POSITION PAPER

Treatment failure in osteoporosis

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Mini abstract

Guidelines concerning the definition of failure of therapies used to reduce the risk of fracture are provided.

Abstract

Purpose To provide guidelines concerning the definition of failure of therapies used to reduce the risk of fracture.

Methods A working group of the Committee of Scientific Advisors of the International Osteoporosis Foundation was convened to define outcome variables that may assist clinicians in decision-making.

Results In the face of limited evidence, failure of treatment may be inferred when two or more incident fractures have occurred during treatment, when serial measurements of bone remodelling markers are not suppressed by antiresorptive therapy and where bone mineral density continues to decrease.

Conclusion The provision of pragmatic criteria to define failure to respond to treatment provides an unmet clinical need and may stimulate research into an important issue.

Keywords: fractures · Osteoporosis · Treatment · Bone mineral density · Markers of bone turnover

Introduction

The efficacy of drug treatment in osteoporosis ultimately depends on the demonstration of a reduction in the risk of fracture. In some instances efficacy against fracture risk is assumed where increases in BMD in one clinical context (e.g. in men) are equivalent to the changes in bone mineral density (BMD) in another clinical setting where efficacy on fracture risk has previously been demonstrated (e.g. in postmenopausal osteoporosis) [1,2]. Although biochemical markers of bone turnover are not considered to provide end-points or outcome measures, they have proved useful in dose-finding for several interventions in phase 2 studies and are commonly incorporated as a pharmacodynamic secondary endpoint in phase 3 studies. Thus, for anti-resorptive treatments, efficacy is assumed by a significant reduction in fracture risk supported by an increase in BMD and a decrease in markers of bone turnover. The converse applies to an ineffective treatment.

The question arises whether these therapeutic agents are effective in all patients who adhere to a treatment regimen. This is not an easy question to resolve. Fractures occur in both placebo and actively treated patients. An effective intervention decreases the risk of fracture but does not eliminate the risk. Typically, risk reductions are in the range of 30-70% for vertebral fractures, 40-50% for hip fractures and 15-20% for non-vertebral fractures [3,4]. Thus fractures during the course of treatment cannot be taken as proof of treatment failure. The situation is no better for the response of BMD and the markers of bone turnover to treatment. In several studies, treatment seems to be equally effective irrespective of the increment induced in BMD or the suppression of markers of bone turnover [5,6]. In addition, patients that lose bone under treatment are reported to have a lower fracture risk compared to control patients that lose bone [7-9]. Such observations suggest that changes in BMD and bone turnover markers are imperfect surrogates for anti-fracture efficacy.

These issues are difficult enough in the context of clinical trials, but become impossible to resolve outside the trial environment when dealing with individual patients. Notwithstanding, physicians are commonly faced with treatment failures in the sense that for the patient, a fracture that arises while on treatment signifies a failure of treatment. The problem is compounded by some reimbursement agencies and health technology

assessments that categorise first and second line drugs [5,6]. Second line drug are recommended when first line agents fail.

Against this background, the Committee of Scientific Advisors (CSA) of the International Osteoporosis Foundation considered that pragmatic advice was needed for medical practitioners who have to deal with treatment failure – or more accurately – perceived treatment failure. The Committee of Scientific Advisors of the International Osteoporosis Foundation set up a Working Group to discuss these issues and this paper reports its recommendations. The Working Group proposes that the response to treatment can be assessed using incident fractures, changes in bone mineral density and bone turnover markers (BTMs).

Incident fracture

Sustaining a fracture is always an undesirable outcome but treatments do not eliminate fracture risk, they reduce it. Thus, it is difficult to infer that a fragility fracture that occurs while on treatment for at least 6 month since its initiation means that treatment has failed. Conversely, the absence of an intercurrent fracture is no arbiter of successful treatment since the majority of placebo-treated patients will not sustain a fracture during the conduct of a typical phase 3 trial. In clinical trials, a second or third fracture during therapy is generally markedly reduced by 80-90% in comparison to the placebo treated [10-13]. In addition, the natural history of fracture events is that after the index fracture, the fracture risk decreases progressively with time [14-16]. These observations provide the rationale for the Working Group to recommend that the occurrence of a second fragility fracture be used to infer that treatment has failed. It is important to note that not all fracture sites are associated with osteoporosis [17,18]. These include fractures of the hand, skull, digits, feet and ankle fractures which appear to be less responsive to interventions for osteoporosis [19].

