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Effect of zoledronic acid with or without methylprednisolone on 3D bone area and bone shape in patients with symptomatic knee osteoarthritis: a post-hoc analysis of the ZAP2 trial

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Running title: Effect of zoledronic acid with or without methylprednisolone on bone shape and bone area

Abstract

Objective

To evaluate the effect of annual infusions of zoledronic acid (ZA) with or without a single injection of methylprednisolone, compared to placebo, on quantitative magnetic resonance imaging 3-D bone area and bone shape in participants with symptomatic knee osteoarthritis (OA).

Methods

This was a post-hoc analysis of the ZAP2 trial. Active appearance modelling was used to assess bone area (mm^2) and femur bone shape (B-score) in 262 participants (mean 61.8±8.0 years, 51% female) at baseline, 6, and 24 months. Radiographic joint space narrowing (JSN) was measured at baseline. An 'OA shape' was defined as a B-score of >1.96.

Results

At baseline 65% of participants demonstrated an OA shape. Treatment with ZA plus methylprednisolone but not ZA alone, compared to placebo, was associated with significantly slower expansion in bone area at the medial femoral (-33.9mm^2, 95% confidence interval [CI] -61.8 to -6.0) and lateral femoral (-22.0mm^2, 95%CI -40.7 to -3.4) compartments over 24 months. B-score increased in all groups, with no significant between-group differences. There were significant interactions of JSN (grade 0 vs grade 1-2) and B-score (≤1.96 vs >1.96) with treatment effect on bone area ($p<0.05$), such that ZA plus methylprednisolone slowed the expansion of medial and lateral femoral bone area over 24 months in participants with JSN grade 1-2 or a B-score of >1.96.

Conclusions

ZA plus methylprednisolone may retard expansion of bone area over 24 months, but ZA alone may not. Neither ZA with or without methylprednisolone slowed progression of bone shape over 6 or 24 months.

Keywords: Bone area; bone shape; methylprednisolone; osteoarthritis; zoledronic acid.

Introduction

Structural deterioration of osteoarthritis (OA) worsens with age [1], but no approved treatments have been shown to reverse or retard its progression. The Osteoarthritis Research Society (OARSI) Clinical Trials Imaging Working Group recommends change in radiographic joint space width (a surrogate measure of cartilage thickness) and magnetic resonance imaging (MRI)-detected cartilage morphometry (e.g., cartilage volume, cartilage thickness) as outcomes for assessing OA structural progression [2]. However, increasing evidence suggests that OA is a disease of the whole joint rather than just the cartilage [3, 4]; thus, the exploration and quantification of non-cartilage MRI pathologies may enable a better understanding of OA progression.

Subchondral bone structure and metabolism interacts with articular cartilage and is closely involved in the pathogenesis of OA [5]. Several studies have found that MRI-based three-dimensional (3-D) bone area and bone shape quantified using active appearance modelling provides a strong predictive validity for the onset and progression of knee OA [6-8]. Moreover, bone area may be a more sensitive marker than cartilage morphometry as it changes significantly over 3 and 6 months in a population at high risk of OA progression [9]. A recent study using data from the Osteoarthritis Initiative (OAI) showed that femur bone shape (termed the B-score) is a highly reliable and precise measure of OA status compared to radiographic Kellgren-Lawrence grade [8]. Despite the high sensitivity of bone area and bone shape measures in assessing structural change of OA, their applicability in detecting treatment effects in clinical trials has not been evaluated.

In our previous randomised controlled trials (RCTs) conducted in participants with symptomatic knee OA and selected for the presence of bone marrow lesions (BMLs), annual infusions of zoledronic acid (ZA) with or without a one-off intravenous injection of methylprednisolone did not change MRI-detected cartilage volume and BML size over 6 and

24 months compared to placebo [10, 11]. These trials provide an additional opportunity to investigate whether ZA and ZA plus methylprednisolone changed other OA pathologies, particularly the subchondral bone. Therefore, this study aimed to compare whether the changes in MRI-based 3-D bone area and bone shape over 6 and 24 months differed among the three treatment groups.

