Viability of a single infusion of zoledronic acid (ZOL) to reduce implant failure rate in THA

Results from a randomized, double-blind, controlled trial

Gerald Friedl¹; Roman Radl¹; Peter Rehak², Reingard Aigner³, and Reinhard Windhager¹

¹ University Clinic of Orthopaedic Surgery, Medical University of Graz (MUG), Austria
² Dept. of Surgery, Unit for Biomedical Engineering and Computing, MUG, Austria
³ Dept. of Radiology, Division of Nuclear Medicine, MUG, Austria
Rationale
Revision in primary THR

The Swedish National Hip Arthroplasty Register (http://www.jru.orthop.gu.se)
1979 – 2005: ~ 30,000 THR

1. Aseptic loosening 75%
2. Deep infection 7%
3. Dislocation 7%
4. Periprosthetic fracture 6%
5. Others 5%
Rationale
Periprosthetic Bone Mass

Substantial bone loss after THR

Maloney WJ, 1996, CORR:
Cementless stems at mean fu 6 years (1.5 – 13.5 yrs)

• Periprosthetic cortical bone area: up to -40%

• Periprosthetic BMD: up to -30%
Rationale
Periprosthetic BMD and Bisphosphonates

Bhandari M, 2005, JBJS Am:
A Meta-Analysis of 6 randomized controlled trials in TJR

- 24-52 wks treatment with Bisphosphonates
- Beneficial effects in maintaining periprosthetic BMD

?? Predictive value of BMD for aseptic loosening??
Rationale
Prosthetic Migration

Mjöberg B, 1997, Orthopedics: Theory based on findings in RSA
  •  Loosening begins at early stage due to insufficiency of initial fixation.

Stocks GW, 1995, JBJS Br: 265 THRs with 4 acetabular systems
  •  Migration rate of cups at 2 years was significantly predictive for loosening within a period of 6.5 yrs

Krismer, 1999, JBJS Br: 240 THR with 3 stem systems
  •  Migration of stems at 2 yrs was related with loosening, fu 10 years
Aim of the Study

Higher failure rate in ON-FH compared with OA was associated with higher migration.

Efficacy of a single infusion of ZOL on reducing the early migration rate of acetabular and femoral components in ON-FH

Secondary endpoints
- Biochemical bone resorption and formation markers
- Clinical outcome
- Safety
Study Design

THR in ON-FH
(n=50)

Plazebo (CTR)
(n=25 -1)

Zoledronic acid (ZOL)
(n=25)

Pharmacy

Follow-up 2 yrs minimum
at 7w → 6 mths → 1 yr → yearly thereafter

• Standardized plain x-rays
  → migration analysis by EBRA (blinded)
• Harris Hip Score (HHS)
• Fasting blood samples
• Side effects
Methods

Approved by local ethics committee (No 12-152ex01/02)

Surgery

• Cementless rectangular straight titanium stem without collar (n=49)
• Cementless titanium-backed press-fit acetabular cup (n=46)
• Weight bearing limited to half of BW for 6 weeks

Study medication

• Staff and patients were fully blinded, randomization by pharmacist
• Infusion of 20 ml intravenously over a 15 minute-period
• Patients were instructed to supplement 1000 mg Ca / 400 IU vitamin D

Endpoint measurements

• EBRA: ≥ 2 independent investigators blinded to randomization
• Fasting-blood analysis by core-facility of the University Hospital (GLP)
• Blinding was opened after all patients had a minimum fu of 2 years and measurements had been finished
# Results

## 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic of Patients</th>
<th>Total (n=49)</th>
<th>ZOL (n=25)</th>
<th>CTR (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, [years]</td>
<td>61.0 ± 12.8</td>
<td>63.9 ± 9.7</td>
<td>57.8 ± 15.0</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, [kg]</td>
<td>79.0 ± 16.1</td>
<td>76.8 ± 16.6</td>
<td>81.1 ± 15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, [kg/m²]</td>
<td>28.4 ± 4.4</td>
<td>28.5 ± 4.8</td>
<td>28.4 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, female / male</td>
<td>27 / 22</td>
<td>17 / 8</td>
<td>10 / 14</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco abuse, n</td>
<td>11 (22%)</td>
<td>5 (20%)</td>
<td>6 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic, n</td>
<td>19 (39%)</td>
<td>10 (40%)</td>
<td>9 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary, n</td>
<td>30 (61%)</td>
<td>15 (60%)</td>
<td>15 (62%)</td>
<td>NS</td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right / left side treated, n</td>
<td>33 / 16</td>
<td>18 / 7</td>
<td>15 / 9</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of THA</th>
<th>Total</th>
<th>ZOL</th>
<th>CTR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem size 2 / 3 / 4 / 5 / 6 / 7 / 8, n</td>
<td>2 / 4 / 9 / 14 / 12 / 6 / 2</td>
<td>2 / 2 / 6 / 5 / 6 / 3 / 1</td>
<td>- / 2 / 3 / 9 / 6 / 3 / 1</td>
<td>NS</td>
</tr>
<tr>
<td>Cup size, [mm]</td>
<td>53.5 ± 4.5</td>
<td>53.0 ± 4.4</td>
<td>54.0 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cups secured with screws, n</td>
<td>17 (37%)</td>
<td>7 (30%)</td>
<td>10 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Inclination of the cups, [°]</td>
<td>41.2 ± 6.2</td>
<td>40.8 ± 3.0</td>
<td>41.7 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Head size S / M / L / XL, n</td>
<td>7 / 11 / 29 / 2</td>
<td>2 / 5 / 16 / 2</td>
<td>5 / 6 / 13 / -</td>
<td>NS</td>
</tr>
</tbody>
</table>

