JAMA | Original Investigation

Effect of Intravenous Zoledronic Acid on Tibiofemoral Cartilage Volume Among Patients With Knee Osteoarthritis With Bone Marrow Lesions
A Randomized Clinical Trial

Guoqi Cai, MMedSci; Dawn Aitken, PhD; Laura L. Laslett, PhD; Jean-Pierre Pelletier, PhD; Johanne Martel-Pelletier, PhD; Catherine Hill, PhD; Lyn March, PhD; Anita E. Wluka, PhD; Yuanyuan Wang, PhD; Benny Antony, PhD; Leigh Blizzard, PhD; Tania Winzenberg, PhD; Flavia Cicuttini, PhD; Graeme Jones, PhD

IMPORTANCE A proof-of-principle study suggested that intravenous zoledronic acid may reduce knee pain and the size of bone marrow lesions in people with knee osteoarthritis, but data from large trials are lacking.

OBJECTIVE To determine the effects of intravenous zoledronic acid on knee cartilage volume loss in patients with symptomatic knee osteoarthritis and bone marrow lesions.

DESIGN, SETTING, AND PARTICIPANTS A 24-month multicenter, double-blind placebo-controlled randomized clinical trial conducted at 4 sites in Australia (1 research center and 3 hospitals). Adults aged 50 years or older with symptomatic knee osteoarthritis and subchondral bone marrow lesions detected by magnetic resonance imaging (MRI) were enrolled from November 2013 through September 2015. The final date of follow-up was October 9, 2017.

INTERVENTIONS Intravenous infusion with either 5 mg of zoledronic acid in a 100-mL saline solution (n = 113) or a placebo saline solution (n = 110) at baseline and 12 months.

MAIN OUTCOMES AND MEASURES The primary outcome was absolute change in tibiofemoral cartilage volume assessed using MRI over 24 months (the minimum clinically important difference [MCID] has not been established). Three prespecified secondary outcomes were change in knee pain assessed by a visual analog scale (0 [no pain] to 100 [unbearable pain]; MCID, 15) and the Western Ontario and McMaster Universities Osteoarthritis Index (0 [no pain] to 500 [unbearable pain]; MCID, 75) over 3, 6, 12, 18, and 24 months and change in bone marrow lesion size over 6 and 24 months (the MCID has not been established).

RESULTS Of 223 participants enrolled (mean age, 62.0 years [SD, 8.0 years]; 52% were female), 190 (85%) completed the trial. Change in tibiofemoral cartilage volume was not significantly different between the zoledronic acid group and the placebo group over 24 months (−878 mm^3 vs −919 mm^3; between-group difference, 41 mm^3 [95% CI, −79 to 161 mm^3]; $P = .50$). No significant between-group differences were found for any of the prespecified secondary outcomes, including changes in knee pain assessed by a visual analog scale (−11.5 in the zoledronic acid group vs −16.8 in the placebo group; between-group difference, 5.2 [95% CI, −2.3 to 12.8]; $P = .17$), changes in knee pain assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (−37.5 vs −58.0, respectively; between-group difference, 20.5 [95% CI, −11.2 to 52.2]; $P = .21$), and changes in bone marrow lesion size (−33 mm^2 vs −6 mm^2; between-group difference, −27 mm^2 [95% CI, −127 to 73 mm^2]; $P = .60$) over 24 months. Adverse events were more common with zoledronic acid than with placebo (96% vs 83%, respectively) and consisted mainly of acute reactions (defined as symptoms within 3 days of administration of infusion; 87% vs 56%).

CONCLUSIONS AND RELEVANCE Among patients with symptomatic knee osteoarthritis and bone marrow lesions, yearly zoledronic acid infusions, compared with placebo, did not significantly reduce cartilage volume loss over 24 months. These findings do not support the use of zoledronic acid in the treatment of knee osteoarthritis.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12613000039785

JAMA. 2020;323(15):1456-1466. doi:10.1001/jama.2020.2938

Visual Abstract

Supplemental content

Author Affiliations: Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia (Cai, Aitken, Laslett, Antony, Blizzard, Winzenberg, Jones); Osteoarthritis Research Unit, University of Montreal Hospital Research Centre, Notre-Dame Hospital, Montreal, Quebec, Canada (Pelletier, Martel-Pelletier); Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia (Hill); University of Sydney, Royal North Shore Hospital, Sydney, Australia (March); Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia (Wluka, Wang, Cicuttini).

Corresponding Author: Graeme Jones, PhD, Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool St, Private Bag 23, Hobart, Tasmania 7000, Australia (graeme.jones@utas.edu.au).

Osteoarthritis is the most common form of arthritis, affecting 250 million people worldwide.[1] Knee osteoarthritis is characterized by knee pain and structural changes, leading to disability, impaired quality of life, and economic burden.[2-4] Alleviating pain and preventing structural progression are 2 major treatment goals for osteoarthritis.[5] However, pain control remains poor in more than half of patients,[6] and no approved disease-modifying therapies have been identified that prevent structural progression of knee osteoarthritis.

Subchondral bone resorption and turnover contribute to the pathogenesis of osteoarthritis. In animals, treatment with bisphosphonates reduced cartilage deterioration by inhibiting subchondral bone resorption in a dose-response manner.[7-9] However, the results from randomized clinical trials (RCTs) in humans have been mixed. A meta-analysis[10] of 7 RCTs concluded that bisphosphonates were ineffective for knee symptoms and radiographic progression in patients with knee osteoarthritis, but the authors stated that bisphosphonates may be beneficial in patients with high rates of bone turnover. Subchondral bone marrow lesions visible on magnetic resonance imaging (MRI) identify regions of high bone turnover that may be associated with greater response to bisphosphonates.[11]

In a pilot study, zoledronic acid (an intravenous bisphosphonate) reduced knee pain and bone marrow lesion size in patients with knee osteoarthritis and subchondral bone marrow lesions after 6 months.[12] Given that bone marrow lesions were associated with faster cartilage volume loss[13] (an important measure of knee structural progression), the current multicenter RCT assessed whether zoledronic acid reduced knee pain, bone marrow lesion size, and cartilage volume loss in patients with knee osteoarthritis and bone marrow lesions at 24-month follow-up. This study assessed the effects of 2 annual infusions with 5 mg of zoledronic acid on knee cartilage volume loss in participants with symptomatic knee osteoarthritis and bone marrow lesions over 24 months.

Key Points

Question Is zoledronic acid effective for reducing knee cartilage loss in patients with symptomatic knee osteoarthritis and bone marrow lesions?

Findings In this randomized clinical trial that included 223 adults, the mean change in tibiofemoral cartilage volume over 24 months was −878 mm^3 in the zoledronic acid group and −919 mm^3 in the placebo group, a difference that was not statistically significant.

Meaning The findings do not support the use of zoledronic acid for slowing cartilage volume loss in patients with knee osteoarthritis.

Methods

Trial Design

The Zoledronic Acid for Osteoarthritis Knee Pain (ZAP2) study was a multicenter, double-blind placebo-controlled RCT conducted in Australia. Participants were recruited via the Osteoarthritis Clinical Trial Network at 4 sites (in Adelaide, Hobart, Melbourne, and Sydney) in collaboration with general practitioners, rheumatologists, and orthopedic surgeons, and with advertising through local and social media. Details of the trial design have been published[14] and are provided in the study protocol (eAppendix in Supplement 1).

