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Perspective Article

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Issues in designing and testing a "cure" for osteoporosis

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The current conventional strategy for treatment of osteoporosis is to start patients on a single treatment, generally a bisphosphonate. Although the ideal duration of treatment is controversial, most physicians would continue treatment indefinitely for patients with severe osteoporosis. The effect of the treatment is sometimes assessed by repeat measurements of BMD to look for small changes; small increases are considered a sign the patient is 'responding' to treatment while loss of BMD may be interpreted as 'non-response.'

The goal of this approach is to maintain BMD, not to reduce the risk of fractures to normal. Assuming (optimistically) that long-term treatment with bisphosphonates reduces the risk of vertebral fractures by 60% and the risk of other types of fractures by about 1/3, a patient who has very low bone density and a vertebral fracture still has a 2- to 3-fold greater risk of fractures than normal, despite treatment.

This conventional approach differs from the strategy for treating several other chronic diseases, such as hypertension, diabetes or HIV infection. In those conditions, clinicians treat patients to achieve a goal of normal – or at least much lower risk of bad outcomes. The goal is to achieve a certain value of the clinical marker, such as blood pressure, that indicates a normal, or best possible, risk of the bad outcome (e.g., stroke).

Applied to osteoporosis, this strategy would mean treatment of patients with whatever agents are necessary, to achieve a 'normal' or near normal risk of fractures. This would be accomplished by treating until a patient had reached a goal level of a measurement of bone strength and risk of fracture.

This strategy requires a treatment that can achieve goals. It requires treatment that can continue to improve bone mass and structure until the goal is reached. For most patients with severe osteoporosis, this cannot be achieved by anti-resorptive treatments alone. As reviewed above, a combination of PTH followed by an anti-resorptive seems to be the most promising approach. In order to reach the goal of achieving or exceeding the goal, it may be necessary to extend PTH beyond the current approved 2-year course or repeat courses until the goal is achieved. It is likely that achievement of goal will need to be followed by maintenance of bone structure with long term anti-resorptive treatment.

It is not clear how to measure the goal. Bone density measurement would be the simplest approach. But, as reviewed by Dr. Bouxsein, it may be better to measure bone mass and structure with more sophisticated methods. However, it is not clear which method is the best index of fracture risk after a patient has been treated.

Testing this approach. Does goal-directed therapy reduce the risk of fractures more than does conventional long-term suppression of resorption? This should be tested in a randomized clinical trial. The most feasible and least expensive trial would test the effect of the two alternatives on the surrogate measure of bone strength, such as CT. Unfortunately, the result would not answer the most important questions and it is 100% certain that goal-directed therapy would have superior effects on bone mass or structure because that is the goal of that goal-directed treatment.

A trial comparing the two approaches to treatment on risk of fractures would be large (at least 3,000 subjects) and expensive (at least $30 million over at least 5 years). Before undertaking such a trial, we need the following information: 1) Which imaging (or bone marker, or combination) measurement is the best predictor of a patient's risk of fractures while on treatment? 2) Can PTH (or another bone forming agent) be safely given for long or repeated periods until a 'goal' is achieved. With this information in hand, the remaining missing element would be sufficient funding for a trial to compare these two fundamentally different paradigms for treating osteoporosis.

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