P003

Zoledronic Acid (ZOL) Infusion Reduces Femoral Bone Loss Following Total Hip Arthroplasty (THA)

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Abstract

Summary: Percentage bone mineral density (BMD) loss at the proximal femur after cementless THA was significantly reduced with ZOL vs. placebo at 2 yrs.

Introduction: Significant proximal femoral remodeling occurs after THA, with regions of bone loss and hypertrophy.

Methods: Fifty-one patients (mean age, 61.2 yrs; range, 33-84 yrs) participated in a prospective, blinded, randomized, placebo-controlled study. ZOL 5 mg intravenous infusion (n=27) or saline placebo (n=24) was administered at 2 weeks and 1 yr after primary cementless THA. Dual energy X-ray absorptiometry (DXA) scans of the 7 femoral region Gruen zones were performed preoperatively and 3-7 days, 6 weeks, 6 months, and 1 & 2 yrs postoperatively. 2-yr data were available for a subset of pts (ZOL, n=21; placebo, n=22). Harris hip scores were recorded to assess post-arthroplasty pain and functionality.

Results: There were no statistical differences in age, gender, or BMI between groups. BMD in Gruen zone 1 decreased 4.0% at 2 yrs in the placebo group, but increased 14.3% in the ZOL group (P <.0001, Wilcoxon/Kruskal-Wallis test). BMD in Gruen zone 7 decreased 27.3% at 2 yrs in the placebo group, but decreased 9.6% in the ZOL group (P <.0001). Harris hip scores were not statistically different between groups at any time point.

Conclusion: Percentage BMD loss at the proximal femur after cementless THA was significantly reduced with ZOL vs. placebo at 2 yrs. By preserving bone, ZOL has the potential to improve long-term outcomes in THA.

Background

- Periprosthetic bone loss following total hip arthroplasty (THA) has been observed on x-ray analysis and documented by measurement of bone mineral density (BMD) on dual-energy x-ray absorptiometry (DXA)[1-3]
- The implantation of a femoral component can cause substantial osteopenia of the proximal femur by radically altering the stresses transferred through the proximal femur (stress shielding)[4,5]
- Zoledronic acid (ZOL) is an intravenous bisphosphonate that prevents BMD loss in osteoporosis when given once-yearly[6,7] and in osteopenia when given once-yearly or once every 2 years[8]
- We evaluated the effect of ZOL on femoral BMD following primary uncemented THA [NOTE: ZOL has not been approved for this use by the US Food and Drug Administration]

Methods

- All subjects took 1500 mg of calcium carbonate and 600 IU of vitamin D daily as a divided dose for the 2-year study period
- The following femoral prosthesis designs/articulating surfaces were used: for the femur, Apex Modular (OMNI LifeScience, Raynham, Massachusetts) or M-COR Modular (Portland Orthopaedics Ltd, Sydney, Australia); for the acetabulum: Conserve Plus with large-diameter/metal-on-metal (MOM) bearings (Wright Medical Technology, Arlington, Tennessee)
- The primary end point of the study was change in BMD of the operated proximal femur measured by dual-energy x-ray absorptiometry (DXA)

Results

- One-year data were available for 24 ZOL patients and 24 placebo patients; 2-year data were available for 21 ZOL patients and 22 placebo patients
- There were no significant differences in gender distribution, age, or BMI between the groups (Table 1)

Table 1. Baseline Characteristics of Study Population

	ZOL (n = 27)	Placebo (n = 24)	*P*-value
Male, no.	12	11	0.57
Female, no.	15	13	0.60
Age, mean (range), y			
Male	55.8 (33-76)	62.9 (51-72)	0.52
Female	64.7 (52-84)	60.7 (51-77)	0.57
BMI, mean (range), kg/m^2			
Male	28.3 (22.4-36.7)	30.0 (25.1-33.5)	0.63
Female	29.8 (22.3-40.2)	29.4 (21.3-37.6)	0.66

BMI = body mass index. *P*-values from chi-square test.

BMD Effects

- Overall, ZOL-treated patients had reduced BMD loss in the 7 Gruen zones over 2 years (Figure 1) compared with the placebo group (Figure 2)
- ZOL was associated with significant effects in preventing BMD loss at 1 year (+13.8% vs +1.4%, ZOL vs placebo; P = 0.0065) and 2 years (+14.3% vs -4.0%, P <0.0001) in Gruen zone 1 and at 1 year (-8.4% vs -25.4%, P <0.0001) and 2 years (-9.6% vs -27.3%, P <0.0001) in Gruen zone 7
- Suppression of BMD loss with ZOL vs placebo was also significant from 6 weeks to end of study in Gruen zone 4 ($P \leq 0.0437$), Gruen zone 6 ($P \leq 0.008$), and Gruen zone 7 ($P \leq 0.0007$)

Figure 1. Mean Percent BMD Change From Baseline With Zoledronic Acid by Gruen Zone