The trial was registered on the Australian New Zealand Clinical Trials Registry prior to recruitment. Ethics approval was obtained from the Tasmania Health and Medical human research ethics committee (H0012941), the Alfred Hospital ethics committee (03/13), the Monash University human research ethics committee (CF14/1064-2014000452), the Northern Sydney Coast human research ethics committee (HREC/13/HAWKE/80), and the Queen Elizabeth Hospital human research ethics committee (TQEH/LMH/MH and HREC/13/TQEHLMH/134). All participants provided written informed consent.

Participants

Inclusion and exclusion criteria are detailed in the published protocol[14] and are identical with that in the pilot study.[12] Participants were eligible if aged 50 years or older with knee pain (defined as a pain score ≥40 mm on a 100-mm visual analog scale [VAS]) on most days during the last month, met the American College of Rheumatology criteria for symptomatic knee osteoarthritis[15] as assessed by a rheumatologist, and had a subchondral bone marrow lesion present on MRI.

Exclusion criteria included prior use of bisphosphonates (except according to a washout schedule), abnormal blood test results (serum calcium level >2.75 mmol/L or <2.00 mmol/L, creatinine clearance <35 mL/min, or serum 25-hydroxyvitamin D <40 nmol/L), grade 3 joint space narrowing (JSN) on radiograph using the Osteoarthritis Research Society International atlas (grade 0 [normal] to 3 [severe]),[16] other forms of arthritis (eg, rheumatoid arthritis), poor dental health, arthroscopy or open surgery in the study knee during the last 12 months, planned knee replacement, cancer, or contraindication to MRI.[14]

When a participant had 2 eligible knees, the knee with the worst pain and mild JSN was selected as the study knee.

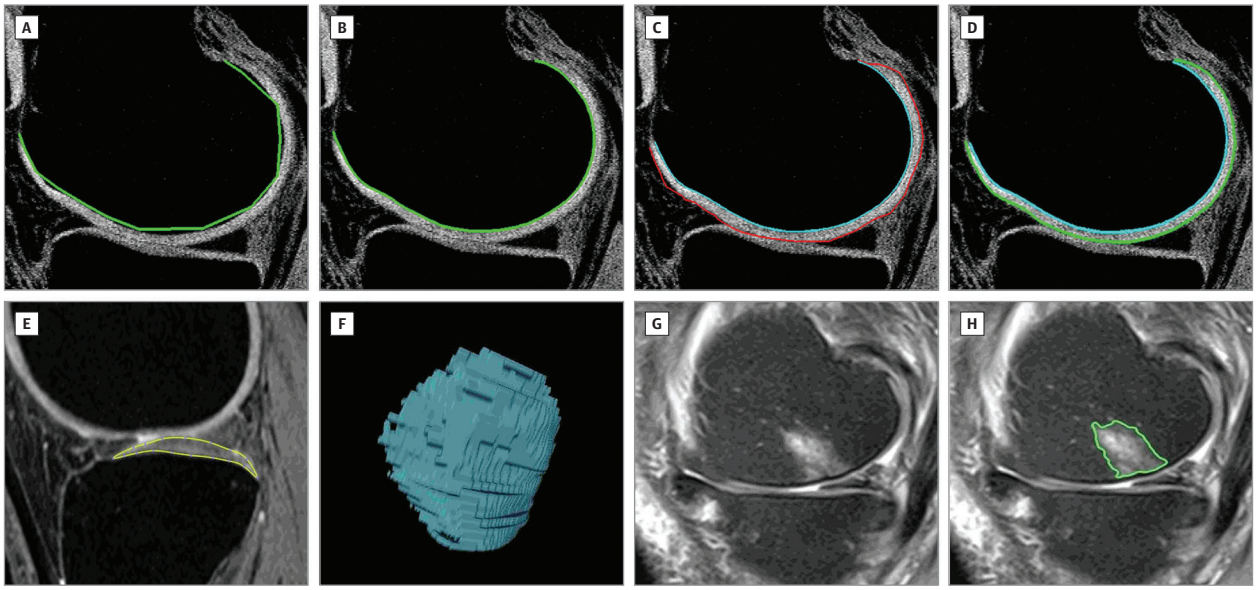
Randomization and Blinding

Stratified randomization was conducted by each study site based on computer-generated block randomization with a block size of 10. This procedure was performed by a staff member without other study involvement. Allocation concealment was ensured using visually identical infusions (ie, clear and colorless) for each group. Research nurses administered the treatments and investigators assessed the outcomes while blinded to treatment allocation.

Interventions

Participants were randomly assigned in a 1:1 ratio to receive a single 15-minute intravenous infusion of either zoledronic acid (5 mg in a 100-mL saline solution) or identical placebo (100-mL saline solution) at baseline and at 12 months and were followed up until 24 months.

Figure 1. Examples of the Measurement of Femoral (A, B, C, and D) and Tibial (E and F) Cartilage Volume and Bone Marrow Lesion Size (G and H)



A, Delineation of an initial estimate of the bone cartilage interfaces. B, Automatic deformation of the bone cartilage contour estimates by the 2- or 3-dimensional active contour process. C, Delineation of an initial estimate of the cartilage soft tissue interfaces. D, Automatic deformation of the cartilage soft contour estimates by the 2- or 3-dimensional active contour process. E, The manual drawing process of disarticulation contours around the tibial cartilage boundaries. This was done on a section-by-section basis, and then a 3-dimensional rendering (F) was conducted to calculate the volume of the tibial cartilage. G, A hyperintensity in the subchondral bone at the medial femoral compartment. H, The manual drawing process of the hyperintense area. Bone marrow lesions on adjacent slices were measured and compared to locate the slice with the maximum lesion size. This was done for the medial femoral, medial tibial, lateral femoral, lateral tibial, and patellar compartments. The total size of the bone marrow lesion was calculated as the sum of every lesion within each compartment.

Outcomes

The primary outcome was absolute change in tibiofemoral cartilage volume assessed using MRI over 24 months. The minimal clinically important difference for cartilage volume loss has not been established.

The secondary outcomes were change in total bone marrow lesion size after 6 and 24 months and change in knee pain after 3, 6, 12, 18, and 24 months (assessed using a VAS pain score [0-100 mm] and the Western Ontario and McMaster Universities Osteoarthritis Index[17] [WOMAC] pain score [0-500 mm]). A proxy for a clinically important difference of 140 mm^2 was defined for change in bone marrow lesion size. This cutoff was used in the pilot study[12] given that a change in bone marrow lesion size of 140 mm^2 was associated with a 1-point change in pain score (as assessed by a WOMAC pain score of 0-45).[18] The minimal clinically important difference was 15 for the VAS pain score and 75 for the WOMAC pain score.[19]

Assessments Using MRI

Magnetic resonance imaging scans of the study knee were performed at screening and at 6 and 24 months using 1.5-T or 3-T whole-body MRI units with a commercial transmit-receive knee coil. For each participant, the same scanner at each site was used throughout the study. The sequences and parameters of the MRI units used at each site were described.[14] Participants who withdrew from the study after 9 months of follow-up were invited to have their final MRI scan at the time of withdrawal to minimize missing MRI data.

