	0.661	263.45
Lumbar spine BMD	2144	0.167	12838.11	174.1	0.1564	1113.45

Table 2. Calculation of CER with Respect to Percentage Difference of Outcomes

Variables	Intervention group (ZOL)			Control group (placebo)		
	Cost	Outcome (Percentage)	CER	Cost	Outcome (Percentage)	CER
Femoral neck BMD	2144	4.145	517.24	174.1	-0.92	-189.29
Hip trochanter BMD	2144	3.27	655.65	174.1	-3.26	-53.42
Total hip BMD	2144	3.53	607.36	174.1	-1.54	-113.08
Lumbar spine BMD	2144	5.98	358.52	174.1	0.31	561.75

3.2. Calculation of ICER of outcomes with respect to numerical difference of outcomes

Calculation of ICER indicated that on femoral neck BMD, one unit increase in BMD requires spending further costs of $386. On hip trochanter BMD, total hip BMD, lumbar spine BMD one unit increase in BMD requires spending further costs of $264, $388 and $347, respectively.

3.3. Calculation of ICER of outcomes with respect to percentage difference of outcomes

Based on the results of this study, one unit increase in femoral neck BMD requires spending further costs of $65,660. On hip trochanter BMD, total hip BMD and lumbar spine BMD, one unit increase in BMD requires spending further costs of $98,491, $44,768 and $185,832, respectively.

3.4. Calculation of the 12-month CBA

The calculated CBA for vertebral and hip fracture was 1.14 and fracture cost in the intervention group is $574 lower than the placebo group. Therefore, the imposed cost was also 1.14 times lower for obtaining a higher outcome (0.6% fewer fractures). The calculated CBA for Non-vertebral fracture and any clinical fracture equals 0.64, and fracture cost in the intervention group was $1,015 lower than the placebo group. Therefore, the imposed cost was 0.64 times lower for obtaining a higher outcome (1.2% fewer fractures). The calculated CBA for all fractures is -0.13 and fracture cost in the intervention group was $4,710 lower than the placebo group. Therefore, the imposed cost was 0.13 times lower for obtaining a higher outcome (0.8% fewer fractures).

3.5. Calculation of the 36-month CBA

The calculated CBA for vertebral and hip fracture was 0.82 and fracture cost in the intervention group was $2,402 lower than the placebo group. Therefore, for obtaining a higher outcome (2.7% fewer fractures), the imposed cost was also 0.8 times lower. The calculated CBA for Non-vertebral fracture and any clinical fracture equals 0.57, and fracture cost in the intervention group was $3,436 lower than the placebo group. Therefore, for obtaining a higher outcome (3.9% fewer fractures), the imposed cost was 0.57 times lower. The calculated CBA for morphometric fracture was 1.06 and fracture cost in the intervention group was $1,855 lower than the placebo group. Therefore, for obtaining a higher outcome (2.1% fewer fractures), the imposed cost was 1.06 times lower. The calculated CBA for all fractures is -0.76 and fracture cost in the intervention group was $2,561 lower than the placebo group. Therefore, for obtaining a higher outcome (3% fewer fractures), the imposed cost was 0.76 times lower.

4. Discussion

Osteoporosis is one of the disasters of the recent century. In 1991, the WHO recognized osteoporosis, cancer, Myocardial infarction, and cerebrovascular accident as the four main enemies of humanity (14). As osteoporosis is related to fracture, it should be considered as one of the major problems of health and treatment authorities in every country (15). Population aging has made osteoporosis appear as an important aspect of public health in developing countries like Iran (16). It should be noted that osteoporosis is a multifactorial disease so that preventing and treating osteoporosis is very complicated (17). Several drugs which may reduce fractures have been approved for preventing or treating osteoporosis. (18). Zoledronic acid was approved for preventing and treating postmenopausal osteoporosis (3). It is also used for treating postmenopausal osteoporosis in Iran, but it is not covered by the main

