

Medical Treatment of Osteoporosis—Increasing Options

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Abstract

Introduction: Many drugs are now available for the prevention and treatment of osteoporosis. They have differing levels of evidence of efficacy and each may be used according to clinical indications. **Methods:** A Medline search of clinical drug trials using various therapeutic agents used for osteoporosis was carried out. **Results:** Several randomised controlled trials have been carried out using many agents. The agents with the best data to date with regards to the prevention of spine as well as hip fractures in patients with prevalent fractures belong to alendronate and risedronate. Parathyroid hormone has been shown in one trial to reduce the risk of non-vertebral fractures. For reduction of spine fractures, in addition to the above two bisphosphonates, many agents, in particular raloxifene, have been shown to be clearly beneficial. Weaker data exist for hormone replacement, calcitonin, cyclical etidronate and the vitamin D analogues calcitriol and alfacalcidol. **Conclusion:** There are many therapeutic agents shown to be clearly effective in the treatment of osteoporosis.

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Introduction

The current practice and management of osteoporosis differs greatly from even the recent past. Up to 15 years ago, bone mineral density (BMD) measurements were not widely available, osteoporosis was still largely diagnosed only at the stage of fractures, the epidemiology of osteoporosis was not well studied yet and the only medications that were indicated for osteoporosis were hormone replacement therapy (HRT) and calcitonin.

Since then, relatively accurate and useful measurements of BMD were possible using dual-energy X-ray absorptiometry (DXA) and the whole concept and definition of osteoporosis has changed. Since 1993,¹ osteoporosis has been defined as a systemic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to fracture. Therefore, osteoporosis can be diagnosed before the stage of an osteoporotic fracture. In 1994,² the World Health Organisation set out the criteria for osteopenia and osteoporosis based on T scores of BMD. Long-term prospective studies worldwide elucidated the risk factors for osteoporosis and fractures,³⁻⁵ improving the understanding of the illness and also facilitating better risk assessment to aid in treatment decisions.

The options for medical treatment have also increased. In the past, there were fewer drugs available and the evidence for efficacy was much less well documented. Older clinical

trials in the late 1980s and early 1990s were generally less stringent in design and execution. They did not always have adequate numbers of study subjects, duration of follow-up was short, fracture risk reduction was not always the outcome measure, dropout rates were high, intention to treat analysis was not done and trials were frequently not randomised, placebo-controlled, double blind in design.

Since the mid-nineties, however, newer agents were introduced which do have evidence of efficacy based on trials carried out under the above stringent conditions. Examples of such medications include alendronate, risedronate and raloxifene.

Nonetheless, the treatment of osteoporosis like many other medical illnesses has to be individualised as there is no one best drug for all. Side effect profile, clinical indications and cost play vital roles in helping to determine the choice of therapeutic agent for a given individual patient.

Bearing this in mind, a brief review of currently available agents is given below.

Calcium and Vitamin D

For too long, calcium and vitamin D were the only medications given for anyone who was diagnosed with osteoporosis. This is clearly inadequate for patients who have a high risk for fractures. It is apparent from the newer clinical trials⁶⁻⁸ that this is so as patients in the placebo arm

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in these trials were supplemented with calcium. This did not prevent them from having a higher risk of fractures compared to patients in the treatment arm.

Calcium and vitamin D, however, have an important adjunctive role in all patients, especially the elderly.⁹⁻¹¹ Chapuy et al¹² demonstrated a 43% reduction in hip fractures over a period of 18 months in patients taking calcium and vitamin D in a French nursing home. On further analysis by the investigators, they were found to be relatively vitamin D deficient. In a similar vitamin D replete population in Rotterdam,¹³ no such effect was demonstrated.

Agents Which Have Been Shown to Reduce the Risk of Spine and Hip Fractures

Bisphosphonates

Usually in a review of medications for osteoporosis, HRT is dealt with first. However, in terms of evidence of efficacy, the newer bisphosphonates, alendronate and risedronate have the advantage, and this group of agents will be reviewed first. The first bisphosphonate to be used for osteoporosis was cyclical etidronate. Those early trials did not show efficacy in preventing hip fractures, and cyclical etidronate seems best suited to prevent spine fractures in those with pre-existing spine fractures.¹⁴ In 1996, the Fracture Intervention Trial¹⁵ was the first study to demonstrate the efficacy of alendronate in preventing hip fractures in patients who have at least one prevalent vertebral fracture. One criticism of this study was that although there was a statistically significant relative risk reduction of 51%, there was a small number of incident hip fractures. Interestingly, the arm of the Fracture Intervention Trial involving patients without pre-existing fractures¹⁶ showed that the risk of fractures was not reduced in patients with osteopenia. Risedronate has also been well-studied and in an older set of patients, the risk of hip fractures was reduced in those with osteoporosis as defined by BMD.¹⁷ These patients were older than in the alendronate trials and had a lower BMD in the range of T score of minus 4. However, in another set of patients who did not have low bone density but who had clinical risk factors for hip fractures such as having factors which increase the possibility of falls, risedronate did not prevent hip fractures. This shows that BMD measurement is important even in the elderly.