Cartilage Volume

Knee tibial cartilage volume was assessed on the sagittal T1-weighted sequences using OsiriX software (University of Geneva) and femoral cartilage volume was assessed using the Cartiscope (ArthroLab Inc).[20] The volumes of the tibial cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled using bilinear and cubic interpolation for the final 3-dimensional images (**Figure 1**). The coefficient of variation was 2.1% to 2.2% for intraobserver and interscan repeatability.[21]

Femoral cartilage volume was measured directly from a standardized view of 3-dimensional cartilage geometry as the sum of elementary volumes for the medial and lateral condyles delineated by the Blumensaat line.[20] The segmentation of the cartilage-synovial interfaces was carried out with a semiautomatic method under reader supervision and with corrections when needed (Figure 1). The coefficient of variation was 1.6% to 2.6% for intraobserver and interscan repeatability.[22]

Tibiofemoral cartilage volume was defined as the sum of both the tibial and femoral compartment cartilage volume and was calculated at screening and at 24 months. Absolute change in tibiofemoral cartilage volume was calculated as tibiofemoral cartilage volume at 24 months minus tibiofemoral cartilage volume at baseline. The percentage change in tibiofemoral cartilage volume per year was calculated as

follows: 100 × [(follow-up cartilage volume − baseline cartilage volume)/baseline cartilage volume]/exact time between 2 scans in years.

Bone Marrow Lesions

The ill-defined hyperintensities in the subchondral bone visualized on MRI were considered to be bone marrow lesions. The bone marrow lesions were assessed on the sagittal proton density-weighted sequences at the medial tibial, medial femoral, lateral tibial, lateral femoral, and patella sites using OsiriX software. The maximum size of each lesion was measured by applying software cursors to the greatest area of the lesion as previously described.[12] Total bone marrow lesion size was calculated as the sum of every lesion within each site at screening and at 6 and 24 months (Figure 1). The intraclass correlation coefficients (2-way mixed-effects model) of bone marrow lesion size ranged from 0.84 to 0.91.

Assessment of Pain

Knee pain was assessed by a 100-mm VAS (a score of 0 [none] to 100 [unbearable]) and the 500-mm WOMAC pain scale (a score of 0 [none] to 500 [unbearable]) over the past 7 days. Five items were assessed, including pain during walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing upright, and were summed to create a total WOMAC pain score.[23] The WOMAC pain score was considered invalid if there was more than 1 missing item.

Adverse Events

Adverse events were monitored throughout the trial. All participants were requested to report any adverse event to the research staff at each study visit and by telephone between visits. Moreover, participants were telephoned 3 days following their infusions at baseline and at 12 months to determine if they experienced any of the following types of adverse effects after the infusion: fever, musculoskeletal, gastrointestinal, or eye symptoms and any other adverse effects as previously described.[24] The presence of serious adverse events (ie, death, life-threatening, disabling, nonelective or prolonged hospitalization, and important medical events such as cancer) was determined by a rheumatologist.

Power Calculations

For change in tibiofemoral cartilage volume, the sample size was calculated based on the assumption that a decrease in bone marrow lesion size would result in a reduction in cartilage volume loss over time. This assumption was based on evidence from observational data demonstrating that bone marrow lesions were associated with cartilage volume loss over time.[25-28] Data from the pilot study showed that zoledronic acid decreased bone marrow lesion size compared with placebo (−199 mm^2 vs −23 mm^2) over 6 months.[12] These data and unpublished observational data from the Tasmanian Older Adult Cohort study were used to estimate the association of a decrease in bone marrow lesion size with change in tibiofemoral cartilage volume over 24 months. Estimates of tibiofemoral cartilage loss expected from the magnitude of changes observed in bone marrow lesion size were −824 mm^3 (SD, 273 mm^3) in the zoledronic acid group and −928 mm^3 (SD, 272 mm^3) in the placebo group (the minimal clinically important difference was not defined for cartilage volume loss). With this difference (104 mm^3), 132 participants in each group would provide 80% power with 5% probability of type I error (α = .05), allowing for a dropout rate of 20% over 24 months. The power to detect a clinically important difference was 99.3% for a VAS knee pain score of 15 (range, 0-100) and 97.3% for a bone marrow lesion size of 140 mm^2.

Statistical Analysis

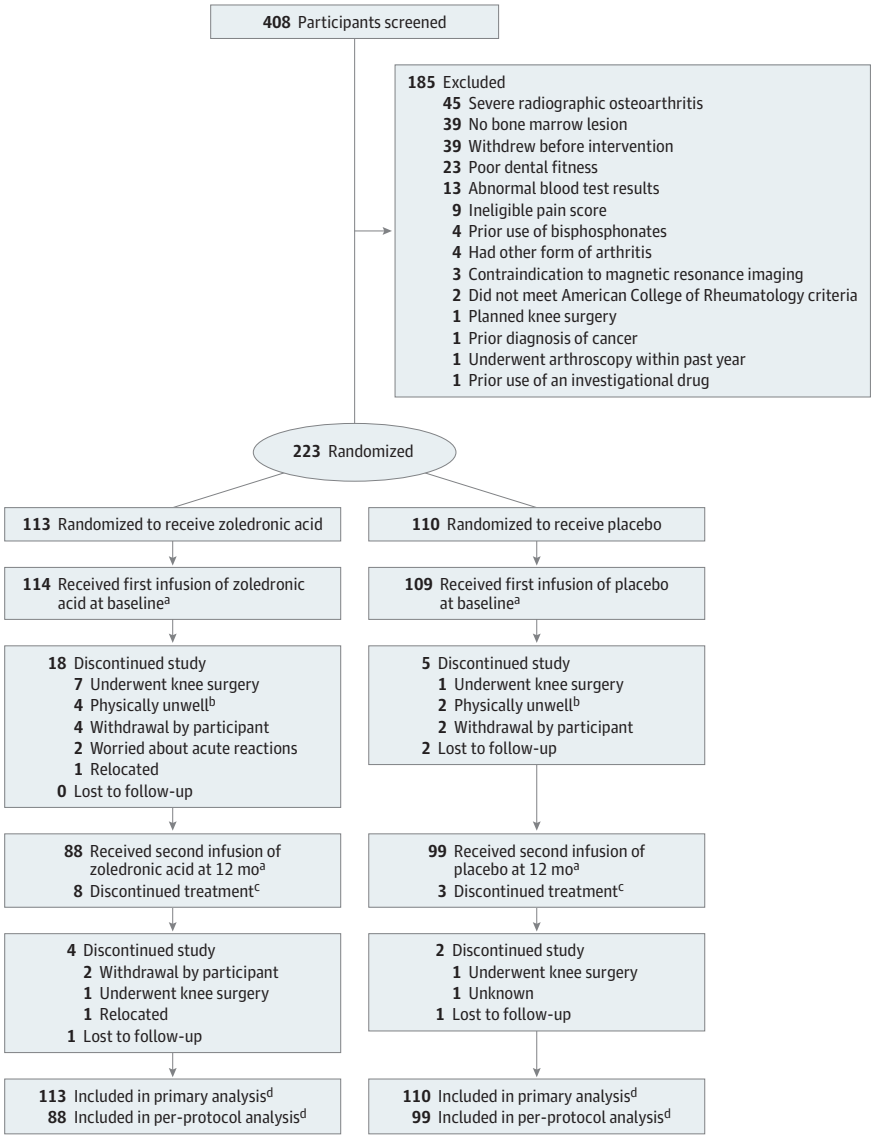
The statistical analysis plan is provided with the study protocol (eAppendix in Supplement 1). The primary analyses were performed based on the original randomization group for each participant. Change in tibiofemoral cartilage volume, knee pain, and bone marrow lesion size were analyzed using linear mixed-effects models with treatment, month, and the treatment × month interaction as covariates. The correlations within trial site and the repeated measures were addressed using trial site and participant identification as random intercepts. Month was treated as a random effect, and an unstructured covariance structure was used to allow different treatment effects over time. Each model was adjusted for the baseline value of the corresponding outcome (eg, change in cartilage volume was adjusted for baseline cartilage volume). Missing data caused by loss to follow-up and nonresponses were addressed by adding baseline complete variables that explained the missingness to the regression models.

