British Journal of Medicine & Medical Research
1(4): 478-485, 2011

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Metabolic Characterization and Follow up of Adult Patients Affected by Osteogenesis Imperfecta in Long-term Treatment with Neridronic Acid

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Research Article

Received 10th July 2011
Accepted 14th August 2011
Online Ready 23rd September 2011

ABSTRACT

Aims: Osteogenesis imperfecta (OI) is a rare inherited disorder causing low bone density and increased fragility. Bisphosphonates (BP) are a treatment of choice for OI. Few studies have investigated the long-term effects of BP in OI patients. Thus, aim of our study was to follow up adults affected by OI to evaluate changes in metabolic, clinical situation and safety of long-term neridronic acid therapy, BP authorized for OI treatment.
Study design*:* Longitudinal observational study.
Place and duration of the Study: Department of Experimental Medicine, Section of Medical Pathophysiology, Endocrinology and Nutrition. Year: 2004 - October 2010.
Methodology*:* 68 patients underwent clinical examination, laboratory endocrine/ metabolic, pro-inflammatory cytokines screening, ECG at baseline and every 3 months and bone mineral density evaluation, by DEXA, once a year.
Results: Skeletal evaluation showed a significant increase of BMD through follow up.

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Patients were evaluated for metabolic and cardiovascular risk factors, which were unmodified by long-term therapy.
Conclusion*:* Long-term neridronic acid treatment increases bone density, does not alter metabolic parameters indicating that this therapy can be considered safe and a valid therapeutic option for OI patients.

Keywords: Osteogenesis imperfect; metabolic markers; skeletal markers; neridronic acid; BMD;

1. INTRODUCTION

Osteogenesis imperfecta (OI) is a rare inherited disorder causing increased bone fragility and low bone mass resulting from mutations in the gene encoding Type I collagen pro-α and pro-α2 chains (Rauch and Glorieux, 2004; Sykers et al., 1990). However, in most case the mutation is unknown and diagnosis is made radiologically and by clinical assessment (Rauch and Glorieux, 2004). OI belongs to a group of severe connective disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, in which symptoms are mainly due to alteration in the connective tissue, due to collagen type I damage, leading to the presence of different alterations and symptoms (Grahame, 2000). OI includes severe bone fragility, impaired dentinogenesis, blue sclerae, hearing loss, with less common alterations in the joints, tendons lassity, cardiovascular system, blood vessels, heart valves, diastolic function and skin.

The severity of clinical features of OI is highly heterogeneous, ranging from neonatal lethality to individuals with skeletal deformities, altered mobility, short stature to nearly asymptomatic individuals with a mild increased risk of bone fractures, normal stature, and normal lifespan. OI includes fractures with minimal or absent trauma, due to severe bone fragility (Adami et al., 2003; Monti et al., 2010; Wong et al., 1995). Furthermore, left ventricular rupture, aortic dissection and heart valves incompetence have been described and death can occur in asyntomatic patients for cardiac failure (Shapiro, 2010).

Indeed, we have previously described that OI patients, even without cardiac symptoms, have an impaired diastolic function, assessed by echo-doppler examination showing both a reduction of E/A ratio and a significant prolongation of IRT and DT (Migliaccio et al., 2009).

Nevertheless, the hallmark of the disease is bone fragility, due to generalized osteopenia, and recurrent bone fractures and deformities are major complications of the disease. A variety of agents (anabolic steroids, sodium fluoride, growth hormone, magnesium oxide, and calcitonin) have been used to increase bone mass and to reduce the frequency of fractures (Sykers et al., 1990), but none have reduced the complications of the disease (Sykers et al., 1990). Bisphosphonates (BP), synthetic analogues of naturally occurring inorganic pyrophosphate (Drake et al., 2008), have been commonly used and considered to be the treatment of choice for moderate to severe OI (Drake et al., 2008; Rauch and Glorieux, 2004; Munns et al., 2005). The rationale of BP treatment in OI is the predominantly inhibitory effect on osteoclasts, leading to a net effect of increased bone

mass in OI patients (Grahame, 2000; Drake et al., 2008; Rauch and Glorieux, 2004; Munns et al. 2005).

