

No effect of risedronate on femoral periprosthetic bone loss following total hip arthroplasty

A 4-year follow-up of 61 patients in a double-blind, randomized placebo-controlled trial

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Background and purpose — We have previously shown that during the first 2 years after total hip arthroplasty (THA), periprosthetic bone resorption can be prevented by 6 months of risedronate therapy. This follow-up study investigated this effect at 4 years.

Patients and methods — A single-center, double-blind, randomized placebo-controlled trial was carried out from 2006 to 2010 in 73 patients with osteoarthritis of the hip who were scheduled to undergo THA. The patients were randomly assigned to receive either 35 mg risedronate or placebo orally, once a week, for 6 months postoperatively. The primary outcome was the percentage change in bone mineral density (BMD) in Gruen zones 1 and 7 in the proximal part of the femur at follow-up. Secondary outcomes included migration of the femoral stem and clinical outcome scores.

Results — 61 of the 73 patients participated in this 4-year (3.9- to 4.1-year) follow-up study. BMD was similar in the risedronate group (n = 30) and the placebo group (n = 31). The mean difference was -1.8% in zone 1 and 0.5% in zone 7. Migration of the femoral stem, the clinical outcome, and the frequency of adverse events were similar in the 2 groups.

Interpretation — Although risedronate prevents periprosthetic bone loss postoperatively, a decrease in periprosthetic BMD accelerates when therapy is discontinued, and no effect is seen at 4 years. We do not recommend the use of risedronate following THA for osteoarthritis of the hip.

Adaptive bone remodeling around the femoral stem following total hip arthroplasty (THA) results in regional loss of bone mass, especially in proximal parts of the femur—most of which takes place within the first postoperative year (Bodén et al. 2006, Sköldenberg et al. 2006). Periprosthetic bone loss

may predispose to periprosthetic fracture, aseptic loosening, and difficulties at revision surgery (Lindahl 2007, Streit et al. 2011, Sköldenberg et al. 2014).

The bisphosphonate (BP) risedronate has been used successfully to prevent osteoporotic fractures, mainly in the hip and vertebrae, by inhibiting osteoclast activity (McClung et al. 2001). In recent years, the possible use of BPs to prevent or ameliorate periprosthetic adaptive bone resorption, osteolysis, and implant migration has been investigated thoroughly in animal models and humans. The short-term results of several studies showing the effects of postoperative BP treatment in reducing periprosthetic bone loss up to a year after the arthroplasty have already been published (Venesmaa et al. 2001, Wilkinson et al. 2001, Hennigs et al. 2002, Wilkinson et al. 2005, Arabmotlagh et al. 2006).

We have previously found that risedronate given once a week for 6 months after THA reduces periprosthetic bone resorption around an uncemented femoral stem in the first and second postoperative year (Sköldenberg et al. 2011). We now report the 4-year outcome in the same cohort.

Patients and methods

Design and setting

This single-center, double-blind, randomized placebo-controlled trial (the PREVENT trial) was carried out from 2006 to 2010 at the orthopedics department of Danderyd Hospital in collaboration with the Karolinska Institute.

We included patients with osteoarthritis (OA) of the hip, 40–70 years old, with a bone stock suitable for uncemented fixation and no previous or concurrent medication with bone-active drugs. The femoral component consisted of an uncemented, tapered, proximally porous-coated and hydroxy-

apatite-coated stem composed of Ti-6Al-4V titanium alloy (Bi-Metric HA; Biomet, Warsaw, IN) and a 28-mm chromium-cobalt head. Further inclusion and exclusion criteria and also the details of surgery were reported in the 2-year follow-up study (Sköldenberg et al. 2011).

We randomized the patients on the second postoperative day to receive a tablet containing either 35 mg of risedronate or placebo once a week for 6 months. All the patients also received daily oral supplements of calcium carbonate (1,000 mg) and vitamin D (400 IU) for 6 months. An attempt was made to contact all the patients for follow-up 4 years after surgery.

