

Paper

# Recombinant PTH: A Study of the Outcome of Teriparatide Therapy for 138 Patients with Osteoporosis

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## ABSTRACT

**Introduction:** Osteoporosis results in significant morbidity and mortality for a large number of patients within Northern Ireland. Recombinant PTH (Teriparatide) is one of a growing number of treatment options for the disease.

**Methods:** A retrospective analysis was carried out for all patients who had been commenced on Teriparatide since it was first used in the Belfast Health and Social Care Trust (BHSCT) in 2007. Patient demographics, clinical history and prior treatment were recorded prior to an eighteen month treatment protocol. Outcome measures including bone densitometry, bone turnover markers and health status were assessed on commencement and completion.

**Results:** 138 patients have commenced teriparatide therapy since 2007 (9 male, 129 female). At the time of analysis 60 patients had completed treatment, 53 patients were receiving ongoing treatment and 25 patients did not complete the 18 month course. On completion vertebral bone mineral density (BMD) had increased by 8.3% while femoral neck BMD had increased by 3.5%. Bone turnover markers demonstrated a significant increase of bone formation and resorption at 4 months, with a smaller increase at 18 months. Health outcome measures (EuroQoL-5 and patient visual analogue scale) indicated improvement in the quality of life of patients of those who completed the treatment course.

**Conclusions:** Experience in the BHSCT with teriparatide since 2007 demonstrates improvement in BMD comparable to published data, changes in bone turnover markers consistent with increased bone remodeling and better health outcomes for patients.

**Keywords:** Osteoporosis, Teriparatide, Bone Density, Bone Turnover Markers, Outcome

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## INTRODUCTION

Osteoporosis has been estimated to affect over 2 million people in the UK.<sup>1</sup> Mistaken as a silent disease it has significant consequences in terms of morbidity and mortality to those afflicted. Calculation of Disability Adjusted Life Years indicates that osteoporosis has a greater impact than most types of cancer.<sup>2</sup> Hip fractures alone are calculated to cost the National Health Service £2 billion per year.<sup>3</sup>

Osteoporosis has been defined as a bone mineral density (BMD) of more than 2.5 standard deviations below the average value.<sup>4</sup> Post-menopausal women are most at risk as falling oestrogen levels cause an increase in bone turnover at the expense of bone microarchitecture and subsequent bone strength.<sup>5</sup>

Teriparatide, recombinant human PTH (1-34), is an anabolic agent indicated in the treatment of osteoporosis. By stimulating osteoblast activity it causes increased bone formation with resultant improved bone strength and mass.<sup>6,7</sup>

Administration is by a once daily subcutaneous injection. Phase III data by Neer et al<sup>8</sup> showed an increase of 9% in BMD at the lumbar spine with a more modest 3% increase

at the neck of femur after 18 months treatment. There was a corresponding reduction in vertebral fractures from 14% on placebo to 5% with active treatment. Initially licensed for a duration of 18 months, extension trials showed further benefit up to 24 months<sup>9</sup> and the licence has changed accordingly.

The National Institute for Health and Clinical Excellence (NICE) issued guidance in 2008 limiting teriparatide use to post-menopausal women who are 65 years or older and have a T-score of  $-4.0$  SD or below, or a T-score of  $-3.5$  SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of  $-4$  SD or below plus more than two fractures.<sup>1</sup>

To date, NICE has not issued guidance for male patients. However trial data demonstrates teriparatide has similar benefits in male patients with significant increases in BMD and reduction in fracture risk.<sup>10</sup>

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Within the Belfast Health and Social Care Trust (BHSCT) teriparatide has been in use since 2007. The aim of this study is to review the clinical experience with Teriparatide so far, assessing compliance with NICE guidance and the clinical outcomes following treatment.

## METHODS

As of January 2011, 138 patients (129 female, 9 male) had been commenced on teriparatide in the BHSCT. Each patient had been under regular review by the regional osteoporosis service. They were put forward for teriparatide after consultant review deemed it necessary.

