Zoledronic acid plus methylprednisolone versus zoledronic acid or placebo in symptomatic knee osteoarthritis: a randomized controlled trial

Guoqi Cai, Laura L Laslett, Dawn Aitken, Flavia Cicuttini, Lyn March, Catherine Hill, Tania Winzenberg and Graeme Jones

Abstract

Background: The aim of this study was to compare the efficacy and safety of zoledronic acid (ZA) plus intravenous methylprednisolone (VOLT01) to ZA, and placebo for knee osteoarthritis.

Methods: A single-center, double-blind, randomized controlled trial (RCT) was carried out. Adults (aged ≥50 years) with knee osteoarthritis, significant knee pain [≥40 mm on a 100 mm visual analog scale (VAS)], and magnetic resonance imaging-detected bone marrow lesion (BML) were randomized to receive a one-off administration of VOLT01, ZA, or placebo. The primary hypothesis was that VOLT01 was superior to ZA in having a lower incidence of acute phase responses (APRs) over 3 days. Secondary hypotheses were that VOLT01 was noninferior to ZA, and both treatments were superior to placebo in decreasing BML size over 6 months and in improving knee pain [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and VAS] and function (WOMAC) over 3 and 6 months.

Results: A total of 117 patients (62.2 ± 8.1 years, 63 women) were enrolled. The incidence of APRs was similar in the VOLT01 (90%) and ZA (87%) groups (p = 0.74). VOLT01 was superior to ZA in improving knee pain and function after 6 months and noninferior to ZA in reducing BML size. However, BML size change was small in all groups and there were no between-group differences. Compared with placebo, VOLT01 but not ZA improved knee function and showed a trend toward improving knee pain after 6 months.

Conclusions: Administering intravenous methylprednisolone with ZA did not reduce APRs or change knee BML size over 6 months, but in contrast to ZA or placebo, it may have a beneficial effect on symptoms in knee osteoarthritis.

Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN12613000039785.

Keywords: acute phase response, bone marrow lesion, methylprednisolone, noninferiority, zoledronic acid

Received: 29 April 2019; revised manuscript accepted: 12 September 2019.

Introduction

Osteoarthritis is the most common form of arthritis, and to the best of our knowledge, there are currently no approved disease-modifying drugs available.1 Subchondral bone turnover is closely associated with the development and structural progression of osteoarthritis and may be a therapeutic target.2–4 Intravenous bisphosphonates are a potential candidate for treating osteoarthritis given their strong effect on bone metabolism, but
they commonly cause high rates of a defined suite of adverse events [referred to as ‘acute phase responses’ (APRs)].

Bisphosphonates inhibit bone resorption and turnover by inducing apoptosis in osteoclasts and preventing apoptosis in osteocytes and osteoblasts. They are effective treatments for osteoporosis, Paget’s disease, and bone metastases. Zoledronic acid (ZA) is the most potent nitrogen-containing bisphosphonate and has a prolonged duration of action. Pilot trials have indicated a therapeutic role of ZA for both pain and structural changes in patients with knee osteoarthritis and bone marrow lesions (BMLs), and patients with back pain and modic changes, suggesting that ZA may have disease-modifying potential.

However, ZA treatment frequently leads to APRs. These are primarily influenza-like symptoms and musculoskeletal pain, but can also include much rarer symptoms such as uveitis. Although APRs occur and resolve within approximately 3 days post-dose, they are unpleasant. Finding ways to reduce rates of APRs is important. APRs are thought to occur via activation of γδ-T cells and upregulation of pro-inflammatory cytokines, as a result of the inhibition of farnesyl pyrophosphate in the mevalonate pathway due to nitrogen-containing bisphosphonates. Possible approaches to preventing nitrogen-containing bisphosphonate-induced APRs include co-administration of paracetamol/ibuprofen, statins, or corticosteroids, given their anti-inflammatory properties.

Preliminary findings suggested that a combination of a one-off administration of 5 mg ZA and 10 mg methylprednisolone (VOLT01) significantly reduces APRs over 3 days and knee pain over 6 months compared with ZA alone in patients with knee osteoarthritis. Indeed, 10 mg methylprednisolone should be sufficient to inhibit pro-inflammatory cytokines, while not causing steroid side effects or any long-term anti-inflammatory effect. To confirm these preliminary findings and evaluate the effect of VOLT01 on knee structural changes, we assessed the superiority of VOLT01 to ZA for reducing APRs and noninferiority of VOLT01 to ZA for knee structure changes (as assessed by the size of knee BML) and knee symptoms, in patients with symptomatic knee osteoarthritis and BMLs, over 6 months.

