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A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density

Kenneth Saag [a,*], Robert Lindsay [b], Audrey Kriegman [c], Emily Beamer [c], Wenchun Zhou [c]

[a] *University of Alabama School of Medicine, 1530 3rd Avenue South, FOT 820D, Birmingham, AL 35294-3408, USA*
[b] *Helen Hayes Hospital, West Haverstraw, NY 10993, USA*
[c] *Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936-1080, USA*

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Abstract

Early data suggest that an annual i.v. infusion of zoledronic acid (ZOL) might have therapeutic use in women with osteoporosis. In this randomized, double-blind, double-dummy, multicenter, 24-week trial, we evaluated the onset of action of a single infusion of ZOL 5 mg ($n=69$) compared with weekly oral alendronate (ALN) 70 mg ($n=59$) in postmenopausal women with low bone mineral density (T score ≤ -2 by DXA) as assessed by reductions in urine *N*-telopeptide of type I collagen (NTX) at week 1. The effects of these therapies on other markers of bone turnover, patient preference for once yearly i.v. vs. oral weekly treatment, and adverse events were also assessed. At week 1, ZOL 5 mg resulted in a significantly greater reduction in mean urine NTX from baseline than ALN 70 mg ($P<0.0001$). Significantly greater reduction in urine NTX and serum β-C-telopeptide of type I collagen (β-CTX) were also observed in the ZOL 5 mg group at all post-baseline time points. Bone-specific alkaline phosphatase (BSAP) levels showed a more gradual reduction in both the ZOL 5 mg and ALN 70 mg groups, reaching premenopausal range by week 12. A comparable proportion of patients reported adverse events in each treatment group (ZOL 5 mg, 91.3%; ALN 70 mg, 86.4%). Transient, flu-like symptoms were the most common adverse events in the ZOL 5 mg group and resulted in a higher frequency of adverse events in this group during the first 3 days of treatment. After 3 days, adverse event rates were similar in the 2 groups. The majority of patients, including those experiencing flu-like symptoms, expressed a preference for annual i.v. therapy (66.4%) compared with weekly oral therapy (19.7%). We conclude that a single i.v. infusion of ZOL 5 mg reduced urine NTX levels more rapidly than weekly oral ALN 70 mg. The majority of study patients preferred an i.v. treatment regimen of ZOL 5 mg over weekly osteoporosis therapy with ALN 70 mg.
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Introduction

Zoledronic acid (ZOL) is a bisphosphonate that has significant efficacy in the treatment of bone disease. The 4-mg i.v. formulation is widely used to reduce skeletal events in patients with advanced cancer [1], and a 5-mg formulation, given as a single infusion, is an efficacious treatment for Paget's disease [2].

Preclinical data indicate that ZOL is the most potent bisphosphonate currently available. In particular, ZOL has a higher binding affinity for hydroxyapatite and is a more potent inhibitor of farnesyl disphosphate synthase and bone resorption than other bisphosphonates [3–5].

ZOL has shown promising results in a dose-ranging, placebo-controlled, 12-month trial in postmenopausal women with low bone mineral density (BMD) [6]. One of the dosing regimens tested in that trial was a single infusion of 4 mg, which was found to be as efficacious in improving BMD and decreasing bone resorption markers at 12 months as more frequent doses. A once yearly dosing regimen is an attractive

* Corresponding author. Fax: +1 205 975 6859.
E-mail address: kenneth.saag@ccc.uab.edu (K. Saag).

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option for treating osteoporosis because it would offer assured adherence over the 1 year of therapy. In addition, i.v. dosing may result in a more rapid onset of activity than oral bisphosphonates.

The study reported here was primarily designed to evaluate whether a single infusion of ZOL 5 mg has a more rapid onset of action than weekly oral alendronate (ALN) 70 mg, as demonstrated by comparing relative change from baseline in the bone resorption marker urine *N*-telopeptide of type I collagen (NTX) at week 1 for both groups. Secondary objectives included assessments of changes in other bone resorption and formation markers over time, patient preference for annual i.v. therapy vs. weekly oral therapy, and adverse events.

Patients and methods

Patients

Postmenopausal women between 45 and 79 years of age were eligible for this study. All patients were required to have a bone density *T* score ≤ -2 at lumbar spine or femoral neck no more than 3 months prior to the screening visit. Unless the total lifetime duration of treatment was less than 8 weeks and no treatment had occurred within 6 months prior to randomization, patients who had been treated with oral or i.v. bisphosphonates within the last 2 years were excluded. Other major exclusion criteria included fractures within 3 months prior to randomization; any treatment with strontium ranelate, sodium fluoride, or parathyroid hormone; treatment with raloxifene, calcitonin, tibolone, or hormone replacement therapy in the 6 months prior to randomization; and creatinine clearance <30 mL/min. Patients with invasive malignant disease or any medical condition that would interfere with the action of the study drug or limit life expectancy to less than 6 months were excluded from this study.

Study design and treatment

The study was designed as a randomized, double-blind, double-dummy, active-controlled trial involving 17 participating centers. The study duration was 24 weeks. The trial was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. Signed, informed consent was given by all patients prior to the start of treatment.