Plus-minus values are mean ± SD.

a Mann-Whitney U test.  b Fisher Exact test.  c Chi-square test.  d NS P > 0.05 for comparisons between randomization groups.

d n=25 in ZOL and n=24 in CTR.  e An alternative cup system had to be implanted in 3 patients (2 in ZOL, 1 in CTR; n=23 in each randomization group).
Results

2.1 Migration Analysis - Stems

Median follow-up 2.8 yrs
Results

2.2 Migration Analysis - Cups

Median follow-up 2.8 yrs
## Results

### 3.1 Harris Hip Rating Scale

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>CTR</th>
<th>ZOL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HHS</td>
<td>Range</td>
</tr>
<tr>
<td>Baseline</td>
<td>31</td>
<td>9 – 55</td>
</tr>
<tr>
<td>7 weeks</td>
<td>86</td>
<td>75 – 100</td>
</tr>
<tr>
<td>6 months</td>
<td>88</td>
<td>78 – 100</td>
</tr>
<tr>
<td>1 year</td>
<td>92</td>
<td>76 – 100</td>
</tr>
<tr>
<td>2 years</td>
<td>96</td>
<td>87 – 100</td>
</tr>
<tr>
<td>3 years(^b)</td>
<td>96</td>
<td>87 – 100</td>
</tr>
</tbody>
</table>

ANOVA on ranks: CTR versus ZOL: P=0.008

Values of Harris hip score (HHS) are median values. IQ: 25%-75% interquartile range.

\(^a\) Mann-Whitney U test; \(^b\) Median follow-up was 2.8 years, last value was carried forward
Results
3.2 Side Effects / Complications

Surgery/Implants

- One revision surgery because of recurrent dislocations
  → excluded (CTR)
- No complications related surgery
- No case of impending loosening during follow-up

Study Medication

- Fairly well tolerated
- No serious adverse event
- “flue-like” symptoms with increase of +1.7°C ± 0.6 SD for < 2 days:
  in ZOL: 14 of 25 (56%)
  in CTR: 3 of 25 (12%)
Results
3.3 Analysis of Covariance

- No influence of age on cup migration
- Outcome was not affected by other covariates (i.e., risk factors of ON-FH, Gender, BW, BMI)
Discussion

1.1 Histogram – Subsidence at 2 yrs

Krismer et al., 1999, JBJS Br. EBRA of 158 stems at 2 yrs

→ Subsidence of ≥ 1.5 mm

Sens 69% / Spec 80% for aseptic loosening at mean fu of 10 years

9/24 (CTR) vs 3/25 (ZOL)
P < 0.05, Fisher Exact Test
Discussion

1.2 Histogram – Total Migration of Cups at 2 yrs

Krismer et al., 1996, JBJS Br.
EBRA of 102 cups at 2 yrs
→ Migration of ≥ 1.0 mm
Sens & Spec > 80% for aseptic
loosening at mean fu of 8.7 years

12/23 (CTR) vs 4/23 (ZOL)
P < 0.05, Fisher Exact Test
Summary

- ZOL was safe, but frequently caused “flue-like” symptoms
- Single-dose ZOL \(\rightarrow\) significant effects on implant migration

<table>
<thead>
<tr>
<th>Implant Migration (CTR)</th>
<th>Cups</th>
<th>Stems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of ZOL</td>
<td>Reached plateau phase</td>
<td>Slowed down, but continued</td>
</tr>
<tr>
<td>Age</td>
<td>Prevented migration</td>
<td>Diminished migration</td>
</tr>
<tr>
<td></td>
<td>Not influenced</td>
<td>Related to age</td>
</tr>
</tbody>
</table>

- Some positive effect on clinical outcome (HHS)
- JBJS Am.; Feb 2009; 91:274-81
Conclusion

A single infusion of ZOL was found to improve initial fixation in cementless THA and shows therefore promise as treatment adjunct in an effort to reduce implant failure in the long term.

Prospective long-term studies needed.
Acknowledgement

- Mag. Barbara Primus and Mag. Dr. Marianne Leitner
  Clinical Pharmacy
  University Hospital of Graz

- Christa Barowitsch
  Laboratory Core Unit
  University Hospital of Graz

- Silvia Ulz and Cornelia Wiedner
  University Clinic of Orthopaedic Surgery