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Original Article

Osteoporotic Fractures among Selective Estrogen Receptor Modulator Users in South Korea: Analysis Using National Claims Database

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Background: We evaluated (1) compliance with selective estrogen receptor modulator (SERM) use in postmenopausal women; and (2) the risk of osteoporotic fractures according to compliance and other patient characteristics. **Methods:** National claims data of postmenopausal women from January 2013 to December 2014 were reviewed. Demographics, comorbidities, type of medical institution, and patient compliance were investigated. Compliance was measured according to medication possession ratio (MPR) and the patients were classified into compliant (MPR ≥80%) or non-compliant (MPR <80%) groups. Osteoporotic fractures were followed up for 2 years after prescription. **Results:** Among 15,166 postmenopausal women, 4,130 were categorized as compliant. Osteoporotic fractures were confirmed in 669 patients. The hip fracture rate in the non-compliant group (0.39%) was marginally higher than that in the compliant group (0.36%; $P=0.06$). Compared to age 50 to 54 years, age 55 to 59 years showed protection against fractures (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.379–0.857; $P=0.007$), while those over 70 years showed a higher risk of fractures (HR, 2.035; 95% CI, 1.485–2.789; $P<0.0001$ for age 70–74 years; HR, 2.197; 94% CI, 1.588–3.041; $P<0.0001$ for age 75–79 years; and HR, 3.53; 95% CI, 2.493–4.999; $P<0.0001$ for age ≥80 years). Patients with mild (HR, 1.29; 95% CI, 1.088-1.530; $P=0.0034$) and moderate (HR, 1.286; 95% CI, 1.002–1.652; $P=0.0486$) comorbidities were associated with higher risks of fractures compared to those without comorbidities. **Conclusions:** Among postmenopausal women with osteoporosis, only 27.2% complied with SERM therapy. A marginal difference in hip fracture rate was observed between the compliant and non-compliant groups. Older age and severe comorbidities were associated with higher risks of osteoporotic fractures.

Key Words: Compliance · Medication adherence · Osteoporosis · Osteoporotic fractures · Selective estrogen receptor modulators

INTRODUCTION

A rising socioeconomic burden of osteoporosis and osteoporotic fractures have been recently recognized as a serious threat to global public health. It is estimated that half of the women and one in 5 men over 50 years of age are likely to suffer an osteoporotic fracture at least once in lifetime.[1] The number of osteoporotic

fractures in the European Union was expected to increase from 3.5 million cases in 2010 to approximately 4.5 million cases in 2025.[2] The features of osteoporosis as a chronic disease underlines the importance of long-term medical therapy.

Osteoporosis medications are categorized into anti-resorptive drugs and anabolic drugs. Selective estrogen receptor modulators (SERMs) are drugs that modulate estrogen receptor with tissue selectivity. As anti-resorptive drugs in anti-osteoporotic medication, SERMs are commonly used in postmenopausal women. Currently, raloxifene, lasofoxifene, and bazedoxifene are approved by the US Food and Drug Administration as treatment for osteoporosis. Raloxifene was proven to be effective in reducing vertebral fractures in postmenopausal women with osteoporosis.[3,4] Lasofoxifene was effective in reducing the vertebral fracture risks up to 42% in a 5-year randomized clinical trial (RCT) on postmenopausal women.[5] The efficacy of bazedoxifene was proven to be comparable to that of raloxifene in fracture reduction.[6]

Even with the advancement of diverse medications to treat osteoporosis, poor adherence to medications remains as a vital issue in deterring the treatment effectivity. It was reported one-year compliance was lower than 25% in all osteoporosis therapies, leaving patients with higher risk for fractures and public health costs.[7] Among the antiresorptive osteoporosis drugs, there are numerus studies on compliance of BP,[8-14] whereas, there are relatively few studies on compliance of SERM.[3,15,16]

The primary objective of this study was (1) to evaluate the compliance to SERM medication in postmenopausal women with osteoporosis; and (2) to determine the risk of osteoporotic fractures according to the compliance or other patient characteristics, using the Korean National Health Insurance (KNHI) claims database.

METHODS

1. Source of database

This was a retrospective registry study using a claims data from the KNHI database. All medical claims from entire South Korean institutions are reported to KNHI. The integrated KNHI data contain demographics, institutional information, comorbidity, and prescriptions of all postmenopausal osteoporotic patients in South Korea. All information was submitted in form of the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic and procedural codes.

This study was approved by the institutional review board (IRB) of Chung-Ang University Hospital (IRB no. 1903-002-16253).

