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Experimental Drug Helps Treat Osteoporosis

By Alice Park

An experimental drug has successfully reduced hip and spine fractures in the two largest patient populations at risk for osteoporosis — postmenopausal women and men being treated for prostate cancer — according to two major studies published online on Aug. 11 by the *New England Journal of Medicine*. The new compound, denosumab, is being reviewed by the Food and Drug Administration. If approved, it has the potential to become a standard treatment for certain patients.

Doctors say they are encouraged by the findings, since hip and spine fractures are among the leading causes of health problems in the elderly. Each year, more than 300,000 Americans over age 65 suffer hip fractures, mostly due to falls, and 15% to 20% die within a year of their injury because of complications from infection or blood clots. While current drug treatments for osteoporosis slow down the destruction of existing bone, the new data suggest that denosumab may be more effective in promoting bone density. In addition, the studies show that denosumab did not cause the serious side effects — including cancer and the disintegration of bone in the jaw — that are associated with bisphosphonate drugs like Boniva, Fosamax and Reclast, the most commonly prescribed osteoporosis drugs on the market. (See TIME's special report "America the Fit.")

In the first study, involving 1,468 prostate-cancer patients receiving testosterone-depleting therapy — which can retard the growth of tumors but increases the risk of brittle bones and osteoporosis — half were given denosumab injections every six months for 36 months, and the other half were given a placebo. Over the course of the three-year study, the treatment group had a 62% lower risk of spinal fracture than the placebo group (1.5% of treated patients suffered a fracture vs. 3.9% of the placebo group) and a 5.6% increase in bone-mineral density in the spine. Patients receiving a placebo saw a 1% decline in bone density over the same time period.

The results of that study, called the Denosumab Hormone Ablation Bone Loss Trial (HALT), were especially welcomed by cancer doctors, since it was the first study to show that a drug can lower the

risk of fractures in men with prostate cancer. So far, most trials of osteoporosis treatments have focused on postmenopausal women, who are at high risk of bone loss with the sudden drop in estrogen that occurs after menopause.

"This really addresses an unmet medical need for fracture prevention in men receiving androgen-deprivation therapy for prostate cancer," says Dr. Matthew Smith, director of genitourinary medical oncology at Massachusetts General Hospital and the lead author of the HALT paper. "Given that we have such little data on fracture prevention in men, these findings are important."

The second trial published in the *New England Journal of Medicine* included 7,868 postmenopausal women between the ages of 60 and 90, who were also given either a placebo or injections of denosumab every six months for 36 months. Compared with the placebo group, the treated patients in this study had a 68% lower risk of vertebral fracture and a 40% lower risk of hip fracture over three years. Overall, 2.3% of women receiving denosumab had a spine fracture and 0.7% had a hip fracture, compared with 7.2% and 1.2% in the placebo group, respectively. (Read "Osteoarthritis: Not Just For Women.")

But it is not clear how denosumab, should it win approval, would fit into the anti-osteoporosis market for treating postmenopausal women. Among these patients, the study suggests, the experimental compound would be slightly more effective at reducing fractures than the bisphosphonate drugs Fosamax (alendronate) and Boniva (ibandronate), but no better than Reclast (zoledronic acid), the once-a-year solution that doctors administer intravenously.

"How much impact this would have on patient care remains to be seen," says Dr. Sundeep Khosla, a professor of medicine at the Mayo Clinic, who wrote an editorial accompanying the two studies in the *Journal*. But because denosumab did not result in any serious side effects, it has the potential of becoming a safer alternative, should its current profile hold up in additional studies.

The new agent works a little differently than the bisphosphonates, which are designed to paralyze bone-destroying cells — cells that increase in number as people age. While the body continually destroys and replaces bone tissue throughout life, the destruction eventually begins to overtake the construction, and the result in older age is a patchier, weaker type of bone that is more prone to breaking. While bisphosphonates block the activity of bone-destroying cells, denosumab prevents new ones from forming altogether. The end result is a tipping of the bone balance away from bone destruction and toward bone formation. Early studies in mice at Amgen, the company that developed denosumab, showed that animals given higher amounts of this compound developed thicker, more robust bone.

But Khosla notes that neither the bisphosphonates nor denosumab actually causes the creation of new bone, which would be the ultimate goal of any osteoporosis treatment. The increases in bone-

mineral density seen in the *Journal* studies is primarily due to minerals filling in the gaps left in the wake of bone destruction, he says. "In my mind, the dramatic changes will be seen with the anabolic agents," he says. "They hold the potential for completely curing the disease, reversing bone loss so you effectively are not osteoporotic any more."

Currently only one anabolic agent, called teriparatide, is available. But because it causes the deposition of new bone, it has the potential to cause uncontrolled bone growth and osteosarcoma tumors; to avoid that, the drug can be given only for short periods of time — about two years. After the drug treatment stops, bone loss resumes.

Amgen is developing an anabolic therapy based on a genetic mutation found in people with abnormally strong bones. So far, says the company's executive vice president of research and development, Roger Perlmutter, early testing of the compound in postmenopausal women has been "spectacular." The agent appears to build bone density, and Perlmutter's team is continuing to study the volunteers to see if they experience improvements in fracture healing.

Read "Health: Bones of Contention."