Methods

Trial design
This study was a single-center, randomized, parallel, double-blind, placebo-controlled trial, performed in Hobart, Australia. This was a substudy to the multicenter Zoledronic Acid for Osteoarthritis Knee Pain (ZAP2) trial. The ZAP2 study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN 1261300039785) while this substudy was not registered separately.

Participants and screening procedure
Participants were recruited from November 2013 to September 2015 using local and social media, and by collaboration with private rheumatologists and the Royal Hobart Hospital, Hobart, Australia. Informed consent was obtained from all participants, and ethics approval for the study was granted by the Tasmanian Human Research Ethics Committee.

Inclusion criteria
Participants were adults aged ≥50 years, with clinical knee osteoarthritis diagnosed according to the American College of Rheumatology (ACR) criteria for knee osteoarthritis, significant knee pain on most days [defined as a 100 mm visual analog scale (VAS) ≥40], and a knee BML visualized on magnetic resonance imaging (MRI). When both knees met the criteria, the study knee was decided by a rheumatologist (GJ) and was generally the more severe knee.

Exclusion criteria
Exclusion criteria were the same as for the ZAP2 trial as previously published. Briefly, we excluded patients with prior use of bisphosphonates except according to a washout schedule, a history of nontraumatic iritis or uveitis, abnormal blood tests (i.e. serum calcium >2.75 mmol/l or <2.00 mmol/l, creatinine clearance <35 ml/min or 25-hydroxyvitamin D concentrations <40 nmol/l), cancer, poor dental health, severe knee osteoarthritis [defined as a joint space narrowing on X-ray of Grade 3 using the Osteoarthritis Research Society International (OARSI) atlas], knee surgery or arthroscopy in the last 12 month, a corticosteroid injection in the last 3 months, or a hyaluronic acid injection in the last 6 months in the study knee. A screening MRI was performed.
when all other inclusion criteria were met, partici-
pants without knee BMLs were then excluded.

Randomization and interventions
Participants were randomized into one of three
study arms, VOLT01, ZA, or placebo based on
computer generated random numbers using adap-
tive allocation. The first participant was recruited
to the ZAP2 trial at the Hobart site on 25
November 2013. Use of the protocol allowing
recruitment of a third arm (VOLT01) began on 7
November 2014, at which time 47 participants
had been recruited (23 placeboes and 24 ZA).
This required 17:16:40 patients (placebo: ZA:
VOLT01) to be recruited according to the study
design, and we used adaptive allocation by adjust-
ing for the randomization thresholds so that par-
ticipants had a higher probability of being allocated
to the VOLT01 group. This was conducted by a
staff member with no direct involvement in the
study. The allocated treatment was dispensed by
one author (LLL) and administered by a nurse. All
participants and assessors were blinded to
treatment allocation throughout the trial.

Drugs were administered according to the follow-
ing procedure. First, an intravenous injection of
either 10 ml saline (for the ZA and placebo
groups) or 10 mg methylprednisolone sodium
succinate (SOLU-MEDROL) in 10 ml saline (for
the VOLT01 group) was given manually through
a peripheral venous catheter over 5 min. Second,
a 10 ml saline flush following the first step was
given to all participants. Third, an IV bag con-
taining either 5 mg/100 ml ZA/saline [Aclasta
(Novartis Pharmaceuticals) for the ZA group and
Zobone 5 (Sun Pharmaceuticals) for the VOLT01
group], or 100 ml saline (for the placebo group)
was attached to the catheter for an intravenous
infusion. Both the ZA and VOLT01 solutions
were visually identical to saline. Study partici-
pants were asked to keep using concomitant med-
ications as stable as possible and to use
paracetamol as a rescue medication.

Outcome assessment
Assessment of APRs. Participants were phoned
3 days after their infusion to determine if they
experienced any symptoms within the defined
suite of APRs. The details of APRs were recorded
by a research assistant using a form based on pre-
determined categories. These are ‘fever’, ‘mus-
culoskeletal’, ‘gastrointestinal’, ‘eyes,’ and ‘other’.
Each category includes descriptive options and
notes to detail these APRs.