Methods

Study design

The Zoledronic Acid for Osteoarthritis Knee Pain (ZAP2) study is a multicentre, randomised, double-blind, placebo-controlled clinical trial conducted in Hobart, Melbourne, Adelaide, and Sydney, Australia [10]. ZAP2 evaluated the effect of annual infusions of ZA (5 mg) or placebo on change in cartilage volume, knee pain, and BML size over 24 months in 223 participants with symptomatic knee OA and BML (Australian New Zealand Clinical Trials Registry: ACTRN12613000039785). A substudy of ZAP2 was conducted in Hobart which introduced an extra trial arm (ZA plus methylprednisolone, n=40) with the aim of evaluating the effect of methylprednisolone (10 mg) on acute-phase adverse events caused by ZA infusions over 6 months (the VOLT01 study) [11]. Data of participants in Hobart site who received ZA (n=39) or placebo (n=38) were used in both the ZAP2 trial and the VOLT01 study (Figure 1). The VOLT01 study stopped at 6 months but all participants in the ZA plus methylprednisolone group were given an infusion of ZA at 12 months and were followed-up until 24 months (same as participants in the ZA group). The current study was a post-hoc analysis of ZAP2 and VOLT01. The study protocol of ZAP2 and VOLT01 has been described elsewhere [12]. Ethics approval of ZAP2 and VOLT01 were granted by ethics committees at each site. All participants provided written informed consent.

Participants

Detailed inclusion and exclusion criteria are described in the published protocol [12] and are identical for ZAP2 and VOLT01. In summary, participants were eligible if aged ≥50 years with significant knee pain (defined as a pain score ≥40 mm on a 100-mm visual analogue scale) on most days during the last month, met the American College of Rheumatology criteria for symptomatic knee OA [13], and had a subchondral BML present on MRI. Participants were excluded if they had prior use of bisphosphonates (unless an adequate washout period had elapsed, according to the following schedule: 2 years (if use > 48 weeks, or any intravenous bisphosphonate use); 1 year (if used > 8 weeks but < 48 weeks); 6 months (if used > 2 weeks but < 8 weeks); 2 months (if used < 2 weeks) [12]), abnormal blood tests that were considered unsuitable for ZA infusions, grade 3 joint space narrowing (JSN) on radiographs according to the Osteoarthritis Research Society International (OARSI) atlas [14], had surgery in the study knee during the last 12 months, cancer, or contraindications to MRI. Eligible participants were randomised to receiving a 15-minute intravenous infusion of ZA (5 mg in 100 ml saline), placebo (100 ml saline), or ZA (5 mg in 100 ml saline) plus a single injection of 10 mg methylprednisolone (for the VOLT01 study at baseline only) at baseline and 12 months and were followed-up until 24 months. The current study included 262 participants from both ZAP2 and VOLT01, with one participant being excluded because the MRI scans were unable to be read for bone shape and bone area.

MRI

MRI scans were performed at baseline, 6 and 24 months using 1.5-T (Hobart, Sydney, and Adelaide) or 3-T (Melbourne) whole-body MRI units with a commercial transmit-receive knee

coil. The same MRI unit was used for each participant throughout the study. Both T1- and proton-density-weighted sagittal MRI were conducted, detailed MRI sequences and parameters of the MRI units at each study site are described in the protocol [12].

Bone area and bone shape of the knee

Bone area and bone shape at baseline, 6, and 24 months were determined with active appearance models provided by Imorphics (Manchester, UK), a type of statistical shape modelling using supervised machine-learning [8, 15]. Bone area (mm^2) at medial femoral, medial tibial, lateral femoral, and lateral tibial compartments were calculated.

Based on MRI data from the Osteoarthritis Initiative study [16], an 'OA vector' was constructed as the line passing through the mean shape of a population with radiographic OA (Kellgren-Lawrence grade ≥2) and a population without radiographic OA (Kellgren-Lawrence grade 0) [8]. Distances along the OA vector are termed 'B-score'. A B-score of 0 indicates the mean shape of the non-OA participants for each sex, and 1 unit is defined as 1 standard deviation (SD) of the non-OA participants along the OA vector (towards the 'OA shape'). Previous studies have consistently shown that B-scores of the femur bone had the greatest discrimination and responsiveness [7, 15, 17-19]; therefore, we only calculated B-scores at the femoral site in this study. A B-score of ≤1.96 was used as a cut-off point to differentiate non-OA shape from OA shape (B-score >1.96) based on the 95% confidence limits of B-scores in the non-OA group, as indicated in the original methodological study [8].