Prespecified subgroup analyses were performed to examine which subgroups may respond better to treatment. One prespecified stratification variable was presence or absence of radiographic JSN (grade 1 or 2 vs grade 0). This was conducted by introducing a 3-way interaction between treatment, month, and radiographic JSN in the linear mixed-effects models. Other prespecified subgroup analyses using MRI readings for pathological effects (ie, cartilage defects and meniscal tears and extrusion) were not conducted because these MRI readings have not been completed.

In the secondary analyses,[14] per-protocol analyses were conducted for the primary and secondary outcomes by the actual treatment that the participants received, and this was limited to those who received infusions at both baseline and 12 months. Multiple imputation with chained equations was used to address missing data, with 20 imputations performed by treatment group using baseline complete variables (age, sex, body mass index, and study site) and nonmissing values of the outcomes at baseline and at each follow-up, and assuming the data were missing at random.

A post hoc subgroup analysis was performed by baseline bone marrow lesion size (larger [>median size] or smaller [<median size]). Post hoc conditional power analyses were performed based on both the designed detectable effects and the clinically important effects on study end points using the observed SDs in this trial. Some participants had missing measurements for tibial, femoral, or both tibial and femoral cartilage volume; therefore, a comparison was conducted to evaluate the effect of zoledronic acid on cartilage volume loss

Figure 2. Population Eligibility and Inclusion in the Zoledronic Acid for Osteoarthritis Knee Pain (ZAP2) Study



[a] One participant allocated to the placebo group incorrectly received zoledronic acid at both baseline and 12 months.

[b] Participants who had major surgery (eg, heart surgery, hip replacement, back surgery) or wished to have an antiresorptive treatment (denosumab).

[c] Participants who did not receive the second infusion but continued with the study visits and assessments.

[d] For change in cartilage volume, 194 participants with data on both tibial and femoral cartilage volume at baseline were included in the primary analysis (93 in the zoledronic acid group and 101 in the placebo group) and 163 were included in the per-protocol analysis (79 and 84, respectively).

in participants with complete data on tibiofemoral cartilage volume vs those with measures of cartilage volume only at either the tibial or the femoral site.

Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary outcomes and for the subgroup analyses should be interpreted as exploratory. All analyses were performed with Stata version 15.1 (StataCorp). A 2-sided *P* value of .05 or less was considered statistically significant.

Results

Participants

The study flowchart appears in **Figure 2**. From November 2013 through September 2015, 408 participants were screened and 223 were randomized to receive zoledronic acid (n = 113) or placebo (n = 110). The final date of follow-up was October 9, 2017. The planned sample size (n = 264) was not achieved due to budgetary limitations. One participant in the placebo group incorrectly received zoledronic acid infusions at both baseline and 12 months. Thirty-three participants (15%) withdrew from the trial (23 [20%] in the zoledronic acid group and 10 [9%] in the placebo group), and 190 participants (85%) completed the study. The baseline characteristics of all participants (both those who completed the study and those who did not) appear in eTable 1 in Supplement 2.

The mean age of the participants was 62.0 years (SD, 8.0 years), and 117 (52%) were women. The baseline characteristics of the 2 study groups were generally well balanced. However, the mean value of knee pain scores was higher and the cartilage volume was lower in the placebo group than in the zoledronic acid group (**Table 1**).

Primary Outcome

Tibiofemoral cartilage volume decreased by a mean value of 878 mm^3 in the zoledronic acid group and 919 mm^3 in the placebo group over 24 months and the between-group difference was not statistically significant (between-group difference, 41 mm^3 [95% CI, −79 to 161 mm^3], P = .50; **Table 2**).

Secondary Outcomes

Knee pain improved in both groups over 24 months and there was no significant between-group difference observed for the VAS pain score (−11.5 for the zoledronic acid group vs −16.8 for the placebo group; between-group difference, 5.2 [95% CI, −2.3 to 12.8]; P = .17) or for the WOMAC pain score (−37.5 vs −58.0, respectively; between-group difference, 20.5 [95% CI, −11.2 to 52.2]; P = .21) or at any other time point (Table 2 and **Figure 3**). Bone marrow lesion size was not significantly changed in either group and no significant between-group differences were observed over 24 months (−33 mm^2 for the zoledronic acid group vs −6 mm^2 for the placebo group; between-group difference, −27 mm^2 [95% CI, −127 to 73 mm^2]; P = .60) or over 6 months (Table 2 and Figure 3).

The results of the prespecified subgroup analyses appear in eFigure 1 in Supplement 2. The effect of zoledronic acid on the change in tibiofemoral cartilage volume was not significantly different in participants with or without radiographic JSN. A significant interaction between treatment and radiographic JSN for change in WOMAC knee pain score was observed after 12 months (P = .01 for interaction). Zoledronic acid significantly improved WOMAC knee pain score among participants without radiographic JSN (n = 44) over 12 months compared with placebo (between-group difference, −67.9 [95% CI, −126.8 to −8.9], P = .01). There were statistically significant interactions between treatment and radiographic JSN for both the WOMAC and VAS knee pain scores after 24 months, but compared with placebo, zoledronic acid did not significantly improve the WOMAC or VAS knee pain score among participants with or without radiographic JSN.

In prespecified secondary analyses, neither the per-protocol analyses nor multiple imputation changed the results meaningfully from the primary analyses (eTables 2 and 3 in Supplement 2).

Post Hoc Analyses

Even though significant interactions between treatment and bone marrow lesion size (>the median size vs <the median size) were found for WOMAC knee pain score after 12 and 18 months and for VAS knee pain score after 6 months, zoledronic acid did not significantly improve knee pain in participants with larger or smaller bone marrow lesions compared with placebo (eFigure 2 in Supplement 2). In the post hoc conditional power analyses, this trial had sufficient power to detect a clinically important difference in cartilage loss (power = 1.0; eTable 4 in Supplement 2). The effect of zoledronic acid on cartilage loss in participants with data on tibial or femoral cartilage volume (n = 188) or with complete data on both tibial and femoral cartilage volume (n = 142) was not meaningfully different from the primary analysis (n = 194; eTable 5 in Supplement 2).

