

Efficacy, Side Effects, Safety and Effects on Bone Turnover Markers of once a Week Sandoz Alendronate Sodium Trihydrate 70 mg

Waikakul S, MD, FRCOST, Sintuvanich N, MD, Assanasuwan T, BSc, Soparat K, MSc(Stat), MSc(Nurses)
Department of Orthopaedic Surgery, Mahidol University, Bangkok, Thailand

ABSTRACT

This open trial study was carried out to evaluate safety, side effects and efficacy of once a week alendronate sodium trihydrate (Sandoz, Pymant, Australia) for inhibiting bone resorption and bone turnover in 35 postmenopausal osteoporotic patients. Serum beta crosslaps was used to evaluate bone resorption, Serum N-MID osteocalcin to estimate overall bone turnover, and serum PINP to estimate bone formation. The patients received the drug every week for 12 weeks. They were examined and evaluated for pain, side effects and bone turnover markers at 6 weeks and 12 weeks after the first dose. Eleven patients had mild side effects, with only one requiring ceasing participation in the trial. At the 12 week follow up, 85.3% had normal serum beta crosslap and all patients had normal serum N-MID osteocalcin. Low serum PINP was found in 6 patients. All patients had significantly improved pain. The trial drug normalizes bone turnover markers in acceptable numbers of patients during the trial.

Key Words:

Osteoporosis, Bone turnover markers, Bisphosphonates

INTRODUCTION

Alendronate is a commonly used antiresorption drug for the prevention of osteoporotic fracture¹. The main mechanism by which this drug works is through apoptotic induction of osteoclasts². Long term use of the drug resulted in the prevention of both primary and secondary osteoporotic fractures³⁻⁵. Alendronate is usually administered to postmenopausal women with bone mineral density (BMD) less than -2.5 and high bone turnover rate, high serum beta crosslaps and N-MID osteocalcin⁶⁻⁸. The original drug, Fosamax®, results in rather rapid onset for inhibition of bone resorption which in turn causes normalization of serum beta crosslaps and serum N-MID osteocalcin in all patients within 12 weeks⁹⁻¹¹. Recently, many generic alendronate formulations have appeared on the market with lower costs of treatment. One of the most interesting generic drugs is the

once a week Sandoz formulation of oral alendronate sodium trihydrate 70mg, which has an encouraging pharmacologic profile. The aim of this study was to investigate the side effects, safety and efficacy of this generic drug including effect on bone turnover markers.

MATERIALS AND METHODS

For sample size calculation, we estimated that 90% of the patients would have normal serum beta crosslap 12 weeks following initiation of alendronate sodium trihydrate 70 mg (Sandoz) administration with an alpha error of 0.05. Utilising nQuery advisor software, Version POCO-1 for Windows, we calculated that the sample size should be 35.

The study was conducted through the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University. Patients were interviewed and physical exams were conducted before beginning the trial. T-scores for BMD below -2.5 at the spine and femoral neck compared to normal young adults were used to diagnose osteoporosis. Blood tests including complete blood count (CBC), fasting blood sugar, uric acid, renal and liver function tests and serum bone turnover markers were conducted in the patients before the trial. Bone turnover markers included: 1) serum parathyroid hormone to check for the possibility of secondary osteoporosis (normal value, 15.00 – 65.00 pg/ml); 2) serum beta crosslap for evaluation of bone resorption (normal value, < 0.32 ng/ml); 3) serum N-MID osteocalcin for evaluation of overall bone turnover rate (normal value, 1.00 – 35.00 ng/ml) and 4) serum procollagen type 1 amino-terminal propeptide (PINP) for evaluation of new bone formation (normal value, 15.00 – 74.00 ng/ml). The bone turnover marker test kits were the products of Roche Diagnostic Company.

Inclusion criteria were: 1) post menopausal osteoporosis with one, or more than one, clinically healed osteoporotic fracture; 2) patients who had T-scores of bone mineral density of the spine and femoral neck below -2.5, compared

to normal young adults, measured by DEXA; 3) normal laboratory results including complete blood count, fasting blood sugar, renal and liver function; 4) normal to high serum N-MID osteocalcin, high serum beta crosslaps (>0.32 ng/ml) and normal to high serum PINP; and 5) no history of having received any medication for the treatment of osteoporosis including bisphosphonates before the study. Exclusion criteria were 1) upper gastrointestinal problems including dyspepsia, peptic ulcer and gastroesophageal reflux disorders (GERD); 2) patients who could not be followed up as per the study schedule; 3) patients who did not want to continue the medication and laboratory tests; 4) patients who could not sit quietly for half an hour after taking the drug and 5) patients who did not want to participate or continue with the study for any other reason. A volunteer who was not a medical professional and was not an author introduced the trial to the patients at our osteoporosis clinic. About 85% of the patients who were asked agreed to participate.