Other measures

A standing anteroposterior semi-flexed radiograph of the study knee was performed at baseline. JSN was graded using the OARSI atlas [14] and was grouped as normal (grade 0) and mild-to-moderate (grade 1-2) for prespecified subgroup analyses [12]. Height and weight were measured by stadiometer and electric scales, respectively.

Statistical analysis

Baseline characteristics were described as mean (SD) or n (%) by treatment groups. The effects of ZA and ZA plus methylprednisolone on each of the medial femoral, medial tibial, lateral femoral, and lateral tibial compartments were analysed separately. B-score and bone area measures were normally distributed at baseline and follow-up visits. Linear mixed-effects models were conducted to evaluate the changes of bone area and bone shape within and between treatment groups over 6 and 24 months, with adjustment for baseline values of the outcome measures (i.e. baseline bone area, or baseline bone shape) as covariates. Fixed effects were treatment group, month, and treatment by month interaction. The correlations within study sites and the repeated measures were addressed by specifying study site and participant identification as random intercept. Month was treated as a random effect, and an unstructured covariance structure was used to allow different treatment effects over time. Diagnosis of model fit was conducted by visual inspection of the distribution of residuals, and the results suggested normal and homoscedastic residuals.

The modification effect of JSN (grade 0 vs grade 1-2) and B-score ($\leq$1.96 vs >1.96) on treatment effects was evaluated by adding a three-way interaction (treatment×month×JSN, or treatment×month×B-score) to the linear mixed-effects models, where two-way interactions were also included. A p-value of an interaction less than 0.05 was considered statistically

significant. All statistical analyses were performed using Stata/SE version 16.1 (StataCorp, College Station, TX, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Participants

Of 262 participants, 238 (90.8%) and 214 (81.7%) had bone area and bone shape measures on MRI at 6 months and 24 months, respectively (Figure 1). Baseline characteristics of participants in the ZA, ZA plus methylprednisolone, and placebo groups were generally well balanced, except that more female participants were enrolled in the placebo group and mean B-score and the proportion of participants with a B-score of >1.96 were higher in the ZA plus methylprednisolone group (Table 1).

The effects of ZA and ZA plus methylprednisolone on bone area and bone shape

Bone area at the medial femoral, medial tibial, lateral femoral, and lateral tibial compartments increased in the ZA and the placebo groups but not the ZA plus methylprednisolone group over 6 and 24 months (Table 2). Compared to placebo and ZA, ZA plus methylprednisolone slowed bone area expansion at the medial and lateral femoral compartments after 24 months of follow-up (Table 2). Further adjustment for age, sex, height, and weight did not change the results (Supplementary Table 1).

B-scores increased in all the three study groups (ZA, ZA plus methylprednisolone, and placebo) over 6 and 24 months. Although the increases in B-scores over 24 months were smaller in participants who received ZA plus methylprednisolone compared to those who received ZA or

placebo, there were no statistically significant differences in changes in B-scores between the three groups over 6 or 24 months (Table 2).

The interactions of baseline JSN and B-score with treatment effects

There were significant interactions by B-score for medial and lateral femoral bone area at 6 months such that the effect of administration of ZA plus methylprednisolone, compared to placebo, on increases in bone area was larger in participants with B-score ≤1.96 compared to those with B-score >1.96 (Figure 2). A similar pattern was seen at 24 months though the interactions did not reach statistical significance. There was also an interaction at the medial tibia at 24 months, but in this case ZA alone resulted in slower bone area expansion compared to placebo in participants with B-score ≤1.96.

There were significant interactions by JSN grade (0 vs 1-2) for medial and lateral tibial bone area at 6 months such that those with JSN grade 0 had greater bone area expansion with administration of ZA plus methylprednisolone, and those with JSN grade 1-2 had slower expansion, compared to participants administered placebo (Figure 3).