Table 1. Patient Demographics and Baseline Characteristics

	Zoledronic acid (n = 113)	Placebo (n = 110)
Age, mean (SD), y	62.6 (8.5)	61.3 (7.3)
Sex, No. (%)		
Female	54 (48)	63 (57)
Male	59 (52)	47 (43)
Body mass index, mean (SD)[a]	30.2 (5.5)	30.8 (6.2)
Radiographic JSN, No./total (%)[b]		
Grade 0 (normal)	21/110 (19)	23/108 (21)
Grade 1 (mild)	39/110 (36)	48/108 (45)
Grade 2 (moderate)	50/110 (45)	37/108 (34)
Tibiofemoral cartilage volume, mean (SD), mm^3	(n = 101) 16 994 (7273)	(n = 93) 16 039 (6807)
Tibial cartilage volume, mean (SD), mm^3	3371 (1213)	3247 (1044)
Femoral cartilage volume, mean (SD), mm^3	(n = 101) 13 529 (6497)	(n = 93) 12 787 (6128)
Bone marrow lesion size, median (IQR), mm^2	476 (255-860)	502 (225-919)
Knee pain score, mean (SD)		
WOMAC[c]	180.8 (103.7)	(n = 109) 219.9 (103.0)
Visual analog scale[d]	47.7 (21.2)	(n = 108) 54.5 (19.2)
Concomitant medications		
No. of analgesics, median (IQR)	1 (0-2)	1 (0-2)
NSAIDs, No. (%)	52 (46)	59 (54)
Paracetamol/acetaminophen, No. (%)	58 (51)	46 (42)
Other analgesics, No. (%)[e]	8 (7)	11 (10)
Glucosamine or chondroitin, No. (%)	31 (27)	33 (30)

Abbreviations: IQR, interquartile range; JSN, joint space narrowing; NSAIDs, nonsteroidal anti-inflammatory drugs; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Calculated as weight in kilograms divided by height in meters squared. A body mass index of 18.5 to 25 was considered a healthy weight; 26 to 30, overweight; and greater than 30, obese.

[b] Assessed according to the atlas from the Osteoarthritis Research Society International (a score of 0 indicates normal; 1, mild; 2, moderate; and 3, severe).

[c] Range is 0 to 500; higher scores indicate more severe symptoms. The index relies on a self-administered questionnaire reflecting pain, stiffness, and limitations to physical function. The pain subscale measures 5 dimensions: walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing upright.

[d] Range is 0 to 100; higher scores indicate more severe symptoms.

[e] Included opioids, prednisolone, and compound analgesics.

Adverse Events

The adverse event rates appear in **Table 3.** One hundred and eight participants (96%) in the zoledronic acid group and 91 participants (83%) in the placebo group experienced at least 1 adverse event. The between-group difference was primarily due to the higher rate of acute reactions with zoledronic acid than with placebo (87% vs 56%, respectively). Acute reactions within 3 days of the infusion consisted primarily of musculoskeletal pain and stiffness (70% in the zoledronic acid group vs 30% in the placebo group), fever (52% vs 8%, respectively), and headache and dizziness (42% vs 26%). These

Table 2. Change in Study Outcomes Between the Zoledronic Acid and the Placebo Group Over 24 Months

	Mean (95% CI)					
	Zoledronic acid		Placebo		Absolute between-group difference[a]	*P* value
	At baseline	Change at 24 mo[a]	At baseline	Change at 24 mo[a]		
Primary outcome						
Tibiofemoral cartilage volume,[b] mm^3	(n = 101) 16 994 (15 558 to 18 429)	(n = 101) −878 (−963 to −793)	(n = 93) 16 039 (14 637 to 17 441)	(n = 93) −919 (−1004 to −835)	41 (−79 to 161)	.50
Annual percentage change in tibiofemoral cartilage volume[c]		(n = 68) −2.66 (−2.97 to −2.34)		(n = 74) −2.73 (−3.04 to −2.43)	0.08 (−0.36 to 0.51)	.73
Secondary outcomes						
WOMAC pain score[d]	(n = 113) 180.8 (161.5 to 200.1)	(n = 113) −37.5 (−59.9 to −15.0)	(n = 109) 219.9 (200.3 to 239.4)	(n = 109) −58.0 (−79.8 to −36.1)	20.5 (−11.2 to 52.2)	.21
Visual analog scale pain score[e]	(n = 113) 47.7 (43.7 to 51.6)	(n = 113) −11.5 (−16.9 to −6.2)	(n = 108) 54.5 (50.8 to 58.1)	(n = 108) −16.8 (−22.0 to −11.6)	5.2 (−2.3 to 12.8)	.17
Bone marrow lesion size, mm^2	(n = 113) 609 (519 to 699)	(n = 113) −33 (−104 to 39)	(n = 110) 630 (525 to 735)	(n = 110) −6 (−75 to 63)	−27 (−127 to 73)	.60

Abbreviation: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] The within-group change and between-group difference were calculated in participants with baseline data of the outcome. Missing data at follow-up were addressed using linear mix-effects modeling (no imputation). Models were adjusted for the baseline value of the corresponding outcome.

[b] Analyzed in participants with data on both tibial and femoral cartilage volume at baseline (n = 194).

[c] Calculated as 100 × [(follow-up cartilage volume − baseline cartilage volume)/baseline cartilage volume]/exact time between 2 scans in years. This formula requires complete data at both time points, therefore participants with tibiofemoral cartilage volume data at both baseline and follow-up (n = 142, fully paired data) were analyzed using a linear regression model (no imputation).

[d] Range is 0 to 500; higher scores indicate more severe symptoms. The index relies on a self-administered questionnaire reflecting pain, stiffness, and limitations to physical function. The pain subscale measures 5 dimensions: walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing upright.

[e] Range is 0 to 100; higher scores indicate more severe symptoms.

symptoms were less prevalent in both groups after the second infusion. Two participants (2%) in the zoledronic acid group withdrew due to acute reactions.

Adverse events other than acute reactions were similar in the zoledronic acid and placebo groups (68% vs 67%, respectively) throughout the trial, except that more knee replacement procedures were performed in the zoledronic acid group compared with the placebo group (9% vs 2%). The incidence of serious adverse events was similar in the zoledronic acid group (20%) and in the placebo group (22%).