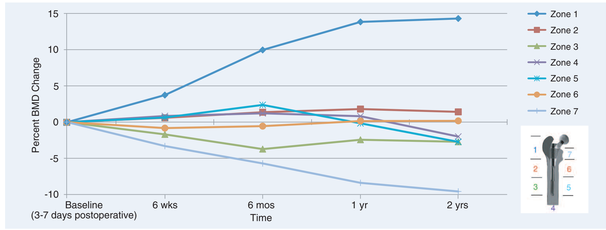


Figure 2. Mean Percent BMD Change From Baseline With Placebo by Gruen Zone

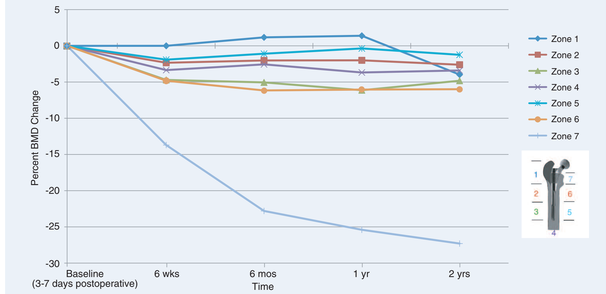
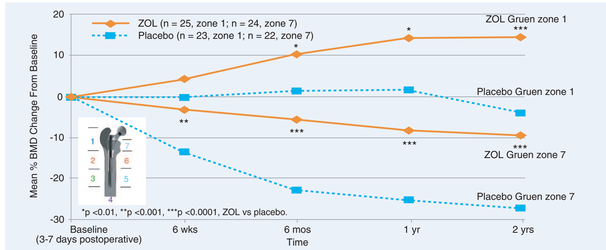


Figure 3. Mean % BMD Change From Baseline for ZOL and Placebo Groups in Gruen Zones 1 and 7



- For all zones combined, there was a progressive loss of BMD from baseline to 2 years with placebo treatment as compared with ZOL treatment, with the differences being significant (P <0.0001) at all time points
- ZOL prevented BMD loss from baseline or reduced BMD loss vs placebo as early as 6 weeks
- ANOVA showed large and significant treatment and Gruen zone effects, a large and significant treatment*Gruen zone interaction, and small but significant time*Gruen zone interaction and time*treatment*Gruen zone effects (all P <0.0001)

Harris Hip Scores

- Harris Hip Scores did not significantly differ between ZOL and placebo groups at 6 weeks, 6 months, 1 year, or 2 years after surgery

Safety

- One patient in the placebo group discontinued participation in the study after receiving the second infusion at 1 year due to a hepatic liver mass. One patient in the ZOL group discontinued participation 6 months into the study due to a diagnosis of liver cancer. Neither adverse event was attributed to study drug
- Two patients in the ZOL group discontinued the study after the first infusion due to flulike symptoms
- At the 24-month time point, one patient in the placebo group required a hip revision due to device failure (implant breakage)
- There were no adverse radiographic or other clinical events

Conclusions

- **Percentage BMD loss at the proximal femur after cementless THA is significantly reduced by ZOL**
  - **BMD loss was observed in 6 of 7 Gruen zones at 1 year and in all 7 zones at 2 years in the placebo group, whereas no loss in BMD or an increase in BMD from baseline was observed in the ZOL group in Gruen zones 1, 2, 4, and 6 at one year and in zones 1, 2, and 6 at two years**
  - **Significant suppression of bone loss with ZOL vs placebo was evident as early as 6 weeks after surgery, and the greatest suppressive effect was seen at the proximal femur (Gruen zones 1 and 7)**
  - **For combined Gruen zones, there was progressive BMD loss from baseline to 2 years with placebo vs ZOL treatment; differences were significant at all time points**
- **Our results were consistent with those from previous studies of bisphosphonate administration following THA**
- **By preserving bone, ZOL has the potential to improve the long-term outcome of THA**

References: **1.** Kiratli JB, et al. *J Orthop Res.* 1992;10:836-844. **2.** Kiratli JB, et al. *J Arthroplasty.* 1996;11:184-193. **3.** Scott DF, Jaffe WL. *J Arthroplasty.* 1996;11:429-437. **4.** Rubash HE, et al. *Orthop Clin North Am.* 1998;29:173-186. **5.** Huiskes R, et al. *Clin Orthop Relat Res.* 1992;274:124-134. **6.** Black DM, et al. *N Engl J Med.* 2007;356:1809-1822. **7.** Lyles KW, et al. *N Engl J Med.* 2007;357:1799-1809. **8.** McClung M, et al. *Obstet Gynecol.* 2009;114:999-1007.

Funding for the conduct of this study and the development of this poster was provided by Novartis Pharmaceuticals, East Hanover, NJ

Poster presented at the 2011 Annual Meeting of the American Academy of Orthopaedic Surgeons; February 15-19, 2011; San Diego, CA