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Compliance, persistence, and preference outcomes of postmenopausal osteoporotic women receiving a flexible or fixed regimen of daily risedronate: A multicenter, prospective, parallel group study

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Objective: The aim of this study was to examine the level of compliance and persistence in patients with postmenopausal osteoporosis (OP) receiving daily risedronate (5 mg) with either fixed dosing of three different timing regimens (A: before breakfast; B: in-between meals; C: before bedtime) or with flexible dosing and the effect on urinary N-terminal telopeptide of Type 1 collagen (NTX-1).

Methods: The study included 448 patients with postmenopausal OP. Patients were randomly assigned into six treatment groups each with a permutation of the treatment sequence (ABC, BCA, etc.) in the crossover phase (3x1 week) and randomized to 23 weeks of either the daily flexible (either regimen A, B or C) or fixed timing (only regimen A, B, or C) in the patient's preference phase. Urinary NTX-1 was tested.

Results: A total of 433 patients participated in the patient's preference phase (49.7% preferred flexible and 50.3% fixed timing). There was no significant difference between the proportion of responders who were both compliant and persistent in the flexible (54.4%) and fixed regimens (53.7%) (p=0.8803). A significant difference between the flexible and fixed regimens was seen in persistence in favor of the flexible regimen (p=0.0306). There was no significant difference between the flexible and fixed regimens in terms of compliance (p=0.4611). Change in urinary NTX-1 did not show any difference between the two regimens. At the final visit, 51% of patients in the flexible and 55% in the fixed regimen group considered the used risedronate regimen as excellent or very good (p=0.1440).

Conclusion: A flexible dosing with daily risedronate appears be a valuable option in terms of compliance and persistence for patients with postmenopausal OP.

Key words: Compliance; daily fixed dosing; daily flexible dosing; osteoporosis; persistence; risedronate.

Medications for the treatment of postmenopausal osteoporosis (OP) require years of persistence and proper compliance to successfully achieve the goal of reducing fracture risk. Increased fracture risks of 30%[1] or 46%[2] with noncompliance and 30% to 40% with non-persistence[1] have been reported in systematic reviews and meta-analyses dealing with patients receiving OP medications. Therefore, patient compliance and persistence in taking of OP medications remain an important issue that may affect treatment efficacy. However, compliance and persistence with OP treatments are poor,[3] with compliance rates ranging from 0.46 to 0.64 as assessed using the medication possession ratio (MPR) and persistence rates for one year ranging from 26.1% to 55.7% for patients receiving daily bisphosphonates.[4] According to a survey investigating why OP patients do not continue with bisphosphonates, side effects and inconvenience-related reasons including the strict regimen that interferes

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with eating and drinking as well as with the taking of other medications, were reported to be among the most commonly-referred factors.[5] Among bisphosphonates, risedronate at a daily dose of 5 mg has been shown to reduce the risk of fracture,[6-10] and can be administered in one of three different timing regimens. In addition to the traditional before breakfast dosing of other oral bisphosphonates, daily risedronate can also be administered in a flexible way allowing patients to choose to take their medications 'in-between meals' or 'before bedtime' freely every day. Three studies exploring the effects of risedronate dosing at a time other than before breakfast on bone mineral density (BMD) and/or on bone turnover markers (BTMs)[11-15] have provided information on compliance[13-15] while two gave information on persistence only.[11,12] Therefore, little information is available on patients' level of compliance and persistence with instructions to take medication at specific times of day or within specified amounts of time in relation to food intake.

The aim of this study was to examine the compliance, persistence and preference between a fixed or flexible dosing regimen of daily risedronate in patients with postmenopausal OP.