Since few studies have investigated the effects and safety of long-term BP treatment of patients with OI, aim of our study has been to characterize and follow up adults patients, in long-term treatment with neridronic acid, a BP authorized for the treatment of this disease, to evaluate potential metabolic changes and worsening of the clinical situation.

2. MATERIAL AND METHODS

2.1 Patient Characteristics

Sixty eight patients (27 men and 41 women) affected by type I, III, and IV OI have been evaluated for the study. All patients have been admitted to the Day Hospital of Department of Experimental Medicine of the Policlinico Umberto I of Rome, for the diagnosis, treatment and follow up. Patients were evaluated at baseline (demographic characteristics in Table 1) and every three months, at the time of therapy infusion, for five years, from 2004 through October 2010. The study abides by the rules of our Internal Review Board and the tenets of the Helsinki protocol. Written consent form was obtained for each patient enrolled in the study.

Patients underwent complete medical history, physical examination (weight, height, heart rate, blood pressure), laboratory analysis for the screening of endocrine/metabolic disorders (blood cells count, coagulation assessment, liver and renal function parameters, lipid profile, homocysteinemia, glucose metabolism, calciotropic hormones, bone turnover markers, complete hormonal assessment), 12-lead electrocardiogram (ECG), echocardiographic evaluation, and bone mineral density (BMD) evaluation, hearing function, neurological function, and orthopaedic evaluation at baseline as also described elsewhere (Migliacco et al., 2009).

In patients with low bone mineral density, thus at high risk for fracture, were prescribed BP therapy. Every three months, patients received treatment with neridronic acid infusion (2 mg/kg i.v.) and underwent physical examination, laboratory analysis and ECG, as above described, while, once a year all patients underwent a complete clinical follow up. Biochemical parameters were measured by standard methods as previously published elsewhere (Migliaccio et al., 2009), while cytokines were evaluated at the laboratory of the Department of Health Sciences at the University of Foro Italico. Mean age and other clinical parameters of OI patients are shown in Table 1.

All the data collected were verified from medical records of the patients.

2.2 Methods

Bone mineral density was evaluated by Dual-Energy-X-Ray Absorptiometry (DXA) (Hologic 4500 RDR). Several cytokines and adipokines (adiponectin, adipsin, c-peptide, ghrelin, GLP-1, GIP, glucagon, insulin, leptin, PAI-1, resistin) were measured using the Bio-plex suspension array system (Bio-Rad).

2.3 Statistical Analysis

Clinical and biochemical data were compared before and after treatment. Data are expressed as means ± standard error (SEM). Kolmogorov-Smirnov test has been used to test the parameter distribution. Paired t-test and Wilcoxon test (for parametric and non-parametric distributed parameters, respectively) have been used to test the parameter changes during the study. A p value <0.05 was taken as statistically significant.

All OI patients are followed in our day hospital and monitored for bone and other systemic disorders. As previously demonstrated by Adami (Adami et al., 2003) and collaborators neridronic acid induced a significant increase in BMD levels in short-term treatment. Our data showed that neridronic acid increased vertebral BMD beginning 12 months of therapy and reached statistically significant difference after 24 months of therapy at lumbar site (Figure 1) and slowly increased through all the treatment period (5 years). Femural BMD increased as well but in a less significant manner (baseline Tscore -1,89±1,6 ; Tscore -1.6 ±0.6, 5 yrs).

Additionally, record of fractures was collected for each subject through the follow up period: interestingly only 4 patients experienced additional fracture: one for a car accident, two had a traumatic wrist fracture and one had traumatic humerus fracture.

