Ibandronat in the Therapy of Osteoporosis in Turner Syndrome

DANA MARIA ALBULESCU[1], ADELINA SMARANDA PREDA[2], ADRIAN CAMEN[3]*, NINA IONOVICI[4]

[1]University of Medicine and Pharmacy of Craiova, Department of Anatomy, 2 Petru Rares Str., Craiova, Romania

[2] University of Medicine and Pharmacy of Craiova, 2 Petru Rares Str., Craiova, Romania

[3]University of Medicine and Pharmacy of Craiova, Department of Oro-Maxilo-Facial Surgery, 2 Petru Rares Str., Craiova, Romania

[4] University of Medicine and Pharmacy of Craiova, Research Center for Microscopic Morphology and Immunology, 2 Petru Rares Str., Craiova, Romania

Turner syndrome represents a condition that associates diverse pathology with somatic, metabolic (diabetes), cardio-vascular, digestive, respiratory and bone involvement along with chromosomal abnormalities. In our study we have analyzed the bone pathology that occurs in Turner syndrome and the response in the therapy with ibandronat. The decrease in value of the bone turn-over biomarkers and the decrease of the T score after the administration of ibandronate p.o. in a monthly dosage demonstrates the efficiency of this bisphosphonate in the treatment of the osteoporosis secondary to sexual hormone deficiency in Turner syndrome.

Keywords: ibandronat, osteoporosis, Turner syndrome

Turner syndrome is characterized by chromosomal abnormalities linked to the total or partial absence of the X chromosome. Various types of karyotypes and phenotypes can coexist. [1] Nowadays this syndrome's prevalence is 1/2000 in female newborns [2].

The osteoporosis and osteopenia are reported by other studies in a proportion of 2/3 of the women that have Turner syndrome. It is believed that the bone density alterations are associated with the ineffective estrogen treatment for the gonadal dysgenesis. The risk for fractures secondary to osteoporosis is also reported in certain studied. [2,3].

In order to appreciate the degree of osteopenia or osteoporosis, bone turn-over biomarkers dosing and DEXA are used.

The administration of anti-resorptive agents is the pharmacological therapy used in Turner syndrome. Ibandronat or acid ibandronic is a part of the bis-phosphonates class with molecular formula $C_9H_{23}NO_7P_2$ and can be administered orally, daily, in a dosage of 2.5 mg or a single dose of 150 mg per month, orally. The purpose of associating estrogen therapy, growth hormone therapy and thyroid hormonal substitution therapy is to reduce osteoporosis. It is well known that estrogen deficiency has several effects upon the structure of the bone: a profound, accelerated and irreversible decrease in bone density through the increase of the frequency of new remodeling units, through the increase of bone turn-over, the excessive supplementation of osteoclastic resorptive activity, the decrease of intestinal calcium absorption and through the induction of decreasing the concentration of calcitriol [4].

Experimental part

Material and method

14 cases with Turner syndrome have been studied with a 45X0 cytogenetic profile. The patients were between 12 and 18 years old. The biochemical tests were made before any hormonal treatments or ibandronic acid therapy were instituted.

The biochemical analysis revealed normal values for glycemia and high seric values for total cholesterol, lipids, triglycerides and LDL-cholesterol.

The values for the ovarian hormones (estradiol-E and plasmatic progesterone-P) were very low. In contrast, the values for the gonadotropic hormones (LH, FSH) were above the superior normal limit.

The plasmatic estradiol had values bewtween 13- 20pg/mL (Normal: 30- 120pg/mL) and those for the progesteron varied between 0.4 -1.2pg/mL (Normal: 4.9-18.8pg/mL).

The LH had variability limits: 190-290miliUI/mL (Normal: 0.110 -190miliUI/mL) and the FSH had values between 180- 240miliUI/mL (Normal: 0.110-190miliUI/mL). Also the measurements of the bone turn-over markers have shown low values which proved to be in agreement with the existence of ostepenia/osteoporosis.

The seric osteocalcin had values between 29.4 and 112.96 ng/mL.

The CrossLaps values were correlated to those of ostecalcin and were situated between 1.40 and 2.10 ng/dL.

The bone denisty was measured using Whole Body DEXA with a Medix 90DXA machine which was calibrated before every scan. The values we obtained showed the existence of osteoporosis in 10 patients (a T score under 2.5) and osteopenia in 4 patients (T score 2-2.5).