Besides efficacy in the prevention of hip fractures, both alendronate¹⁸ and risedronate^{6,7} are also effective in reducing spine fractures in osteoporotic patients with or without prevalent fractures.

It must be remembered that not all bisphosphonates are the same. Other bisphosphonates, such as clodronate, are effective in the treatment of metastatic bone disease and hypercalcaemia of malignancy but their evidence for use in osteoporosis is far weaker than alendronate or risedronate.¹⁹

Parathyroid Hormone

Parathyroid hormone (PTH) has been studied in the recent past as a potentially useful bone-forming agent.²⁰ A recent study showed that daily subcutaneous administration of PTH improved BMD and also reduced the risk of non-vertebral fractures.²¹ Up to now, bone-forming agents such as anabolic steroids and fluoride have weak evidence of efficacy²² and their side effect profile limits their usefulness. Prolonged use of anabolic steroids may lead to androgenisation effects and liver abnormalities. Some studies on the use of fluorides show an increase in fractures rather than a reduction.²³ If further studies strengthen the evidence for PTH, it will represent an advance in the treatment of osteoporosis. The exciting prospect of having combination therapy using both a bone-forming agent and an anti-resorptive drug might then become reality.

Agents Which Have Been Shown to Reduce the Risk of Spine Fractures

In this category of agents, the level of evidence for hip fracture efficacy is weak, the studies being either observational in nature or randomised, placebo-controlled, double-blind trials which did not show evidence of efficacy. However, the evidence for reduction in spine fractures is fairly robust.

Of all the agents in this category, the medication with the best data to date is raloxifene. This is the first selective oestrogen receptor modulator (SERM) to be used extensively in clinical practice. Besides other benefits on lipid profiles and reduction of breast cancer risk²⁴ in oestrogen receptor positive subjects, the data on osteoporosis clearly show a benefit in reduction of spine fractures in osteoporotic patients with or without prevalent fractures.⁸ Existing published studies do not show reduction in the risk of hip fractures but ongoing studies looking at this as the primary outcome are in progress. There are also studies being done to see if there is a reduction in fracture risk in patients who are in the osteopenic range of BMD.

Besides alendronate, risedronate and raloxifene, other agents currently used for osteoporosis have weaker data because of differences in availability, design and execution of clinical trials. Nonetheless, it is acceptable to use these agents if there are reasonable grounds for their choice, such as cost of treatment. However, it would be prudent to monitor response using serial measurements of BMD or bone turnover markers to ensure there is at least surrogate evidence of improvement.

Hormone replacement therapy has been in use for several decades.²⁵⁻²⁷ Most trials clearly show beneficial changes in serial BMD with HRT. There is also some evidence for fracture risk reduction. However, the thinking that long-term use would offer other benefits such as a reduction in

the risk of cardiovascular disease²⁸ has changed in light of several recent studies. There is also concern over the increased risk of breast cancer with long-term use.²⁹

Calcitonin is also an agent that has been in use for some time.³⁰ Earlier trials were small and the design was suboptimal. A recent larger trial,³¹ using 200 iu a day, showed efficacy for reducing spine fractures but not hip fractures. This trial suffered from a high dropout rate and intention to treat analysis was not used. A unique benefit of calcitonin is the reduction of pain that arises from an acute osteoporotic fracture.³²

Vitamin D analogues, such as calcitriol³³ and alfacalcidol, have been used in osteoporosis. These agents should not be regarded as supplements but rather as drugs. The trial on calcitriol by Tilyard et al was done in calcium replete patients and benefit was shown mainly in the subset of patients with prevalent spine fractures. Efficacy was shown for reduction in spine fractures but not hip fractures.

Anabolic steroids, such as nandrolone^{22,34} and stanozolol, have been used but they may cause considerable side effects such as androgenisation and liver abnormalities. BMD is increased but evidence for fracture risk reduction is weak. Their use should be limited to not more than 6 months and reserved for the frail elderly patient undergoing rehabilitation.

Fluoride salts²³ have been shown to increase BMD. However, poor quality bone is formed and fracture risk in fact increases. Strontium salts are now being evaluated.