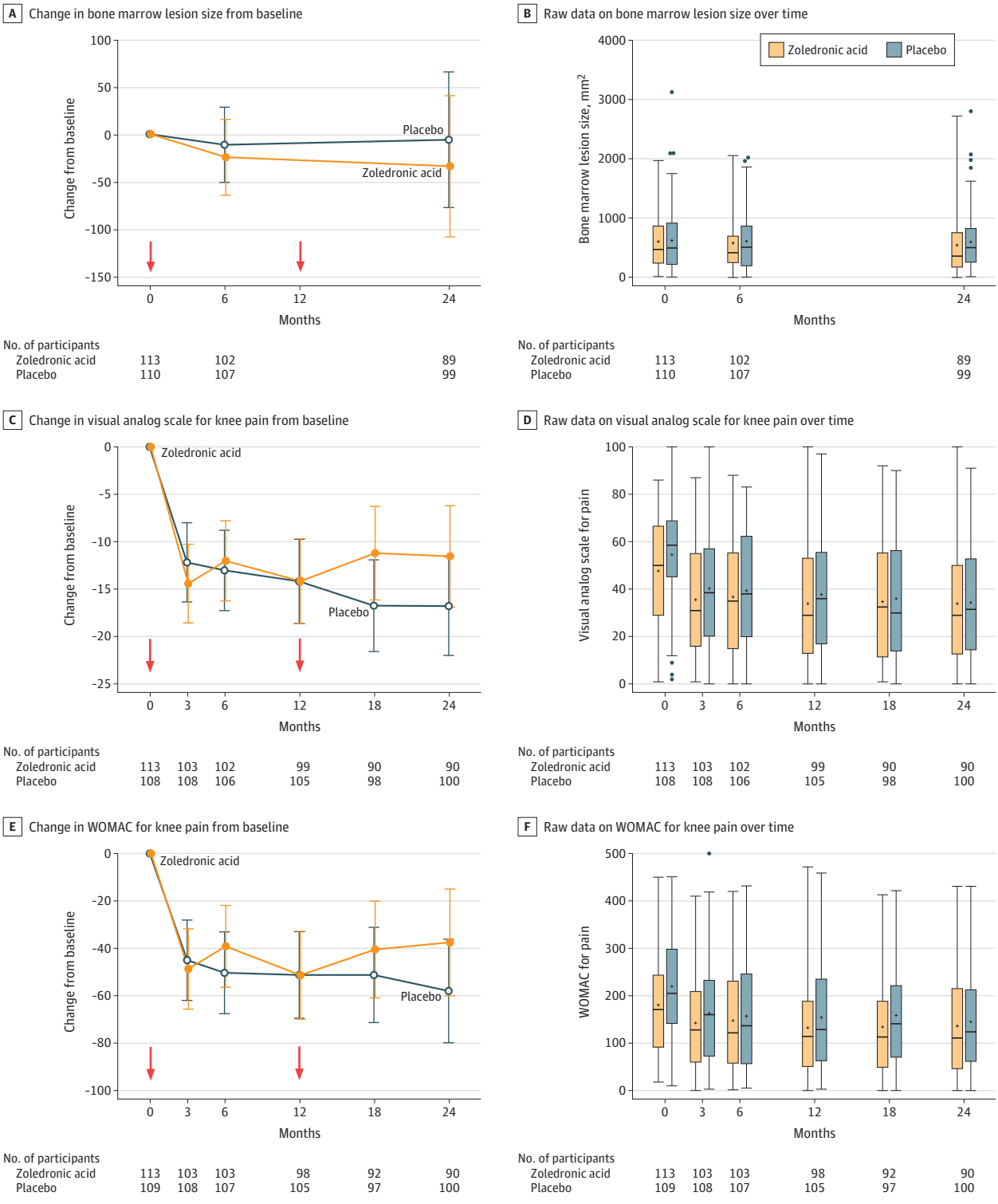
Discussion

During a 2-year period, 2 annual infusions with 5 mg of zoledronic acid compared with placebo did not significantly decrease cartilage volume loss, knee pain, or bone marrow lesion size in participants with symptomatic knee osteoarthritis and subchondral bone marrow lesions. These findings do not support the use of zoledronic acid for slowing cartilage volume loss or alleviating knee pain in patients with knee osteoarthritis.

This trial adds in several ways to 2 prior clinical trials (n = 2483 and n = 284) that showed no effect of bisphosphonates on progression of knee osteoarthritis.[29,30] First, this study was designed for patients with a subchondral bone marrow lesion who may be more likely to benefit from bisphosphonate therapy.[31] Second, the exclusion of patients with severe radiographic JSN minimized a floor effect,[32] given that patients with severe radiographic JSN have only a small volume of cartilage remaining. Third, in contrast to prior trials, the current trial directly measured cartilage volume using MRI, which is more sensitive to change compared with a surrogate measure of cartilage volume (ie, radiographic JSN).[33] Fourth, the current trial followed up participants for 2 years. In contrast, the 1-year follow-up in 1 of the prior trials[29] may have been too short to observe change in radiographic JSN (as a measure of disease progression). Fifth, the most potent intravenous bisphosphonate (ie, zoledronic acid) was used. Sixth, the annual administration of zoledronic acid increased patients' adherence to treatment.[34]

This trial was designed to detect a between-group difference of 104 mm^3 in cartilage volume loss over 2 years based on pilot RCT data[12] and a surrogate marker (bone marrow lesion) of cartilage loss. Neither of these outcomes has a defined minimal clinically important difference. It is important to know whether the threshold effect that the study was designed to detect (104 mm^3) is clinically important. Cartilage loss has been associated with an increased risk of knee replacement, and every 1% per-year increase in cartilage loss is associated with a 20% increase in the risk of knee replacement surgery over 4 years.[35] Based on this, the amount of cartilage loss equivalent to 1% per year in this clinical trial population was calculated to be 331 mm^3 over 2 years (mean cartilage volume at baseline = 16 536 mm^3 and 331 = 16 536 mm^3 × 1% × 2 years). Therefore, this trial was designed to detect a small effect (104 mm^3), and one that was much smaller than the estimated clinically important effect (331 mm^3).

Figure 3. Effect of Zoledronic Acid on Knee Pain and Bone Marrow Lesion Size Compared With Placebo



A, C, and E show changes from baseline in bone marrow lesion size, visual analog scale pain score, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Results were estimated using linear mixed-effects modeling (no imputation). The models included treatment, month, and treatment × month interaction with adjustment for the baseline value of the corresponding outcome. Error bars indicate 95% CIs. The red arrows indicate infusions at baseline and at 12 months. B, D, and F show the raw data for the outcomes at each point. The boxes indicate 25th and 75th percentiles; horizontal lines and "+" within boxes indicate median and mean, respectively; whiskers indicate the highest and lowest values within 1.5 × interquartile range; and points beyond the whiskers indicate outliers. The WOMAC index relies on a self-administered questionnaire reflecting pain, stiffness, and limitations to physical function. The WOMAC pain subscale measures 5 dimensions: walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing. Higher WOMAC and visual analog scale knee pain scores indicate more severe symptoms.

Table 3. Adverse Events

	No. (%)	
	Zoledronic acid (n = 113)	Placebo (n = 110)
Adverse events		
Any	108 (96)	91 (83)
Any serious[a]	23 (20)	24 (22)
Any acute reactions[b]	98 (87)	61 (56)
Acute reaction after first infusion	97 (86)	50 (46)
Acute reaction after second infusion	41 (36)	28 (26)
Acute reaction categories		
Eye inflammation and pain	11 (10)	6 (6)
Fever	59 (52)	9 (8)
Gastrointestinal symptoms	30 (27)	13 (12)
Musculoskeletal pain and stiffness	79 (70)	33 (30)
Other	82 (73)	44 (40)
Fatigue	44 (39)	16 (15)
Headache and dizziness	47 (42)	29 (26)
Influenzalike illness	21 (19)	3 (3)
Malaise and insomnia	33 (29)	11 (10)
Pain	24 (21)	7 (6)
Unclassified	23 (20)	12 (11)
Nonacute reaction categories	77 (68)	74 (67)
Cancer	3 (3)	3 (3)
Cardiovascular diseases	7 (6)	9 (8)
Disk degeneration	2 (2)	2 (2)
Elective hospital admissions[c]	35 (31)	44 (40)
Gastrointestinal symptoms	2 (2)	6 (5)
Hernia	1 (1)	1 (1)
Injuries[d]	12 (11)	8 (7)
Knee replacement	10 (9)	2 (2)
Malaise and insomnia	1 (1)	4 (4)
Musculoskeletal pain and stiffness	39 (35)	35 (32)
Neuropathy	1 (1)	4 (4)
Other problems[e]	0	5 (5)
Pneumonia	1 (1)	2 (2)
Skin diseases	1 (1)	1 (1)

[a] Defined as death, life-threatening, disabling, nonelective or prolonged hospitalization, or important medical events such as cancer.

[b] Typically occur and resolve within 3 days of zoledronic acid infusion; these include fever, musculoskeletal, gastrointestinal, eye, or other symptoms.