Baseline data was collected as part of the initial assessment and subsequent review, then entered into a database used to monitor patients progress while taking the drug. Patient consent for storage of personal information was sought at the time of starting teriparatide. Ethical approval was not sought for this study as the analysis relates to a retrospective review of teriparatide administration.

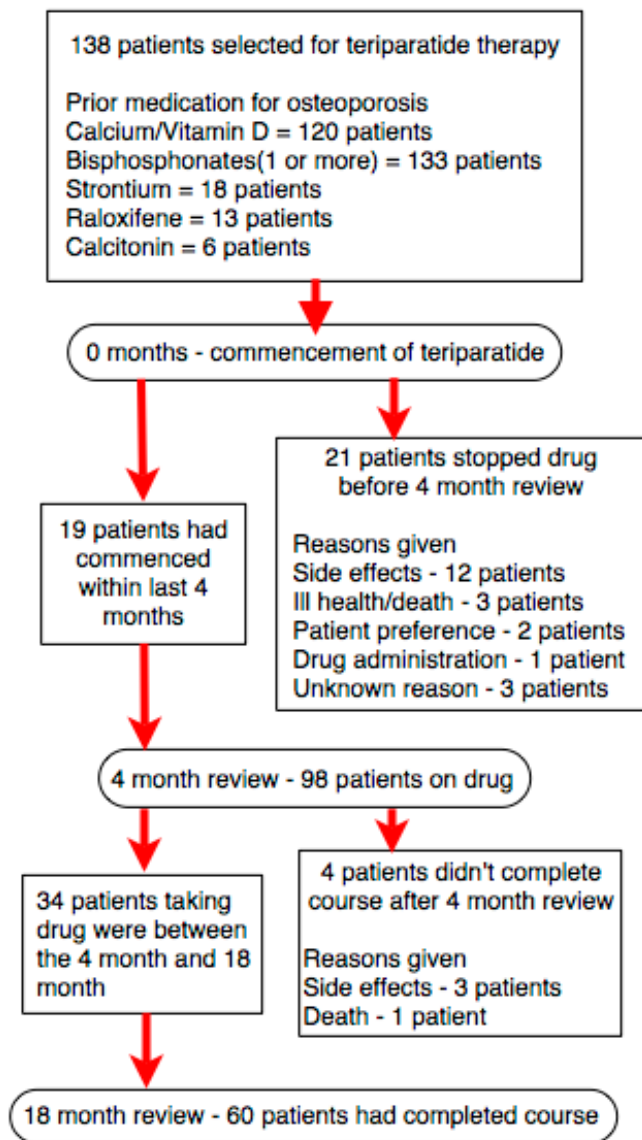


Fig 1. Progressive of patients through treatment course

At the time of analysis a total of 60 patients had completed a full 18 month treatment course, while 25 patients had stopped taking the drug prior to completing the treatment course and 53 patients were still in the process of completing their treatment regime. (Fig 1)

Bone mineral density at the lumbar spine and femoral neck was assessed using dual-energy x-ray absorptiometry at baseline and completion of treatment. The reference population for hip measurements included NHANES gender and ethnically matched populations<sup>11</sup>, with the manufacturer Hologic and Lunar reference populations for spinal measurements<sup>12,13</sup>. Measurements are given in g/cm<sup>2</sup> and also in terms of standard deviation (SD) to the reference populations above.

Bone turnover was assessed using two markers measured at baseline, 4 months and on completion of treatment. PINP (Procollagen type 1 N-terminal Propeptide) is a measure of bone formation (normal range 20.3 - 76.3 ng/mL) while CTX (C-terminal Telo peptide Collagen breakdown product) is a measure of bone resorption (normal range: female <1.008 pg/mL, male <0.854 pg/mL). These were measured in the Royal Victoria Hospital by immunoassay<sup>14</sup>

Two different patient-reported measures of health status were performed at commencement and completion of the treatment course. EuroQoL-5 is a validated measure of patient quality of life involving five items of patient health, specifically: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression<sup>15</sup>. Each item is coded using 3-levels (1 = no problems; 2 = some problems; 3 = severe problems). Calculation of the EuroQoL-5 gives a range of results varying from -0.549 to 1 (-0.549 represents worse possible health state, 0 equates with death and 1 correlates with perfect health).