Sample size

Before starting the study, we had conducted a power analysis (Sköldenberg et al. 2011). In a previous study of hip fracture prevention with risedronate, a 4.8% increase in BMD in the greater trochanter and a 3.4% increase in BMD in the femoral neck (roughly equivalent to Gruen zones 1 and 7) in the risedronate group was associated with a 30% reduction in the risk of hip fracture (absolute risk reduction, 1.1%) (McClung et al. 2001, Sköldenberg et al. 2014). Zones 1 and 7 were chosen as outcome areas since this is where most of the bone remodeling occurs during the early postoperative period, and since this is the location for Vancouver A, B1, and B2 fractures (Schmidt and Kyle 2002, Sköldenberg et al. 2014). We assumed that an increase in BMD of 10% (roughly twice as large as the increase in that study) could be clinically relevant in preventing future periprosthetic fractures in the present trial. However, the study was not powered for the endpoint of lowering either the incidence of periprosthetic fractures or of preventing future loosening of the THA. The sample size was therefore designed simply to determine whether we could detect a difference in BMD in the zones of interest after risedronate treatment. We calculated that 60 patients (30 in each group) would be required to provide a power of 90% to detect a difference of 10% in bone mineral density in zones 1 and 7 in the 2 groups, assuming an SD of 11% (Sköldenberg et al. 2006) and considering a 2-sided p-value of 0.05 to be significant.

Outcome measures

The primary endpoint was the change in BMD at 4 years, compared to immediate postoperative values, in Gruen zones 1 and 7 (proximal-lateral and proximal-medial, respectively) around the femoral stem. Secondary endpoints included change in BMD in individual zones (zones 2–6), as well as the entire periprosthetic region (zones 1–7), vertical migration of the femoral stem, clinical outcome scores, and the occurrence of adverse events.

Bone mineral density (BMD) was measured as previously reported (Sköldenberg et al. 2011) and with the same scanner, using dual X-ray absorptiometry (DXA) in the 7 Gruen zones around the femoral stem in the frontal plane. The patient was placed supine with standard knee and foot supports, with

the femur in neutral rotation. The scanner was equipped with the software for femoral periprosthetic bone mineral measurement. The software detected the interface between the bony part and the stem of the prosthesis. We performed double examinations at 1 year on 20 patients. Differences in values were between 1.0% (zone 2) and 4.2% (zone 5) in the 7 Gruen zones.

The BMD at the operated proximal femur and vertebrae L1 to L4 was measured and categorized preoperatively according to the World Health Organization (WHO) classification for osteoporosis. The bone density of the vertebrae was also recorded 4 years postoperatively. The migration of the femoral stem was examined using EBRA femoral component analysis (EBRA-FCA) software (University of Innsbruck, Innsbruck, Austria), after taking digital anteroposterior and lateral radiographs (Bucky Diagnostics; Philips, Eindhoven, the Netherlands). The radiographs were also evaluated for heterotopic ossification at 4 years. Using the Harris hip score and the EuroQoL (EQ-5D) questionnaire, we evaluated hip function and health-related quality of life, respectively. The occurrence of adverse events and reoperations was recorded.

Statistics

The analyses were performed on the basis of the intention-to-treat principle, and all patients who received at least 1 dose of either risedronate or placebo were included in the final analysis. We used Student's t-test and Levene's test for comparison of BMD data between the groups. A Bonferroni correction was used to handle multiplicity and a type-1 error rate of 0.01 was protected. We used paired t-test to compare the 4-year values with the 2-year values within the whole cohort. We used a linear regression analysis to reduce variance, and adjusted for group (placebo/risedronate) and stratification factor (male/female) in order to evaluate the effect of treatment at 4 years. The Mann-Whitney U test was used for between-group comparisons of clinical outcome scores at each follow-up visit because these values were not normally distributed. Any p-value of ≤ 0.05 was considered significant.

Ethics and registration

The study was conducted in accordance with the ethical principles of the Helsinki declaration. It was approved by the ethics committee of the Karolinska Institute and has been registered at ClinicalTrials.gov (identifier NCT00772395).