2. Patients

To evaluate the compliance to SERM medications and subsequent fracture risk, patients who were prescribed with SERMs for osteoporosis medication at least once from January 2013 to December 2014 were searched in the Health Insurance Review and Assessment Service (HIRA) database. The first prescription date of SERMs during the study period was defined as the index date. Patients with following conditions were excluded: (1) patients who are under 50 years of age; (2) patients who were not treated with bisphosphonates (BPs), calcitonin, or SERMs within 1 year before the index date; (3) patients who were treated with BPs or calcitonin during the study period; (4) patients who were diagnosed as cancer or Paget's disease; (5) patients who died within 1-year after index date; (6) patients who suffered osteoporotic fractures within 2 years before or 1 year after the index date; and (7) patients who lacked basic demographic data. BPs and calcitonin treatments during the study period or underlying cancer or Paget's disease could be a confounding factor in assessing the fracture risk regardless to the SERM compliance.[17,18] Osteoporotic fractures that occurred within 2 years before the index date is itself a independent risk factor for the secondary osteoporotic fracture.[19] Osteoporotic fractures within 1 year after the prescription of SERMs does not represent the fracture risk related to SERMs but rather it is related to the prior medication.[20]

The basic demographic data was collected. Age groups were stratified with 5-year intervals into 7 groups from 50 years of age to ages over 80 years. Information on the medical institutions where SERMs were prescribed at the index date was also collected. The type of medical institution was classified into tertiary hospitals (number of beds $\geq$500, number of departments $\geq$9), general hospitals (number of beds $\geq$100, number of departments $\geq$7), hospitals (number of beds $\geq$30), and clinics (number of beds $<$30). Underlying comorbidities of included patients were stratified using Charlson's comorbidity index (CCI).[21]

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3. Operational definition and outcome measures

The diagnosis of osteoporosis was specified as ICD-10 codes, M80*, M81*, or M82*. The SERMs used in South Korea during the study period included raloxifene and bazedoxifene. Anatomical Therapeutic Chemical code of G03XC indicated SERMs (G03XC01 as raloxifene and G03XC02 as bazedoxifene). Osteoporotic fractures were defined with ICD-10 codes of hip fractures (S72.0, S72.1), vertebral fractures (S22.0, S22.1, S32.0, S32.7, T08.0),[22] distal radius fractures (S52.5, S52.6),[23] and proximal humerus fractures (S42.2, S42.3).[24] The surveillance of osteoporotic fractures was conducted until 2 years after the prescription date.

The compliance to SERM medications were measured with medication possession ratio (MPR), which is the ratio of available doses of medication against the expected doses over a fixed period of time.[25] Patients were categorized into compliant group (MPR ≥80%) and non-compliant group (MPR <80%) in one year after the index date. A refill prescription was considered to have been continued without a break if there was a continuous gap of 30 days or more between the expected refill date and the actual refill date during the study period.

4. Statistical analysis

All patient data and osteoporotic fractures were compared between compliant group and the non-compliant group. Multivariable Cox proportional hazard models were used to analyze the hazard ratios of osteoporotic fracture occurrence between different compliance, age groups, type of institutions, and CCIs. All statistical analyses were carried out using SPSS for Windows software (version 25.0; SPSS Inc., Chicago, IL, USA). It was considered statistically significant when *P* was less than 0.05.

The approval of design and protocol of this study was exempted by the Institutional Review Board of our hospital with waived informed consent from all the involved patients as it was retrospective registry study.

RESULTS

1. Patient demographics

A total of 145,923 patients who were prescribed with SERMs for osteoporotic treatment from January, 2013 to December, 2014 were identified in KNHI database. After the exclusion process, 15,166 patients (all women) were included (Fig. 1).

Among the 15,166 included patients, compliant group accounted for 4,130 patients (27.2%) while remaining 11,036 patients (72.8%) were non-compliant. The distribution of age, level of medical institution, and comorbidities between 2 groups are summarized in Table 1.

The most common age group for SERM prescription was 65 to 69 years both in compliant group and noncompliant group. SERMs were most commonly prescribed from clinics followed by general hospitals, hospitals, and tertiary hospitals in both groups. More than half of the included patients had no comorbidities and less than 5% of patients had severe comorbidities (CCI ≥3).