Patients gave written informed consent to participate in the study, and were instructed that they could choose to discontinue participation in the trial at any time. This study was approved by the Siriraj Ethics Committee, project number 239/2552 (ECI), 31/07/2552.

Biographic data of the patients and pain characteristics were recorded. Pain severity at or around fracture sites was evaluated with the use of a visual analogue scale (VAS, possible scores 0-10, with higher numbers indicating more severe pain). Pain in other areas was also assessed and recorded. Associated and underlying diseases of the patients were reviewed and recorded. All laboratory tests, plain radiographs and T-scores of BMD of the patients were rechecked and recorded.

Following the enrollment procedures noted above, study participants were prescribed once a week, oral alendronate sodium trihydrate (Sandoz, Pyrmant, Australia) of 70 mg. The patients were instructed to take the drug in the morning before breakfast with a glass of water. They had to sit quietly for at least half an hour after taking the drug before taking part in any activities or eating their breakfasts. Patients were also prescribed an oral multivitamin with 800 IU of vitamin D and 1,000 mg of calcium carbonate per day for the study period. Paracetamol and NSAIDs were prescribed to be taken as needed for patients who still had pain related to osteoporosis or other musculoskeletal conditions continuing during the study.

Follow-up visits were conducted at the end of the 2nd, 6th and 12th week following the first study medication dose. Physical examination, re-evaluation of pain, and evaluation of drug side effects were performed and the results were recorded. At the 6th and 12th week follow up laboratory tests for CBC, renal function, liver function and bone

turnover markers were performed. In particular patients, who still had severe pain at follow-up visits (VAS > 30 , at the fracture site or related areas underwent physical examination, plain radiography and all indicated blood tests to check for any other possible underlying conditions.

Descriptive analysis was conducted for all data. Student-T test was used for analysing continuous data. Chi-square test and analysis of variance were used for analysing discrete data.

RESULTS

Thirty-five postmenopausal osteoporotic patients with healed fractures were enrolled and 34 completed the trial. Their ages ranged between 51 and 89 years with an average of 72.74 ± 9.51 years. All patients were female. Participant BMI ranged between 18.49 and 33.68 with an average of 23.41 ± 3.47 . Twenty-four patients (68.6%) had associated osteoarthritis and most had knee complaints. One patient had degenerative disease of the spine. All patients had osteoporotic fractures: 27 spinal fractures, 5 fractures in the hip region, 2 Colles fractures and 1 fracture of the femoral condyle. All patients had clinical and radiological fracture healing. Deformities of the spine were found in 19 patients (54.3%), kyphosis in 16 patients and scoliosis in three patients. Diabetes mellitus with good control was present in 13 patients (37.1%).

Before the trial, all patients had significant pain with VAS > 3 , mean 6.23 ± 1.81 , (Table I). All patients had normal renal and liver function according to laboratory results. Additionally, all patients had normal serum parathyroid hormone with an average of 47.46 ± 18.55 pg/ml; normal to high serum N-MID osteocalcin; mean 26.34 ± 9.92 ng/ml; serum PINP, 67.28 ± 33.68 ng/ml; and high serum beta crosslap, >0.32 ng/ml, with an average of 0.59 ± 0.23 ng/ml (Table I).

At the 2 week follow up, significant improvement in pain was noted in 20 of 35 (57.1%), patients with an average VAS of 3.37 ± 2.82 (Table I). Seven patients experienced mild side effects including; nausea in 1, dyspepsia in 2, oedema in 1 patient, and muscle pain in 3 patients (Table II), although all patients were able to continue the trial.

