Bone recovery after zoledronate therapy in thalassemia-induced osteoporosis: a meta-analysis and systematic review

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CRD summary
The authors concluded that zoledronate was a promising bisphosphonate that improved bone mineral density in thalassemia-induced osteoporosis, but that more research is required to understand its potential adverse effects. The review suffered from poor reporting and had potential methodological weaknesses, including the uncertain quality of included trials, which limits the reliability of the authors’ conclusion.

Authors' objectives
To evaluate the effectiveness of zoledronate for the treatment of thalassaemia-induced osteoporosis.

Searching
MEDLINE, EMBASE, and CINAHL were searched for published studies. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of zoledronate for the treatment of thalassaemia-induced osteoporosis in thalassaemic patients were eligible for inclusion.

The included RCTs all defined osteoporosis as low bone mineral density in at least one site including lumbar spine, femur neck, wrist, trochanter, total hip and whole body. Patients received zoledronate at a dose of 4mg every three or six months for one year. The co-interventions included calcium supplementation, vitamin D supplementation, and hormone replacement therapy. The age of participants ranged from 23 to 44 years. Baseline lumbar spine bone mineral density values ranged from -2.77 to -3.30.

The authors did not state how many authors undertook the selection process.

Assessment of study quality
The authors did not state if quality assessment was undertaken.

Data extraction
Data was extracted on the change from baseline bone mineral density at one-year and used to calculate standardised mean differences (SMD) together with 95% confidence intervals (CIs). Data on markers of bone turnover, pain, and adverse events were also extracted.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The pooled standardised mean differences and 95% confidence intervals were calculated using Hedges’ g transformation random-effects meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic. Publication bias was assessed using funnel plot analysis and Egger’s test.

Results of the review
Four RCTs were included in the review (n=103 patients). The sample size of included trials ranged from 12 to 29 patients. The length of follow-up ranged from nine to 12 months. There was no evidence of publication bias.

Bone mineral density: There was a statistically significant improvement in femur neck bone mineral density with zoledronate at follow-up compared with baseline (SMD 0.41, 95% CI 0.09 to 0.74; three trials; $I^2=0\%$). There was also a statistically significant improvement in lumbar spine bone mineral density with zoledronate at follow-up compared...
with baseline (SMD 0.91, 95% CI 0.61 to 1.20; four trials; \(I^2=77\%\)). In both the femur neck and the lumbar spine there was a statistically significant improvement in bone mineral density with zoledronate at follow-up compared with baseline (SMD 0.69, 95% CI 0.47 to 0.90; four trials; \(I^2=67\%\)). There was no statistical difference in zoledronate at follow-up in the other body sites; the authors did not show these results. Subgroup analysis revealed that when zoledronate was given every three months, the benefit in terms of bone mineral density was sustained (SMD 0.74, 95% CI 0.50 to 0.97; four trials).

**Markers of bone turnover:** The authors reported that zoledronate decreased markers of bone resorption, bone formation, and other markers. Markers of osteoclast function were inconclusive.

**Pain:** Two trials reported a reduction in pain with zoledronate at follow-up compared with baseline.

**Adverse events:** There were no reports of atrial fibrillation in any of the trials. One trial reported an acute cardiac death.

**Authors’ conclusions**
Zoledronate (4mg every three months) was found to be a promising bisphosphonate that improved bone mineral density in thalassemia-induced osteoporosis, but more evidence is required to understand the mechanisms of its actions and side-effects.

**CRD commentary**
The research question was clear, supported by brief inclusion criteria for study design, patient population and intervention. The search strategy was limited to published studies, which could have introduced publication bias into the analysis. Search dates were not reported. The authors did not state how many reviewers performed study selection and data extraction or if a quality assessment was undertaken, which could be poor reporting or could indicate limitations in the review methodology.

A random-effects meta-analysis was undertaken and statistical heterogeneity was explored, but the sample size of the included trials was small and trial quality was not reported, which raised questions as to the reliability of the results. Also, the authors appeared to combine data from the same patients more than once in the meta-analysis, which artificially increased the sample size of the analysis.

Overall, the review suffered from poor reporting and had potential methodological weaknesses, which limits the reliability of the authors’ conclusion. The authors call for more research seems justified.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that larger studies with longer follow-up are needed to more fully understand the potential adverse effects of zoledronate.

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