Patients and Methods

The study included 448 women with postmenopausal OP enrolled in 10 centers in Turkey and 9 centers in Poland and treated with risedronate 5 mg daily, supplemented with 1000 mg of calcium and 400 IU of vitamin D, for 26 weeks. Inclusion criteria were as follows: ambulatory women aged 55 to 85 years and appropriate for OP treatment based on the investigator's judgment (a T-score of ≤-2.5 of the spine and/or hip or ≤-1 plus low trauma fractures as measured by dual-energy X-ray absorptiometry) willing to participate in the study. Patients presenting at screening with any of the following were excluded: evidence of clinically significant organic or psychiatric disorder, any mental condition causing inability to understand the nature and possible consequences of the study, abnormal laboratory parameters (including renal or hepatic insufficiency, gastrointestinal disease), use of oral and parenteral glucocorticoids (≥5 mg prednisone or equivalent/day) for more than one month within six months of entry to the study or any use within three months of beginning risedronate, history of cancer, known hypersensitivity to bisphosphonates and/or excipients, likelihood of requiring treatment during the study period with drugs not permitted by the study protocol, hypocalcaemia, and history of alcohol abuse.

Patients were instructed to take risedronate while in an upright position with a glass of plain water, either a minimum of 30 minutes before the first food or drink of the day, or at least two hours apart from any food or drink intake at any other time of the day, or at least 30 minutes before going to bed/lying down.

The study protocol was approved by independent ethics committees in Turkey and Poland. Written informed consent was obtained prior to the conduct of any study-related procedures.

This crossover study comprised a screening phase (2 to 4 weeks) and a treatment phase (26 weeks), for a total of 5 visits. In the screening phase, the period between screening (Visit 1) and the baseline (Visit 2), patients were given 1000 mg of calcium and 400 IU of vitamin D. The treatment phase consisted of a crossover phase (from Visit 2 to Visit 3 at three weeks) and a patient's preference phase (from Visit 3 until Visit 5 at 26 weeks). For treatment in the crossover phase, each subject was given a container with two blisters of 14 tablets of risedronate and was randomly assigned to one of six different treatment groups, each of which had three treatment sequences (ABC, BCA, etc.), using a computer-generated randomization schedule. The timing regimens were; A: before breakfast, B: in-between meals, or C: before

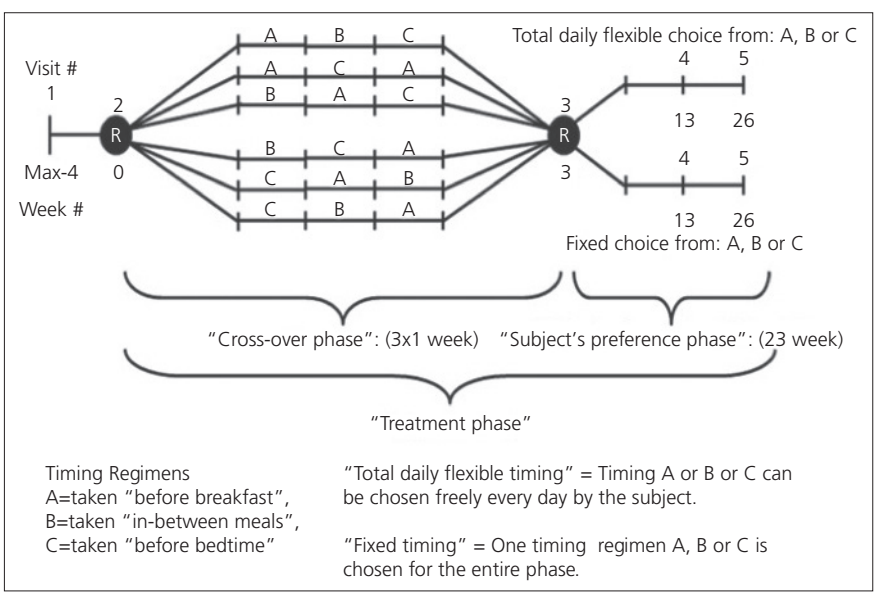

Fig. 1. Study design.