After trial drug administration for 6 weeks, 30 patients (85.7%) reported significant improvement in pain with an average VAS score of 2.62 ± 3.07 (Table I). Twenty-nine patients reported mild pain with VAS < 3 . Thirty-three patients continued with normal results for blood sugar, renal and liver function tests; 2 patients had increased serum alkaline phosphatase. Normal serum parathyroid hormone, N-MID osteocalcin and PINP was noted in most patients, and normal serum beta crosslap, <0.32 ng/ml, in 24 patients, 68.6% (Figure 1). The trial was continued in six patients who experienced mild side effects from the trial drug at the 2nd week follow up, but one patient with progressively worsening

Table I: Changes of pain severity, serum alkaline phosphatase and bone turnover makers

Pain Laboratory test	Before trial N = 35	At 2nd week N = 35	At 6th week N = 35	At 12th week N = 34	P value Student t-test
Visual analog scale	6.23± 1.81	3.37±2.82	2.62± 3.07	1.68± 2.83	0.001
Alkaline phosphatase (IU)	72.88±28.22	-	76.80±25.72	70.13±32.82	0.91
PTH (ng/ml)	47.46±18.55	-	63.47±30.05	61.66±31.23	0.038
Beta cross lab (ng/ml)	0.59± 0.23	-	0.20± 0.15	0.21± 0.15	0.001
N-MID osteocalcin (ng/ml)	26.34± 9.92	-	22.56± 8.76	18.80± 6.68	0.071
P1NP (ng/ml)	67.28±33.68	-	43.44±24.10	32.66±22.52	0.021

Table I: Numbers of the patients who had side effects of the trial drug during the follow up.

Side effects	Before trial N = 35	At 2nd week N = 35	At 2nd week N = 35	At 2nd week N = 34
Nausea	-	1	1	1
Vomiting	-	-	-	-
Dyspepsia	-	2	2	3
Muscle pain	-	3	3	4
Edema	-	1	1	2
Fever	-	-	-	1
Total	-	7	7	11 (+1)

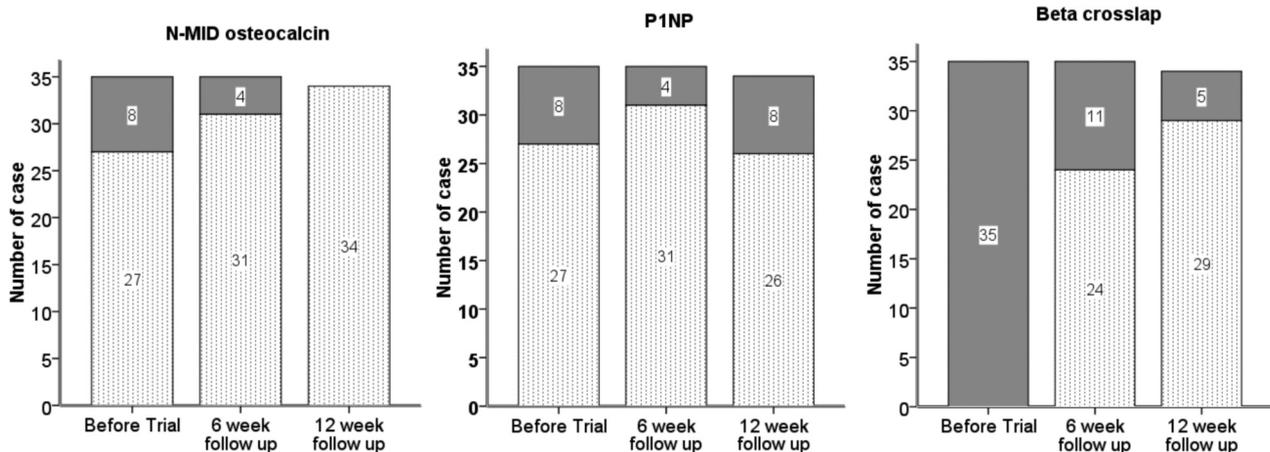


Fig. 1: Changes of bone turnover markers.

nausea discontinued the trial. That same patient also had a significant increase in serum alkaline phosphatase. No new cases of side effects were reported at the 6 week follow up (Table II).

At the 12 week follow up, all patients reported minimal pain with VAS <3 with an average of 1.68±2.83 (Table I). Thirty-four patients had normal laboratory results for renal and liver function, except one patient who still had a slightly increase serum alkaline phosphatase continuing from the 6 week follow up. Although the 12 week serum alkaline phosphatase was higher than normal, it was lower than at the 6 week follow up. She had no other side effects. Five additional patients

experienced mild side effects at the 12 week follow up (nausea in 1, dyspepsia in 1, muscle pain in 1, oedema in 1, and fever in 1 patient; Table II). There were 11/34 patients, 32.3%, who had mild side effects and the trial drug could be continued until the end of the 12 weeks. Serum parathyroid hormone was below normal in 1 and normal to slightly high in 33 patients. All patients had normal N-MID osteocalcin with an average of 18.8±6.68 (Figure 1). Eight patients had abnormal serum P1NP, with 6 patients below normal and 2 patients with high serum P1NP; 26 patients had normal P1NP (Figure 1). Serum beta crosslap was <0.32 ng/ml in 29 (85.3%) patients, and 5 patients still had serum beta crosslap >0.32 ng/ml (Figure 1).