Bone mineral density

Osteoporosis is characterised by progressive loss of bone and BMD is a predictor of fracture risk [20,21]. It is therefore intuitively appealing to presume that an increase in BMD

represents a favourable response to treatment and, conversely, that a decrease in BMD during the course of treatment is a sign of failure of treatment.

The principal problem in assessing this issue is that rates of bone loss or gain are most often modest compared to the errors incurred in the measurement of BMD. For example, the rate of loss in BMD at the femoral neck in untreated women with postmenopausal osteoporosis is typically 1-2% per year, which is approximately the same as the precision error of the measurement of BMD at this site. The measurement error is greater when assessing change in BMD in an individual since a change in BMD requires at least two measurements of BMD to be made - each with the attendant errors of measurement. Thus, a change in areal BMD is, as expected, a weak predictor of fracture risk reduction [22-25].

The change in BMD that can be confidently detected is termed the least significant change (LSC). LSC depends upon the precision error of the technique applied and the confidence needed to assume a change. In clinical research, at least 95% confidence is demanded when inferring that a change has occurred. This is approximately 2.77 times the coefficient of variation (CV) using a two-sided test (Table 1). If one is assessing failure to respond, then a one-sided test ($2.33 \times$ the CV) is appropriate since in clinical practice only one of the possibilities of BMD variation is of concern, the decrease. Furthermore, an 80% confidence might be accepted. Then, the LSC with a one-tailed test would be $1.19 \times$ the individual coefficient of variation.

In the context of clinical research, the CV of BMD estimates at the femoral neck or lumbar spine lie in the order of 1.0 to 1.6% [26,27]. In clinical practice, the CV is approximately 2% at the lumbar spine and 1.6% at the hip [28,29]. Thus, to be 95% confident that a decrease in BMD has taken place (i.e. a one-sided test) a change of 4-5% should have been observed. Decreases in BMD greater than the LSC at 95% confidence are rarely found in patients who adhere to therapy [30,31]. This forms the rationale for the Working Group to propose that a decrease in BMD greater than the LSC at 95% confidence is considered as an indicator of failure to respond to treatment.

Table 1. Derivation of least significant change (%) from the coefficient of variation (expressed as a percent) and the confidence assumed for the difference.

Confidence %	Multiple of CV	Δ LS BMD % (CV 2%)	Δ FN BMD % (CV 1.6%)	Δ PINP % (CV 10%)	Δ CTX % (CV 10%)
Two-sided					
99	3.64	7.3	5.8	36	36
95	2.77	5.5	4.4	28	28
90	2.33	4.7	3.7	23	23
85	2.04	4.1	3.3	20	20
80	1.81	3.6	2.9	18	18
One-sided					
99	3.29	6.6	5.3	33	33
95	2.33	4.7	3.7	23	23
90	1.81	3.6	2.9	18	18
85	1.47	2.9	2.4	15	15
80	1.19	2.4	1.9	12	12

Markers of bone turnover

The treatment of osteoporosis with anti-resorptive agents is associated with an early decrease in markers of bone resorption and a later decrease in markers of bone formation. In the case of teriparatide (or PTH 1-84), the principal index of response is an increase in indices of bone formation. Several studies suggest that, in general, the larger the decrease in turnover markers with anti-resorptive agents, the greater the reduction in fracture risk [32-38]. Thus failure to observe a change in these response variables might be considered as a failure to respond to treatment.

Since a change in markers is the response variable, the same considerations apply to the measurement of change in marker values as apply to changes in BMD, discussed above. In the case of the markers, the precision error is much higher (5 to 10-fold greater) but is offset by the larger response to treatment. A further consideration is the many markers available, often measured with different technologies, each with different precision errors. The role of bone markers in monitoring response to treatment has been reviewed by the

International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine [39] and recommends that serum C-telopeptide of type I collagen (β CTX) and serum procollagen I N-propeptide (PINP) are considered as reference markers. The CVs provided by the manufacturers are 4.3-6.5% for P1NP and 1.3-4.3% for β CTX [38] but the inter-laboratory errors are larger [40]. Under clinical conditions a precision error of approximately 10% is estimated for both analytes [39] so that LSC estimates for serum β CTX and PINP are approximately 25% (see Table 1).