Secondly, a visual analog scale (VAS) of current health state, ranging from 0 (worst imaginable) to 100 (best imaginable), was used. It has been validated as a tool to measure global rating of current health<sup>16</sup>.

An online Wilcoxon rank sum test was used to assess change in BMD and health outcome measures<sup>17</sup>. The test was carried out two tailed and considered significant if  $p < 0.05$ . Standard error of the mean was used to interpret change in bone turnover markers.

## RESULTS

Prior to commencement of teriparatide the mean number of vertebral fractures was 4.3/pt and non-vertebral fractures was 1.4/pt. The prior medication use for osteoporosis is noted in fig 1. Of the 129 female patients commenced on teriparatide, 59.6% of them met the criteria suggested by NICE for when patients should receive the drug<sup>1</sup>.

The mean age of patients at commencement was 74.0 years (Standard error (SE) - 0.72 yrs) with a range from 46 to 90. (fig 2)

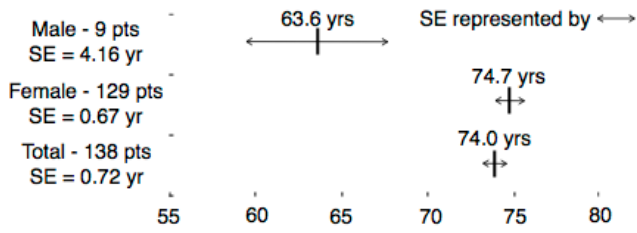


Fig 2. Age at commencement of teriparatide

**VERTEBRAL BMD**

At commencement, mean vertebral BMD was 0.715 g/cm<sup>2</sup> with a mean T score of -3.52 SD (total 118 patients). Following 18 months treatment the mean vertebral BMD was 0.772 g/cm<sup>2</sup> with a mean T score of -3.09 SD (total 53 patients).

A complete data set was available for 49 patients of vertebral BMD at commencement and completion. For this subgroup, initial mean spinal BMD was 0.707 g/cm<sup>2</sup> (T-score -3.67 SD) and on completion mean vertebral BMD was 0.766 g/cm<sup>2</sup> (T-score -3.16 SD). There was a 8.3% increase in vertebral BMD following 18 months of teriparatide treatment (p=0.031).

**FEMORAL NECK BMD**

At commencement, mean femoral neck BMD was 0.574 g/cm<sup>2</sup> with a mean T score of -2.88 SD (total 127 pts). Following 18 months treatment the mean femoral neck BMD was 0.592 g/cm<sup>2</sup> with a mean T score of -2.80 SD.

A complete data set was available for 52 patients of femoral neck BMD at commencement and completion. For this subgroup, initial mean femoral neck BMD was 0.576 g/cm<sup>2</sup> (T-score -2.83 SD) and on completion mean femoral neck BMD was 0.596 g/cm<sup>2</sup> (T-score -2.78 SD). There was a 3.5% increase in femoral neck BMD following 18 months of teriparatide treatment (p=0.455).