health insurance companies of the country. Therefore, patients are often required to pay the total price of the drug. High cost of the drug, especially the imported type, and weakness of public sector resources in Iran necessitated a comprehensive evaluation of the drug and its related diagnosis tests. No study has ever been conducted in Iran on the economic assessment of Zoledronic acid in preventing and treating postmenopausal osteoporosis; therefore, this study aimed at comparing its cost-effectiveness with routine medical treatment in preventing and treating postmenopausal osteoporosis. As the outcomes used in this analysis were reported on a 12-month and 36-month basis, the applied model was also on a 12-month and 36-month basis. In this study, the costs were also calculated first. The calculated costs for the 36-month period in the intervention group (Zoledronic acid) and the control group (placebo) were $2,143.9 and $174.1, respectively. The costs for a 12-month period for the intervention group and control group were $727 and $70.5, respectively. Effectiveness unit was considered as femoral neck BMD, hip trochanter BMD, total hip BMD, and lumbar spine BMD, and different bone fractures, with their values shown by Table 1 and 2. CER and ICER of outcomes were calculated once by considering the numerical difference of the outcomes under study and once by considering percentage difference of the outcomes as follows: On femoral neck BMD, CERs of the intervention group and control group (placebo) were $3,764 and $322, respectively. Mean cost in the intervention group (Zoledronic acid drug) was higher, but it had higher outcomes in comparison with the control group. The CERs calculated for other BMDs including hip trochanter BMD, total hip BMD and lumbar spine BMD, such as femoral neck BMD, their values in U.S. dollar, the mean cost of the intervention group (Zoledronic acid drug) was higher, but it had higher outcomes in comparison with the control group. ICER was calculated by considering numerical difference of outcomes as follows: On femoral neck BMD, one unit increase in BMD requires spending $65,660. On hip trochanter BMD, one unit increase in BMD requires spending $98,491. On total hip BMD, one unit increase in BMD requires spending $44,768. On lumbar spine BMD, one unit increase in BMD requires spending a further $185,832. The CERs were obtained with respect to the percentage difference of the outcomes, as follows: On femoral neck BMD, CERs of the intervention group (Zoledronic acid drug) and the control group (placebo) were $517 and $189, respectively; however, the outcome of the intervention group was higher than the control group. On the CERs calculated for other BMDs including hip trochanter BMD, total hip BMD, and lumbar spine BMD, mean of cost in the intervention group (Zoledronic acid drug) was higher, but its outcome was higher than the control group. Table 2 shows the values of CERs in $. ICERs of the outcomes were calculated with respect to percentage difference of outcomes as follows: On femoral neck BMD, one percent increase in BMD requires spending further $386.2. On hip trochanter BMD, one percent increase in BMD requires spending further $264. On total hip BMD, one percent increase in BMD requires spending further $388.5. On lumbar spine BMD, one percent increase in BMD requires spending further $347.4. The final outcome used for determining effectiveness unit was the calculation of rate and cost of fracture in the intervention group and control group. It was used because this outcome could be expressed in currency through CBA that measures cost and benefits of programs as a similar unit – usually money – assuming that other outcomes – including BMD - are equal or difference of outcomes are automatically reflected in some fractures. Since fracture outcome was reported as 12-month and 36-month periods here, CBA of Zoledronic acid was also calculated for these two periods. The calculated CBA (36 month) for vertebral and hip fractures was 0.82 which implies that the imposed cost was 0.8 times smaller for obtaining a higher outcome. In other words, based on the economic assessment, consumption of the Zoledronic acid drug was a cheaper and better approach and it can be considered as a dominant approach. The calculated CBA (36 month) for non-vertebral fracture and any clinical fracture was 0.57 which implies that the imposed cost was lower for obtaining an outcome higher than 0.57. In other words, based on the economic assessment, consumption of the Zoledronic acid drug was a cheaper and better approach and it can be considered as a dominant approach. The calculated CBA (36 month) for morphometric fracture was 1.06 which implies that the imposed cost was lower for obtaining an outcome higher than 1.06. In other words, based on the economic assessment, consumption of the Zoledronic acid drug was a cheaper and better approach and it can be considered as a dominant approach. The calculated CBA (36 month) for all fractures was -0.76 which implies that the imposed cost was lower for obtaining an outcome higher than 0.76. In other words, based on the economic assessment, consumption of the Zoledronic acid drug was a cheaper and better approach and it can be considered as a dominant approach. The calculated CBA (12 month) for vertebral and hip fractures was 1.14 which implies that the imposed cost was 1.14 times smaller for obtaining a higher outcome. Furthermore, the calculated CBA (12 month) for non-vertebral fracture and any clinical fracture was 0.64, which implies that the imposed cost was lower for obtaining an outcome higher than 0.64. The calculated CBA (12 month) for all fractures is -0.13 which implies the imposed cost was lower for obtaining an outcome higher than 0.13. In other words, based on the economic assessment, consumption of the Zoledronic acid drug was a cheaper and better approach and it can be considered as the most dominant approach in all above cases. In 2010, Patrice Fardellone et al. proved that the overall medical cost of Zoledronic acid was lower than the current treatment strategies in any clinical fractures. The obtained cost was £1,178 versus £1,440 for vertebral fractures,