Results and discussions

In patients with osteopenia the major objectives for the profilaxy of hipogonadic osteoporosis were: to ensure the developmenet of the sexualisation process as close to the normal parameters as possible, to mentain the stability of the bone mass, to fight against the factors that lead to osteoporosis and it's consequences (the raising number of fractures secondary to osteoporosis).

The non-pharmaceutical recomendations for the patients we included in this study were:

-a diet with an adequate intake of calcium (1200-1500 mg/day) and vitamin D (400-800UI/day);

-changes in their lifestyle and light daily phisical exercises, at least 30 minutes every day;

-avoiding smoking and alcohol for patients with early onset of ovarian disfunction.

For the statural hipotrophy we administerd recombined growth hormone (GH) in a 30 U.I/m^2/week dose over a period of 6 to 12 months in order to achieve complete somatic developement, including bone and muscular maturity.

* email: adycamen@icloud.com

For inducing secondary sexualisation we have administered sequential estrogenic ovarian substitution by using etynylestradiol 0.02-0.035mg/day.

Regarding autoimune hipothyroidism we used the sustitution with thryoidian hormones 50-100 mg/day.

In the cases with osteoporosis and hipogonadic osteopenia that we included in our study the main goal for the pharmacological therapy was to prevent and reduce de risk of fractures.

We have administered drugs from the two classes that are used in treating osteoporosis:

-anti-resoptive agents which block the bone resorption by innabling the osteoclastic activity: ibandronat 150mg/ month, 24 months;

-anabolic agents which stimulate bone formation by acting prioritary on the osteoblasts: L arginin 1000 mg/ day.

After 3 months of treatment with IBANDRONAT a decrease in the concentration of CrossLaps in the serum was noticed with 38.5% compared to the basal level and the concentration of Osteocalcin in the serum decreased with 41.3% after 6 months of treatment.

By monitoring the bone denisity using DEXA examinations after 6 months from the beginning of the treatment with ibandronic acid, a decrease of the T score values was noticed with 30-4-%. However, this interval varried with individual receptivity.

The anti-resorptive medication has as a front runner the bisphosphonates class which is currently the most used. From this class of drugs we used in our study ibandronate administered orally 150mg/month.

This therapy's choice was based on the results from studies regarding the efficiency of ibandronic acid in postmenopausal osteoporosis and also in the secondary osteoporosis that occurs in other conditions (Cushing syndrome, osteogenesis imperfecta, Padget disease, bone metastasis in breast, prostate cancer etc). The Ibandron is the most powerful bisphosphonate with nitrogen content used in the hypercalcemia secondary to tumors and bone metastasis. It's use in the therapy of osteoporosis is based upon important preclinic evaluations [6-8].

The bisphosphonates are stable analogues of natural inorganic pyrophosphate and it has an affinity for mineral bone and for hydroxyapatite. The cellular action mechanisms include the absorption of the bis-phosphonates at the surface of the bone in close contact with the osteoclasts [9, 10].

The action mechanisms of ibandronate in inhibiting bone resorption are due to the selective absorption on the surface of the bone where it interferes with the resorptive action of the osteoclasts, more specifically with specific biochemical processes [11].

The bisphosphonates have the property to inhibit the dissolution of hydroxyapatite crystals [12] and to affect the biochemical bone activity by inhibiting the farnesyl pyrophosphate syntase (FPPS) enzyme [9].

Different types of bisphosphonates with various affinities for the mineral bone will enter in different degrees in the numerous skeletal compartments such as the trabecular and cortical bone or the endosteum or periosteum. Microscopically speaking the distribution of the bisphosphonates in the areas of bone formation and resorption as well as inside the intercanalicular network, which contains the detection system for mechanical bone modifications of the osteocytes, can depend of the mineral affinity of the different types of bisphosphonates [9].

More exactly, the bisphosphoantes raise the bone mass and lower the risk of fractures in the vertebral column with a percentage of 30-70% [13]. These data refer to the bisphosphonates effects in primary osteoporosis with vertebral implication where bone resorptive processes take place in the central area of the vertebral body especially involving the horizontal trabeculas which are considered to be connectin trabeculas. This will lead to compression and fractures of the vertebral body [14].

Studies regarding the osteoporosis in Turner syndrome show a slight decrease of the bone's cortical density with the preservation of the trabecular bone which predisposes to bone fragility and fractures, especially at the femoral neck [15]. These aspects are in contradiction with the evolution of the primary osteoporosis where the bone resorption occurs firstly in the trabecular bone and the involvement of the cortical occurs in later stages. The atrophic modifications in primary osteoporosis are more intense in the femoral neck in comparison to the femoral head [16].