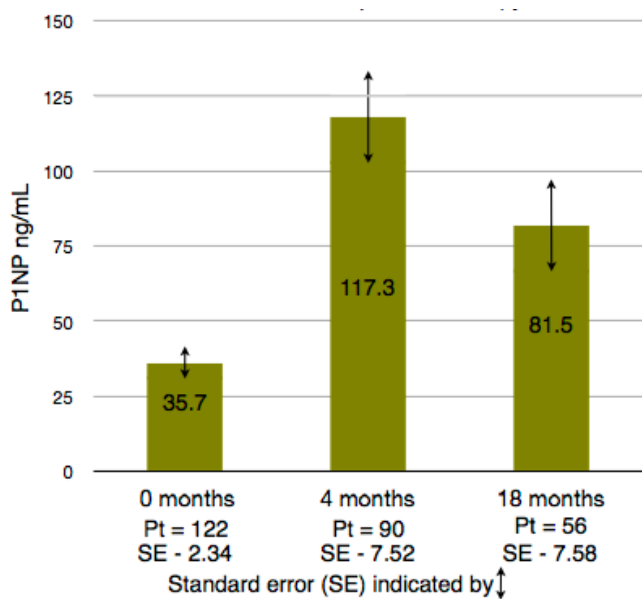


Fig 3. Change in mean P1NP level over the duration of Teriparatide therapy

**BONE TURNOVER MARKERS**

P1NP (normal range 20.3 - 76.3 ng/mL)

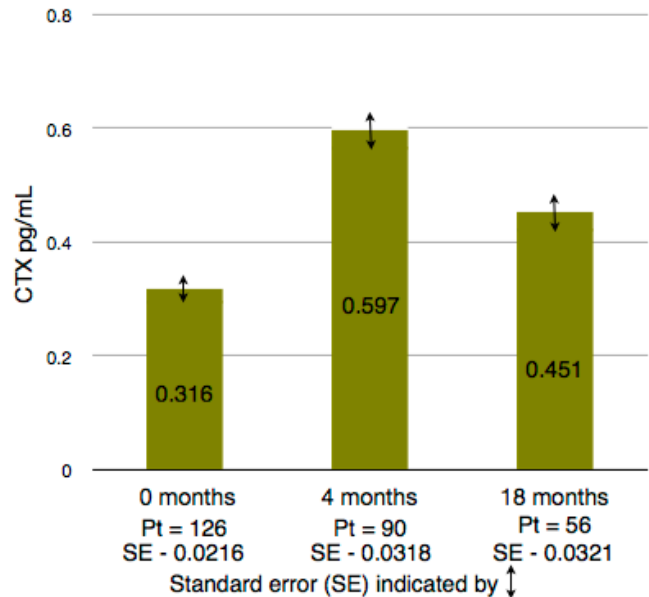


Fig 4. Change in mean CTX level over the duration of Teriparatide

At commencement the mean P1NP level for 122 patients was 35.7 ng/mL (SE - 2.34). At 4 months of treatment the mean P1NP was 117.3 ng/mL (SE - 7.52) for a total of 90 patients. On completion of the 18 month course the mean P1NP value was 81.5 ng/mL (SE - 7.58) for a total of 56 patients. (fig 3)

CTX (normal range: female <1.008 pg/mL, male <0.854 pg/mL)

At commencement the mean CTX level for 126 patients was 0.316 pg/mL (SE - 0.0216). At 4 months of treatment the mean CTX was 0.597 pg/mL (SE - 0.0318) for a total of 90 patients. On completion of the 18 month course the mean CTX value was 0.451 pg/mL (SE - 0.0321) for a total of 56 patients. (fig 4)

**HEALTH OUTCOME MEASURES**

29 patients contributed sufficient information to fulfill a complete data set of health outcome measures. On starting mean EuroQoL-5 was 0.450 (SE - 0.306) improving to a value of 0.611 (SE - 0.256) after 18 months (p=0.008).

Mean patient-reported VAS on commencement was 53.2 (SE - 11.9) with an increase to 64.3 (SE - 18.6) on completion (p=0.003). However these two results have to be approached with caution as 31 of the 60 patients who completed the treatment schedule didn't supply any health outcome data.

**DISCUSSION**

In the treatment of osteoporosis, teriparatide represents a viable second line treatment option after standard therapy has proved unhelpful. The use of teriparatide in daily practice has been restricted based on the guidance by NICE which advocates it's use after key clinical criteria have been met.