For these reasons, the Working Group propose that a decrease in β CTX and PINP less than the LSC at 95% confidence is considered as an indicator of failure to respond to treatment with anti-resorptive agents and that an increase in PINP less than the LSC at 95% confidence is considered as an indicator of failure to respond to treatment with parathyroid hormone peptides.

Clinical assessment of response to treatment

In a patient receiving treatment in whom no new fractures have occurred, BMD has increased and bone markers have decreased with antiresorptive treatment, to the extent expected from the intervention used (greatest with denosumab, least with raloxifene or calcium supplements), fracture risk is likely to be attenuated and the treatment should be maintained. If these response criteria are not fulfilled within a year of starting treatment, modification of treatment should be considered. This includes a review of adherence, which is the most likely reason for a poor response and a search for occult secondary causes of osteoporosis [41,42].

If adherence cannot be further improved and other causes of secondary osteoporosis are excluded, the Working Group recommends that treatment be changed in the following circumstances:

- a) Two or more incident fragility fractures
- b) One incident fracture and elevated serum β CTX or PINP at baseline with no significant reduction during treatment, a significant decrease in BMD, or both

- c) Both no significant decrease in serum β CTX or PINP and a significant decrease in BMD.

Note that:

1. Fractures of the hand, skull, digits, feet and ankle are not considered as fragility fractures.
2. The overall decline in BMD should be in the order of 5% or more in at least two serial BMD measurements at the lumbar spine or 4% at the proximal femur
3. Sequential measurement of markers of bone turnover should use the same assay. A significant response is a decline of 25% from baseline levels for anti-resorptive treatments, and 25% increase for anabolic agents (PTH) after 6 months. For anti-resorptive treatments, if baseline levels are not known, a positive response is a decrease below the average value of young healthy adults. It is assumed that the response is similar between men and women.
4. Falls are an important driver of fracture. Therefore this problem should be considered when analysing response to treatments.

No evidence is available on the effectiveness of alternative treatments when one has been deemed to have failed. Almost no studies have explored the issue and, therefore, the available data are scarce [43]. Some data based on indirect comparisons or surrogate endpoints can be of help [44-47]. Three general rules, based on the opinion of the Working Group, are recommended:

- a) A weaker anti-resorptive is reasonably replaced by a more potent drug of the same class
- b) An oral drug is reasonably replaceable by an injected drug
- c) A strong anti-resorptive is reasonably replaceable by an anabolic agent

Discussion

The available evidence does not permit a firm assessment of the success or failure of a treatment. The recommendations that we make are therefore based on expert opinion that provides the lowest level of evidence. Nevertheless, pragmatic criteria for failure to respond

to treatment are a need for the practicing clinician. Three parameters that modify fracture risk and that are commonly measured in clinical practice are incident fractures, changes in BMD and changes in markers of bone turnover and form the basis of our recommendations. The recommendations themselves have the merit of being conservative. There is, however, a dearth of evidence that patients deemed to have failed treatment respond favourably to an alternative. This needs further research.

If failure of therapy is a real state in adherent patients, this may arise because treatment is offered too late in the natural history of the disorder when disruption of skeletal architecture is well advanced [42]. Studies are needed to relate structure to treatment-induced fracture outcomes so patients at high risk can be targeted early enough to prevent irreversible architectural losses. Whether or not individuals with high remodelling rates may require more potent remodelling suppressants, and patients with low remodelling require less potent anti-resorptive or anabolic agents is an open question. So too is whether patients with marked deterioration of microarchitecture require anabolic agents rather than anti-resorptives.

We conclude that a significant minority of patients who adhere to treatment fail to respond to available treatments. The reasons for this remain uncertain. In some cases treatment has failed perhaps because the bone is too severely disrupted, in others the treatment may be inappropriate, perhaps failing to access remodelling sites in bone. Nevertheless, no treatments eliminate the risk of fragility fractures so that treatments will be perceived as failing in those who sustain a further fracture by patients, carers and physicians alike. This paper identifies the unmet need to identify the morphological basis for treatment failure and success, mechanisms of drug therapy that may contribute to failed therapy and so advance our understanding of how best to identify patients at need for treatment, the mechanisms responsible and target treatment in a reasoned disease specific and individualized fashion.

