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CLINICAL TRIAL REPORT

Defining Zoledronate's Duration of Action and Optimal Dosing Interval for an Effective Therapy

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Trial

Grey A, Boland M, Wattie D, et al.: Prolonged antiresorptive activity of zoledronate: a randomized control trial. *Gen Bone Miner Res* 2010, 25:2251–2255.

Introduction

Zoledronic acid (ZA) is a potent nitrogen-containing bisphosphonate with a long skeletal half-life that is administered annually by intravenous (IV) infusion. In the Horizon trial, ZA significantly reduced the risk of vertebral fracture by 70%, the risk of hip fracture by 40%, and the risk of nonvertebral fracture by 20% [1]. ZA also reduced the risk of clinical fracture by 35% and decreased mortality by 28% after hip fracture in the Recurrent Fracture Trial [2]. A combination of antifracture efficacy, low rate of adverse events, and infrequent dosing make it a desirable agent for the future.

Aims

Defining the duration of action of zoledronate and the optimal dosing interval may help reduce the cost of an effective therapy.

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Methods

Andrew Grey performed a 3-year randomized placebo-controlled trial of the effects on bone turnover and bone mineral density (BMD) of a single infusion of 5 mg IV zoledronate. Fifty postmenopausal women with osteoporosis were randomized to either a single infusion of IV ZA or placebo. The primary end points were bone turnover markers such as β CTX (C telopeptide) and P1NP (procollagen type I N-terminal propeptide). Secondary end points were BMD of the lumbar spine, total hip, and total body. After 3 years, bone markers, serum β CTX, and P1NP were 44% and 40% lower in the zoledronate group ($P<0.001$ vs placebo for each marker). BMD was higher in the zoledronate than in the placebo group by an average of 6.8% in the lumbar spine, 4.0% total hip, and 2.0% of total body ($P<0.001$ for each skeletal site). Between-group differences in makers of bone turnover and BMD were stable from 12 to 36 months.

Discussion

The data demonstrate the antiresorptive effects of a single 5-mg IV dose of zoledronate was sustained for 3 years and suggests we may wish to consider investigating the antifracture efficacy of ZA in dosing intervals longer than 1 year. However, it is important to note that the Horizon trial, which required IV once yearly for 3 years, is the only trial that has shown fracture efficacy as an end point in the treatment of patients at risk for osteoporotic fracture.

A recent report by Black et al. [3] at the 2010 American Society for Bone and Mineral Research Meeting in Toronto of a 3-year extension of the Horizon trial addresses another related issue, the possibility of a holiday after 3 years

treatment. Black et al. [3] identified 1,233 patients in the Horizon trial at year 3 who were randomized to either continued infusions of IV ZA or placebo. BMD remained constant at all sites in the 6-year ZA group, whereas there was a slight drop in femoral neck BMD of about 1% in the group that received 3 years of placebo injection after 3 years of ZA but the BMD remained well above pretreatment levels.. Results for other sites of BMD were similar. Biochemical markers remained constant in the group receiving ZA for 6 years but rose slightly in the group receiving placebo for 3 years. New morphometric vertebral fractures were significantly lower in the group receiving six ZA injections (RR=0.48, P=0.04), whereas other categories of fractures including nonvertebral, hip, and clinical vertebral were not different between study groups.

Conclusions

The data demonstrate that the antiresorptive effect of IV ZA is sustained for 3 years. Future studies of different dosing intervals may be considered. However, for now we do know that once-yearly IV ZA for 3 years is effective in reducing fracture risk.

Disclosure Conflicts of interest: S.L. Silverman: has received grant support from Novartis.

References

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