All other questionnaires (including assessments
of knee pain and function, quality of life, and con-
comitant medication) were dispensed and col-
lected by mail.

MRI assessments. MRI scans were performed at
the Royal Hobart Hospital at screening and
6 months with a 1.5T noncontrast scan (GE
Optima 450W, Milwaukee, USA) using a dedi-
cated 8-channel knee coil. The study knee was
scanned in the sagittal plane using a proton den-
sity-weighted, fat saturation, 2-dimension fast spin
echo MRI sequence (repetition time 3800 ms,
echo time 39 ms), with a slice thickness of 3 mm
and spacing 1.5 mm, flip angle 150°, 512×512-
pixel matrices, and a field of view 16 cm.

A BML was defined as an area of increased signal
intensity adjacent to the subchondral bone. The
presence of BMLs at the screening was assessed
by an experienced MRI reader (DA) for the pur-
poses of patient enrolment. BMLs were scored
blinded to treatment allocation by a trained
observer (GC) using OsiriX software (University
of Geneva, Geneva, Switzerland). Screening and
6 months scans were read in pairs with the chron-
ological order known to the observer. For each of
the medial femoral, lateral femoral, medial tibial,
lateral tibial, and patellar sites, the maximum area
(mm²) on MRI slices was measured indepen-
dently and then summed to create a total BML
area. Intraclass correlation coefficients (two-way
mixed effects model) of the total BML area
ranged from 0.86 to 0.94.

Pain and function assessments. Knee pain and
function were self-assessed by each participant
using WOMAC at baseline, 3, and 6 months. Each
of the 5 (WOMAC pain) and 17 (WOMAC function) items were measured using a 100 mm VAS from 0 (none) to 100 (unbearable), using the last 7 days as the reference period. Missing items on WOMAC subscales were managed according to the WOMAC user guide. In data analyses, WOMAC pain (0–500) and function (0–1700) scores were converted to a 0–100 scale for ease of interpretability, because the noninferiority margins were defined based on a 0–100 scale.

Knee pain was also assessed using a 100 mm VAS at baseline, 3, and 6 months by asking ‘On this line, thinking about your right/left knee, where would you rate your pain? Use the last 7 days as a time frame’.

Other measures. Radiographic knee osteoarthritis was assessed at screening using X-rays according to the OARSI atlas. A four-dimensional assessment of quality of life (AQLoL-4D) questionnaire was used for the calculation of utility (0–1) at baseline, in which health states range from 0 (death) to 1 (best health). We also recorded the use of concomitant medications at baseline.

Height (cm) and weight (kg) were measured at baseline. Participants were asked to remove shoes, socks, and any headgear before measuring height using a stadiometer (MedTech Melbourne, Australia), and shoes and any heavy clothing before measuring weight using a scale (A&D Medical Sydney, Australia). Body mass index (BMI) was calculated [weight (kg)/height (m2)].

Statistical analysis

This study aimed to demonstrate the superiority of VOLT01 to ZA in having a lower incidence of APRs, the noninferiority of VOLT01 compared with ZA in reducing BML size and knee pain, and function scores, and the superiority of VOLT01 and ZA to placebo in reducing BML size, knee pain, and function scores. The noninferiority margin for BML size was set at 140 mm2 because we have demonstrated this amount is clinically significant based on observational and clinical trial data. For knee pain and function scores we chose a conservative margin of 8 mm (assessed using a 0–100 scale), which preserves 60% of the 95% confidence interval (CI) difference between ZA and placebo over 6 months as informed from a previous randomized controlled trial (RCT) (–14.5, 95% CI –28.1 to –0.9). Therefore, an upper limit for the 95% CI for the difference of reduction in BML size (VOLT01: ZA) less than 140 mm2, and in knee pain, and function scores less than 8 mm would demonstrate noninferiority of VOLT01 to ZA.

The sample size was calculated according to the primary hypothesis of this study. Preliminary data from our collaborator (n = 20, unpublished) indicated that 60% of the participants in the ZA group and none in the VOLT01 group experienced at least one APR. Assuming a two-sided α = 0.05, β = 0.20 and no loss to follow-up during the first 3 days, 40 participants per group would enable us to detect at least a 50% reduction of APRs in the VOLT01 group compared with ZA (30% versus 60%).