2. Osteoporotic fractures

There was total 669 (4.41%) osteoporotic fractures that occurred during the study period. Although osteoporotic

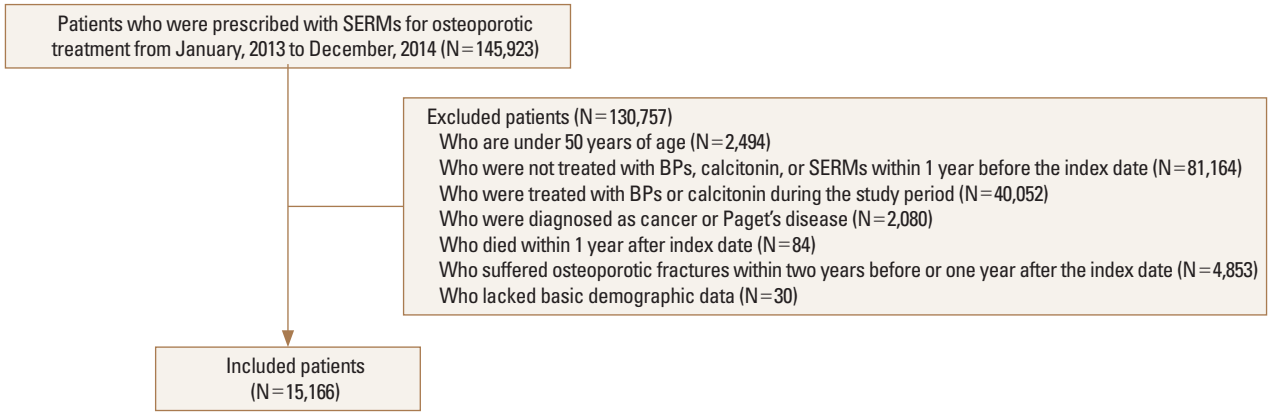

Fig. 1. Flowchart of included patients. SERMs, selective estrogen receptor modulators.

Table 1. Patient characteristics of compliant and non-compliant group

Characteristics	Non-compliant group (N=11,036)	Compliant group (N=4,130)	*P*-value
Age (yr)			<0.001
50-54	961 (8.7)	394 (9.5)	
55-59	1,673 (15.2)	673 (16.3)	
60-64	1,951 (17.7)	765 (18.5)	
65-69	2,313 (21.0)	906 (21.9)	
70-74	1,884 (17.1)	681 (16.5)	
75-79	1,454 (13.2)	437 (10.6)	
≥80	800 (7.2)	274 (6.6)	
Institutions			<0.001
Tertiary hospital	1,292 (11.7)	881 (21.3)	
General hospital	3,012 (27.3)	1,179 (28.5)	
Hospital	2,834 (25.7)	763 (18.5)	
Clinic	3,898 (35.3)	1,307 (31.6)	
CCI			0.722
0	6,292 (57.0)	2,347 (56.8)	
1	3,235 (29.3)	1,191 (28.8)	
2	1,004 (9.1)	389 (9.4)	
≥3	505 (4.6)	203 (4.9)	

CCI, Charlson's comorbidity index.

Table 2. Osteoporotic fractures after selective estrogen receptor modulator treatment

Location	Non-compliant group (N=11,036)	Compliant group (N=4,130)	*P*-value
Hip (N=58)	43 (0.4)	15 (0.4)	0.06
Spine (N=437)	331 (3.0)	106 (2.6)	0.16
Distal radius (N=143)	104 (0.9)	39 (0.9)	0.99
Proximal humerus (N=31)	23 (0.2)	8 (0.2)	0.86
Total (N=669)	501 (4.5)	168 (4.1)	0.21

fracture rate showed higher tendency in the non-compliant group than in the compliant group (4.54 % vs. 4.07 %), the difference was insignificant (*P*=0.21).

The most common location of osteoporotic fracture was spine (2.88%) followed by distal radius (0.94%), hip (0.38%), and proximal humerus (0.2%). This tendency was apparent in both groups. For spine, distal radius, and proximal humerus fractures, the prevalence of osteoporotic fractures was higher in non-compliant group compared to compliant group, but the difference did not reach statistical significance (Table 2). The prevalence of hip fractures was marginally higher in non-compliant group (0.39%) compared to compliant group (0.36%; *P*=0.06).

