

First Indian prospective randomized comparative study evaluating adherence and compliance of postmenopausal osteoporotic patients for daily alendronate, weekly risedronate and monthly ibandronate regimens of bisphosphonates

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ABSTRACT

Aim: The aim of the following study is to evaluate adherence and compliance of postmenopausal osteoporotic patients for different regimens of bisphosphonates (BP).

Materials and Methods: A prospective observational randomized comparative 1 year study was undertaken to evaluate the adherence/compliance rates of most commonly prescribed daily alendronate (ALN), weekly risedronate (RIS) and monthly ibandronate (IBN) BP regimens.

Results: Nearly 40% was the 1 year adherence rate with BP and 41.33% of non-compliance. Whereas, 8.66% was interrupted compliance rate and 6% switched over to other anti-osteoporotic treatment. The three treatment arm did not vary significantly. However, numerically maximum adherence rate of 56% was recorded in monthly BP regimen followed by weekly (36%) and daily regimen (32%). Medication possession rate confirmed on a follow-up visit was maximum with monthly regimen as 84.61% followed by daily (62.5%) and weekly (61.11%) respectively. Average time in days for non-adherence was 48, 56 and 92 day with daily ALN, weekly RIS and monthly IBN regimen respectively. Age, mean age at menopause, demographical profile failed to influence the adherence. Concomitant treatment for co-morbid condition (57.14%), unawareness about osteoporosis (OP) (50%), cost of treatment (45.33%), belief that drugs is for their general disability (39.28%), physician's failure to stress the need and necessary calcium + vitamin D daily requirement (23.80%) each were the most prevalent factors responsible for non-adherence. Intolerance and adverse drug reactions were responsible for only 13.09% and 11.90% of non-adherence.

Conclusion: Treatment compliance is poor with daily ALN, weekly RIS and monthly IBN regimen along with calcium and vitamin D3 in Indian paramedical workers suffering OP.

Key Words: Adherence, alendronate, bisphosphonates, compliance, ibandronate, postmenopausal osteoporosis, risedronate

INTRODUCTION

Bisphosphonates (BP) are recommended world-wide including India as first-line drugs for the treatment of postmenopausal osteoporosis (OP), with proven efficacy in the prevention of vertebral and non-vertebral fractures, including hip fractures.^[1-6] BP are generally safe and well-

tolerated group of drugs. However, concerns have emerged about adverse drug reactions (ADRs) related to long-term use, such as osteonecrosis of the jaw and atypical femur fractures.^[7]

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Access this article online

Quick Response Code:



Website:
www.jmidlifehealth.org

DOI:
10.4103/0976-7800.127788

Fracture intervention trial and vertebral efficacy with risedronate (RIS) therapy trials established safety and efficacy of BP beyond 5 and 7 years, respectively.^[8,9] Robust data exist from numerous placebo-controlled trials demonstrating efficacy in fracture risk reduction over 3-5 years of treatment.^[10]

Alendronate (ALN) can produce 55% significant reduction in spine fracture. RIS can reduce up to 49% in new vertebral fracture and 39% reduction in non-vertebral fractures. Oral ibandronate (IBN) can reduce vertebral fracture by 62%. Treatment with yearly zoledronic acid (ZA) can reduce the incidence of vertebral fracture by 70% over 3 years.^[6]

BP, such as ALN, RIS, IBN and ZA are well studied for their efficacy and safety. However, no data exist comparing these agents neck to neck for their ant fracture efficacy to recommend any particular BP over other. In the Indian setup most commonly prescribed BP remain daily ALN, weekly RIS and monthly IBN along with calcium and vitamin D3.

As the current recommendations^[1-6] issued by various menopause societies including Indian Menopause Society, long-term treatment of BP for the prevention and treatment of postmenopausal osteoarthritis is recommended. Thus, the adherence and compliance to the prescribed BP treatment is utmost important for the favorable outcome of treatment in regards to its anti-fracture efficacy.

Poor adherence to prescribed treatments is apparently widespread in clinical practice particularly for OP treatment but the causes of discontinuation and low compliance are very complex, poorly defined and minimally researched in Indian setup for BP. Apparently it appears monthly regimen may find more adherence and compliance in comparison to daily and weekly regimens, but it may not be true.

The studies do exist to address this problem from western world^[11-21] but to the best of our knowledge no study exist from India evaluating adherence and compliance of most commonly prescribed BP in India. Hence, the current study was undertaken for the first time from India to evaluate adherence and compliance of postmenopausal osteoporotic patients with different treatment regimens of BP.