An intention-to-treat principle was applied for all analyses. Mean [standard deviation (SD)] and median [interquartile range (IQR)] were used to describe continuous data as appropriate, n (%) was used to describe categorical data. Incidences of APRs were compared between the VOLT01 group and the ZA group using the chi-squared and Fisher’s exact tests, without adjustment for multiple comparisons. To rule out the potential influence of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and statins to APRs, a log-binomial regression was performed adjusting for use of these medications at baseline. Changes in BML size, knee pain, and function scores were analyzed using linear mixed effects models, in which fixed effects were month, treatment group, and their interaction, the random effect was participant identification. As was prespecified in the study protocol, analyses of outcome measures were adjusted for clinically important characteristics where there was an imbalance between treatment groups at baseline. Missing values (2–3% missing) on any outcome measure were addressed using maximum-likelihood estimation assuming Missing At Random by adding baseline complete variables that can explain the missingness to the regression models. Analyses were performed using Stata version 15 (Stata Corporation, TX, USA). A two-sided p value of 0.05 was considered statistically significant.

Results

Participants

A total of 172 participants were screened and 117 participants were randomized to receive VOLT01.
(n = 40), ZA (n = 39), or placebo (n = 38). Recruitment of study participants stopped without reaching the anticipated sample size (n = 40 per group) due to budgetary issues. A total of 114 (97%) participants completed questionnaires and 113 (97%) had knee MRIs at 6 months. Only 3 participants (3%) withdrew from the study during the 6 months follow-up (Figure 1).

At baseline, the placebo group had a higher proportion of women (66% compared with 41% in the VOLT01 group and 54% in the ZA group), higher knee pain, utility scores, and concomitant medications, specifically NSAID and glucosamine, than the active treatment groups (Table 1).

**Primary outcomes**
Most APRs were musculoskeletal and nonmusculoskeletal pain, fever, gastrointestinal problems, and nonspecific symptoms (e.g. influenza-like symptoms, headache, fatigue, malaise, and insomnia) (Table 2). Overall 90% of the participants in the VOLT01 group, 87% in the ZA group, and 55% in the placebo group experienced at least one APR. Compared with ZA, the incidence of APRs was similar in the VOLT01 group (p = 0.74). The results were not changed after adjustment for use of NSAIDs, paracetamol, and statins at baseline (data not shown).

**Secondary outcomes**
Results for secondary outcomes are presented in Table 3. VOLT01 was noninferior to ZA for changing BML size over 6 months (Figure 2). However, knee BML size changed little in all groups, and there were no significant differences in the change of BML size between the active groups (ZA and VOLT01) and the placebo group.

VOLT01 was noninferior to ZA after 3 months and superior to ZA after 6 months in reducing knee pain and function scores (Figure 2). Compared with placebo, VOLT01 significantly reduced WOMAC function scores after 6 months and showed a trend to reduce WOMAC function scores after 3 months (p = 0.052) and WOMAC pain scores (p = 0.055) after 6 months.

**Other adverse events**
Adverse events other than APRs were common, with 59% of participants in the ZA group, 69% in the VOLT01 group, and 68% in the placebo group reporting at least one other adverse event over 6 months (Table 4). These were primarily increased musculoskeletal pain and stiffness. In the ZA group, one participant had a knee replacement (nonstudy knee), and one was diagnosed with bowel cancer. No participant withdrew due to adverse events.
### Table 1. Baseline characteristics of participants.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>VOLT01 (n = 40)</th>
<th>ZA (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.5 (7.4)</td>
<td>60.9 (8.1)</td>
<td>64.4 (8.4)</td>
</tr>
<tr>
<td>Women [%]</td>
<td>25 (66)</td>
<td>17 (43)</td>
<td>21 (54)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.0 (5.4)</td>
<td>30.4 (6.0)</td>
<td>31.0 (5.2)</td>
</tr>
<tr>
<td>WOMAC, 0–100†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>47.2 (18.5)</td>
<td>43.0 (19.5)</td>
<td>36.8 (21.8)</td>
</tr>
<tr>
<td>Function</td>
<td>42.1 (17.0)</td>
<td>39.2 (20.6)</td>
<td>36.6 (21.4)</td>
</tr>
<tr>
<td>Knee pain VAS, 0–100</td>
<td>57.1 (17.9)</td>
<td>48.1 (18.3)</td>
<td>45.4 (18.8)</td>
</tr>
<tr>
<td>BML area [mm²]</td>
<td>518.8 (438.0)</td>
<td>576.8 (531.3)</td>
<td>466.0 (396.7)</td>
</tr>
<tr>
<td>Radiographic osteoarthritis, n [%]</td>
<td>24 (63)</td>
<td>30 (75)</td>
<td>28 (72)</td>
</tr>
<tr>
<td>Utility, 0–1</td>
<td>0.62 (0.24)</td>
<td>0.72 (0.14)</td>
<td>0.73 (0.16)</td>
</tr>
</tbody>
</table>