[c] Mostly diagnostic examinations (eg, bronchoscopy, cystoscopy, colonoscopy, and gastroscopy), planned surgery for injuries, or long-term conditions unrelated to the knee or musculoskeletal system.

[d] Mostly due to falls and accidents. Five injuries were related to the knee (1 in the zoledronic acid group and 4 in the placebo group).

[e] Single adverse events included enlarged prostate, gluten sensitivity, sore throat, whooping cough, and type 2 diabetes.

This trial may have included an unnecessarily large sample size for the outcome of cartilage volume, increasing the precision for estimating treatment effects. Post hoc conditional power analyses also suggested that this trial had sufficient statistical power to detect the estimated clinically important effect on cartilage loss (331 mm^3; eTable 4 in Supplement 2). The observed 95% CI for cartilage loss (−79 to 161 mm^3) did not include the estimated clinically important effect (331 mm^3), indicating the effect of zoledronic acid on cartilage loss was small and did not meet the criterion for a clinically important effect. For the secondary outcomes, the observed 95% CIs did not include clinically important differences for either pain or bone marrow lesion size. Based on these results, it is unlikely that a clinically important effect was missed. A larger study is unlikely to yield a different result.

In a previously completed pilot study of patients with knee osteoarthritis, zoledronic acid significantly reduced both knee pain score (−14.5 [95% CI, −28.1 to −0.9]) and bone marrow lesion size (−176 mm^2 [95% CI, −327 to −24 mm^2]) compared with placebo over 6 months,[12] but these preliminary findings were not replicated in this larger multicenter trial using the same protocol. In this trial, the between-group difference in knee pain score over 6-month follow-up was 1.0 (95% CI, −5.0 to 7.0) and in bone marrow lesion size was −13 mm^2 (95% CI, −67 to 42 mm^2). The comparison of the 95% CIs suggests that the statistically significant results in the pilot study were likely due to chance.

Subgroup analyses showed an interaction of JSN for the effects of zoledronic acid treatment on knee pain, in which patients without radiographic JSN had greater improvement in WOMAC knee pain score vs those with radiographic JSN. However, compared with placebo, zoledronic acid did not significantly improve knee pain score using the WOMAC or the VAS in participants with or without JSN. There was a significant improvement for WOMAC knee pain score over 12 months among those without JSN in the zoledronic acid group. These results are consistent with previous findings that zoledronic acid improved back pain in patients with mild but not severe disc degeneration.[36] A possible explanation is that bone resorption increases in early-stage osteoarthritis but decreases as the disease progresses.[37] Antiresorptive agents may help to improve knee pain in those without radiographic JSN (early-stage osteoarthritis) but not in those with radiographic JSN (later-stage osteoarthritis). These observations should be viewed as exploratory.

Adverse events in this trial were common and there was a higher frequency of acute reactions (eg, musculoskeletal pain, fever, and headache and dizziness) within 3 days of treatment in patients who received zoledronic acid compared with placebo. This is consistent with a prior report.[24] More knee replacements occurred in the zoledronic acid group (9%) compared with the placebo group (2%) over 24 months. This finding differs from 2 observational studies[38,39] that suggested a lower risk of knee replacement in patients with bisphosphonate use compared with those without bisphosphonate use. The reasons for this discrepancy are unclear.

Limitations

This study has several limitations. First, the planned sample size was not reached. However, as discussed above, it is unlikely that a clinically important effect was missed for any of the primary and secondary outcomes.

Second, 1 patient assigned to the placebo group incorrectly received zoledronic acid treatment at both baseline and 12 months. However, the per-protocol analyses produced

similar results compared with the primary analyses, suggesting no effect from misallocation.

Third, baseline WOMAC pain score was substantially different between the groups, but this was adjusted for in the regression models evaluating the treatment effect on knee pain.

Fourth, there was a differential rate of follow-up. The loss to follow-up rate was 20% in the zoledronic acid group compared with 9% in the placebo group. This differential follow-up rate has the potential to influence the missing at random assumption used for addressing missing data. The difference in loss to follow-up rates per group was mainly due to the higher incidence of knee replacement surgery in the zoledronic acid group (9% vs 2% in the placebo group).

Conclusions

Among patients with symptomatic knee osteoarthritis and bone marrow lesions, yearly zoledronic acid infusions, compared with placebo, did not significantly reduce cartilage volume loss over 24 months. These findings do not support the use of zoledronic acid in the treatment of knee osteoarthritis.

ARTICLE INFORMATION

Accepted for Publication: February 24, 2020.

Author Contributions: Dr Jones had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Cai and Dr Aitken contributed equally to this work.
Concept and design: Aitken, Hill, March, Wluka, Cicuttini, Jones.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cai, Aitken, Laslett, Pelletier, Martel-Pelletier, Antony, Cicuttini, Jones.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Cai, Blizzard, Jones.
Obtained funding: Aitken, Hill, March, Cicuttini, Jones.
Administrative, technical, or material support: Aitken, Laslett, Pelletier, Martel-Pelletier, Hill, Wluka, Wang, Antony, Cicuttini, Jones.
Supervision: Aitken, Laslett, Hill, Wluka, Winzenberg, Cicuttini, Jones.

Conflict of Interest Disclosures: Dr Aitken reported being a recipient of a level 1 National Health and Medical Research Council of Australia (NHMRC) future fund career development fellowship. Dr Laslett reported being a recipient of an NHMRC early career fellowship. Dr Pelletier reported being a shareholder in ArthroLab Inc; and receiving grants and speaker's fees from Mylan and TRB Chemedica. Dr Martel-Pelletier reported being a shareholder in ArthroLab Inc; and receiving grants and speaker's fees from TRB Chemedica. Dr Wluka reported being a recipient of an NHMRC translating research into practice fellowship. Dr Wang reported receiving grants from Monash University. Dr Jones reported being a recipient of an NHMRC practitioner fellowship; and receiving personal fees for serving as a consultant to multiple unnamed pharmaceutical companies. No other disclosures were reported.

Funding/Support: The ZAP2 study was funded by project grant APP1045415 from the National Health and Medical Research Council of Australia.

Role of the Funder/Sponsor: The National Health and Medical Research Council of Australia had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank all the study participants who made this study possible. We also thank the following professionals for their compensated role in the coordination and execution of the study from the University of Tasmania: Kathy Buttigieg, B Biotech, Emma Bavage, MNNP, Sarah Day, MMedSci, Jodie Lamont, BA, LLB, Joan Clough, Kate Probert, BA, Janette Gyselman, Jason Jin, PhD, Tim Albion, BE, and Rob Warren, BSc (Hons); Monash University: Molly Bond, B Biotech (Hons), Cameron Redpath, BNeuroSci (Hons), Clare Bellhouse, MPsych (Clin), Judy Hankin, BA, and Andrew Teichtahl, PhD; the Queen Elizabeth Hospital: Courtney Davis, PhD, Sarah Downie-Doyle, PhD, Peter Rogers, Grad Dip (Nurs Educ), and Carlee Ruediger, PhD; and the University of Sydney: Emma Smith, PhD, Marita Cross, PhD, and Monique Macara, MPH.

