CORRESPONDENCE

Safety of Zoledronic Acid in Patients with Thalassemia Associated Low Bone Mineral Density

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To the Editor,

Zoledronic acid (ZA) is effective in thalassemia associated low bone mineral density [1–3]. We have recently documented 75–100% incidence of osteoporosis in Indian patients with thalassemia [4].

We performed a prospective study to assess the safety of ZA in patients with transfusion dependent thalassemia with osteoporosis/osteopenia. The Institute's ethics committee approved the study. Twenty-seven patients (17 males) with median age of 18 years (16–38 Years) were enrolled. All patients were receiving 500 mg of calcium carbonate twice daily and 0.25 µg alfacalcidol once daily. Reconstituted ZA diluted with 100 ml of 0.9% w/v sodium chloride solution was given as a 15-min intravenous infusion.

With first dose of 4 mg ZA, 4 patients developed grade 4 hypocalcemia and 3 developed tetany (Table 1). All 4 patients were treated with intravenous calcium gluconate. Joint swelling with pain and fever were present in another patient, which started 24 h after the drug injection. Fever subsided the same day. Pain resolved in 4 days. She was given paracetamol for pain relief. Joint swelling resolved

after 11 days. There is no residual joint deficit. There was no recurrence with repeat dose. Another girl developed fever with chills and joint pains which resolved with paracetamol. Joint symptoms abetted in 8–10 h and fever resolved after 36 h. She reported excessive sleepiness with the second dose. This lasted for 2 days. She refused further doses.

After these adverse effects, an in-house (departmental faculty) committee reduced dose of ZA to 1 mg as one study had already shown efficacy of 1 mg ZA in thalassemia associated osteoporosis [2]. Girl with hypoparathyroidism was not administered any further doses of zoledronic acid. Other 3 patients with hypocalcemia, however, received further doses at 1 mg.

All new enrolled (18) patients were subsequently given 1 mg ZA. There were no episodes of hypocalcemia after 1 mg ZA dose in these and any of the subsequent patients enrolled. After the revised schedule of 1 mg dose, one patient developed body pain and fever after 10–12 h after the dose. The symptoms lasted for 5–6 h and responded to paracetamol. There was no recurrence with repeat doses. Another girl developed nausea and dizziness after the second dose. The symptoms started 8 h after the injection and lasted for about 6 h. Remaining all patients tolerated the drug well. Zoledronic acid was efficacious even at 1 mg dose and data is being reported separately.

Diffuse bone pain and fever lasting <24 h after the first infusion of ZA were reported by Voskaridou et al. [3] in 9 and 20% patients, respectively. Otrock et al. [1] reported joint pain in 50% patients after the first dose and in 11.1% after the second dose. They did not observe any episode of hypocalcemia. Perifanis et al. [2] used 1 mg dose and no side effects were noted at this dose.

There are anecdotal reports of patient developing symptomatic hypocalcemia following IV administration of ZA in myeloma patients [5] but have not been reported in

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Table 1 Hypocalcemia and tetany in thalassemia patients after 4 mg zoledronic acid

Patient	Age/gender	Calcium	Symptoms	Parathyroid	Comment
1.	21 Year/F	5.6 mg/dl	Tetany of hands started 12 h after the infusion and continued intermittently for 6 days	Hypoparathyroidism	No further doses
2.	22 Year/F	4 mg/dl	Tetany 24 h after infusion and continued for 3 days despite therapy	Normal parathyroid	Further dose 1 mg
3.	19 Year/M	6.2 mg/dl	Tetany of left hand 24 h after the injection. Symptoms lasted for 2 days	Normal parathyroid	Further dose 1 mg
4.	17 Year/M	4 mg/dl	Asymptomatic He required intravenous calcium gluconate for 5 days.	High parathyroid HIV	Further dose 1 mg

patients with thalassemia. In most of the published reports, apart from nutritional deficiency of Vitamin D, impaired renal function had been sighted as the main reason for development of symptomatic hypocalcemia. Significant adverse effects in our patients at 4 mg dose could be due to high prevalence of Vitamin D deficiency in our population, unmasking hypoparathyroidism and lower mean weight of our patient population (44 vs 57 kg in another study) [1].

We conclude that zoledronic acid produces significant adverse effects at 4 mg dose and is safe at 1 mg dose in patients with thalassemia associated low bone mineral density.

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Compliance with Ethical Standards

Conflict of interests All the authors declares that they have no conflict of interests.

Informed Consent Informed consent was obtained from all individual participants included in the study. This was part of DM thesis.

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