Patients were randomized to treatment with either ZOL 5 mg or ALN 70 mg in a 1:1 ratio according to a computer-generated schedule. Patients in the ZOL arm received a single infusion of ZOL 5 mg plus oral placebo once weekly for 24 weeks, while those in the ALN arm received oral ALN 70 mg once weekly for 24 weeks plus a single infusion of i.v. placebo. All patients also received elemental calcium (1000 mg/day) and vitamin D (400 IU/day) by mouth throughout the study. Study medication was packaged in a double-blind, double-dummy format to allow investigators and site personnel to be blinded to trial medication. Blinding of ALN 70 mg was performed with standard overencapsulation with gelatin capsule shells. To reduce the incidence of flu-like symptoms that sometimes occur in bisphosphonate-naïve patients, all patients were instructed to take acetaminophen 1000 mg every 6 h starting at randomization.

Assessment of outcomes

Biochemical markers

Patients were asked to provide a second morning or subsequent urine sample for measurement of biochemical markers. The majority of patients were fasting at the time of the urine and serum collections. Measurement of biochemical markers was performed in a central laboratory facility (Synarc, Lyon, France). Urine NTX corrected for creatinine (Analyser Vitros ECI, NTx Reagent pack; intra-assay variability, 1.1%–6.7%; inter-assay variability, 3.8%–6.1%) and serum C-telopeptide of type I collagen (β-CTX) (Analyzer Elecsys 2010, Beta-CrossLaps serum pack; intra-assay variability, 1.6%–3.0%; inter-assay variability, 1.3%–4.3%) were evaluated to assess the rate of bone resorption. Serum bone-specific alkaline phosphatase (BSAP) (Access Ostase Reagent Pack; intra-assay variability, 2.3%–3.7%; inter-assay variability, 4.4%–9.8%) was evaluated to assess the rate of bone formation. To minimize the assay variability within and between the patients, all samples were shipped in batches from a central laboratory (Covance, Indianapolis, IN) for analysis at the end of the study. Samples from the same patient were analyzed in the same batch.

Patient preference of treatment modality

At the end of the study, patients were asked 4 questions to determine their preferences for the different treatment modalities (annual i.v. vs. weekly oral capsule): (1) which treatment delivery they considered more convenient, (2) which they considered more satisfying, (3) which they would be willing to take for a long period of time, and (4) which they preferred.

Dyspepsia symptoms

The Nepean Dyspepsia Index–Short Form (NDI–SF) was used to assess the frequency, intensity, and "bothersomeness" of upper gastrointestinal symptoms on a scale of 0 (not at all) to 4 (daily) for frequency, 0 (not at all) to 5 (very severe) for intensity, and 0 (not at all) to 4 (extremely bothersome) for bothersomeness [7].

Endpoints

The primary study endpoint was the relative change from baseline in urine NTX at week 1, defined as the $\log_e$ ratio of the post-baseline measurement divided by the baseline measurement. Other endpoints included the relative change in urine NTX (weeks 2, 4, 8, 12, 24), serum β-CTX (weeks 1, 2, 4, 8, 12, 24), serum BSAP (weeks 4, 12, 24) over time, as well as patient preference of treatment modality at study end.

Clinical evaluation of adverse events and laboratory measurements including serum chemistry, urinalysis, and hematology were performed at screening, week 1, and week 24. Vital signs were recorded at screening, week 1, and week 24 and concomitant medication use was recorded at each visit. Upper gastrointestinal symptoms were assessed using NDI–SF Symptom Checklist scores at weeks 2 and 24.

Statistical analysis

The sample size was calculated as the number of patients needed to detect a difference between the ZOL 5 mg group and the ALN 70 mg group of at least 25% in the percent change in urine NTX from baseline to 1 week. Given a non-central *t*-distribution with a significance level of 0.05, a power of 90%, and a standard deviation of 42%, we calculated that 60 patients per group were needed.

For ease of interpretation, summary statistics of biochemical markers in their original scales are displayed instead of the percent change from baseline. The natural log transformation ($\log_e$ ratio of the post-baseline measurement divided by the baseline measurement at each time point, referred to hereafter as *relative change*) was used in statistical analyses of biochemical markers in order to achieve an approximately normal distribution [8].

An analysis of variance (ANOVA) model with treatment and center as explanatory variables was performed to estimate differences between treatment groups for biochemical markers and NDI–SF scores. All comparisons were tested at a 2-sided level of significance of 0.05. Associated 2-sided 95% confidence intervals were constructed as well. No adjustment for multiple comparisons was performed for secondary endpoints. All analyses were performed according to the intent-to-treat principle using all available data from all patients who received study drug. Missing values due to withdrawal from the study were not imputed. However, values below the lower limit of detection (LOD) for the biochemical markers were imputed using LOD/2 in analyses (urine NTX: LOD<10 nmol BCE and serum β-CTX: LOD<0.010 ng/mL).

The analysis of the primary efficacy variable urine NTX was repeated using data from all patients who completed the study without any major protocol violations (per-protocol population), and was done using available observed values without imputation of those that were missing because they were below the LOD.

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