REFERENCES

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393(10182):1745-1759. doi:10.1016/S0140-6736(19)30417-9

2. Martel-Pelletier J, Barr AJ, Cicuttini FM, et al. Osteoarthritis. *Nat Rev Dis Primers*. 2016;2:16072. doi:10.1038/nrdp.2016.72

3. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330. doi:10.1136/annrheumdis-2013-204763

4. Bitton R. The economic burden of osteoarthritis. *Am J Manag Care*. 2009;15(8)(suppl):S230-S235.

5. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *BMJ*. 2012;345:e4934. doi:10.1136/bmj.e4934

6. Conaghan PG, Peloso PM, Everett SV, et al. Inadequate pain relief and large functional loss among patients with knee osteoarthritis. *Rheumatology (Oxford)*. 2015;54(2):270-277. doi:10.1093/rheumatology/keu332

7. Hayami T, Pickarski M, Wesolowski GA, et al. The role of subchondral bone remodeling in osteoarthritis. *Arthritis Rheum*. 2004;50(4):1193-1206. doi:10.1002/art.20124

8. Muehleman C, Green J, Williams JM, et al. The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage. *Osteoarthritis Cartilage*. 2002;10(3):226-233. doi:10.1053/joca.2001.0506

9. She G, Zhou Z, Zha Z, et al. Protective effect of zoledronic acid on articular cartilage and subchondral bone of rabbits with experimental knee osteoarthritis. *Exp Ther Med*. 2017;14(5):4901-4909. doi:10.3892/etm.2017.5135

10. Vaysbrot EE, Osani MC, Musetti MC, et al. Are bisphosphonates efficacious in knee osteoarthritis? *Osteoarthritis Cartilage*. 2018;26(2):154-164. doi:10.1016/j.joca.2017.11.013

11. Kuttapitiya A, Assi L, Laing K, et al. Microarray analysis of bone marrow lesions in osteoarthritis demonstrates upregulation of genes implicated in osteochondral turnover, neurogenesis and inflammation. *Ann Rheum Dis*. 2017;76(10):1764-1773. doi:10.1136/annrheumdis-2017-211396

12. Laslett LL, Doré DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year. *Ann Rheum Dis*. 2012;71(8):1322-1328. doi:10.1136/annrheumdis-2011-200970

13. Barr AJ, Campbell TM, Hopkinson D, et al. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. *Arthritis Res Ther*. 2015;17(1):228. doi:10.1186/s13075-015-0735-x

14. Aitken D, Laslett LL, Cai G, et al. A protocol for a multicentre, randomised, double-blind, placebo-controlled trial to compare the effect of annual infusions of zoledronic acid to placebo on knee structural change and knee pain over 24 months in knee osteoarthritis patients—ZAP2. *BMC Musculoskelet Disord*. 2018;19(1):217. doi:10.1186/s12891-018-2143-2

15. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. *Arthritis Rheum*. 1986;29(8):1039-1049. doi:10.1002/art.1780290816

16. Altman RD, Hochberg M, Murphy WA Jr, et al. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage*. 1995;3(suppl A):3-70.

17. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC. *J Rheumatol*. 1988;15(12):1833-1840.

18. Dore D, Quinn S, Ding C, et al. Natural history and clinical significance of MRI-detected bone marrow lesions at the knee. *Arthritis Res Ther*. 2010;12(6):R223. doi:10.1186/ar3210

19. Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2012;64(11):1699-1707. doi:10.1002/acr.21747

20. Raynauld JP, Kauffmann C, Beaudoin G, et al. Reliability of a quantification imaging system using magnetic resonance images to measure

cartilage thickness and volume in human normal and osteoarthritic knees. *Osteoarthritis Cartilage*. 2003;11(5):351-360. doi:10.1016/S1063-4584(03)00029-3

21. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development. *Arthritis Rheum*. 2000;43(11):2543-2549. doi:10.1002/1529-0131(200011)43:11<2543::AID-ANR23>3.0.CO;2-K

22. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum*. 2004;50(2):476-487. doi:10.1002/art.20000

23. Bellamy N. WOMAC osteoarthritis index user guide version XI. Accessed July 11, 2018. http://www.womac.com/womac/womac_userguide.htm

24. Reid IR, Gamble GD, Mesenbrink P, et al. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab*. 2010;95(9):4380-4387. doi:10.1210/jc.2010-0597

25. Davies-Tuck ML, Wluka AE, Forbes A, et al. Development of bone marrow lesions is associated with adverse effects on knee cartilage while resolution is associated with improvement. *Arthritis Res Ther*. 2010;12(1):R10. doi:10.1186/ar2911

26. Dore D, Martens A, Quinn S, et al. Bone marrow lesions predict site-specific cartilage defect development and volume loss. *Arthritis Res Ther*. 2010;12(6):R222. doi:10.1186/ar3209

27. Hunter DJ, Zhang Y, Niu J, et al. Increase in bone marrow lesions associated with cartilage loss. *Arthritis Rheum*. 2006;54(5):1529-1535. doi:10.1002/art.21789

28. Wluka AE, Hanna F, Davies-Tuck M, et al. Bone marrow lesions predict increase in knee cartilage defects and loss of cartilage volume in middle-aged women without knee pain over 2 years. *Ann Rheum Dis*. 2009;68(6):850-855. doi:10.1136/ard.2008.092221

29. Spector TD, Conaghan PG, Buckland-Wright JC, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis. *Arthritis Res Ther*. 2005;7(3):R625-R633. doi:10.1186/ar1716

30. Bingham CO III, Buckland-Wright JC, Garnero P, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee. *Arthritis Rheum*. 2006;54(11):3494-3507. doi:10.1002/art.22160

31. Castañeda S, Roman-Blas JA, Largo R, Herrero-Beaumont G. Subchondral bone as a key target for osteoarthritis treatment. *Biochem Pharmacol*. 2012;83(3):315-323. doi:10.1016/j.bcp.2011.09.018

32. McAlindon TE, Driban JB, Henrotin Y, et al. OARSI clinical trials recommendations. *Osteoarthritis Cartilage*. 2015;23(5):747-760. doi:10.1016/j.joca.2015.03.005

33. Guermazi A, Roemer FW, Burstein D, Hayashi D. Why radiography should no longer be considered a surrogate outcome measure for longitudinal assessment of cartilage in knee osteoarthritis. *Arthritis Res Ther*. 2011;13(6):247. doi:10.1186/ar3488

34. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates. *Osteoporos Int*. 2008;19(6):733-759. doi:10.1007/s00198-007-0540-8

35. Cicuttini FM, Jones G, Forbes A, Wluka AE. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty. *Ann Rheum Dis*. 2004;63(9):1124-1127. doi:10.1136/ard.2004.021253

36. Cai G, Laslett LL, Aitken D, et al. Effect of zoledronic acid and denosumab in patients with low back pain and modic change. *J Bone Miner Res*. 2018;33(5):773-782. doi:10.1002/jbmr.3376

37. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol*. 2012;8(11):665-673. doi:10.1038/nrrheum.2012.130

38. Neogi T, Li S, Peloquin C, et al. Effect of bisphosphonates on knee replacement surgery. *Ann Rheum Dis*. 2018;77(1):92-97. doi:10.1136/annrheumdis-2017-211811

39. Fu SH, Wang CY, Yang RS, Wu FL, Hsiao FY. Bisphosphonate use and the risk of undergoing total knee arthroplasty in osteoporotic patients with osteoarthritis. *J Bone Joint Surg Am*. 2017;99(11):938-946. doi:10.2106/JBJS.16.00385