MATERIALS AND METHODS

A prospective observational randomized comparative 1 year study was undertaken after Institutional Ethics Committee clearance to evaluate the adherence/compliance rates of most commonly prescribed BP regimens in the form of daily ALN, weekly RIS and monthly IBN along with calcium and vitamin D3 among Indian paramedical

workers (PMW) in a tertiary care teaching hospital in India. 150 PMW (with cessation of menstruation for 1 year) requiring BP treatment for postmenopausal OP as per the Indian clinical practice guidelines on postmenopausal OP^[1-6] were allocated to one of the BP regimen in the form of daily ALN 10 mg ($n = 50$), weekly RIS 35 mg ($n = 50$) and monthly IBN 150 mg ($n = 50$) along with the recommended dose of calcium and vitamin D3 using block permutation randomization method.

Non-standardized brief (5 min) pre-treatment counseling (face to face conversation) with regard to their disease, details and importance of treatment and the need for follow-up was allowed to be carried before allocation of treatment in each arm by the prescribing doctor.

Patients with only stable co-morbid conditions, ambulatory, non-hospitalized, non-critically ill, requiring BP therapy were included in the current study. The patients were followed for 1 year from the commencement of their inclusion. Treatment adherence rate, non-compliance rate and switching over to other treatment were recorded at the end of the study and compared among each arm. Furthermore, a face-to-face and telephonic enquiry was undertaken with predesigned questioner to come to the conclusion for various reasons and factors for non-adherence to BP among Indian PMW not adhering to the three respective treatment arms.

Statistical analysis

Analysis was carried out with the help of computer software SPSS Version 15 for windows. The data was expressed in n (%). Chi-square test was applied for some of the parameters to prove their statistical significance. $P < 0.05$ was considered to be significant.

RESULTS

The current study recorded 40% of 1 year adherence rate with BP therapy. Nearly 41.33% of the total population showed non-compliance. Whereas, 8.66% of the population recorded interrupted compliance and 6% switched over to other anti-osteoporotic treatment during the study period. 4% lost to follow-up during the study. While comparing these parameters among the three treatment arm the result did not vary significantly among each other. However, numerically maximum adherence rate of 56% was recorded with monthly BP regimen followed by weekly (36%) and daily regimen (32%) as expected. Maximum non-compliance rate (52%) was observed with daily regimen. Whereas maximum interrupted compliance rate (12%) and switch over rate to other anti-osteoporotic treatment (8%) was observed with weekly and daily BP regimen [Table 1].

Medication possession rate confirmed on a follow-up visit was maximal with monthly regimen as 84.61% followed by daily (62.5%) and weekly (61.11%) regimen respectively. The medication possession rate confirmed by telephone was maximum (38.88%) with weekly regimen. Average time in days for non-adherence was 48, 56 and 92 days with daily ALN, weekly RIS and monthly IBN regimen respectively.

Age, mean age at menopause, demographical profile failed to influence the adherence rate among three treatment arms. Concomitant treatment for co-morbid condition (57.14%), unawareness about their OP (50%), cost of treatment (45.33%), belief that drugs is for their general disability (39.28%), physician's failure to stress the need and necessary calcium + vitamin D daily requirement (23.80%) each were the most prevalent factors responsible for non-adherence and non-compliance of BP. Intolerance and ADRs were only responsible for 13.09% and 11.90% of non-adherence. The detail of other factors is depicted in Table 2.

DISCUSSION

The study undertaken by Rossini *et al.*^[11] recorded overall 19.1% of discontinuation rate of prescribed anti-osteoporotic treatment. The most frequent reasons suggested for discontinuation were drug related side-effects, insufficient motivation to treatment and fear of side-effects unlike our study. Safety concerns were very common for hormone replacement therapy, lack of motivation was the most common cause for calcium and vitamin D and drug related side-effects for RIS, ALN and raloxifen. However, result of our study recorded an alarmingly high discontinuation rate of BP and concomitant treatment, priority for co-morbid conditions, unawareness, cost of treatment and daily requirement of calcium and vitamin D were the most frequent reasons for non-adherence.

Papaioannou *et al.*^[12] in their study suggested that 20-30% of patients taking daily or weekly treatments of BP may suspend their treatment within 6-12 months of initiating therapy due to drug-induced ADR and fear of ADR. Factors associated with medication adherence suggested by their study were fractures, regular exercise, female sex, fewer non-OP medications and co-morbidities, early menopause, willingness to take medications, awareness of OP status. However, ADR, intolerance and fear of ADR were not the most common factors responsible for discontinuation of BP in our study. This clearly indicates that BP are well-tolerated by Indian PMW.