Moreover, all patients were screened for endocrine and metabolic disorders at baseline and parameters were then evaluated every year. No specific modifications were found in either metabolic or endocrine parameters at baseline or during the period of infusion with neridronic acid (Table 2). However, as expected bone specific markers such as alkaline phosphatase decreased over time with a max effect between the 1° and 2° year of treatment to remain stable throughout the period of follow up (Table 2). OI patients had Vitamin D in the low range, but no alterations were found in PTH values or in either total and ionized calcium levels (Table 2).

Since our previously data (Migliaccio et al., 2009) showed significant alterations in heart parameters as measured by cardiac ultrasound, we also evaluated potential alterations in cardiovascular risk factors such as lipid, glicemic and homocystein levels. No changes were found over time in the metabolic parameters (Table 2) in OI patients treated with bisphosphonates for 5 yrs. Interestingly, fibrinogen levels decreased over time, without however reaching statistically significant changes (Table 2). No significant alteration was found in cytokines levels among those evaluated (data not shown). Homocysteine levels were found to be higher in a subset of patients whom were prescribed folic acid supplementation which, as expected, maintained homocysteine within normal levels.

OI impairs collagen type I metabolism, and subjects affected have a decreased amount of this protein, leading to alteration of several tissue homeostasis but the hallmark of this disease is significant low BMD and severe bone fragility, leading to frequent spontaneous or traumatic fractures (Grahame, 2000; Drake et al., 2008; Rauch and Glorieux, 2004).

Pharmacological treatment should always be considered as part of a coordinated multidisciplinary approach to the treatment of patients affected by OI, including timely corrective surgery, physiotherapy, occupational and physical activity. Until a gene therapy aimed to either replacement or silencing of the mutant allele is feasible (Cheung and Glorieux, 2008), the causal defect of the disease cannot be corrected. At present, ‘symptomatic’ therapeutical options are available since medical therapy to treat the causal

defect is not as yet possible. The goals of pharmacological therapy in OI are: increase in BMD and increase in bone strenght; decrease in the incidence of fractures; decrease of pain; and finally an increase of mobility and independence of these subjects (Phillipi et al., 2008).

Also, several different physical exercises might be appropriately designed by specialized trainers in order to increase skeletal and joints mobility. However, several obstacles must be considered when evaluating a physical activity including prior fracture history, degrees of bending of long bones, degree of muscle weakness, joint stiffness or laxity (looseness), joint alignment, poor exercise tolerance. For instance, long-term sitting in a wheelchair may be associated with hip flexion contractures and compensatory back curvatures, often associated with back pain, joint stiffness, osteoporosis, and obesity.

In terms of pharmacological approach, BP have been demonstrated to be the first choice therapy in patients affected by OI and their activity, which result in suppression of bone turnover, result in improved vertebral shape and mass, increased cancellous bone volume as also shown by previous histomorphometric studies (Drake et al., 2008). Our data demonstrate that indeed BPs can be considered a safety choice which increases BMD in OI patients, without altering other metabolic parameters, which might be critical in these subjects to avoid potential worsening of cardiological and/or metabolic risk factors (Migliaccio et al., 2009).

In conclusion, our present study indicate that a long-term neridronic acid treatment of patients induces a persistent increase in BMD, does not alter metabolic parameters, is safe and well-tolerated and, in the context of a multidisciplinary evaluation, BP therapy, along with appropriate physical exercise, can be considered a valid therapeutic option for patients affected by osteogenesis imperfecta.

