

Is it time for alendronate?

Susan M. Ott, MD April 27, 1998

Alendronate is a potent new bisphosphonate that blocks bone resorption without direct inhibition of bone formation. This results in an increase in bone density and, in the short term, bone strength. The physiology of bone is so slow that "short term" means 5-10 years.

The clinical trials showing efficacy in terms of both bone density and fracture reduction are impressive. These have been well publicized to both physicians and consumers. While I find the intensive media advertising distressing, it does have the positive benefit of increasing the awareness of osteoporosis and leading to discussions about this disease between physicians and their patients.

There are some aspects about treatment with alendronate that are not mentioned in the advertisements, and I think these should be taken into consideration by physicians who decide to prescribe this drug.

1) What is the ten-year effect of alendronate on the skeleton? Will there be short-term gain but long-term pain? This question is particularly important in view of the long half-life of the drug: it is deposited in bone and remains there longer than 10 years (1). Alendronate blocks bone resorption by mechanisms that are not yet understood. In normal bone, resorption is initiated by fatigue damage to the bone, seen as micro-stress fractures (2). The subsequent bone remodeling repairs this damage. The long-term effects of blocking the bone's repair mechanism are unknown.

2) What is the mechanism for the small increases in bone density after the first year of alendronate treatment? Normal bone remodeling removes old, dense, brittle bone and replaces it with newer, more elastic bone. This new bone gradually becomes denser as mineral is packed more tightly into the collagen. It is not usually recognized that some late increases in bone density might reflect hypermineralization (3) which does not improve bone strength (4). More research is needed to understand these changes.

3) What happens when the drug is stopped? Limited information suggests that bone loss in the first year after stopping is similar to rates in untreated controls (5), but it is not known how long any beneficial effects persist.

4) Are there any long-term effects on white blood cells, which show some subtle changes with alendronate? For example, when exposed to alendronate, human peripheral blood monocytes do not express antigens after stimulation with lectins (6).

In the future we will know the answers to these questions, and hopefully the long-term side effects will be minimal. But lack of knowledge should not be equated with lack of risk. It may not seem just, but a conservative physician will consider a new drug unsafe until proven otherwise.

In a 70 year-old woman who already has vertebral compression fractures, the risk of a new vertebral fracture in the next 3 years is about 20% (7). Clearly the gain in bone strength and reduction in fracture incidence with alendronate therapy outweigh the theoretical long-term risks. In these women the optimal duration of alendronate treatment is unknown.

Elderly women with osteoporosis (defined by low bone mass) without vertebral fractures have only a 2% chance of a new vertebral fracture in the next 3 years (7), making treatment with alendronate less cost effective. But a 50 year old woman - even one with a bone density in the "osteopenic" range - is not expected to develop osteoporotic fractures for another 15 to 20 years.

The paper by Hosking et al. (8) in this issue is the first published study in which postmenopausal women in their 50's were randomly assigned to treatment with either estrogen or alendronate. This study is important because it extends our knowledge about alendronate to a younger age group, and because it directly compares the drug to both estrogen/progesterone and placebo. The alendronate group, at the 5mg dose, showed improvement at a time that the placebo group was losing bone. The improvement in bone mass was significantly better with estrogen/progesterone than with alendronate. The study conclusively documented that alendronate prevented bone loss over 2 years with a good safety profile during that time. But this does not necessarily mean that alendronate will protect women from osteoporosis or from future fractures.

A potential problem with using alendronate as prevention of osteoporosis in relatively young women is that it would replace estrogen. This may result in a reduction of overall benefit, because cardiovascular disease is much more common than osteoporosis. Studies are underway to clearly define the risks and benefits of long-term estrogen use. But the available data show substantial benefits to the cardiovascular system (9). Also, large

epidemiological studies document that the effects of estrogen on the heart and the skeleton continue to be beneficial after many years of continuous use. For example, elderly women in the Study of Osteoporotic Fractures who had been taking estrogen since menopause had about 1/3 as many hip fractures as women who didn't take estrogen (10).

A colleague asked what I thought about using alendronate for prevention of osteoporosis in the early postmenopausal woman. I replied that I would not use a new drug to prevent a disease that wasn't expected to occur for 20 years unless I knew the safety data for 20 years. He exclaimed, "But that would take a long time!"

Precisely.

Before I was born Fuller Albright first postulated that postmenopausal osteoporosis was caused by estrogen deficiency. Perhaps we will understand all the risks and benefits of estrogen replacement therapy while I'm still alive - but not before I have to decide whether to take it! And the full potential uses and risks of the bisphosphonates will not be known until my daughter has to make that decision.

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