

MANAGEMENT OF THALASSAEMIA-INDUCED OSTEOPOROSIS

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Prevention and general principles: Prevention and treatment of early bone loss consists the best policy. Annual checking of BMD starting in adolescence is considered indispensable. Physical activity must always be encouraged. Moderate and high impact activities are to be supported. Exercise has additional benefits: it improves cardiovascular system, reduces the risk of diabetes and prevents depression. Smoking should be discouraged. Adequate calcium and zinc intake during skeleton development can increase bone mass in adult life and in combination with administration of low doses of vitamin D, may prevent bone loss and fractures (Lasko *et al*, 2001). Early diagnosis and treatment of diabetes mellitus is also important, as the association between diabetes and low bone mass in TM patients has been well documented (Jensen *et al*, 1998). Adequate iron chelation may prevent iron toxicity in the bone and sufficient blood transfusions may inhibit uncontrolled bone marrow expansion.

Hormonal replacement: Prevention of hypogonadism seems to be the most effective way for preventing osteoporosis and other bone deformities in TM patients (Jensen *et al*, 1998). Continuous hormonal replacement therapy with transdermal oestrogen for females or human chorionic gonadotrophin for males improves bone density parameters (Anapliotou *et al*, 1995).

Calcitonin: It's a potent inhibitor of osteoclasts. It has evaluated the effect on bone mass in 14 patients with TM (100 IU x 3/w x 1 year) in combination with 250 mg calcium daily. At the end of treatment period, bone pain had disappeared, radiological findings of osteoporosis had been improved and the number of fractures had been

decreased in the treatment group but not in controls. CT had no important side effects (Canatan *et al*, 1995).

Hydroxyurea: Ten patients with TM were given hydroxyurea (1.5 g per os daily), in an attempt to reduce marrow hyperplasia diagnosed by MRI. Hydroxyurea improved bone pain and MRI findings (Angastiniotis *et al*, 1998). However, these results have not been confirmed by other studies.

Bisphosphonates: The increased bone resorption observed in patients with thalassaemia-induced osteoporosis has led to the use of bisphosphonates in the management of osteoporosis in this cohort of patients. Bisphosphonates are potent inhibitors of osteoclastic bone resorption. They act by inhibiting osteoclastic recruitment and maturation, preventing the development of monocyte precursors into osteoclasts, inducing osteoclast apoptosis and interrupting their attachment to the bone (Suda *et al*, 1997). In thalassaemia osteoporosis, almost all generations of bisphosphonates have been used in an attempt to increase the BMD and improve the abnormal bone remodelling. Morabito *et al* (2002) investigated the effects of two years daily oral administration of alendronate or intramuscular administration of clodronate on BMD, bone turnover markers, safety and tolerability in 25 thalassaemia patients with osteoporosis. After two years of follow-up, the lumbar spine and femoral neck BMD had decreased significantly in the placebo group. Clodronate reduced bone resorption markers, deoxypyridinoline and pyridinoline, and inhibited bone loss but it was unable to increase BMD at all studied sites. Daily treatment with alendronate normalised the rate of bone turnover, and resulted in a rise in BMD of the spine and the hip. The ineffectiveness of clodronate was also confirmed by Pennisi *et al* (2003).

Pamidronate, a second generation aminobisphosphonate, was firstly given by Wonke (2001) at doses ranged between 15 mg and 60 mg, in a 40 minutes infusion, at monthly intervals. A significant improvement in BMD was observed in most patients. Our group compared the effects of two different doses of pamidronate, 30 mg vs. 60 mg, on BMD of the lumbar spine, the femoral neck and the forearm and on markers of bone remodelling and osteoclast function in 26 patients with thalassaemia and

osteoporosis. Thirteen patients with thalassaemia major and 5 patients with thalassaemia intermedia were given pamidronate at a dose of 30mg in a two hour iv infusion, once a month for 12 months; another 8 patients (4 with thalassaemia major and 4 with thalassaemia intermedia) received a dose of 60 mg/month, in an attempt to explore whether increasing the dose of pamidronate might have any additional effect. The intravenous was preferred against to oral administration to override the problem of gastrointestinal malabsorption of oral bisphosphonates, which is less than 10%, and it is further reduced by food containing milk or iron. Both groups included patients with comparable degrees of osteoporosis and hypogonadism. All patients were also receiving calcium, and vitamin D supplement prior and during the 12-month follow-up period of the study. Administration of 30 mg of pamidronate resulted in a significant increase of the BMD of the lumbar spine in all patients, but not the BMD of the femoral neck and the forearm. The 60 mg of pamidronate group showed a similarly significant increase in the BMD of the lumbar spine in both transfusion dependent and transfusion independent patients. Administration of both doses of pamidronate was also followed by a clear decrease of markers of bone resorption (NTX, and TRACP-5b), OPG, and osteocalcin that was similar in patients of both treatment groups. Furthermore, most patients complaining for severe bone pain at the onset of the study had a significant reduction of pain after treatment period. No severe adverse-events were reported in this study (Voskaridou *et al*, 2003).

In another recent study, 29 patients with transfusion-dependent beta-thalassaemia and severe osteoporosis were given zoledronic acid, the most potent third generation bisphosphonate to-date, at a dose of 1 mg intravenously every 3 months over 12 months period. All patients were also receiving calcium and vitamin D supplement prior to and during the study. Administration of zoledronic acid was followed by a clear increase in the BMD of the lumbar spine, as well as by a significant decrease in IGF-1 and a significant increase in OPG serum levels. No treatment-related side-effects were observed in this study (Perifanis *et al*, 2004).

These studies confirm the effectiveness of bisphosphonates in the treatment of thalassaemia-induced osteoporosis. Alendronate, pamidronate and zoledronic acid

seem to have the greater efficacy. However, more trials must be conducted in order to clarify the exact role of each biphosphonate, the long-term benefit and side-effects as well as the effects of the combination of bisphosphonates with other effective agents, such as hormonal replacement, in thalassaemia-induced osteoporosis.

CONCLUSION

Thalassaemia-induced osteoporosis is multifactorial and therefore, very difficult in its management. Adequate hormonal replacement, effective iron chelation, improvement of haemoglobin levels, calcium and vitamin D administration, physical activity, and no smoking, consist the main to-date measures for the management of the disease. However, novel pathogenetic data suggest that the reduced osteoblastic activity, which is believed to be the basic mechanism of bone loss in TM, is accompanied by a comparable or even greater increase in bone resorption, through the RANK/RANKL/OPG pathway. Therefore, the role of bisphosphonates, that are potent inhibitors of osteoclast activation, arises as major in the management of osteoporosis in these patients. However, many aspects have to be clarified before the broad use of bisphosphonates in TM-induced osteoporosis: which one? how long? and at what dose? The combination of bisphosphonates with other effective agents has also to be evaluated in randomised trials. Other novel agents that stimulate bone formation such as teriparatide, a recombinant peptide fragment of parathyroid hormone, strontium ranelate, a second anabolic agent, that seem to prevent osteoporotic fractures in postmenopausal women, are being studied but their effects in TM-induced osteoporosis remains to be proven. Finally, recombinant OPG, and anti-RANKL, which reverses osteopenia in ovariectomised mice and reduces osteoclast activation in humans with myeloma and breast cancer bone disease may be another future agent that may help in the management of this difficult complication of thalassaemia.