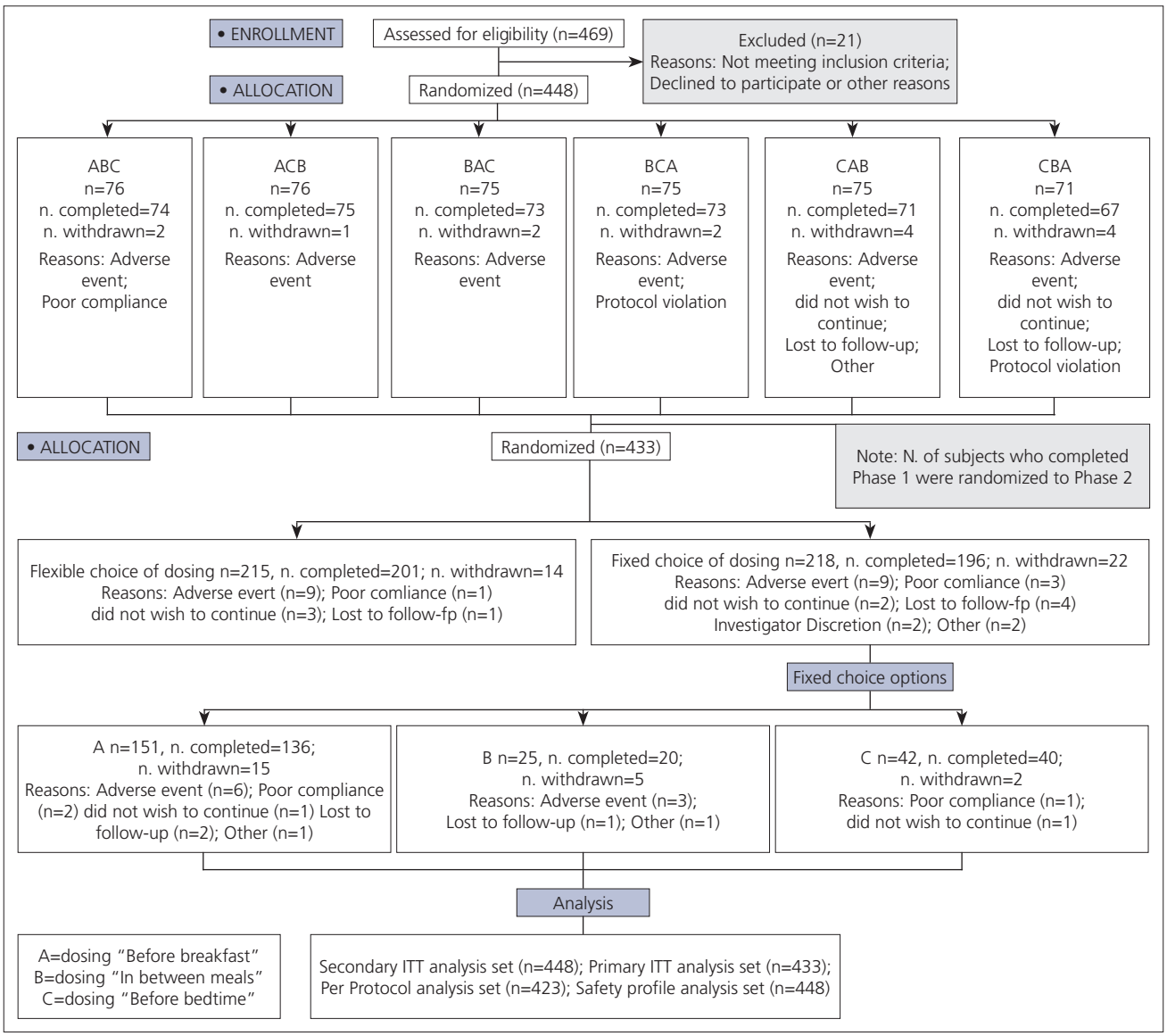

Fig. 2. Study flow diagram: participants from the first phase to the analyses. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

bedtime. At the end of the third crossover sequence, on Visit 3, each subject was given a container of risedronate with six blisters of 14 tablets for treatment for Week 4 to Week 13 and assigned (based on preference) to 23 weeks of either daily flexible (regimen A, B, or C chosen freely each day) or daily fixed timing (regimen A, B, or C chosen for the remaining study period) groups. At Visit 4, patients were given their last container with seven blisters of 14 tablets for treatment for Weeks 14 to 26 (Fig. 1). The number of tablets returned at each study visit was recorded on the case report form.