Table 3. Multivariable Cox proportional hazard model of baseline characteristics for osteoporotic fractures

Baseline characteristics	HR (95% CI)	*P*-value
Compliant group (MPR ≥80) compared to non-compliant group (MPR<80)	0.93 (0.781-1.108)	0.4183
Age group with age 50-54 years as reference		
Age 55-59 years	0.57 (0.379-0.857)	0.007
Age 60-64 years	0.858 (0.601-1.226)	0.4007
Age 65-69 years	1.088 (0.781-1.516)	0.6189
Age 70-74 years	2.035 (1.485-2.789)	<0.0001
Age 75-79 years	2.197 (1.588-3.041)	<0.0001
Age ≥80 years	3.53 (2.493-4.999)	<0.0001
Type of institution with tertiary hospital as reference		
General hospital	0.918 (0.375-2.246)	0.8509
Hospital	1.053 (0.433-2.561)	0.9098
Clinic	0.984 (0.407-2.38)	0.9721
CCI with CCI 0 as reference		
CCI 1	1.29 (1.088-1.53)	0.0034
CCI 2	1.286 (1.002-1.652)	0.0486
CCI ≥3	1.31 (0.953-1.801)	0.0967

MRP, medication possession ratio; HR, hazard ratio; CI, confidence interval.

Among the baseline characteristics, age and CCI was related to osteoporotic fractures (Table 3). With age group 50 to 54 years as a reference, age group 55 to 59 years was protective of fractures (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.379-0.857; *P*=0.007) while fracture risk increased in ages over 70 years (HR, 2.035; 95% CI, 1.485-2.789; *P*<0.0001 for age 70-74 years; HR, 2.197; 95% CI, 1.588-3.041; *P*<0.0001 for age 75-79 years; HR, 3.53; 95% CI, 2.493-4.999; *P*<0.0001 for age ≥80 years). With patients with no underlying comorbidity (CCI, 0) as a reference, those with mild comorbidity (CCI 1; HR, 1.29; 95% CI, 1.088-1.530; *P*=0.0034) and those with moderate comorbidity (CCI 2; HR, 1.286; 95% CI, 1.002-1.652; *P*=0.0486) were related to higher risk of osteoporotic fractures. Other factors such as compliance and type of institutions where the patients were treated were not related to the osteoporotic fracture occurrence.

DISCUSSION

Patients who were compliant to SERM treatment (MPR ≥80%) for 2 years only accounted for 27.2% of total SERM prescribed patients in South Korea. Among the SERM pre-

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scribed population, 4.41% suffered osteoporotic fractures. Compared to non-compliant group, compliant group tend to show lower prevalence of osteoporotic fractures both in total or by subtypes but the difference was marginal in hip and otherwise insignificant. Osteoporotic fractures were less likely to occur in patients with ages of 50 to 54 years and more likely to occur in patients with ages over 70 years and in those with severe comorbidities.

Adherence to osteoporotic medications has been considered as a serious threat to public health. Although Ringe et al. [15] reported the rate of compliant patients of raloxifene, alendronate, and risedronate as 80%, 79%, and 76%, respectively, other studies reported far inferior adherence to osteoporotic drugs. In 2004, McCombs et al. [7] found that 1-year compliance rate was below 25% in 58,109 patients treated with hormone replacement therapies, BPs, or raloxifene. They also reported 1.32% of osteoporotic fracture (categorized into vertebral, hip, Colles, and other fractures) in a year after raloxifene therapy. In 2007, Kothawala et al. [16] conducted a meta-analysis and reported adherence rates ranging from 34% to 53% in 6 studies. Pooled estimates of adherence rate was 53% in 6 months and decreased to 43% for treatments that lasted 7 to 24 months. The authors concluded that nearly 1/3 to 1/2 of osteoporotic patients were not compliant to medication and that nonadherence starts soon after commencement of therapy. Low adherence to drugs are not only limited to SERM therapy, but it is also observed in other osteoporotic medications.[7,16,26,27] The reported MPR of osteoporotic drugs from 2 meta-analyses range from 67% to 68%,[12,16] which is lower than the suggested optimal level of 80%. This is probably because osteoporosis is asymptomatic before the occurrence of consequent osteoporotic fractures, and the direct benefits are difficult to be recognized by patients.

Low compliance to SERM treatment could be related to its form of administration. Commonly given SERMs in South Korea, namely raloxifene and bazedoxifene, are prescribed in once daily oral form. In previous report by Durden et al. [26], compliance of oral agents (20%-31%) were inferior to compliance of injectable agents (34%-41%) in osteoporosis therapy. Interestingly, the authors reported compliance of raloxifene as 36.6% in 12 months and 28.7% in 24 months. [26] Our findings of low compliance in SERM treatment mostly agree with the previous reports with only minor differences in adherence rates which might be affected by the different threshold of MPR - 66%,[28] 75%,[27] 80%. [7,26] - used to dichotomize the compliant and non-compliant groups. However, approaches to increase the low adherence to osteoporotic medications still require further researches. Kripalani and colleagues [29] conducted a systematic review on diverse measures including behavioral or informative interventions suggested to increase the adherence to drugs for chronic conditions. They reported behavioral interventions increased adherence but only few significantly changed the related clinical outcomes.[29] Even with the effective interventions in similar settings in chronic diseases, methods to increase adherence were reported to lack cost-effectiveness.[30,31]