There were no significant interactions by baseline JSN (grade 0 vs grade 1-2) or B-score (≤1.96 vs >1.96) for change in B-score over 6 and 24 months (data not shown).

Discussion

Using data from the ZAP2 trial and its substudy VOLT01, we found that overall increases in MRI-based 3-D bone area at medial and lateral femur over 24 months were lower in people receiving ZA plus methylprednisolone than ZA or placebo. However, increases in B-score indicated that progression in OA bone shape were similar in all three treatment groups. The

effects on medial and lateral femoral bone area over 24 months were especially evident in those with pre-existing structural abnormalities (i.e., JSN grade 1-2, or B-score >1.96). These findings suggest that ZA plus methylprednisolone may slow increases in bone area in OA patients with structural abnormalities but do not support an effect of ZA, with or without methylprednisolone, in slowing deterioration in bone shape.

An increased subchondral bone area measured by both dual x-ray absorptiometry (DXA) and MRI is well documented in pre-, early, and radiographic knee OA [20, 21], and predicts the progression of knee symptoms [6], cartilage defects and the risk of joint replacement [22]. Therefore, bone area may be a potential biomarker for evaluating the effect of interventions in OA trials [6]. Our results contrast to those of a small propensity-score matching study using data from the OAI, in which bisphosphonate use was associated with reduced odds of expansion in bone area (measured using the same methodology in this study) over 24 months [23]. In contrast, this analysis, using data from an RCT, we found that ZA alone, the most potent bisphosphonate [24], did not retard increases in bone area over 6 or 24 months compared to placebo, though ZA plus methylprednisolone did. Thus, these results regarding the effect of bisphosphonates on bone area is conflicting. This could be due to the different study designs (cohort study vs clinical trial), different population characteristics (degree of knee symptoms and structural abnormality) or different definitions of expansion of bone area (dichotomous vs continuous). However, overall, explanations for the contrasting results remains unclear.

An interesting finding from this study is that bone area remained relatively stable over 6 and 24 months in participants receiving ZA (baseline and 12 months) plus a single injection of 10 mg methylprednisolone (baseline only). Compared to participants in both the placebo group and the ZA group, those who received ZA plus methylprednisolone had significantly slower expansion in bone area at the medial and lateral femur over 24 months. While we did not have a group of participants who received methylprednisolone alone, these results suggest that

methylprednisolone could have stopped the expansion of bone area. Increases in bone area could be driven by more than one mechanism [15], including the formation or enlargement of osteophytes and a general spreading of the subchondral surfaces, both of which are related to inflammation. The anti-inflammatory effect of glucocorticoids has been well documented [25]. Thus, methylprednisolone may have a role in inhibiting the formation and enlargement of osteophytes and in reducing inflammation-driven bone loss [26-28], which would translate to a lower increase in bone area according to Wolff's law [29]. Moreover, previous study indicates a sensitive bone effect of glucocorticoids [30], but the dose of methylprednisolone used in our study was very small and its effect on bone resorption was thought to be negligible (i.e., readily inhibited by ZA). Thus, the possibility of a chance finding cannot be excluded. Although increased bone area predicts greater cartilage defects [22], we are uncertain whether the effect of methylprednisolone on bone area, if truly present, would translate to reductions in cartilage defects.

There were significant interactions of JSN and B-score with the treatment effects of ZA plus methylprednisolone and ZA alone on bone area. Specifically, ZA plus methylprednisolone, or potentially a single dose of methylprednisolone itself, compared to placebo, led to slower expansion in bone area in participants with structural abnormalities (i.e., JSN grade 1-2, or B-score >1.96) and greater increases in those without structural abnormalities (i.e., JSN grade 0, or B-score ≤1.96). The reason for these diverse effects is unclear. A potential explanation is that the effect of steroids on bone loss are complex. While steroids may inhibit bone loss by suppressing inflammation [26-28], they could also lead to bone loss and osteoporosis [31]. Given the small sample size in the ZA plus methylprednisolone group (n=40), these findings should be interpreted with caution. In contrast, ZA alone showed no statistically significant effect on bone area in any subgroup, and the only statistically significant interaction between

ZA and ‘OA shape’ (B-score > or ≤ 1.96) for medial tibial bone area over 24 months could be due to chance.