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Competing interests

A Diez-Perez has given lectures and provided advice for Novartis, Amgen, Lilly and MSD. His institution has received research grants from Amgen and Servier. JD Adachi has given lectures and is a consultant for Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Procter & Gamble, Roche, Sanofi Aventis, Warner Chilcott. D Agnusdei is an employee of Eli Lilly. J Bilezikian is a consultant for Amgen, Merck, Lilly and GlaxoSmithKline, gives lectures for Amgen, Lilly and has received research grant from Amgen. J Compston has no disclosure. S Cummings is consultant for Merck, Amgen and Lilly. R Eastell serves as a consultant, has received honoraria for speaking, and has received grant support from Amgen, AstraZeneca, California Pacific Medical Center, GlaxoSmithKline, Hologic, Kyphon Inc., Lilly Industries, Maxygen, Natestch Pharmaceuticals, Nestle Research Center, New Zealand Milk Limited, Novartis, Novo Nordisk, ONO-Pharma, Organon Laboratories, Osteologix, Pfizer, Procter & Gamble Pharmaceuticals, Roche Diagnostics, Sanofi-Aventis, Servier, Shire, Tethys, TransPharma Medical Limited, Unilever, and Unipath. E Eriksen has given lectures and has provided advice for Novartis, Amgen, Eli Lilly and MSD. J González-Macías has given lectures and provided advice for Amgen, Lilly, Servier and MSD. U Liberman has given lectures for MSD. D Wahl declares no conflict of interest. E Seeman serves as advisory board member and gives lectures at symposia organized by several pharmaceutical companies including, variously Amgen, Warner Chilcott, MSD, Eli Lilly, Sanofi-Aventis, Novartis. J A Kanis receives research funding and consults with many companies involved with skeletal metabolism. C Cooper has received honoraria and consulting fees from Servier, Amgen, Eli Lilly, Merck, Medtronic and Novartis.

References

1. Food and Drug Administration (1994) Guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis. Rockville, MD, Division of Metabolism and Endocrine Drug Products, Food and Drug Administration, 1994
2. Committee for Medicinal Products for Human Use (CHMP) (2006) Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis. Ref CPMP/EWP/552/95Rev.2. London, CHMP. Nov 2006
3. Body JJ, Bergmann P, Boonen S et al (2010) Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. *Osteoporos Int* 2:1657-1680
4. MacLean C, Newberry S, Maglione M et al (2008) Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 148:197-213
5. National Institute for Health and Clinical Excellence (2010a) Final appraisal determination. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE, London
6. National Institute for Health and Clinical Excellence (2010b) Final appraisal determination. Alendronate, tidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE, London
7. Chapurlat RD, Palermo L, Ramsay P, Cummings SR (2005) Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. *Osteoporos Int* 16:842-848
8. Watts NB, Geusens P, Barton IP, Felsenberg D (2005) Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res* 20:2097-2104
9. Ettinger B, Black DM, Mitlak BH (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomised clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 282:637-645
10. Levis S, Quandt SA, Thompson D et al (2002) Alendronate reduces the risk of multiple symptomatic fractures: results from the fracture intervention trial. *J Am Geriatr Soc* 50:409-415
11. Watts NB, Josse RG, Hamdy RC et al (2003) Risedronate prevents new vertebral fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab* 88:542-549
12. Barrett-Connor E, Nielson CM, Orwoll E, Bauer DC, Cauley JA (2010) Epidemiology of rib fractures in older men: Osteoporotic Fractures in Men (MrOS) prospective cohort study. *BMJ* 340:c1069