The osteoporosis fracture risks for the compliant and the non-compliant group were 4.07% and 4.57%, respectively ($P=0.21$). In 2006, Huybrechts et al. [32] found that only a quarter of the women on osteoporotic drugs are compliant and the low compliance was associated with 17% increase in the fracture rate. This finding was supported by a meta-analysis by Imaz et al. [12], in which they reported the pooled fracture risk was 46% higher in the non-compliant group. In addition, compliant patients are found to experience 16% to 37% less hospitalization in several studies.[32,33] In our study, difference in the fracture risk according to the dichotomized compliance groups did not reach statistical significance. The low compliance to SERMs might, in fact, affect the fracture risk less compared to low compliance in other osteoporotic drugs, especially denosumab. The rebound phenomenon after denosumab discontinuation has been reported to be associated with almost 5-fold higher risk of vertebral, hip, and other osteoporotic fractures.[34,35] Multiple vertebral fractures, or rebound associated vertebral fractures, are specifically increased in patients who discontinue denosumab even compared to those who were not treated for osteoporosis at all.[36] Although similar phenomenon is observed after SERM discontinuation, the bone loss after cessation was not significantly different from the placebo group.[37,38] Idolazzi et al. [39] suggested that after discontinuation, SERM users with low fracture risk should be reassessed after 1 or 2 years without pharmacologic prevention as BP users, while denosumab users should use BPs after cessation.

The risk of osteoporotic fracture was lower in ages of 50 to 60 years and higher in ages over 70 years. It was also re-

lated to higher comorbidities represented by higher CCIs in this study. These findings align well with the known risk factors of imminent osteoporotic fractures – previous fractures, low BMD, older age, previous falls, comorbidities that affect physical and cognitive functioning.[40-42] In this study, we also evaluated the influence of the level of institutions where the SERMs were prescribed on the subsequent fracture risk, but no significant difference was found. This is in line with the previous reports by Yoon et al. [43] where the knowledge on osteoporosis of prescribers were not related to the level of medical institute. As osteoporotic fracture risk and the knowledge for treatment does not vary among the level of institutions, patients need not be treated from higher level of medical institutions expecting for higher treatment outcomes. Instead, the regular follow-up in clinics and smaller hospitals in the vicinity could be more beneficial.

There are certain limitations in current study. First, difference in osteoporotic fracture risk between 2 groups was marginal in hip and insignificant in other locations. The retrospective sample size analysis on osteoporotic fracture risk in compliant vs. non-compliant group revealed that at least 29,274 patients in each group were required to significantly differentiate between 2 groups ($\alpha=0.05$, $\beta=0.8$). The number of study patients in current study was 11,036 and 4,130 for non-compliant group and compliant group, respectively. When analyzed with the larger population, significant change between 2 groups might be found, especially in hip fractures. Second, data on compliance were derived from claims data involving drug prescription. This approach accompanies the underlying assumption, which patients that fill prescription eventually use the medication. However, patients may not use the drugs prescribed, leading to underestimation or overestimation of the association to fracture risks. Nevertheless, compared to patient self-reported questionnaires where patients might tend to exaggerate the compliance to please physicians, the database-derived approach might have some advantages.[44] Third, data on persistence of the included patients were not available from the database. The notion of adherence usually include both compliance and persistence in numerous studies.[25,45] In further studies, acquiring data on persistence would enable the comparison between adherent group and non-adherent group for more accurate analysis.

CONCLUSION

Among postmenopausal women with osteoporosis, only 27.2% were compliant to SERM therapy from 2013 to 2014 in South Korea. The overall osteoporotic fracture rate within 2 years of SERM prescription was 4.41%. The difference in hip fracture rate showed marginal difference between non-compliant and compliant group. Older age and more severe comorbidities were related to higher risk of osteoporotic fractures.

DECLARATIONS

Acknowledgement

This study was supported by Alvogen Korea.

Ethics approval and consent to participate

The approval of the design and protocol of this study was exempted by the Institutional Review Board of our hospital with waived informed consent from all the involved patients as it was a retrospective registry study.

Conflict of interest

Young-Kyun Lee has been the Editor-in-Chief of the Journal of Bone Metabolism since January 1, 2022, but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported.

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