B-score increased in all treatment groups over 6 and 24 months, with no between-group differences. These results suggest that B-score is a sensitive measure for structural changes of OA, and that bone shape turns towards the ‘OA shape’ over time irrespective of antiresorptive treatment. This is consistent with previous RCTs showing no effects of bisphosphonates on other structural changes including cartilage volume, BML, and radiographic JSN [10, 32, 33]. ZA plus methylprednisolone had a statistically significant effect on bone area but not bone shape, this could suggest that change in bone area is more sensitive than bone shape, given that in another study that used the same measurement strategy, the authors found that bisphosphonate use was associated with a reduced odds for the expansion of bone area but had no effect on bone shape [23].

The strengths of this study include the well-defined patient group (as it used data from an RCT and its substudy [10, 11]) and the measurements of bone area and bone shape over both short- and long-time horizons. There are several limitations in this study. First, while outcomes were measured prospectively and readers blinded to treatment allocation, these are post-hoc hypotheses being tested, therefore results must be interpreted with caution. Second, the number of participants who received ZA plus methylprednisolone was small (n=40) and multiple tests were conducted in this study, making the effect of ZA plus methylprednisolone on bone area and bone shape hypothesis generating. Third, baseline measures of bone area and bone shape differed between the intervention groups; however, we have taken this into account by adjusting for these baseline values in the regression models and thus reducing the risk of bias.

In conclusion, in these post-hoc analyses, ZA plus methylprednisolone may retard expansion of bone area over 24 months, but ZA alone may not. Neither ZA with or without methylprednisolone slowed progression of bone shape over 6 or 24 months.

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Conflict of Interest Disclosures

LLL reports personal fees from Amgen Pty Ltd, outside the submitted work. MB is an employee of Imorphics Ltd, a company providing measurement of imaging biomarkers, which is wholly owned by Stryker Corp, and MB has share options in that company. PGC has done consultancies or speakers bureaus for AbbVie, Amgen, AstraZeneca, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Novartis, Pfizer, Stryker and UCB. LM has received funding unrelated to this study with grants from Janssen and speaker fees from Pfizer, Abbvie, Lilly. TW reports personal fees from AMGEN, outside the submitted work. GJ reports personal fees

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Authors' contributions

GC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Obtained funding: GJ, FC, LM, CH. Study design: GC, DA and GJ. Acquisition, analysis, or interpretation of data: All authors. Statistical analysis: GC and DA. Drafting of the manuscript: GC. Critical revision of the manuscript for important intellectual content: All authors.

Figure legends

Figure 1. Study flowchart.

Figure 2. Subgroup analyses by B-score (≤1.96 or >1.96) for the effects of zoledronic acid and zoledronic acid plus methylprednisolone on bone area. B-score ≤1.96: n=93; B-score >1.96: n=169.

Figure 3. Subgroup analyses by joint space narrowing (Grade 0 or grade 1-2) for the effects of zoledronic acid and zoledronic acid plus methylprednisolone on bone area. JSN, joint space narrowing. JSN grade 0: n=53; JSN grade 1-2: n=204.

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449 **Table 1.** Baseline characteristics of patients.

	Placebo (n = 109)	Zoledronic acid (n =113)	Zoledronic acid plus Methylprednisolone (n=40)
Age, years	61.3 (7.4)	62.6 (8.5)	60.9 (8.1)
Female, n (%)	62 (57)	54 (48)	17 (43)
Height, cm	168.7 (10.1)	169.7 (9.9)	170.2 (8.9)
Weight, kg	88.2 (20.3)	87.1 (18.7)	87.9 (17.0)
Joint space narrowing grade 1-2, n (%)	85 (79)	89 (81)	30 (75)
Bone area, mm^2			
Medial femoral	2556.6 (376.8)	2599.6 (374.0)	2704.6 (374.1)
Medial tibial	1214.6 (194.9)	1231.3 (193.7)	1273.9 (180.6)
Lateral femoral	1819.1 (298.5)	1841.9 (298.9)	1915.2 (306.8)
Lateral tibial	943.9 (152.0)	956.9 (152.6)	994.4 (159.1)
B-score, SD	2.6 (1.9)	2.8 (2.0)	3.5 (2.2)
B-score >1.96 (OA shape), n (%)	69 (63)	71 (63)	29 (72)

450 SD, standard deviation; OA, osteoarthritis. Results are shown as mean (standard deviation)
451 unless stated otherwise (n (%).