Table 1: Demographic characteristics of patients

Patients number	68
Sex (male-female)	27-41
Age (mean age)	34±7,5
Weight (Kg)	57,11±17
Height (cm)	153±17
Lumbar T score	-3,26±1,50
Lumbar BMD (gr/cm2)	0,75±0,17
Femoral T score	-1,4±1,12
Femoral BMD (gr/cm2)	0,82±0,17
Neck T score	-1,89±1,6
Neck BMD (gr/cm2)	0,62±0,21

Table 2: Metabolic and bone turnover markers

	Baseline	12 months	24 months	36 months	48 months	60 months	p
Fibrinogen	314±69	300±62	295±45	281±51	285±47	290±48	ns
T Cholesterol	200±42	190±35	207±42	205±37	203±35	205±37	ns
LDL	123±29	122±30	115±26	145.22±37	125.89±34	130.00±29	ns
Tryglicerydes	119±76	109±49	126±52	117±52	122±53	130±56	ns
HDL	46.66±9	45.82±12	45.08±12	45.49±14	48.39±13	45.10±11	ns
Total Ca	9,34±0,41	9,28±0,38	9,31±0,52	9,07±0,5	9,53±0,38	9.35±0.42	ns
Ca ++	1,23±0,03	1,23±0,04	1,22±0,04	1,20±0,05	1,23±0,04	1.22±0.05	ns
Vitamin D	21.05±9.4	24,07±9.1	22.01±9.8	26.13±9.7	24.10±7	25.58±6.7	ns
Phosphorus	2.98±0.58	3.03±0.48	3.13±0.54	3.03±0.56	3.17±0.45	2.85±0.28	ns
Homocysteine	10±6	9±4	10±4	9±3	10±3	10±2	ns
PTH	32.25±14	32.07±15	32.82±15	32.84±15	32.6±12	31.83±14	ns
Alkaline Phosphatase	167,22±52	145,06±47*	126,41±39**	99,46±34***	83,58±30***	75,68±22***	*p<0,01 **p<0,001 ***p<0,0001
Bone Alkaline Phosphatase	30,74±11	25,91±9*	20,88±7**	16,70±5***	16,88±5***	15,99±6***	*p<0,01 **p<0,001 ***p<0,0001