Analysis of urine samples for N-terminal telopeptide of Type 1 collagen (NTX-1) was performed using Osteomark® NTX-1 Point-of-Care (Ostex International Inc., Seattle, WA, USA)[16] at the baseline, 13th and 26th weeks at each study center in Poland (with communication of the results to the subjects). These tests were not performed in the Turkish study centers due to difficulties in supplying the NTX-1 device.

Each subject completed a Subject's Preference Questionnaire at the baseline, 3rd and 5th visits along with a questionnaire on subjects' opinion of the risedronate treatment.

Frequency of all treatment-emergent adverse events (TEAEs) was summarized by body system and preferred term including summaries of the severity as mild, moderate, or severe, and relationship to the study drug of all TEAEs.

Compliance was defined as >50% dose taken and was measured by tablet count based on the collected study medication at visits 3, 4 and 5. Compliance was calculated as follows: % compliance=[#of tablets supplied-#of tablets returned]/#of tablets to have been taken x 100.

Persistence was defined as the continuation of treatment at Week 26.

Response was defined as a composite of the subject's compliance and persistence. A subject being both compliant and persistent at Week 26 was considered a responder.

Statistical analyses were performed using the SAS software v.8.2 (SAS Institute Inc., Cary, NC, USA) for all patients and by country, for the primary intension-to-treat (ITT) and the per protocol (PP) analysis sets. The chi-square and Cochran-Mantel-Haenszel tests were used for the analysis of categorical data, while numerical data (relevant to NTX-1) were analyzed using analysis of covariance (ANCOVA). Statistical significance was set at a p value of ≤0.05.

Results

A total of 448 patients participated in the first, crossover phase (Fig. 2). Of these, 433 continued in the second, patient preference phase and 215 (49.7%) chose the flexible regimen and 218 (50.3%) the fixed regimen. In the fixed regimen, 151 (70.2%) opted for regimen A (p=0.0001). Overall and country specific compliance, persistence and response rates for the primary ITT group are shown in Table 1. The persistence rate in the flexible regimen (86.0%) was significantly higher than that of the fixed regimens (78.9%) (p=0.0306). The difference in terms of compliance between groups was not statistically significant (p=0.4611). In the fixed dosing group, patients taking their medication before bedtime had higher compliance and persistence rates. The proportion of responders did not differ between the two dosing regimens (54.4% vs. 53.7%) (p=0.8803), however, was higher for regimen C than those for regimen A and B within the fixed timing group.

At the final visit, 50.8% of patients in the flexible and 55.2% in the fixed regimen group considered the used risedronate regimen as excellent or very good (p=0.1440). Patients' opinion of the risedronate regimen is shown in Table 2. There was no difference between fixed and flexible dosing in the efficacy of risedronate on the decrease of BTMs as shown by change from baseline in NTX-I levels at either Visit 4 or Visit 5 (Table 3).

Frequencies of all TEAEs are summarized in Table 4.

Discussion

Our findings revealed that, apart from a significantly higher rate in persistence noted in patients under the flexible regimen, flexible and fixed dosing of daily risedronate therapy revealed similar findings in postmenopausal osteoporotic women in terms of compliance, responder and patient preference rates as well as efficacy on reduction in BTMs.

Data on 6-month compliance rates in studies assessing before-breakfast dosing of bisphosphonates are inconsistent. A trial comparing the effects of once-monthly versus once-daily risedronate use in postmenopausal OP reported a compliance level of >97% using pill counts.[17] Studies using healthcare claims databases reported compliance rates of 70% (with an MPR ≥80%),[18] 40% (with an MPR ≥80%),[19] 75% (for those with an MPR

Table 1. Compliance, persistence, and response in the population comprising all patients who had been randomized and had received at least one dose of treatment during the second phase of the study. [n (%) of patients].