Results

Follow-up and demographics

Of the 73 patients included, 61 were available for follow-up (at median 4 years (3.9–4.1 years)). Consent was withdrawn by 8 patients (4 in each group) because of illness (n = 2) or not wanting to participate (n = 2). Another 4 patients (2 in each group) had moved from our catchment area and could not be

Table 1. Baseline characteristics of the patients

	Placebo (n = 31)	Risedronate (n = 30)
Age, years ^a	60 (5)	62 (5)
Male sex, n	18	20
BMI ^a	27 (4)	28 (5)
ASA classification, n		
1 or 2 / 3 or 4	30/1	29/1
Charnley class, n		
A/B/C	17/11/2	15/12/4
EQ-5D preoperatively ^a	0.35 (0.30)	0.43 (0.29)
HHS preoperatively ^a	46 (14)	45 (14)
Bone mineral density, total hip		
WHO classification, n		
normal/osteopenia/osteoporosis	26/3/2	22/8/0
Density (g/cm ²) ^a	1.06 (0.20)	1.01 (0.17)
Bone mineral density, lumbar spine		
WHO classification, n		
normal/osteopenia/osteoporosis	23/6/2	24/5/1
Density (g/cm ²) ^a	1.30 (0.30)	1.24 (0.21)
Stem size, n		
8–10/11–13/14–15 mm	7/21/3	12/14/4

^a mean (SD).

WHO: World Health Organization BMD classification;
ASA: American Society of Anaesthesiologists;
EQ-5D: EuroQol 5 dimensions; HHS: Harris hip score.

reached. None of the patients had been revised or reoperated, according to information obtained from telephone interview or through the Swedish Hip Arthroplasty Register. At enrollment, the baseline characteristics of the 2 groups were similar (Table 1).

Efficacy

BMD was not significantly higher in the risedronate group than in the placebo group at follow-up. The mean difference was -1.8% in zone 1 and 0.5% in zone 7, respectively (Table 2). When comparing 2-year and 4-year follow-up, both groups had a statistically significant decrease in periprosthetic BMD, but the rate of bone loss in zones 1 and 7 was higher in the risedronate group than in the placebo group. Between 2 and 4 years, the placebo group lost 4.7% in zone 1 and 4.4% in zone 7. The risedronate group lost 5.8% in zone 1 and 5.2% in zone 7.

We did not find any statistically significant differences between groups in the other periprosthetic zones at 4 years. Only zone 3 had a lower bone resorption in the risedronate group than in the placebo group, with a difference of 5.1% , but this was no longer statistically significant when we used Bonferroni's correction to adjust for multiplicity (Table 2). The

results were confirmed in the linear regression model where treatment with risedronate did not affect bone resorption at 4 years, when adjusted for gender. Females had significantly higher bone resorption in zones 1 and 7, but this correlation disappeared when we adjusted for their lower BMD preoperatively.

We did not find any statistically significant differences between groups for all other secondary endpoints, including vertebral BMD, HHS, EQ-5D, stem migration, heterotopic ossification, and the occurrence of adverse events. Regarding hip-related complications, 1 patient in the control group had a dislocation, which was treated with closed reduction, and the joint remained stable. There were no stem or cup revisions. Apart from the dislocation, there were no serious adverse events in the study.

Discussion

In this double-blind, randomized placebo-controlled trial, we found no significant effect of 6 months of oral treatment with risedronate in preventing femoral periprosthetic bone resorption, up to 4 years. This decline in efficacy (difference between the groups) could also be seen in our previous report where, as soon as risedronate was discontinued after

Table 2. The effect of risedronate on primary and secondary endpoints at 4 years. A Bonferroni correction has been applied to all p-values

Outcome	Placebo (n = 31)	Risedronate (n = 30)	Difference (95% CI)	p-value
Primary endpoint, change in BMD (%) ^a				
zone 1	-21 (13)	-19 (14)	-1.8 (-8.6 to 4.9)	1.0
zone 7	-22 (15)	-23 (16)	0.5 (-7.5 to 8.4)	1.0
Secondary endpoints, change in BMD (%) ^a				
zone 2	-2.5 (7.8)	-0.6 (7.9)	-1.9 (-10.3 to 6.4)	1.0
zone 3	-3.4 (7.8)	1.7 (10.6)	-5.1 (-9.9 to 5.9)	0.3
zone 4	-3.3 (9.3)	-1.7 (6.0)	-1.6 (-5.6 to 2.4)	1.0
zone 5	-2.8 (7.0)	2.8 (6.4)	0.0 (-3.4 to 3.4)	1.0
zone 6	-6.2 (11.9)	3.9 (10.4)	-2.3 (-8.1 to 3.4)	1.0
zones 1–7	-6.8 (6.5)	-4.3 (4.8)	-2.5 (-5.4 to 0.5)	0.8
BMD L1–L4, g/cm ²	1.3 (0.24)	1.3 (0.27)		
Other endpoints				
Vertical migration of the stem, mm ^a	-1.7 (1.5)	-1.7 (1.2)		
Harris hip score ^a	94 (7)	94 (10)		
EuroQoL ^a	0.9 (0.2)	0.8 (0.2)		
Heterotopic ossification, n				
none	23	20		
Class I–II	7	8		
Class III–IV	1	2		
Adverse events, n				
hip dislocation	1	0		
cardiovascular events	3	2		
malignancy	1	2		
respiratory events	2	1		
other	6	4		