Concomitant medications, n [%]

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>VOLT01 (n = 40)</th>
<th>ZA (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>24 (63)</td>
<td>13 (33)</td>
<td>20 (51)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>17 (45)</td>
<td>16 (40)</td>
<td>25 (64)</td>
</tr>
<tr>
<td>Statins</td>
<td>8 (21)</td>
<td>6 (15)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Glucosamine–chondroitin</td>
<td>13 (34)</td>
<td>7 (18)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Fish oil</td>
<td>11 (29)</td>
<td>5 (13)</td>
<td>12 (31)</td>
</tr>
</tbody>
</table>

BMI, body mass index; BML, bone marrow lesion; NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analog scale; VOLT01, zoledronic acid plus methylprednisolone; WOMAC, Western Ontario and McMaster University Index; ZA, zoledronic acid.

Results are shown as mean (SD) unless specified otherwise. For example, n [%].

†WOMAC pain and function scores were converted to a 100 mm scale.

### Table 2. Acute phase responses among the three groups.†

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>VOLT01 (n = 40)</th>
<th>ZA (n = 39)</th>
<th>VOLT01 versus ZA p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one APR, n [%]‡</td>
<td>21 (55)</td>
<td>36 (90)</td>
<td>34 (87)</td>
<td>0.74</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (11)</td>
<td>22 (55)</td>
<td>18 (46)</td>
<td>0.43</td>
</tr>
<tr>
<td>Musculoskeletal pain and stiffness</td>
<td>13 (34)</td>
<td>28 (70)</td>
<td>27 (69)</td>
<td>0.94</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>6 (16)</td>
<td>13 (33)</td>
<td>16 (41)</td>
<td>0.43</td>
</tr>
<tr>
<td>Eye problems</td>
<td>2 (5)</td>
<td>3 (8)</td>
<td>5 (13)</td>
<td>0.48</td>
</tr>
<tr>
<td>Other problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (16)</td>
<td>22 (55)</td>
<td>23 (59)</td>
<td>0.72</td>
</tr>
<tr>
<td>Malaise and insomnia</td>
<td>8 (21)</td>
<td>23 (58)</td>
<td>20 (51)</td>
<td>0.58</td>
</tr>
<tr>
<td>Headache &amp; dizziness</td>
<td>12 (32)</td>
<td>20 (50)</td>
<td>16 (41)</td>
<td>0.42</td>
</tr>
<tr>
<td>Nonmusculoskeletal pain</td>
<td>6 (16)</td>
<td>18 (45)</td>
<td>15 (38)</td>
<td>0.56</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>1 (3)</td>
<td>9 (23)</td>
<td>9 (23)</td>
<td>0.95</td>
</tr>
<tr>
<td>Other</td>
<td>6 (16)</td>
<td>6 (15)</td>
<td>7 (18)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

APR, acute phase response; VOLT01, zoledronic acid plus methylprednisolone; ZA, zoledronic acid.

†Results are shown as n [%].

‡A patients may experience more than one APR.

*p values were calculated using chi-squared and Fisher’s exact tests.
Discussion

In this RCT, co-administration of 10 mg methylprednisolone and 5 mg ZA (VOLT01) did not reduce APRs compared with 5 mg ZA alone and was noninferior to ZA for changing knee BML size and superior to ZA for relieving knee symptoms in patients with knee osteoarthritis. VOLT01 significantly improved knee function compared with placebo after 6 months but not after 3 months. These results do not support the use of 10 mg intravenous methylprednisolone to reduce APRs associated with ZA but in contrast to ZA alone, the combination may have symptomatic benefit in knee osteoarthritis with BML.