Our study demonstrates the experience in daily clinical practice of teriparatide therapy when utilized in the outpatient setting.

In the original phase III trials for teriparatide the mean vertebral BMD was approximately 0.820 g/cm<sup>2</sup> and at femoral neck was 0.640g/cm<sup>2</sup>(8). Only 15% of patients had been on previous osteoporotic therapy and the history of vertebral fractures averaged 2.3±1.8(8). This represents a considerable variation from the typical patient in this study. Our reported fracture incidence is considerably higher while all patients had been on some form of osteoporotic therapy prior to teriparatide. Initial BMD values in our cohort showed a value of 0.722 g/cm<sup>2</sup> (T-score -3.52 SD) at the spine and a value of 0.570 g/cm<sup>2</sup> (T-score -2.91 SD) at the femoral neck.

Therefore patients commenced on teriparatide in the BHSCT represent osteoporosis patients with much lower BMD values, implying that their disease was more advanced and that they had accumulated more damage from fractures related to their disease. The guidance by NICE for selection of patients suitable for teriparatide will identify those patients with more advanced disease and this is reported in our study population.

However only 59.6% of our study population started on teriparatide have met NICE guidance for commencement of the drug. There are a number of considerations when assessing this figure. With more advanced osteoporosis there will naturally be more accumulation of osteoporotic damage. This will have an effect on BMD assessment by DEXA scanning where the presence of an osteoporotic fracture will give an artificially higher BMD reading at that vertebral level, resulting in a higher average BMD reading across the spine despite the presence of significant vertebral osteoporosis.

Another potential confounding factor is that the group of patients put forward for teriparatide in the BHSCT will also include patients who have been intolerant or have had complications with prior osteoporotic medication. Where there is ongoing need for osteoporotic treatment and all other treatment options have failed, teriparatide may have been used as the only alternative treatment despite patients not fully meeting NICE guidance.

In our study, we report improvement of vertebral BMD of 8.3%, which was statistically significant, and femoral BMD of 3.5% over the treatment course. The percentage changes in BMD is comparable with the data reported in the initial trials where there was a reported improvement in vertebral BMD of 9% and femoral neck BMD of 3%(8). Both these changes were significant as the studied population was much larger than in our case.

Measurement of P1NP and CTX in our population suggests correlation with the known increase in bone formation and bone turnover that occurs with teriparatide therapy. Within the limits of our measurements it appears bone turnover reaches a peak after commencement. At the completion of the treatment course both markers remain elevated but at a lower level than when measured at four months.

Studies have shown that P1NP levels correlate with the formation of new bone and have been demonstrated to rise on initiation of treatment, remaining elevated for over a year(18). There is also the suggestion that monitoring of P1NP levels shortly after starting the drug may be a useful means of identifying patients who will respond to teriparatide therapy(19). CTX levels have been shown to drop in the first 2-3 weeks of teriparatide therapy before there is evidence of increased bone turnover.(20) It has not been possible to demonstrate this in our population due to the timing of CTX measurement.

The measurement of health outcome using EuroQoL-5 and patient reported VAS may indicate an improvement on quality of life following teriparatide treatment. However there are significant deficiencies in data to draw any meaningful conclusions from this. With 31 patients who completed treatment not supplying responses for health outcome and 25 patients not completing the treatment course the true picture is not clear.

As teriparatide was being given over an 18 month duration it is inevitable that there will be a number of patients who are unable to complete the course. Other co-morbidities will develop which take precedence over the treatment of osteoporosis while changes in health status will alter a patient's ability to self inject. Side effects secondary to the medication itself will also have a bearing, as highlighted in our case by the 14 patients out of 25 who cited it as a reason for stopping the drug.

A total of 25 patients not completing the 18 month treatment course may seem to be a significant proportion, however compliance with other osteoporotic medication is considerably worse. Patients persisting with bisphosphonate therapy after 1 year of commencing has been reported to be anywhere between 18% and 78%(21).