^a mean (SD); p-value from unpaired Student's t-test.

6 months, the periprosthetic BMD started to drop from the 1-year follow-up to the 2-year follow-up.

Periprosthetic bone remodeling in the proximal zones is faster than the normal ageing of the femoral bone in the long term—with possible implications for increased incidence of periprosthetic fractures with well-fixed, uncemented implants decades after surgery (Lindahl 2007, Streit et al. 2011). There is now some evidence that this local decrease in periprosthetic bone, at least in patients with uncemented implants, can have clinical consequences in the form of fractures (Streit et al. 2011, Sköldenberg et al. 2014). Whether or not a decrease in BMD around femoral stems truly has any influence on the longevity of THA is, however, still very much under debate; larger observational studies evaluating BMD during long follow-up are needed. As clinicians, we certainly experience occasional periprosthetic fractures around implants in patients with radiological signs of stress shielding. To link this to scientific evidence of decrease in periprosthetic BMD leading to later fractures and/or loosening is much more difficult. It would require follow-up of hundreds of patients for many years, with repeated BMD measurements. To our knowledge, no such study exists today. In addition, after 2 decades of clinical trials on bisphosphonates, there is still no evidence that these drugs can affect revision rates after THA (Aspenberg 2009, Zhu et al. 2013).

When we planned the PREVENT trial, we anticipated that the immediate loss of periprosthetic bone that occurs during the first 6 months could be halted (which it could), and that this effect would last for the entire study period (which it did not). Instead, after 4 years, the treatment group had the same decrease in BMD around the stem as the placebo group.

This rebound effect with risedronate has not been presented earlier for THA, because most studies on risedronate are aimed at preventing hip fractures or vertebral fractures in osteoporotic patients, and have a much longer treatment period. Bisphosphonates bind to bone mineral and are deposited on the surfaces of the bone throughout the skeleton. It has been suggested that some of the drug is then recirculated within the bone when bone resorption occurs, binding again to nearby hydroxyapatite surfaces. This phenomenon, together with the long half-life of the drug in the bone, could therefore explain the only gradual decrease in BMD towards pretreatment levels. In the VERT-NA study, BMD at the spine, femoral neck, and trochanter decreased 1 year after discontinuation of a 3-year risedronate treatment period in osteoporotic patients (Watts et al. 2008). Serological markers of bone turnover in this report remained well below pretreatment levels 1 year after the last dose. There are also data on the effect of 1 year discontinuation of risedronate use in postmenopausal women with osteoporosis who had previously received risedronate for 2–7 years. The BMD in the femoral trochanter (roughly equivalent to Gruen zone 1, as in our study) had returned to baseline values at 1 year (Eastell et al. 2011). As mentioned, these were all trials with osteoporotic patients with fragility

fractures and, to our knowledge, our study has had the longest follow-up of treatment of OA patients with risedronate to be published so far. There have been several medium-term (4- to 5-year) follow-up reports on prevention of osteoporotic fractures using risedronate, but there have only been 2 previous RCTs on risedronate therapy following THA. Both had a follow-up of only 6 months (Kinov et al. 2006, Yamasaki et al. 2007) and had small sample sizes (24 and 42 patients in each trial, respectively). Both trials showed positive results in reducing periprosthetic bone loss.