£1,146 versus £1,235 for Non-vertebral fractures, and £1,087 versus £1,251 for hip fractures, respectively. Therefore, consumption of Zoledronic acid has been more effective than the current treatment strategies in any clinical fractures (1). In 2004, Shelby D. Reed et al. obtained the mean of direct costs of $5,365 for the patients diagnosed with prostate cancer consuming Zoledronic acid and direct costs of $5,689 for the patients receiving placebo (cost difference= $324). The nominal cost per skeletal complication avoided was $12,300 and the cost per additional patient free of skeletal complications was $51,400. Cost per quality adjusted life-year (QALY) was calculated in the value of $159,200. CER for bisphosphonates were higher than commonly cited thresholds for conferring cost-effectiveness (20). The study of M. Botteman et al. on patients diagnosed with breast cancer with bone metastases in 2006, showed that all bisphosphonates (oral ibandronate, injection ibandronate, pamidronate), as compared with no therapy, were cost-effective with costs of £2,400 for any obtained QALY (21). The highest rate of cost-effectiveness belonged to Zoledronic acid and oral ibandronate, pamidronate, and injection ibandronate were ranked the second, the third, and the fourth, respectively. Treatment using bisphosphonates had a high rate of cost-effectiveness for preventing SREs in breast cancer patients. They also demonstrated that treatment of patients diagnosed with breast cancer with bone metastases by Zoledronic acid, improves outcomes and saves on costs (20). The study of M. Botteman et al. on patients diagnosed with bone metastases secondary to advanced renal cell carcinoma in 2011 showed that the patient who received Zoledronic acid experienced 1.07 fewer skeletal-related events (SREs) than patients on placebo. Cost for any QALY obtained for the Zoledronic acid patients versus the placebo group patients was below £30,000 for any obtained QALY in 93-94% of the multivariate sensitivity analysis. As a result, Zoledronic acid led to save costs and increased quality of life as compared with placebo in the above patients in France, Germany, and England (22). Similar to many studies, the present study had limitations, weaknesses, and strengths. One limitation was the difficulty of obtaining required information, because the drug was not widely used for treating osteoporosis when the study was being conducted. The second limitation was accessibility to reliable databases for many variables under study in the developing countries, and Iran is no exception. We had to use a survey study on population of patients and outpatients and hospitalization records to evaluate the costs of the disease. One of the strengths was to carry out the study in the country of Iran for the first time. Another strength is the calculation of cost-benefit in addition to cost-effectiveness for economic assessment of the drug under study.

5. Conclusions

This research has been conducted to examine the cost-effectiveness of Zoledronic acid in preventing and treating postmenopausal osteoporosis as compared with the routine medical treatment. Prevention of fractures is the main objective in treating those diagnosed with osteoporosis. Fractures caused by osteoporosis impose heavy costs on an individual and society. Overall results of the study indicated that with respect to the cost-effectiveness of Zoledronic acid in preventing and treating post-menopause osteoporosis and the interests gained from the drug, despite its costs and due to the high costs paid by patients and no insurance coverage for that, an insurance coverage should be considered for the drug. It means that it will reduce the costs imposed on patients and the economic burden on the society, especially due to fractures. As all studies compiled in this study to determine the cost effectiveness of zoledronic acid, the drug was compared with placebo, another method that is suggested here is determining the cost benefit with indirect comparisons using studies that examined strategies for zoledronic acid compared with other drugs from bisphosphonates groups.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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