Male Osteoporosis

A male with osteoporosis may have to be evaluated for hypogonadism or other causes of secondary osteoporosis. Nonetheless, ageing alone predisposes a male to osteoporosis and hip fractures, the female to male ratio is 2:1. Besides treating any underlying illness,³⁵ the only agent with proven anti-fracture efficacy in men is alendronate.³⁶ Trials using risedronate are underway and it is also likely to be of benefit. HRT and raloxifene are not options but other agents have increasingly been studied for male osteoporosis.³⁷⁻⁴⁰

Corticosteroid-induced Osteoporosis

This is an important subset of osteoporosis as there are several medical illnesses requiring long-term use of oral corticosteroids. Generally, topical steroids are preferred to systemic use, where indicated, as they have considerably fewer side effects. If there is a need for long-term systemic use, then one should aim at the lowest possible dose and try not to use more than 5 mg prednisolone daily. Steroid sparing agents have to be considered and monitoring of BMD is needed. For patients with steroid osteoporosis, calcium and vitamin D supplements are not adequate.^{41,42}

Agents which have been shown to be beneficial include alendronate,^{43,44} risedronate,^{45,46} cyclical etidronate,⁴⁷ HRT,⁴⁸ calcitriol,⁴⁹ alfacalcidol,⁵⁰ calcitonin⁵¹ and nandrolone.⁵²

Conclusion

The medical options for treating osteoporosis have really increased tremendously in the past decade. Not only have the number of drugs available increased but the availability of good clinical trials presents the clinician with the assurance that treatment does indeed work to prevent the occurrence of fractures. The future promises the availability of more medications such as newer SERMs, other bisphosphonates and hormonal treatments such as with growth factors and strontium salts. The problem, however, lies in the fact that clinicians are relatively slow to adopt a change in the paradigm for treating osteoporosis.⁵³ In a recent study in the US,⁵⁴ only 13% of patients with osteoporosis received adequate treatment as defined by clinical practice guidelines. This is true world wide, including Singapore, where many patients with prevalent osteoporotic fractures are not started on medication to prevent further fractures. In the light of clearly available effective treatment, this outdated approach will increasingly become unacceptable.

REFERENCES

1. Consensus development conference: prophylaxis and treatment of osteoporosis. *Am J Med* 1991; 90:107-10.
2. Kanis J A, Melton L J 3rd, Christiansen C, Johnston C C, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994; 9:1137-41.
3. Nyugen T V, Center J, Sambrook P N, Eisman J A. Risk factors for proximal humerus, forearm and wrist fractures in elderly men and women: the Dubbo Osteoporosis Epidemiology Study. *Am J Epidemiol* 2001; 153:587-95.
4. Lau E M, Cooper C. The epidemiology of osteoporosis. The oriental perspective in a world context. *Clin Orthop* 1996; 323:65-74.
5. Cummings S R, Nevitt M C, Browner W S, Stone K, Fox K M, Ensrud K E, et al. Risk factors for hip fractures in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; 332: 814-5.
6. Harris S, Watts N, Genant H, McKeever C D, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA* 1999; 282:1344-52.
7. Reginster J, Minne H, Sorensen O, Hooper M, Roux C, Brandi M L, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 2000; 11:83-91.
8. Ettinger B, Black D M, Mitlak B H, Knickerbocker R K, Nickelsen T, Genant H K, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year

- randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999; 282:637-45.
9. Chan H H, Lau E M, Woo J, Lin F, Sham A, Leung P C. Dietary calcium intake, physical activity and the risk of vertebral fracture in Chinese. *Osteoporos Int* 1996; 6:228-32.
 10. Cumming R, Nevitt M. Calcium for prevention of osteoporotic fractures in postmenopausal women. *J Bone Miner Res* 1997; 12:1321-9.
 11. Dawson-Hughes B, Harris S, Krall E, Dallal G. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997; 337:670-6.
 12. Chapuy M C, Arlot M E, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992; 327:1637-42.
 13. Lips P, Graafmans W C, Ooms M E, Bezemer P D, Bouter L M. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996; 124:400-6.
 14. Storm T, Thamsborg G, Steiniche T, Genant H K, Sorensen O H. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990; 322:1265-71.
 15. Black D M, Cummings S R, Karpf D B, Cauley J A, Thompson D E, Nevitt M C, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996; 348:1535-41.
 16. Cummings S, Black D, Thompson D, Applegate W B, Barrett-Connor E, Musliner T A, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; 280:2077-82.
 17. McClung M, Geusens P, Miller P, Zippel H, Bensen W G, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001; 344:333-40.
 18. Black D, Thompson D, Bauer D, Ensrud K, Musliner T, Hochberg M C, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 2000; 85:4118-24.
 19. McCloskey E, Selby P, de Takats D, Bernard J, Davies M, Robinson J, et al. Effects of clodronate on vertebral fracture risk in osteoporosis: a 1-year interim analysis. *Bone* 2001; 28:310-5.
 20. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997; 350:550-5.
 21. Neer R, Arnaud C, Zanchetta J, Prince R, Gaich G A, Reginster J Y, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344:1434-41.
 22. Geusens P. Nandrolone decanoate: pharmacological properties and therapeutic use in osteoporosis. *Clin Rheumatol* 1995; 14(Suppl 3): 32-9.
 23. Hagenauer D, Welch V, Shea B, Tugwell P, Adachi J, Wells G. Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. *Osteoporos Int* 2000; 11:727-38.
 24. Cauley J, Norton L, Lippman M, Eckert S, Krueger K A, Purdie D W, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat* 2001; 65:125-34.
 25. Komulainen M, Kroger H, Tuppurainen M, Heikkinen A M, Alhava E, Honkanen R, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas* 1998; 31:45-54.
 26. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. *JAMA* 1996; 276:1389-96.
 27. Torgerson D, Bell-Syer S. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001; 285:2891-7.
 28. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; 280:605-13.
 29. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 1996; 347: 1713-27.
 30. Kanis J, McCloskey E. Effect of calcitonin on vertebral and other fractures. *QJM* 1999; 92:143-9.
 31. Chesnut C, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. *Am J Med* 2000; 109:267-76.
 32. Lyritys G P, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritys P G. Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. *Acta Orthop Scand Suppl* 1997; 275:112-4.
 33. Tilyard M W, Spears G F, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992; 326:357-62.
 34. Passeri M, Pedrazzoni M, Pioli G, Butturini L, Ruys A, Cortenraad M. Effects of nandrolone decanoate on bone mass in established osteoporosis. *Maturitas* 1993; 17:211-9.
 35. Eastell R, Boyle I T, Compston J, Cooper C, Fogelman I, Francis R M, et al. Management of male osteoporosis: report of the UK Consensus Group. *QJM* 1998; 91:71-92.
 36. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000; 343:604-10.
 37. Anderson F, Francis R, Bishop J, Rawlings D. Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures. *Age Ageing* 1997; 26:359-65.
 38. Erlacher L, Kettenbach J, Kiener H, Graninger W, Kainberger F, Pietschmann P. Salmon calcitonin and calcium in the treatment of male osteoporosis: the effect on bone mineral density. *Wien Klin Wochenschr* 1997; 109:270-4.
 39. Anderson F H, Francis R M, Peaston R T, Wastell H J. Androgen supplementation in eugonadal men with osteoporosis: effects of six months' treatment on markers of bone formation and resorption. *J Bone Miner Res* 1997; 12:472-8.
 40. Orwoll E, Scheele W H, Clancy A D. Recombinant human parathyroid hormone (1-34) therapy reduces the incidence of moderate/severe vertebral fractures in men with low bone density. *J Bone Miner Res* 2001; 16(Suppl 1):S162.
 41. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-induced Osteoporosis. *Arthritis Rheum* 2001; 44:1496-503.
 42. Compston J, Audran M, Avouac B, Bouvenet G, Devogelaer J, Eastell R, et al. Recommendations for the registration of agents used in the prevention and treatment of glucocorticoid-induced osteoporosis. *Calcif Tissue Int* 1996; 59:323-7.
 43. Saag K, Emkey R, Schnitzer T, Brown J P, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-induced Osteoporosis Intervention

- Study Group. *N Engl J Med* 1998; 339:292-9.
44. Adachi J, Saag K, Delmas P, Liberman U A, Emkey R D, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001; 44:202-11.
 45. Cohen S, Levy R, Keller M, Boling E, Emkey R D, Greenwald M A, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999; 42:2309-18.
 46. Wallach S, Cohen S, Reid D, Hughes R A, Hosking D J, Laan R F, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000; 67:277-85.
 47. Adachi J, Roux C, Pitt P, Cooper C, Moniz C, Dequeker J, et al. A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol* 2000; 27:2424-31.
 48. Hall G, Daniels M, Doyle D, Spector T. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum* 1994; 37:1499-505.
 49. Sambrook P, Birmingham J, Kelly P, Kempner S, Nguyen T, Pocock N, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 1993; 328:1747-52.
 50. Reginster J, Kuntz D, Verdict W, Wouters M, Guillemin L, Menkes C J, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. *Osteoporos Int* 1999; 9:75-81.
 51. Cranney A, Welch V, Adachi J, Hornik J, Shea B, Suarez-Almazor M E, et al. Calcitonin for the treatment and prevention of corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 2000:CD001983
 52. Adami S, Fossaluzza V, Rossini M, Bertoldo F, Gatti D, Zamberlan N, et al. The prevention of corticosteroid-induced osteoporosis with nandrolone decanoate. *Bone Miner* 1991; 15:73-81.
 53. Leong K H. Osteoporosis—the need for a paradigm shift. *Ann Acad Med Singapore* 1998; 27:100-4.
 54. Bellantonio S, Fortinsky R, Prestwood K. How well are the community-living women treated for osteoporosis after hip fracture? *Geriatr Soc* 2001; 49:1197-204.
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