DISCUSSION

The finding of normalized serum beta crosslap in 85.3% of the patients after 12 weeks of alendronate sodium trihydrate (Sandoz, 70mg) confirmed efficacy for inhibition of bone resorption Figure I. In previous practice at our institution, the original drug, Fosamax[®], also normalized serum beta crosslap in all postmenopausal osteoporotic patients with high bone turnover within 12 weeks. Thus, trial drug was slightly less efficacious than the original drug.

Serum parathyroid hormone slightly increased at the 6 week follow up, which may be the results of changing serum calcium due to the effects of the drug (Table II). However, serum parathyroid hormone of most patients decreased to previous levels at the 12 week follow up. Serum N-MID osteocalcin of most patients was normal at the 6 and 12 week follow up, indicating good bone turnover suppression due to the trial drug (Figure 1). At the 12 week follow up, 6 patients (17.6%) had low serum P1NP which revealed low bone formation or over-suppression of bone formation. This finding is commonly found in the patients who used the original drug. Two patients experienced an increase in serum alkaline phosphatase. There was no clear explanation for this issue as alendronate has no direct effect on liver function and there was no similar report from our literature review. Close observation in more patients may be needed when the trial drug is used again.

Interestingly, all patients reported significantly improved pain during the trial, which may be the result of both bone anti-resorption effects of the trial drug and the use of pain medication. As pain medication before and during the 12 week-trial was similar, we hypothesize that the trial drug may have provided significant pain improvement.

Side effects were experienced in 34.3% of the patients during the trial, but discontinuation of the trial drug was necessary in only one patient. Alendronate is slowly absorbed and carries a rather high risk of oesophageal irritation^{14, 15}. Various preparations of once a week 70 mg alendronate on the market in most ASEAN countries contain different ratios of alendronate monosodium and alendronate sodium trihydrate. Changes in the ratio may cause differences in drugs pharmacokinetics and pharmacodynamics, which may result in different outcomes in terms of side effects and inhibition of bone resorption. Various formulations of generic alendronate on the markets vary in disintegration time, between 14 to 342 seconds¹⁶. Alendronate with shorter

disintegration time usually have better drug absorption but may result in increased incidence of oesophageal irritation. On the other hand, drugs with longer disintegration times will usually result in poorer drug absorption but they decreased incidence of oesophageal irritation. The original drug, Fosamax[®], has a disintegration time of 86 seconds^{17, 18}, and a prevalence of oesophageal and gastrointestinal complication of approximately 2 – 3 % which was comparable to placebo^{15, 19}. In the present trial, 5 patients (14.3%) had mild to moderate oesophageal and gastrointestinal side effects with nausea in 2 patients and dyspepsia in 3 patients. This increased percentage of oesophageal and upper gastrointestinal complication may be due to the shorter disintegration time of the trial drug formulation; of note, our findings regarding gastrointestinal side effects of this generic alendronate are comparable to some previous reports of studies in other generic formulations¹⁹⁻²¹.

Although the trial drug was slightly less efficacious for bone resorption inhibition and we found higher prevalence of side effects than the original drug, this generic formulations costs 30 - 45% less for treatment when compared to the original drug. Thus, the trial formulation may be suitable for primary osteoporotic fracture prevention in patients who cannot afford the cost of the original drug. The drug is also suitable for the patients in developing countries where per capita annual income is less than \$5,000 US. It is important that patients be notified of the slightly higher chance of mild GI side effects than the original drug. Longer term studies are needed to test efficacy of the trial formulation for prevention of osteoporotic fractures.

CONCLUSION

Once a week oral alendronate sodium trihydrate (Sandoz, 70 mg) normalized serum bone turnover markers in an acceptable number of postmenopausal patients who had high bone turnover prior to the trial. However, mild GI complications were more common in patients prescribed the trial formulation when compared to patients taking the original drug, Fosamax[®].