As our study is based in daily clinical practice the non-completion of the treatment course by 25 patients would be comparable with the percentages highlighted above. However this number of patients not finishing the course will limit the degree to which the final results can be extrapolated to other populations.

## CONCLUSION

This study demonstrates the efficacy of teriparatide therapy for patients in clinical practice with severe osteoporosis, with significant gains in bone mineral density at both the spine and hip comparable to outcome data reported in phase III trials. The adherence to treatment in clinical practice was good with few reported side effects.

The authors have no conflict of interest. We gratefully acknowledge the assistance of Dr Hugh Taggart and Dr Pooler Archbold in obtaining information from subjects treated at Belfast City Hospital.

The authors have no conflict of interest



## REFERENCES

1. National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE Technology Appraisal Guidance 161. London: NICE; 2008. Available from: <http://www.nice.org.uk/nicemedia/live/11748/42508/42508.pdf>. Last accessed March 2013.
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;**17**(12): 1726-33
3. National Osteoporosis Society. Promoting fragile bones: a strategy to reduce the impact of osteoporosis and fragility fractures in England. Bath, England: National Osteoporosis Society; 2009. Available from: <http://www.nos.org.uk/document.doc?id=491>. Last accessed March 2013.
4. World Health Organization. WHO Scientific Group on the assessment of osteoporosis at Primary Health Care Level. Summary meeting report. Brussels, Belgium, 5-7 May 2004. Geneva: WHO; 2007. Available from: <http://www.who.int/chp/topics/Osteoporosis.pdf>.
5. Pietschmann P, Rauner M, Sipos W, Kersch-Schindl K. Osteoporosis: an age-related and gender-specific disease--a mini-review. *Gerontology*. 2009; **55**(1): 3-12
6. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, *et al*.
7. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med*. 2005;**165**(15):1762-8.
8. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. The effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. *J Bone Min Res*. 2007; **22**(1): 149-57
9. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;**344**(19): 1434-41
10. Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, EUROFORIS Investigators, *et al*. Effects of two years of daily teriparatide treatment on BMD in post-menopausal women with severe osteoporosis with and without prior antiresorptive treatment. *J Bone Mineral Res*. 2008; **23**(10): 1591-1600
11. Audran MJY. A review of the clinical management and treatment of male patients with osteoporosis. Presented at Eular, Barcelona 2007. *Annals of the Rheumatic Disease* 2008: 67(suppl II); 26
12. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, *et al*. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int*. 1998; **8**(5): 468-89.
13. Mazess RB, Barden H. Bone density of the spine and femur in adult white females. *Calcif Tissue Int*. 1999; **65**(2): 91-9.
14. QDR 1000. Operators Manual. Bedford, MA: *Hologic The Women's Health Company*; 1989.
15. Roche Diagnostics GmbH, Mannheim, Germany: F. Hoffmann-La Roche Ltd; 2012.
16. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;**33**(5):337-43
17. de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC, *et al*. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res*. 2004; **13**(2); 311-20
18. Avery, L. Mann-Whitney U Test: equivalent to the Wilcoxon rank sum test. Richmond, VA: Virginia Commonwealth University; 2012. Available from: <http://elegans.som.vcu.edu/~leon/stats/utest.html>
19. Bauer DC, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ, *et al*. Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. *J Clin Endocrinol Metabol*. 2006; **91**(4) 1370-5
20. Miyauchi A. [Monitoring bone turnover markers during treatment with anabolic agent Teriparatide: in particular, treatment using daily and weekly subcutaneous injections.] *Clin Calcium*. 2012; 22(3); 387-98. Japanese.
21. Glover SJ, Eastell R, McCloskey EV, Rogers A, Garnero P, Lowery J, *et al*. Rapid and robust response of biochemical markers of bone formation to teriparatide therapy. *Bone*. 2009; **45** (6); 1053-8
22. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007; **18**(8); 1023-31