We observed a similar incidence of APRs in the VOLT01 and ZA groups (90% versus 87%) in a sample size of 79, unlike the findings from the previous pilot study where VOLT01 significantly reduced APRs compared with ZA (13% versus 56%),26 with a sample size of 32. A potential reason for the inconsistent findings could be that our study was double-blind (both patients and assessors), whereas the pilot study was single-blind (i.e. only patients were blinded). This may have introduced bias in assessing outcomes in the pilot study.

APRs are thought to be inflammatory responses to bisphosphonates by activated γδ-T cells and elevated pro-inflammatory cytokines (e.g. interferon-γ and TNF-α), which should be effectively controlled by methylprednisolone given its anti-inflammatory properties.23 However, adding 10 mg intravenous methylprednisolone failed to reduce any type of APRs in this study. Potential reasons include that the dose of methylprednisolone was too small to suppress the inflammatory responses, or that APRs following ZA cannot be fully explained by inflammatory responses. Kalyan and colleagues observed a slight peak in Vγ9Vδ2 T cells (a major subset of γδ-T cells) in osteoporotic...
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**Figure 2.** Noninferiority analysis of zoledronic acid plus methylprednisolone versus zoledronic acid alone. BML, bone marrow lesion; CI, confidence interval; VAS, visual analog scale; VOLT01, zoledronic acid plus methylprednisolone; WOMAC, the Western Ontario and McMaster Universities Osteoarthritis Index. Noninferiority was confirmed if the upper limits of 95% CI less than the margin (140 mm² for BML size and 8 for WOMAC scores).

**Table 4.** Adverse events other than acute phase responses among the three groups.†

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n = 38)</th>
<th>VOLT01 (n = 40)</th>
<th>ZA (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one other adverse event‡</td>
<td>26 (68)</td>
<td>27 (68)</td>
<td>22 (56)</td>
</tr>
<tr>
<td>Musculoskeletal pain and stiffness</td>
<td>12 (32)</td>
<td>14 (37)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Elective hospital admissions other than knee surgery</td>
<td>6 (16)</td>
<td>6 (16)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Injuries</td>
<td>1 (3)</td>
<td>4 (11)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cardiovascular problems</td>
<td>4 (11)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4 (11)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>3 (8)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other problems</td>
<td>3 (8)</td>
<td>5 (13)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Serious adverse events*</td>
<td>1 (3)</td>
<td>0</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

VOLT01, zoledronic acid plus methylprednisolone; ZA, zoledronic acid.
†Results are shown as n (%).
‡A patient may experience more than one adverse event.
*Serious adverse events were categorized based on the type and seriousness of each adverse event.
patients immediately after bisphosphonate therapy, but did not observe any APR.\textsuperscript{39} This implies that activated $\gamma\delta$-T cells may not necessarily cause APRs, suggesting some mechanisms other than $\gamma\delta$-T cells induced inflammatory responses may underlie bisphosphonate-related APRs.

In the present study, adding 10 mg methylprednisolone to ZA was noninferior to ZA alone in changing BML size. However, statistically significant reductions in the size of knee BML were not observed in any group. This was unlikely to be due to the relatively modest sample size since we did not observe a significant reduction in BML size in the main ZAP2 study either.\textsuperscript{40} Furthermore, change in BML size in all three groups was lower than the amount which is clinically meaningful (i.e. $>140 \text{mm}^2$).\textsuperscript{37} Similarly to our study, a randomized controlled superiority trial indicated that an intra-articular injection of 40 mg methylprednisolone plus exercise did not increase the size of knee BML over 26 weeks, and the therapy even decreased the size of knee BML over 14 weeks, compared with placebo plus exercise.\textsuperscript{41} While the route of injection of methylprednisolone differs (intra-articular versus intravenous), this combined with our data supports that the administration of methylprednisolone does not have a detrimental effect on the size of osteoarthritis-related BML.