DISCLOSURE

This study was fully supported by Sandoz Business Unit, Novartis Thailand.

REFERENCES

1. Lin JH, Russell G, Gertz B. Pharmacokinetics of alendronate: an overview. *Int J Clin Pract* 1999; 101(Suppl): 18-26.
2. Sharpe M, Noble S, Spencer CM. Alendronate: An update of its use in osteoporosis. *Drugs* 2001; 61(7): 999-1039.
3. Boonen S, Laan RF, Barton IP, Watts NB. Effect of osteoporosis treatments on risk of non-vertebral fractures: Review and meta-analysis of intention-to-treat studies. *Osteoporos Int* 2005; 16(10): 1291-8.
4. Nguyen ND, Eisman JA, Nguyen TV. Anti-hip fracture efficacy of bisphosphonates: A Bayesian analysis of clinical trials. *J Bone Miner Res* 2006; 21(2): 340-9.
5. Holder KK, Kerley SS. Alendronate for fracture prevention in postmenopause. *Am Fam Physician* 2008; 78(5): 579-81.
6. Camacho PM, Lopez NA. Use of biochemical markers of bone turnover in the management of postmenopausal osteoporosis. *Clin Chem Lab Med* 2008; 46(10): 1345-57.
7. Soontrapa S, Soontrapa S, Bunyaratavej N. Serum concentration of undercarboxylated osteocalcin and the risk of osteoporosis in Thai elderly women. *J Med Assoc Thai* 2005; 88(Suppl 5): S29-32.
8. Garnero P. Biomarkers for osteoporosis management: Utility in diagnosis, fracture risk prediction and therapy monitoring. *Mol Diagn Ther* 2008; 12(3): 157-70.
9. Zikan V, Stepan JJ. Marked reduction of bone turnover by alendronate attenuates the acute response of bone resorption marker to endogenous parathyroid hormone. *Bone* 2009; 44(4): 634-8.
10. Chailurkit LO, Jongjaroenprasert W, Rungbunnapun S, Ongphiphadhanakul B, Sae-tung S, Rajatanavin R. Effect of alendronate on bone mineral density and bone turnover in Thai postmenopausal osteoporosis. *J Bone Miner Metab* 2003; 21(6): 421-7.
11. Chailurkit LO, Aunphongpuwanart S, Ongphiphadhanakul B, Jongjaroenprasert W, Sae-tung S, Rajatanavin R. Efficacy of intermittent low dose alendronate in Thai postmenopausal osteoporosis. *Endocr Res* 2004; 30(1):29-36.
12. Bunyaratavej N. Practical experience in some aspects of bone markers. *J Med Assoc Thai* 2009; 92(Suppl5): S116-20.
13. Bunyaratavej N, Kitimanon N, Boonthitikul S. Study of the level of biochemical bone markers: NMID osteocalcin and bone resorptive marker (beta CTx) in Thai women. *J Med Assoc Thai* 2001; 84(Suppl 2): S560-5.
14. Biswas PN, Wilton LV, Shakir SA. Pharmacovigilance study of alendronate in England. *Osteoporos Int* 2003; 14(6): 507-14.
15. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. *Int J Clin Pract* 1999; 101(Suppl): 51-61.
16. Dansereau RJ, Crail DJ, Perkins AC. In vitro disintegration studies of weekly generic alendronate sodium tablets (70 mg) available in the US. *Curr Med Res Opin* 2009; 25(2): 449-52.
17. Porras AG, Holland SD, Gertz BJ. Pharmacokinetics of alendronate. *Clin Pharmacokinet* 1999; 36(5): 315-28.
18. Alendronate monograph. USP 33, NF 28. Available at URL:<http://www.uspnf.com>
19. Dansereau RJ, Crail DJ, Perkins AC. In vitro disintegration and dissolution studies of once-weekly copies of alendronate sodium tablets (70 mg) and in vivo implications. *Curr Med Res Opin* 2008; 24(4): 1137-45.
20. Grima DT, Papaioannou A, Airia P, Ioannidis G, Adachi JD. Adverse events, bone mineral density and discontinuation associated with generic alendronate among postmenopausal women previously tolerant of brand alendronate: a retrospective cohort study. *BMC Musculoskelet Disord* 2010; 11: 68.
21. Bunyaratavej N. Bisphosphonate in general view. Bone forum 2011. Bangkok: *Concept Medicus* 2011: 33-41.