The efficiency of the ibandronate in treating Turner syndrome osteoporosis was quantified through the bone turnover biomarkers values which have decreased considerably after 6 months of treatment.

It is unanimously accepted that the bone turn-over biochemical biomarkers [17-19] can provide information regarding the rate at which the bone is formed or resorbed and can be useful in the diagnosis of osteoporosis.

By analyzing the results we obtained we consider that seric osteocalcin reflects the rate of bone formation. This is being useful in identifying the risk of osteoporosis in patients with late puberty onset and in monitoring bone metabolism during the treatment with substitutional sexual hormones.

Given the fact that the CrossLaps values, as an indicator of bone resorption, are correlated with those of seric osteocalcin, we consider that with this indicator's aid it is possible to monitor the exchanges that occur during bone reshuffling due to the anti-resorptive therapy in cases with osteopenia or osteoporosis (hormonal substitution, bisphosphonates). In addition, it allows the follow-up in skeletal response (bone mineral density) during the anti-resorptive treatment.

The results we obtained in this study are correlated to the data regarding the efficiency of ibandronate in the reduction of bone turn-over [9, 20-22].

We believe that monitoring the results of anti-osteoporotic therapy through the evaluation of the bone turn-over biochemical markers is an accessible method in clinical practice. It is to be mentioned that these tests must be interpreted in a complete context along with a full evaluation of the patient, including the determination of associated risk factors.

However, the use of DXA examinations for measuring bone density represents the golden standard in the diagnosis and monitorization of the osteoporosis or osteopenia degree.

In our study the osteoporosis has been confirmed through osteodensitometry (DEXA) in 10 cases for which the T score was situated between -2.73 DS and -5.16 DS and in 4 cases the T score was suggestive for osteopenia (-1.7DS to -2.20DS). DEXA showsed a decrease in T score values after ibandronat was administered on a monthly basis. The cumulated ibandronat dose that was administered monthly is higer than the cumulated dose when it was administerd orally every day [23].

Among the side effects that were noticed after administering the ibandronate [24] in our lot we can list gastrointestinal manifestations: dyspepsia, nausea.

We believe this type of therapy can be considered a viable alternative for other conditions that associate secondary osteoporosis, such as paraneoplasic syndromes

or bone metastasis in different types of cancer. Although new methods are starting to be used that aim to ensure early diagnosis or complete resection of tumors, as is the case today in head and neck cancers [25,26], bone metastasis remain a difficult situation to manage. In such cases a curative treatment is not an option anymore, but any method that can increase the quality of life of our patients is worth considering. New methods of osteosynthesis are being researched [27], but preventing a pathologic fracture remains far more valuable.

However, in severe cases we must take into account the overall state of the patient. Chronic diseases, hepatic failure, diabetes or dialysis patients may have a different response to any type of therapy, as it has been demonstrated by studies in other areas of expertise [28]. In such patients, care and precautions must be the first step when introducing any new type of therapy. The direction of research still remains a valuable one, especially considering the complex pathology we are discussing.

Conclusions

In conclusion we believe that the concurrent evaluation of bone mineral density and of the bone turn-over biochemical markers for the patients we included in our study has offered useful information regarding the remodeling bone process in Turner syndrome. In addition, the administration of ibandronate has proven efficient in treating secondary osteoporosis linked to sexual hormonal deficiency.

References

1.LEVITSKY LL, O DONNELL LURIA AH, HAYES FJ, LIN AE, Curr Opin Endocrinol Diabetes Obes , **22**, 2015, p. 65-72.

2. HOLROYD CR, DAVIES JH, TAYLOR P, JAMEON K, RIVETT C, COOPER C, DENNISON EM, Osteporos Int **21**, 2010, p. 2093-2099

3. GRAVOLTH CH, VESTERGAARD P, HERMANN AP, MOSCKLIDE L. BRIXEN K, CHRISTIANSEN JS, Clin Endocrinol, **59**(1), 2003, p. 89-96

4.TANKO LB, BAGGER YZ, ALEXANDERSON P, DEVOGELAER JP, REGINSTER JY, CHICK R, OLSON M, BENMAMMAR H, MINDEHOLM L, AZRIA M, CHRISTIANSEN C, J Bone Miner Res, **19**, 2004, p. 1531 - 1538

5. MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN: 2010 POSITION STATEMENT OF THE NORTH AMERICAN MENOPAUSE SOCIETY. Menopause **17**(1), 2010, p. 25-54