		Fixed dosing				
	Daily flexible dosing	Before breakfast	In-between meals	Before bedtime	Total	p
Compliance						
Poland	74/105 (70.5)	58/83 (69.9)	3/10 (30.0)	14/19 (73.7)	75/112 (67.0)	0.6488
Turkey	54/110 (49.1)	38/68 (55.9)	4/15 (26.7)	18/23 (78.3)	60/106 (56.6)	0.1488
Overall	128/215 (59.5)	96/151 (63.6)	7/25 (28.0)	32/42 (76.2)	135/218 (61.9)	0.4611
Persistence						
Poland	96/105 (91.4)	72/83 (86.7)	7/10 (70.0)	17/19 (89.5)	96/112 (85.7)	0.1813
Turkey	89/110 (80.9)	47/68 (69.1)	10/15 (66.7)	19/23 (82.6)	76/106 (71.7)	0.0892
Overall	185/215 (86.0)	119/151 (78.8)	17/25 (68.0)	36/42 (85.7)	172/218 (78.9)	0.0306
Response						
Poland	70/105 (66.7)	52/83 (62.7)	3/10 (30.0)	13/19 (68.4)	68/112 (60.7)	0.3638
Turkey	47/110 (42.7)	29/68 (42.6)	4/15 (26.7)	16/23 (69.6)	49/106 (46.2)	0.5430
Overall	117/215 (54.4)	81/151 (53.6)	7/25 (28.0)	29/42 (69.0)	117/218 (53.7)	0.8803

Table 2. Patients' opinion of risedronate treatment at Week 3 and Week 26 (primary ITT population) [n (%) of patients].

		Fixed dosing				
	Daily flexible dosing	Before breakfast	In-between meals	Before bedtime	Total	Flexible vs. Fixed
Week 3						
Excellent/very good	88/215 (40.9)	51/147 (34.7)	7/24 (29.2)	20/42 (47.6)	78/213 (36.6)	p=0.4214
Good/fair	127/215 (59.1)	96/147 (65.3)	17/24 (70.8)	22/42 (52.4)	135/213 (63.4)	
Poor	0/215	0/147	0/24	0/42	0/213 (0)	
Week 26						
Excellent/very good	101/199 (50.8)	71/134 (53.0)	13/19 (68.4)	23/41 (56.1)	107/194 (55.2)	p=0.1440
Good/fair	95/199 (47.7)	61/134 (45.5)	6/19 (31.6)	18/41 (43.9)	85/194 (43.8)	
Poor	3/199 (1.5)	2/134 (1.5)	0/19	0/41	2/194 (1.0)	

Table 3. Urinary NTX-1 levels in Polish patients (primary ITT population).

	Urinary NTX-1 levels (nM BCE/mM creatinine)					
	Daily flexible dosing		Fixed dosing			
	Actual	Change from baseline	Actual	Change from baseline	Adjusted difference*	95% CI
Baseline						
n	105		112			
Mean±SD	72.9±112.1		62.1±33.6			
Median (Range)	55.0 (9.0-931.0)		59.0 (12.0-158.0)			
Visit 4						
n	102	107				
Mean±SD	58.6±87.6	-15.2±72.7	43.9±33.2	-18.7±36.0	8.25	(-4.05, 20.56)
Median (Range)	35.0 (10.0-586.0)	-13.0 (-571.0-328.0)	34.0 (8.0-230.0)	-14.0 (-121.0-124.0)		
n	103		107			
Mean±SD	54.4±104.2	-19.0±61.6	42.3±37.0	-19.6±38.3	3.48	(-9.27, 16.22)
Median (Range)	29.0 (7.0-850.0)	-15.0 (-406.0-303.0)	26.0 (2.0-195.0)	-18.0 (-124.0-108.0)		

*ANCOVA adjustment for baseline scores flexible vs. fixed. BCE: Bone collagen equivalents, n: Number of available patients, SD: Standard deviation.

>50%),[20] 61.6% and 55.6% (with an MPR≥80% in those with and without a previous fracture, respectively),[21] and 78.5% (for those with an MPR ≥50%.[22]

The overall percentage of compliant patients in this study (approximately 60% in both regimens) was lower than that reported in a randomized clinical trial[17] or in observational database studies[18,20,22] based on drug dispensing data reflecting a real-world setting. However, it is difficult to make comparisons between our results and those studies defining compliant subjects with an MPR of 80%.[18,19,21] The difference between studies in terms of MPR definitions, the likelihood of cumulative compliance levels with a variety of medications for OP, and the compliance rates in patients with or without a previous fracture can be considered amongst the factors compromising the comparison. The findings of the IMPACT study indicating more patients in the before-breakfast dosing being compliant compared with flexible dosing of oral risedronate 5 mg daily[15] were in contradiction with those of ours being similar in both regimens.