With hindsight, our 6-month treatment period was too short. However, it is doubtful whether a longer period of treatment with risedronate would bring clinically relevant positive effects for THA patients with OA. The PREVENT trial was designed as a “proof of concept” to demonstrate that it is possible, in the clinical setting (as reflected by our use of an intention-to-treat analysis), to reduce bone resorption sufficiently to be clinically relevant. Based on previous studies of hip fracture populations and BP use, we stipulated that a 10% increase in BMD in Gruen zones 1 and 7 (which are roughly equivalent to the BMD zones measured in a standard screening setting for osteoporosis) would be relevant in preventing future periprosthetic fractures. Now, with the 4-year results at hand, we no longer believe this. With the reported occasional occurrence of atypical subtrochanteric or diaphyseal femoral fracture in patients with long-term use of alendronate (Sellmeyer 2010) and risedronate (Alfahad et al. 2012), the risk outweighs the merits of treatment in our opinion.

Several studies have evaluated the short-term antiresorptive effect of other BPs on periprosthetic bone (Venesmaa et al. 2001, Wilkinson et al. 2001, Hennigs et al. 2002, Wilkinson et al. 2005, Arabmotlagh et al. 2006), and have found positive results. However, only 2 medium-term reports with a minimum follow-up of 4 years exist. Venesmaa et al. (2001) were among the first to demonstrate efficacy of alendronate in their small pilot study ($n = 13$) with 6 months of treatment and follow-up as soon as treatment was discontinued. The same research group then published a follow-up 5 years later, and could not show that the positive effect noted in the early postoperative period was still maintained 5 years after the operation (Tapaninen et al. 2010). As in our study, the active drug group had increased bone resorption up to the follow-up, with there no longer being any difference between the groups. In contrast to this, Arabmotlagh et al. (2009) demonstrated in their trial with alendronate treatment that efficacy could be maintained up to 6 years after surgery, with only 6 months of treatment. In addition, there has been one 5-year follow-up published on pamidronate therapy. Shetty et al. (2006) followed up their original cohort of patients, but they did not use DXA to study their endpoints. They concluded that pamidronate had no positive effect on the clinical outcome; nor did it prevent the development of osteolytic lesions 5 years after total hip replacement. In a recent meta-analysis of BPs for joint arthroplasties involving 17 trials with a total of 781 patients (including total

knee arthroplasty), no long-term efficacy of BPs was observed (Zhu et al. 2013).

The difference in results with BPs at longer follow-up times between trials has several explanations. Firstly, femoral stems have different properties regarding how much proximal disuse atrophy they induce (Kim et al. 2011). Almost all studies on BPs and THA have used different implants. Secondly, individual BPs have their own affinities for bone, their own half-life in vivo, and their own inhibitory effects on osteoclasts. The relative contributions of these properties differ among BPs, and help to determine their clinical behavior and effectiveness. Thirdly, there are numerous aspects of protocols that are worth scrutinizing when conducting and comparing clinical trials. Differences in patient selection, in when drugs are given (i.e. preoperatively, intraoperatively, or postoperatively), in the length of treatment and follow-up, and in the configurations of the DXA scanners used will all have significant effects on the results. Lastly, there is always the possibility of publication bias—where negative or neutral results from longer follow-up (as in our study) are simply not published.

The strengths of the present study include an adequate follow-up rate and validated methods for measuring periprosthetic BMD and implant migration. The study was also performed in double-blind fashion, and the analysis of efficacy was performed according to the intention-to-treat principle—an approach that has been lacking, or not reported, in most previously published studies on this topic (Venesmaa et al. 2001, Wilkinson et al. 2001, Hennigs et al. 2002, Wilkinson et al. 2005, Arabmotlagh et al. 2006). This distinction between intention-to-treat analysis and as-treated analysis is important, because exclusion of patients who have discontinued the medication will increase the reported effect of the drug being studied. Reporting of negative or neutral results is also important to avoid publication bias.

One limitation of our study—as previously discussed—was the short duration of risedronate treatment. The study was also underpowered for the clinically relevant endpoint of preventing future periprosthetic fracture. This is, however, true of all clinical trials on the subject of BPs and THA.

In conclusion, although risedronate prevented periprosthetic bone loss in the first year(s) postoperatively, periprosthetic BMD decreased when therapy was discontinued, and no effect was seen at 4 years. We do not recommend the use of risedronate following THA for OA of the hip.

OM, HB, and TE operated on patients and wrote the manuscript. EA and AS wrote the manuscript. MS initiated the study, collected data, operated on patients, and wrote the manuscript. OS initiated the study, collected data, operated on patients, supervised EA, and wrote the manuscript.

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