13. vanStaa TP, Leufkens HG, Cooper C (2002) Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int* 13:624-629
14. Johnell O, Oden A, Caulin F, Kanis JA (2001) Acute and long term increase in fracture risk after hospitalization for vertebral fracture. *Osteoporosis Int* 12:207-214
15. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Pettersen C, De Laet C, Jonsson B (2004) Fracture risk following an osteoporotic fracture. *Osteoporos Int* 15:175-179.
16. Kanis, JA (1984) Treatment of osteoporotic fracture. *Lancet* 1:27-33.
17. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR (1991) Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 115: 837-42
18. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int* 12: 417-427
19. Mackey DC, Black DM, Bauer DC et al (2011) Effects of antiresorptive treatment on nonvertebral fracture outcomes. *J Bone Miner Res* 26:2411-2418
20. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Br Med J* 312:1254-1259
21. Johnell O, Kanis JA, Oden A et al (2005) Predictive value of bone mineral density for hip and other fractures. *J Bone Miner Res* 20:1185-1194
22. Cummings SR, Karpf DB, Harris F (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 112:281-289
23. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 17:1-10
24. Delmas PD, Li Z, Cooper C (2004) Relationship between changes in bone mineral density and fracture risk reduction with anti-resorptive drugs: some issues with meta-analyses. *J Bone Miner Res* 19:33-37
25. Delmas PD, Seeman E (2004) Changes in bone mineral density explain little of the reduction in vertebral or non-vertebral fracture risk with anti-resorptive therapy. *Bone* 34:599-604
26. CRCPD's Task Force on Bone Densitometry (2006) Technical White Paper: Bone Densitometry. October 2006. <http://crcpd.org/Pubs/BoneDensitometryWhitePaper.pdf>
27. El-Hajj Fulehian G, Testa MA, Angell JA, Porrino N, Leboff MS (1995) Reproducibility of DXA Absorptiometry: A Model for Bone Loss Estimates. *J Bone Miner Res* 10: 1004-1014.

28. Lodder MC, Lems WF, Ader HJ et al (2004) Reproducibility of bone mineral density measurement in daily practice. *Ann Rheum Dis* 63:285-9.
29. El Maghraoui A, Do Santos Zounon AA, Jroundi I et al (2005) Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. *Osteoporos Int* 16:1742-8.
30. Bell KJL, Hayen A, Macaskill Pet al (2009) Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. *BMJ* 338:b2266
31. Cummings SR, Lui LY, Vittinghoff E et, al (2010) The value of monitoring hip BMD during treatment with denosumab: one year changes in BMD and reductions in fracture risk. *J Bone Miner Res* 25 S1: S9
32. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD (2003) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 18:1051-1056
33. Eastell R, Hannon RA, Garnero P, Campbell MJ, Delmas PD (2007) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate: review of statistical analysis. *J Bone Miner Res* 22:1656-1660
34. Reginster J-Y, Sarkar S, Zegels B et al (2004) Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 34:344-351
35. Sarkar S, Reginster J-Y, Crans GG, Diez-Perez A, Pinette KV, Delmas PD (2004) Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Miner Res* 19:394-401
36. Bauer DC, Black DM, Garnero P et al (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. *J Bone Miner Res* 19:1250-1258
37. Delmas PD, Munoz F, Black DM et al (2009) Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J Bone Miner Res* 24:1544-1551
38. Glover SJ, Gall M, Schoenborn-Kellenberger O et al (2009) Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. *J Bone Miner Res* 24:389-397
39. Vasikaran S, Eastell R, Bruyere O et al for the IOF-IFCC Bone Marker Standards Working Group (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 22:391-420
40. Meier C, Seibel MJ, Kraenzlin ME (2009) Use of Bone Turnover Markers in the Real World: Are We There Yet? *J Bone Miner Res* 24: 386-388
41. Adami S, Isaia G, Luisetto G et al (2006) Fracture incidence and characterization in patients on osteoporosis treatment: the ICARO study. *J Bone Miner Res* 21:1565-1570

42. Díez-Pérez A, Olmos JM, Nogués X et al (2012) Risk factors for prediction of inadequate response to antiresorptives. *J Bone Miner Res* 27: 817-24
43. Jobke B, Muche B, Burghardt AJ, Semler J, Link TM, Majumdar S (2011) Teriparatide in bisphosphonate-resistant osteoporosis: microarchitectural changes and clinical results after 6 and 18 months. *Calcif Tissue Int* 89: 130-9
44. Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K (2012) Femoral strength in osteoporotic women treated with teriparatide or alendronate. *Bone* 50: 165-70
45. Hadji P, Gamberdinger D, Spieler W et al (2012) Rapid Onset and Sustained Efficacy (ROSE) study: results of a randomised, multicentre trial comparing the effect of zoledronic acid or alendronate on bone metabolism in postmenopausal women with low bone mass. *Osteoporos Int* 23: 625-33
46. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W (2007) A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. *Bone* 40: 1238-43
47. Freemantle N, Satram-Hoang S, Tang ET et al (2012) Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int* 23: 317-26