The percentage of patients who persisted with treatment also vary in the literature, ranging from 40 to 71%.[19,21,23-28] While the overall persistence levels in the flexible (86.0%) and fixed (78.9%) regimen groups in this trial were higher than those in the literature, the differences might be due to the difference in methodology between clinical studies and a real-world setting. Siris et al. found that an MPR of ≥50% was associated with substantial fracture reduction.[29] Similar results have been seen with bisphosphonates in compliant and/or persistent patients in both randomized clinical trials and real world practice in terms of fracture risk reduction.[30]

In the literature, NTX-1 monitoring has been associated with improved persistence[31] and adherence.[32] In our study, NTX-1 monitoring was performed in the

Table 4. All treatment emergent adverse events (TEAEs) and treatment-related (possibly or probably) TEAEs (safety set).

Body system	All patients (n=448)		
	Patients		Events
	n	%	n
All TEAEs			
Any TEAE	105	23.4	140
Adverse events leading to withdrawal	25	5.6	30
Serious adverse events	1	0.2	1
TEAEs by body system			
Digestive system	37	8.3	40
Gastritis	11	2.5	11
Dyspepsia	5	1.1	4
Body as a whole	27	6.0	28
Accidental injury	7	1.6	7
Allergic reaction	4	0.9	4
Back pain	4	0.9	4
Respiratory system	14	3.1	13
Pharyngitis	9	2.0	10
Nervous system	12	2.7	13
Dizziness	4	0.9	4
Musculoskeletal system	11	2.5	11
Cardiovascular system	9	2.0	9
Hypertension	5	1.1	5
Metabolic and nutritional disorders	4	1.0	4
Urogenital system	7	1.6	7
Special senses	6	1.3	6
Skin and appendages	4	0.9	4
Blood and Lymphatic system	2	0.4	2
Endocrine system	1	0.2	1
Treatment related TEAEs			
Any adverse event	33	7.0	39
Digestive system	23	5.0	26
Dyspepsia	4	1.0	4
Gastritis	9	2.0	9
Body as a whole	6	1.0	6
Musculoskeletal system	3	<1	3
Skin and appendages	2	<1	2
Cardiovascular system	1	<1	1
Metabolic and nutritional disorders	1	<1	1

Polish patients but not in the Turkish patients, and may account for the higher compliance and persistence rates in the Polish patients. However, as another study reported no differences in persistence rates between patients who received BTM results and those who did not,[33] the role of NTX-1 monitoring in the reinforcement of persistence and/or compliance remains a speculation. In addition, the discrepancy between the results in Turkey and Poland may also be attributed to geographical differences.[15]

Regarding the efficacy of risedronate on the decrease as measured by urinary NTX-1 testing, there was no significant adjusted difference between the baseline and 6th month findings of flexible and fixed daily dosing regimens. However, Hosking et al.[13] reported greater changes in NTX-1 at 6 months (approximately -35%) with between-meal dosing of daily risedronate than those observed in our study.

The before bedtime subgroup in the fixed dosing regimen in our study had the highest percentage of responders and the in-between meals subgroup the lowest. Mitchell et al. reported that risedronate absorption was comparable when administered either before breakfast or before bedtime and implied a similar effectiveness.[34] Therefore, it can be extrapolated that before bedtime dosing is an alternative means to achieve the desired efficacy.

