

Summary - Curing Osteoporosis

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The current conventional strategy for treatment of osteoporosis is to start patients on a single treatment, generally a bisphosphonate. The goal of this approach is to maintain BMD, not to reduce the risk of fractures to normal. Long-term treatment of patients with severe osteoporosis still leaves them at substantially greater risk of fractures than normal.

The ideal is to cure osteoporosis. Cure may mean a one-time fix without need for future treatment, but all agreed this was not feasible to envision for osteoporosis. Returning older patients to the low risk of younger patients would require reversing other aspects of aging, such as increased risk of falling. So 'normal' must be age-specific.

Curative strategies require bone forming agents which, today, means treatment with PTH. The trial of teriparatide showed that 19 months of treatment improved microarchitecture with a 65% reduction in risk of vertebral fracture. A curative strategy would require flexibility in duration of treatment. Teriparatide has its greatest effects on bone remodeling during the first 6 to 12 months of treatment and continues to increase for a period of at least 30 months, suggesting that repeated short courses may be optimal.

PTH increases bone turnover so adding an anti-resorptive would seem synergistic, but trials have found the concurrent combination to be no better than either treatment alone. PTH after chronic alendronate therapy effectively increases BMD, but perhaps less so than after chronic raloxifene use. Clinical studies have found that PTH followed by alendronate supports a continued increase in BMD. PTH followed by an anti-resorptive with repeat of PTH as necessary seems the most promising approach but which anti-resorp-

tive remains to be resolved.

The goal of treatment would likely be imaging (and perhaps biochemical testing) to determine that normal bone strength has been restored. Bone densitometry (BMD) is the current common and gold standard in practice because it predicts fractures. However, whole bone strength (in response to a load) also depends upon the intrinsic properties of the material(s) of which the bone is comprised, how much of this material is present (i.e., the mass) and how this material is distributed (i.e., the geometry and microarchitecture). Thus, in theory, the ideal imaging methodology would reflect a bone's geometry and microarchitecture, as well as characteristics of the bone matrix, such as the degree of mineralization, amount and nature of existing microdamage, amount of collagen, and extent of collagen cross-linking. Scans cannot be performed on all patients, and scan acquisition is expensive. One promising approach for *in vivo* prediction of bone strength is QCT-based finite element analysis using measurements available from QCT to create a model of the bone, to predict strength in response to loading. MRI has theoretical promise but many practical difficulties that preclude near-term use as a 'goal' for curative therapy.

Ultimately, we need to prove that goal-directed therapy reduces the risk of fractures more than does conventional long-term suppression of resorption. This requires a randomized trial comparing the effects of the two approaches on risk of fractures. Such a trial would involve at least 3,000 subjects over a 5-year study, and would cost \$30 million. It was concluded that we need to determine the best combinations of therapies and compare the predictive value of bone measurements on treatment before such a trial could be confidently started.

The author has no conflict of interest.

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Accepted 4 August 2004