Total dropout rate was 18% in the ALN group because of side-effects (39%). The most frequent side-effect was abdominal pain (42.8%) and other reasons were a fear of side-effects and high drug price in (30%) and inconvenience caused by medication use in 14.3% in the ALN group in the study of Segal *et al.*^[13] The results of the current study are in accordance as far as cost of therapy is concerned for discontinuation.

Serial increase was recorded in discontinuation of treatment with an increase in duration of therapy in the continuation study of Segal and Ish-Shalom.^[14] After 6 months, 77% patients adhered to the treatment and 23% discontinued it. 2 years after initiating the therapy 43.8% continued the treatment and 21.9% discontinued and 9.6% changed the initial drug to another anti-OP therapy in their study.

One of the studies^[15] recommended that effective communication between doctor and patient and follow-up visits would greatly improve adherence to OP treatment modalities. Data also indicate that patients with OP who have good long-term medication compliance experience

Table 1: Comparative 1 year adherence/compliance of daily, weekly and once monthly regimen of BP among Indian postmenopausal women

Parameters of adherence/compliance of BP	Daily BP (ALN) N = 50 (%)	Weekly BP (RIS) N = 50 (%)	Monthly BP (IBN) N = 50 (%)	Total N = 150 (%)	P value
Complete 1 year adherence	16 (32)	18 (36)	26 (52)	60 (40)	$\chi^2=4.67$ P=0.09 NS
Complete non-compliance	26 (52)	22 (44)	14 (28)	62 (41.33)	NS
Interrupted compliance	2 (4)	6 (12)	5 (10)	13 (8.66)	NS
Switching over to other anti-osteoporosis treatment	4 (8)	3 (6)	2 (4)	9 (6)	NS
Lost to follow-up	2 (4)	1 (2)	3 (6)	6 (4)	NS
Medication possession rate confirmed on follow-up visit	10/16 (62.5)	11/18 (61.11)	22/26 (84.61)		$\chi^2=6.57$ P=0.03 significant
Medication possession rate confirmed by telephone	6/16 (37.5)	7/18 (38.88)	4/26 (15.38)		$\chi^2=3.80$ P=0.14 NS
Average time in days for non-adherence	48	56	92		NS

BP: Bisphosphonates, ALN: Alendronate, RIS: Risedronate, IBN: Ibandronate, NS: Not significant

Table 2: Factors for non-adherence to BP among Indian postmenopausal women

Factors for non-adherence	Daily BP (ALN) N = 32 (%)	Weekly BP (RIS) N = 31 (%)	Monthly BP (IBN) N = 21 (%)	Total N = 84 (%)	P value
Age (mean±SD)	59.63±5.94	60.13±4.94	58±6.94		NS
Mean duration since menopause	2.81 years	3.01 years	2.99 years		NS
Rural versus urban population	14 (43.75) versus 18 (56.25)	13 (41.93) versus 18 (58.06)	10 (47.61) versus 7 (33.33)		$\chi^2=1.39 P=0.49$ NS
Concomitant treatment for co-morbid condition	18 (56.25)	13 (41.93)	17 (80.95)	48 (57.14)	$\chi^2=8.39 P<0.01$ significant
Ignorance	6 (18.75)	4 (12.90)	5 (23.80)	15 (17.85)	$\chi^2=1.04 P=0.59$ NS
Lack of motivation	4 (12.5)	6 (19.35)	1 (4.76)	11 (13.09)	$\chi^2=2.36 P=0.30$ NS
Specific administration requirements	7 (21.87)	3 (9.67)	2 (9.52)	12 (14.28)	$\chi^2=2.43 P=NS$
Physician's failure to stress the need	7 (21.87)	5 (16.12)	8 (38.09)	20 (23.80)	NS
Unawareness of their osteoporosis	12 (37.5)	17 (54.83)	13 (61.90)	42 (50)	$\chi^2=3.05 P=0.21$ NS
Cost of treatment	12 (37.5)	13 (41.93)	13 (61.90)	38 (45.23)	NS
Fear of ADR	3 (9.37)	3 (9.67)	3 (14.28)	9 (10.71)	$\chi^2=37 P=0.82$ NS
ADR	3 (9.37)	4 (12.90)	3 (14.28)	10 (11.90)	$\chi^2=44 P=0.80$ NS
Gastrointestinal tract side-effects	1 (3.12)	1 (3.22)	2 (9.52)	4 (4.76)	$\chi^2=1.40 P=0.49$ NS
Intolerance	3 (9.37)	2 (6.44)	6 (28.56)	11 (13.09)	$\chi^2=5.14 P=0.07$ NS
Patient's belief that there is no obvious relief	7 (21.87)	6 (19.35)	7 (33.33)	20 (23.80)	NS
Belief that drugs is for their general disability	7 (21.87)	13 (41.93)	13 (61.90)	33 (39.28)	NS
Because of necessary calcium and vitamin D daily drug requirement	7 (21.87)	5 (16.12)	8 (38.09)	20 (23.80)	NS