6. BAUSS F, RUSSEL RGG, Osteoporos Int, **15**, 2004, p. 423-433

7. TRIPATHY D, BUDDE M, BERGSTROM B, Ann Oncol, **13**(Suppl 5), 2002, p. 168

8. BODY JJ, DIEL JJ, LICHINITSER MR ET AL, Ann Oncol, **14**, 2003, p.1399-1405.

9. RUSSELL R.G.G, WATTS N.B, EBETINO F.H, ROGERS M.J, Osteoporos Int, **19**, 2008, p. 733-759

10. EBETINO FH, FRANCIS MD, ROGERS MJ ET AL, Rev Contemp Pharmacother , **9**, 1998, p. 233-243

11. RUSSELL RGG, Bone **49**, 2011, p. 2-19.

12. RUSSEL RGG, MUHLBAUER RC, BISAZ S, WILLIAMS DA, FLEISCH H, Calcif Tissue Res, **6**, 1970, p. 83-196

13. BOONEN S, LAAN RF, BARTON IP ET AL, Osteoporos Int, **16**(10), 2005, p.1291-1298

14. IONOVICI N, NEGRU M, GRECU D, VASILESCU M, MOGOANTA L, BOLD A, TRAISTARU R, RJME, **50** (1), 2009, p.79-84

15. HOLROYD CR, DAVIES JH, TAYLOR P, JAMEON K, RIVETT C, COOPER C, DENNISON EM, Osteporos Int, **21**, 2010, p. 2093-2099

16. DRAGOI D, POPESCU R, TRAISTARU R, MATEI D, BUZATU AM, IONOVICI N, GRECU D, RJME, **51**(4), 2010, p. 707-711

17.DELMAS PD, Osteoporos Int, **11**, 2000, (Suppl 6), p. 66 - 76

18.DELMAS PD, EASTELL R, GARNERO P, Osteoporosis Int, **11**, 2000, (Suppl 6) p. 2 – 17

19.DONESCU OS, BATTIE MC, VIDEMAN, Osteoporosis Int, vol **17**, 2006, (Suppl 1) p.18 - 23

20.S.A. PREDA, M. BISTRICEANU, I. BISTRICEANU, D.M. ALBULESCU, C.CONSTANTIN, O.M. MARIOARA, A.TURCULEANU, A.COVEI, A.CAMEN, Osteoporosis International with other metabolic bone diseases WCO-IOF-ESCEO, World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, 14-17April 2016, Malaga, Spain Malaga, volume **27** supplement 1, april 2016 p. 293

21.S. A. PREDA, M. BISTRICEANU, I. BISTRICEANU, D.M. ALBULESCU, C.CONSTANTIN, O.M. MARIOARA, A.TURCULEANU, A. COVEI, A. CAMEN. Osteoporosis International with other metabolic bone diseases WCO-IOF-ESCEO, World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, 14-17April 2016, Malaga, Spain Malaga, volume **27** supplement 1, april 2016 p. 293

22.BONDARI S, A. COVEI, A. TURCULEANU, D. M. ALBULESCU, O. M. MARIOARA, A. CAMEN, Osteoporosis international with other metabolic bone diseases world congress of osteoporosis, osteoarthritis and musculoskeletal diseases 26/29 march, 2015 Milan, Italy, volume **26** supplement 1, March 2015, p. 216

23. PAPAPOULOS SE, SCHIMMER RC, Ann Rheum Dis, **66**, 2007, p.853-858

24. LAZAR, A. C.,PACURAR, M.,CAMPIAN, R. S., Rev. Chim. (Bucharest), **68**, no. 2, 2017, p. 246

25. STEFANESCU, D.C., CEACHIR, O., ZAINEA, V., HAINAROSIE, M., PIETROSANU,C., IONITA, I.G., HAINAROSIE, R.,Rev. Chim.(Bucharest), **67**, no. 7, 2016, p. 1255

26. STEFANESCU, D.C., CEACHIR O., ZAINEA, V., HAINAROSIE, M., PIETROSANU, C., IONITA, I.G., HAINAROSIE, R., Rev. Chim. (Bucharest), **67**, no. 7, 2016, p. 1327

27. PITURU T.S., BUCUR A., GUDAS C., PITURU S.M., DINCA O.M. J. of Cranio-maxillofacial Surgery, **44**, nr. 4, 2016, p. 500-505.

28. NECHITA A.M., PITURU S., RADULESCU D., PERIDE I., NEGREANU L., NICULAE A., FERECHIDE D., CHECHERITA I.A., SINESCU R.D. Farmacia, **64**, nr. 3, 2016, p. 348-357.

Manuscript received: 8.01.2018