The risedronate regimen used was rated as excellent or very good by more than half of the patients in both the flexible and fixed regimens, indicating treatment satisfaction. Barrett-Connor et al. pointed to the lower likelihood of medication discontinuation in women with higher satisfaction.[35]

Adverse events experienced with risedronate in this study were few and mild in nature, mainly affecting the upper gastrointestinal system and were comparable with those in previous studies using flexible dosing.[11-15]

There were several limitations to this study. The response rate in the fixed dosing group was considerably lower than 70% and may weaken the comparison between groups. While a sample size of around 460 patients was planned, only 448 patients were enrolled and 397 completed the study. However, given the data available from the existing sample size, it can be concluded that the flexible regimen is not significantly different than the fixed regimen in terms of compliance. Other limitations may include the lack of categorical evaluation of MPRs of ≥80%, which might allow for a more detailed assessment of compliance and facilitate comparison with some other studies. However, the cut-off point of 50% utilized in this study is a commonly used definition of compliant use.[36] The measurement of change in BMD at six months would have also added value in terms of efficacy of different timing of risedronate use if it had been measured. Failure to measure urinary NTX-1 in Turkey may have also affected the overall compliance and persistence rates. We may also speculate that the assessment of the effects of influencing factors on compliance and/or persistence such as prior lack of adherence with other medications, concerns about side effects, beliefs about OP and associated disability, benefits of OP medications and use of alcohol[37,38] might have given more insights on the rates of compliance and persistence if those assessments had been performed.

In conclusion, flexible dosing resulted in better persistence rates than fixed dosing but did not affect compliance rates. A similar percentage of patients preferred daily flexible and fixed dosing, and both regimens were rated as excellent or very good by the patients. Alternate timing for the use of risedronate may assist patients with difficulty following the traditional before-breakfast dosing regimen and offer an option which could easily be incorporated into the individuals' personal schedules. However, because approved treatment regimens vary between countries, these findings may not be applicable worldwide. Additional large scale studies including categorical evaluation of MPR, measurement of change in BMD and the assessment of the additional factors likely to influence compliance and/or persistence will enable more accurate assessment of compliance and persistence with daily risedronate regimens in patients with postmenopausal OP.

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References

1. Ross S, Samuels E, Gairy K, Iqbal S, Badamgarav E, Siris E. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value Health 2011;14:571-81. CrossRef
2. Imaz I, Zegarra P, González-Enríquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int 2010;21:1943-51.
3. Silverman SL, Schousboe JT, Gold DT. Oral bisphosphonate compliance and persistence: a matter of choice? Osteoporos Int 2011;22:21-6. CrossRef
4. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 2007;18:1023-31. CrossRef
5. International Osteoporosis Foundation. The adherence gap: Why osteoporosis patients don't continue with treatment; 2005 [cited 2011 October 17]. Available from: http://www.iofbonehealth.org/publications/the-adherence-gap.html.
6. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;1:CD004523.
7. Jansen JP, Bergman GJ, Huels J, Olson M. The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: a network meta-analysis. Semin Arthritis Rheum 2011;40:275-84. e1-2.
8. Reginster JY. Antifracture efficacy of currently available therapies for postmenopausal osteoporosis. Drugs 2011;71:65-78. CrossRef
9. Gates BJ, Das S. Risedronate's Role in Reducing Hip Fracture in Postmenopausal Women with Established Osteoporosis. Clin Med Insights Arthritis Musculoskelet Disord 2012;5:1-14. CrossRef
10. Zhong ZM, Chen JT. Anti-fracture efficacy of risedronic acid in men: A meta-analysis of randomized controlled trials. Clin Drug Investig 2009;29:349-57. CrossRef
11. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int 1997;7:488-95. CrossRef
12. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab 1998;83:396-402. CrossRef
13. Hosking D, Adami S, Felsenberg D, Andia JC, Välimäki