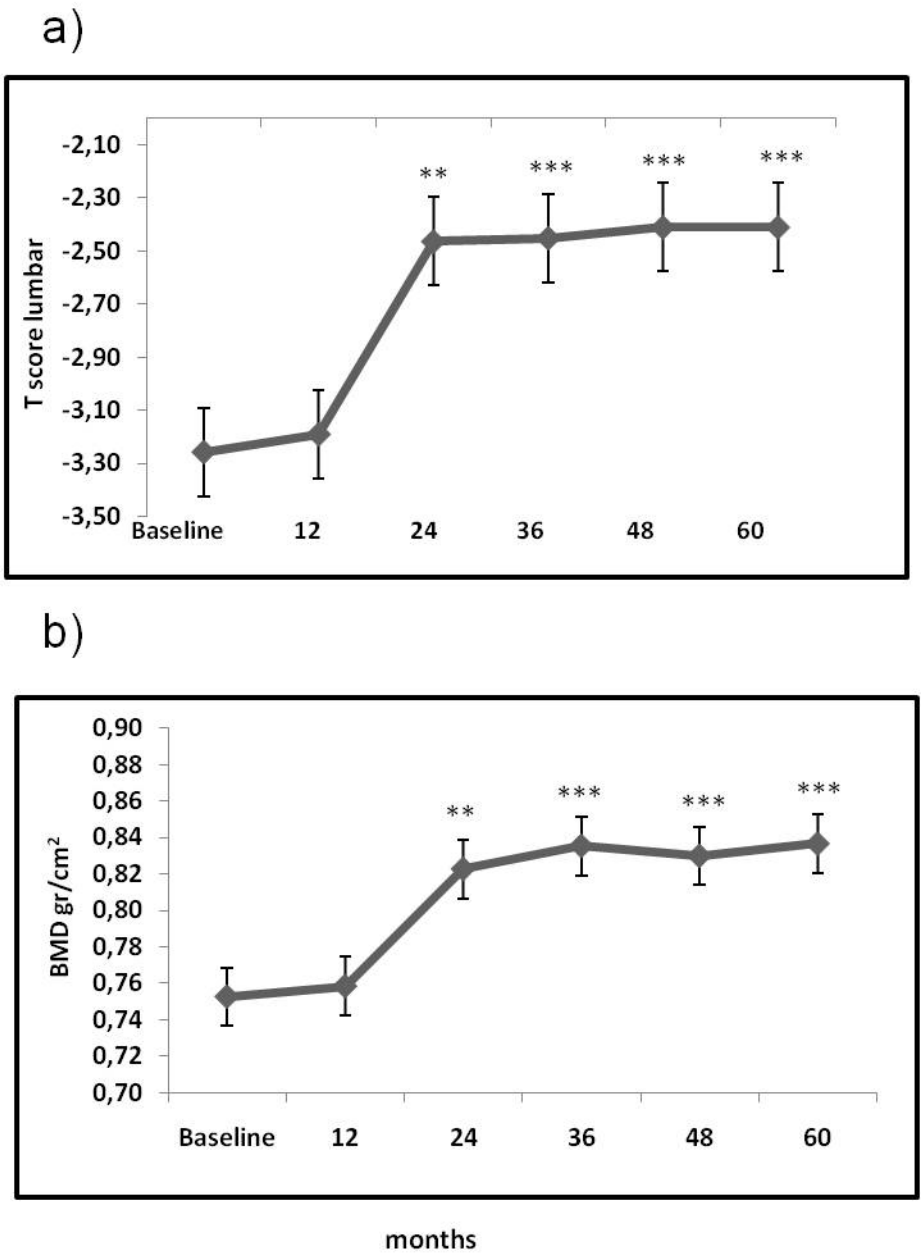

Figure 1: Modification of BMD and Tscore at vertebral site as measured by DEXA.

Data are expressed as mean ± SEM.

4. CONCLUSION

The results of our study indicate that long-term neridronic acid treatment increases BMD, reducing fracture risks, does not alter metabolic parameters indicating, in the context of a

multidisciplinary evaluation, that this pharmacological therapy can be considered safe and a valid therapeutic option for patients affected by OI.

REFERENCES

Adami S., et al. (2003). Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res., 18, 126–130.

Cheung, M.S., Glorieux, F.H. (2008). Osteogenesis Imperfecta: update on presentation and management. Rev Endocr Metab Disord., 9, 153-60.

Drake, M.T., et al. (2008). Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc., 83, 1032-45.

Grahame, R. (2000). Heritable disorders of connective tissue Baillieres Best Pract Res Clin Rheumatol., 14, 345-61.

Ichikawa, H. et al. (1996). Left ventricular rupture following aortic and mitral valve replacement in a patient with osteogenesis imperfecta: a case report. Kyobu Geka., 49,294-6.

Migliaccio, S., et al. (2009). Impairment of diastolic function in adult patients affected by osteogenesis imperfecta clinically asymptomatic for cardiac disease: casuality or causality? Int J Cardiol., 131, 200-3.

Monti, E. et al. (2010). Current and emerging treatments for the management of osteogenesis imperfecta. Ther Clin Risk Manag., 6, 367-81.

Munns, C.F., et al. (2005). Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. J Bone Miner Res., 20, 1235–1243.

Phillipi, C.A., et al. (2008). Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev., 8, 4-8.

Rauch, F., Glorieux, F.H. (2004). Osteogenesis imperfecta. Lancet., 363, 1377-85.

Shapiro, J.R. (2010). Bone mineral density and fracture rate in response to intravenous and oral bisphosphonates in adult osteogenesis imperfecta. Calcif Tissue Int., 87, 120-9.

Sykers, H., et al. (1990). Consistent linkage of dominantly inherited osteogenesis imperfecta to the type of collagen loci: COL1A1 and COL1A2. Am J Hum Genet., 46, 293-307.

Wong, R.S., et al. (1995). Osteogenesis imperfecta and cardiovascular diseases. Ann Thorac Surg., 60, 1439-43.