Improvements in WOMAC knee pain and function in the VOLT01 group reached or approached statistical significance compared with placebo over 6 months (albeit with wide confidence intervals), and reductions in both knee pain and function scores were clinically important (i.e. $>12\%$ of baseline score and $>6\%$ of maximal score).\textsuperscript{42} In contrast, ZA alone did not improve knee symptoms. Therefore, combining intravenous methylprednisolone and ZA for knee symptoms may potentially have therapeutic value. Alternatively, improvements in knee symptoms may be due to intravenous methylprednisolone itself. However, methylprednisolone has a short biological half-life of 18–36 h making the long-term symptomatic effect surprising. Despite this, Dorleijn and colleagues found that a one-off intra-muscular injection of 40 mg triamcinolone acetate significantly improved pain symptoms in patients with hip osteoarthritis over 12 weeks,\textsuperscript{43} suggesting a mid-to-long-term symptomatic benefit of systemic treatment with corticosteroids. In comparison, localized intra-articular injection of corticosteroids needs more frequent and much higher doses, but only has a short-term effect on knee pain and function.\textsuperscript{44} While both localized inflammation (synovitis)\textsuperscript{45} and systemic inflammation\textsuperscript{46} have been implicated in the pathogenesis and progression of osteoarthritis, only intra-articular injection of corticosteroids is recommended for management of knee osteoarthritis.\textsuperscript{47} Our study suggests that intravenous injection of 10 mg methylprednisolone may be beneficial for knee symptoms in patients with knee osteoarthritis, but these findings need to be confirmed further because we did not have a group in which methylprednisolone was administered without ZA, in order to assess the effect of intravenous methylprednisolone alone.

In this study, VOLT01 showed a trend to reduce WOMAC knee pain but not VAS pain, suggesting that the WOMAC pain scale may be more sensitive. This was probably due to the comprehensive measurement of the WOMAC scale for osteoarthritic knee pain because it combines five items including pain during walking, using stairs, in bed, sitting or lying, and standing upright, therefore, any improvement in knee pain would be more likely to be captured.

The strengths of our study include the prospective, double-blind nature of the observations and the very low rates of loss to follow-up (3\%) at 6 months. This study has some limitations. First, we did not reach our target of 120 participants (although we approached the number) due to the early termination of recruitment. However, this study was sufficiently powered to detect a meaningful difference in APRs, and we demonstrated the noninferiority of VOLT01 to ZA in reducing BML size and improving knee symptoms. Second, while we conclude that VOLT01 was superior to ZA in improving knee symptoms, this hypothesis was not prespecified, and the sample size was not set up for superiority comparison. However, it is acceptable to switch the objective from noninferiority to superiority if such a relationship was observed,\textsuperscript{48} as we have done. Third, some baseline characteristics were not well balanced, but we have taken this into account by adjusting for them in data analyses according to the trial protocol.\textsuperscript{28} Four, the sample size was calculated based on the primary hypothesis. The noninferiority test between ZA and VOLT01 and superiority tests of ZA and VOLT01 with placebo on knee symptoms and BMLs may be underpowered, making the results hypothesis generating. Five, the current sub-study of ZAP2 was not registered separately in a
clinical trial registry. However, the published protocol for ZAP2 did include this substudy,\textsuperscript{28} as required by the ethics committee. Finally, the zoledronic acid used in the ZA and VOLT01 groups were sourced from different pharmaceutical companies, but this should not influence the results because they have the same dose of the active ingredient.

**Conclusion**

Administering intravenous methylprednisolone with ZA did not reduce APRs or change knee BML size over 6 months and, in contrast to ZA, may have a beneficial effect on symptoms in knee osteoarthritis.

**Acknowledgements**

The authors thank all patients and staffs who made this study possible.

**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. Study design: LLL, DA, FC, LM, CH, and GJ. Acquisition of data: GC, LLL, DA, and GJ. Analysis and interpretation of data: GC, LLL, DA, TW, and GJ. Manuscript preparation and approval: GC, LLL, DA, FC, LM, CH, TW and GJ.

**Funding**

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The ZAP2 main study was funded by a project grant from the National Health and Medical Research Council of Australia (NHMRC, APP1045415). Voltarra Pharmaceuticals provided part funding for this substudy. LLL is a recipient of an NHMRC Early Career Fellowship. DA is a recipient of an NHMRC/MRFF Career Development Fellowship (Level 1). GJ is a recipient of an NHMRC Practitioner Fellowship.

**Role of the funder/sponsor**

The funders played no role in the design and implementation of the study; collection, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

**Conflict of interest statement**

The authors declare that there are no conflicts of interest.

**Ethics approval and consent to participate**

The study was approved by the Tasmanian Health and Medical Research Ethics Committee, and written informed consent was obtained from all participants.

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**Supplemental material**

Supplemental material for this article is available online.

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