A clinical trial of zoledronate for increasing bone density

The drug zoledronate (also known as zoledronic acid and sold under several brand names including Aclasta, Zometa and Reclast) is one of the drugs that doctors can prescribe to help maintain or increase bone density. This drug belongs to a class of medicines called bisphosphonates and works by interfering with cells that break down bones. By impairing the activity of such cells (called osteoclasts), bone density can be maintained or increased. Zoledronate is given at a dose of 5 mg intravenously once a year.

Researchers in Barcelona, Spain, conducted a clinical trial of zoledronate by randomly assigning participants to receive one of the following interventions:

- one dose of zoledronate + dietary counselling
- dietary counselling alone

After about one year, participants who had received zoledronate were again randomized to one of the following interventions:

- a second dose of zoledronate
- continued dietary counselling

Over the course of this two-year study, bone density in the spine of participants who received counselling alone decreased by about 2%. Among participants who received zoledronate for one year, bone density of the spine increased by 5%. Among participants who received the drug for two years, bone density increased by 8%.

These changes in bone density may seem small but clinical trial data from thousands of HIV-negative people suggest that such increases are associated with a reduced risk for fractures.

Study details

Researchers enrolled 31 participants who were mostly male (only a handful were women) and who had been on a stable anti-HIV regimen for at least six months. At the start of the study, participants were randomly assigned to receive one of the following interventions in a 2:1 ratio:

- zoledronate + dietary counselling – 21 participants
- dietary counselling – 10 participants

Zoledronate was administered intravenously at a dose of 5 mg over 15 to 30 minutes.

Dietary counselling was given every four months to educate participants and remind them to eat sufficient calcium from food. Participants also received 800 IU/day of vitamin D₃. This dose of vitamin D helps the absorption of calcium from the intestine but is unlikely to have a significant impact on bone density.

After 48 weeks, zoledronate users were further randomized to receive either a second dose of the drug or no additional dose.

The average profile of participants at the start of the study was as follows:

- age – late 40s
- time since HIV diagnosis – 14 years
- at least 60% were taking a tenofovir-containing regimen
- CD4+ count – between 500 and 600 cells/mm³
- vitamin D levels – at least 15 ng/ml (about 38 nmol/L)
Results—Week 48

Percent changes in bone density in the spine were as follows:

- dietary counselling – minus 2%
- zoledronate + dietary counselling – plus 6%

This difference was statistically significant; that is, not likely due to chance alone.

Percent changes in bone density in the hips were as follows:

- dietary counselling – plus 0.9%
- zoledronate + dietary counselling – plus 3.5%

This difference was also statistically significant.

Results—Week 96

Percent changes in bone density of the spine were as follows:

- dietary counselling – minus 2%
- one dose of zoledronate + dietary counselling – plus 5%
- two doses of zoledronate + dietary counselling – plus 8%

These differences were statistically significant when comparing the effects of dietary counselling alone to one or two doses of zoledronate. However, there was no significant difference when assessing changes in bone density between the different doses of zoledronate.

Percent changes in bone density of the hips were as follows:

- dietary counselling – plus 2%
- one dose of zoledronate + dietary counselling – plus 4.5%
- two doses of zoledronate + dietary counselling – plus 5%

Although the increase in bone density in the hips among participants who only received dietary counselling might seem helpful, it was described by researchers as “modest” and they noted that there was no increase in the bone density of the spine among participants who received dietary counselling alone (without zoledronate).

A statistically significant difference in bone density was found when comparing the effects of dietary counselling to the use of two doses of zoledronate. However, there was no significant difference in bone density when either one or two doses of zoledronate were compared to each other.

Bone turnover

Although most people think of bones as hard and largely inactive, at the cellular level bones are very dynamic. Parts of bones are always being repaired, torn down and strengthened. This activity—whereby small parts of bones are torn down and repaired—is referred to as bone turnover by researchers.

Some proteins in the blood, called bone turnover markers, can be measured. These proteins can sometimes provide a rough idea of the balance taking place within the body between tearing down and building up bone. Assessment of these proteins is done as part of research studies and not part of routine care. Assessing changes in these proteins, in addition to X-rays, can give researchers an idea of what is happening in bones.

Overall, in the present study, the level of bone turnover markers fell significantly among participants who received zoledronate compared to those who did not get this drug. This suggested that among participants who received zoledronate bone density was more likely increasing rather than decreasing.

Side effects and complications
Three participants who received zoledronate had the following side effects that lasted for between one and two days after the drug was infused:

- lack of energy
- fever

**Bear in mind**

The results of this study suggest that one or two doses of zoledronate have broadly similar benefits on bone density and are better at increasing bone density than dietary counselling coupled with low-dose vitamin D₃. However, bear in mind that this study cannot provide firm results when it comes to comparing the effectiveness of the two zoledronate dose regimens. Although the study was randomized and had a control group (those who received dietary counselling), it enrolled a relatively small number of participants. The study results can serve as a guide to developing a longer and larger study to assess the impact of different doses and schedules of zoledronate in HIV-positive people.

**About zoledronic acid**

Studies with HIV-negative people who have thinning bones due to use of corticosteroids or menopause have found that zoledronate is more effective at maintaining or increasing bone density than other bisphosphonates such as risedronate (Actonel) and alendronate (Fosamax, Fosavance).

The improvement in bone density as a result of zoledronic acid in the Barcelona study is similar to that reported in small studies with HIV-positive people. The results of the Barcelona study confirm that a single dose of zoledronate can have activity that lasts up to two years.

Although rare cases of osteonecrosis of the jaw have been reported in some HIV-negative people who used zoledronate in other clinical trials, serious toxicity from zoledronate did not occur in the Barcelona study.

The Barcelona researchers stated: “Based on our results, doses [of zoledronate] could be spaced to prevent acute and long-term toxicity.” They added, “Both [a single dose and two consecutive yearly dosings] could facilitate adherence in patients who are already receiving a wide array of treatments.” They also noted that the intravenous administration of zoledronate bypasses the gastrointestinal problems that sometimes occur in users of oral bisphosphonate therapy. The researchers stated that zoledronate is processed by the kidneys and did not interact with anti-HIV drugs taken by participants (though the latter was not formally assessed in the present study).

—Sean R. Hosein

**REFERENCE:**

Disclaimer

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