Table 2. Change in bone area and bone shape within and between treatment groups over 6 and 24 months.

	Within-group change, mean (95% Confidence Interval)			Between-group difference, mean (95% Confidence Interval)		
	Placebo (n=109)	Zoledronic acid (n=113)	Zoledronic acid plus Methylprednisolone (n=40)	Zoledronic acid – Placebo	Zoledronic acid plus Methylprednisolone – Placebo	Zoledronic acid plus Methylprednisolone – Zoledronic acid
Baseline to 6 months						
Bone area, mm^2						
Medial femoral	15.1 (7.4 to 22.8)	15.2 (7.5 to 22.9)	11.0 (-1.7 to 23.6)	0.1 (-10.8 to 11.0)	-4.2 (-19.0 to 10.7)	-4.2 (-19.1 to 10.6)
Medial tibial	6.7 (2.3 to 11.1)	11.0 (6.5 to 15.4)	3.0 (-4.2 to 10.3)	4.3 (-2.0 to 10.5)	-3.7 (-12.2 to 4.8)	-7.9 (-16.4 to 0.6)
Lateral femoral	5.8 (0.2 to 11.3)	10.8 (5.1 to 16.4)	3.2 (-6.0 to 12.4)	5.0 (-2.9 to 12.9)	-2.6 (-13.4 to 8.2)	-7.6 (-18.3 to 3.2)
Lateral tibial	4.5 (0.7 to 8.3)	5.8 (2.0 to 9.7)	0.5 (-5.8 to 6.8)	1.3 (-4.1 to 6.7)	-4.0 (-11.4 to 3.4)	-5.3 (-12.7 to 2.1)
B-score, SD	0.15 (0.09 to 0.20)	0.10 (0.04 to 0.16)	0.11 (0.02 to 0.21)	-0.05 (-0.13 to 0.03)	-0.04 (-0.14 to 0.07)	0.01 (-0.10 to 0.12)
Baseline to 24 months						
Bone area, mm^2						
Medial femoral	40.7 (27.1 to 54.3)	38.3 (24.2 to 52.5)	6.8 (-17.4 to 31.0)	-2.3 (-21.9 to 17.2)	**-33.9 (-61.8 to -6.0)**	**-31.5 (-59.6 to -3.5)**
Medial tibial	18.8 (11.7 to 25.9)	18.6 (11.1 to 26.0)	10.0 (-2.7 to 22.8)	-0.2 (-10.5 to 10.1)	-8.8 (-23.4 to 5.9)	-8.5 (-23.3 to 6.2)
Lateral femoral	23.1 (14.1 to 32.1)	25.2 (15.8 to 34.6)	1.0 (-15.2 to 17.3)	2.1 (-11.0 to 15.2)	**-22.0 (-40.7 to -3.4)**	**-24.2 (-42.9 to -5.4)**
Lateral tibial	12.8 (7.2 to 18.5)	13.3 (7.4 to 19.2)	8.0 (-2.2 to 18.2)	0.5 (-7.7 to 8.6)	-4.8 (-16.5 to 6.9)	-5.3 (-17.0 to 6.5)
B-score, SD	0.38 (0.27 to 0.49)	0.36 (0.25 to 0.47)	0.20 (0.01 to 0.40)	-0.02 (-0.18 to 0.14)	-0.18 (-0.40 to 0.04)	-0.16 (-0.38 to 0.06)

SD, standard deviation. Bold denotes statistically significant results.

Models were adjusted for baseline values of the corresponding outcome measure.