M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opin 2003;19:383-94. CrossRef
14. Agrawal S, Krueger DC, Engelke JA, Nest LJ, Krause PF, Drinka PJ, et al. Between-meal risedronate does not alter bone turnover in nursing home residents. J Am Geriatr Soc 2006;54:790-5. CrossRef
15. Kendler DL, Ringe JD, Ste-Marie LG, Vrijens B, Taylor EB, Delmas PD. Risedronate dosing before breakfast compared with dosing later in the day in women with postmenopausal osteoporosis. Osteoporos Int 2009;20:1895-902. CrossRef
16. Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR. A specific immunoassay for monitoring human bone resorption: quantitation of type I collagen cross-linked N-telopeptides in urine. J Bone Miner Res 1992;7:1251-8. CrossRef
17. Ste-Marie LG, Brown JP, Beary JF, Matzkin E, Darbie LM, Burgio DE, et al. Comparison of the effects of once-monthly versus once-daily risedronate in postmenopausal osteoporosis: a phase II, 6-month, multicenter, randomized, double-blind, active-controlled, dose-ranging study. Clin Ther 2009;31:272-85. CrossRef
18. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;38:922-8. CrossRef
19. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int 2006;17:1645-52. CrossRef
20. Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2008;19:511-7.
21. Höer A, Seidlitz C, Gothe H, Schiffhorst G, Olson M, Hadji P, et al. Influence on persistence and adherence with oral bisphosphonates on fracture rates in osteoporosis. Patient Prefer Adherence 2009;3:25-30.
22. Halpern R, Becker L, Iqbal SU, Kazis LE, Macarios D, Badamgarav E. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. J Manag Care Pharm 2011;17:25-39.
23. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin 2005;21:1453-60. CrossRef
24. Penning-van Beest FJ, Goettsch WG, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. Clin Ther 2006;28:236-42. CrossRef
25. Hadji P, Claus V, Ziller V, Intorcia M, Kostev K, Steinle T. GRAND: the German retrospective cohort analysis on compliance and persistence and the associated risk of fractures in osteoporotic women treated with oral bisphosphonates. Osteoporos Int 2012;23:223-31. CrossRef
26. Landfeldt E, Ström O, Robbins S, Borgström F. Adherence to treatment of primary osteoporosis and its association to fractures-the Swedish Adherence Register Analysis (SARA). Osteoporos Int 2012;23:433-43. CrossRef
27. Netelenbos JC, Geusens PP, Ypma G, Buijs SJ. Adherence and profile of non-persistence in patients treated for osteoporosis--a large-scale, long-term retrospective study in The Netherlands. Osteoporos Int 2011;22:1537-46. CrossRef
28. Li L, Roddam A, Gitlin M, Taylor A, Shepherd S, Shearer A, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. Menopause 2012;19:33-40. CrossRef
29. Siris ES, Pasquale MK, Wang Y, Watts NB. Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older, 2001-2008. J Bone Miner Res 2011;26:3-11. CrossRef
30. Wilkes MM, Navickis RJ, Chan WW, Lewiecki EM. Bisphosphonates and osteoporotic fractures: a cross-design synthesis of results among compliant/persistent postmenopausal women in clinical practice versus randomized controlled trials. Osteoporos Int 2010;21:679-88. CrossRef
31. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2007;92:1296-304.
32. Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB. Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. J Bone Miner Res 2011;26:1662-9. CrossRef
33. Silverman SL, Nasser K, Nattrass S, Drinkwater B. Impact of bone turnover markers and/or educational information on persistence to oral bisphosphonate therapy: a community setting-based trial. Osteoporos Int 2012;23:1069-74.
34. Mitchell DY, Heise MA, Pallone KA, Clay ME, Nesbitt JD, Russell DA, et al. The effect of dosing regimen on the pharmacokinetics of risedronate. Br J Clin Pharmacol 1999;48:536-42. CrossRef
35. Barrett-Connor E, Wade SW, Do TP, Satram-Hoang S, Stewart R, Gao G, et al. Treatment satisfaction and persistence among postmenopausal women on osteoporosis medications: 12-month results from POSSIBLE US™. Osteoporos Int 2012;23:733-41. CrossRef
36. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7.
37. Solomon DH, Brookhart MA, Tsao P, Sundaresan D, Andrade SE, Mazor K, et al. Predictors of very low adherence with medications for osteoporosis: towards development of a clinical prediction rule. Osteoporos Int 2011;22:1737-43.
38. Lee S, Glendenning P, Inderjeeth CA. Efficacy, side effects and route of administration are more important than frequency of dosing of anti-osteoporosis treatments in determining patient adherence: a critical review of published articles from 1970 to 2009. Osteoporos Int 2011;22:741-53.