Patients have more than one factor responsible for non-adherence to BP therapy. BP: Bisphosphonate, ADR: Adverse drug reaction, SD: Standard deviation, ALN: Alendronate, RIS: Risedronate, IBN: Ibandronate, NS: Not significant

substantially lower risk of fracture. Persistence with therapy also correlates with better bone mineral density (BMD) and improved suppression of bone turnover markers.^[18] However, no attempt was made to confirm the compliance by undertaking BMD or fracture prevention analysis in the current study.

However, contrary to above studies including ours adherence to therapy was recorded very high during in one of the recent study.^[16] The patients remaining compliant after a year in 95.08 ± 1.39% (mean ± standard error of mean) of cases and the mean persistence with medication was 347.05 ± 5.07 days on ALN 70 mg therapy, administered once a week due to more frequent monitoring of treated patients.

Apparently, it appears monthly regimen may find more adherence and compliance in comparison to daily and weekly regimens, but it may not be true. Once-weekly and once-monthly oral BP therapy has been shown equivalent with once daily medications in their adherence rates^[17,20] as has been recorded in our study. This may be due to the requirement of must daily intake of calcium and vitamin D3 along with these BP. Moreover, asymptomatic nature of the disease and the lack of options for patient self-monitoring are some of the other factors which may influence compliance and adherence to any BP regimens.

Continuous reinforcement of the importance of treatment is a key approach to improve persistence. Patients should receive feedback and individualized reminder systems should be recommended to help the patient adhere to the treatment plan.^[19]

OP is a major public health problem of advancing age, which needs long clinical observation and constant adherence to medication in order to prevent fractures and disability, as patients with poor adherence may have an increased risk of OP fractures.

The results of current study warrant an urgent need to understand the reasons relevant in Indian contest for non-adherence and thus continuous reinforcement of importance of the treatment, periodic clinical monitoring, confirmation of effect of treatment and addressing ignorance and myths of patients and setting up of the priorities of their treatment for co-morbid conditions shall go a long way to ameliorate the associated morbidity and mortality associated with OP fracture in PMW. Moreover, cost of treatment is an issue which at the highest government level can be addressed by including this group of drug along with calcium and vitamin D therapy in essential drug list making them most affordable to general masses. Treatment compliance was particularly poor for calcium and vitamin D and this emphasizes the need for new ways of supplementation of calcium and vitamin D.

The result of the current study strongly recommend the need of extensive pre and continuous post-treatment counseling with regard to their disease, details and importance of treatment of OP and the need for follow-up by the prescribing doctor.

There is a limitation of our study that is no attempt was made to confirm the compliance by undertaking BMD or fracture prevention analysis in the current study. A baseline and follow-up BMD should be included in management protocol to ensure compliance.

Other strategies to enhance adherence such as reducing administration frequency, monitoring patients with bone markers, providing adequate instructions, physician feedback support, providing educational materials and undertaking educative session during follow-ups shall go a long way to improve the compliance of BF.

CONCLUSION

Treatment compliance is poor with daily ALN, weekly RIS and monthly IBN along with calcium and vitamin D3 in Indian PMW suffering OP. Concomitant treatment for co-morbid condition, unawareness about their OP, cost of treatment, belief that drugs is for their general disability and physician's failure to stress the need are some of the common factors for non-compliance. Future studies are needed to design strategies to increase adherence to OP medications.

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How to cite this article: Tandon VR, Sharma S, Mahajan S, Mahajan A, Khajuria V, Gillani Z. First Indian prospective randomized comparative study evaluating adherence and compliance of postmenopausal osteoporotic patients for daily alendronate, weekly risedronate and monthly ibandronate regimens of bisphosphonates. *J Mid-life Health* 2014;5:29-33.

Source of Support: Nil, **Conflict of Interest:** None declared.