Introduction

Beta-Thalassemia (βTh) is a congenital disease in which the genes related to the production of beta-polypeptide chains of hemoglobin are damaged. It manifests as severe hemoglobinopathy with a variety of genotype forms and the degree of gene damage dictates the final ability of the body to produce from practically none at all (“Thalassemia Major”) to relatively satisfactory (“Thalassemia Intermedia”) beta-chain levels and normal hemoglobin HbA1. The total population of patients with βTh is estimated today to amount to 100,000
persons worldwide\textsuperscript{2,3}. Clinically, the disease is characterized by ineffective erythropoiesis, extensive hemolysis, severe anemia and hepatosplenomegaly. Therapeutically, frequent blood transfusions of packed red cells are usually required, a condition which leads to especially harmful deposition of cytotoxic iron in the tissues and organs of the patients\textsuperscript{1,3}. As a result, regular chelation therapy is strongly recommended. The serious cardiovascular manifestations, endocrine gland disorders, the severe bone disease, the high incidence of hepatitis B and C, as well as the accompanying chronic liver disease are mentioned as just some of the numerous complications present in \(\beta T h\)\textsuperscript{1,3}.

Because of the impressive increase in patient survival rates, the bone disease which accompanies beta-thalassemia (TBD) affects the large majority of the cases in our days. It is characteristically mentioned that just the frequency of decreased bone mineral density (BMD) amounts to 40-50\% in older and/or inadequately treated individuals\textsuperscript{4-6}. The spine seems to be the most affected location, followed by the distal radius and femur\textsuperscript{7}. Separate studies have demonstrated an incidence of fractures ranging from 12\% to 71\%, depending on the characteristics of the population being studied\textsuperscript{4,5,8-10}. It has been described that these are observed mostly in the upper limbs (33-53.3\%), followed by spinal, pelvic and hip fractures, with significantly lower frequency\textsuperscript{8-11}. Of special interest is the observation that bone complications are observed with the same frequency between the sexes, while more severe bone disease seems to develop in patients with \(\beta T h\)-intermedia who had been transfused at extremely sparse intervals in the past\textsuperscript{12-15}. Finally, we must emphasize that TBD is clearly differentiated from classical postmenopausal osteoporosis. Although low BMD and typical osteoporotic changes in the bone architecture are present, these changes develop at much younger ages -often as early as the second decade of life- while additional disorders also coexist\textsuperscript{16}. Indicatively, mention is made of abnormal growth of the long bones, hyperplasia of the erythropoietic bone marrow, osteomalacia and metabolic bone disorders arising from the endocrine complications of the disease\textsuperscript{7,17,21}.

### Methods

In order to carry out this research, we reviewed the international literature from 1988 to 2017 via the PubMed database. As keywords, we used the terms: Thalassemia AND Bone disease (or Thalassemia AND Osteoporosis) AND Management, Treatment, Hypercalciuria, Calcium, Vitamins, Zinc, Bisphosphonates, Denosumab, Teriparatide, Activin-A. We focused on twenty-five interventional trials and nine older reviews pertaining to the pathogenesis, prevention and treatment of TBD. We also consulted medical books specific to \(\beta T h\), with significant references to the skeletal complications of the disease. Finally, we utilized information on the results to date of phase-III interventional clinical trials that are underway, as these were presented at 21\textsuperscript{st} and 22\textsuperscript{nd} annual congresses of the European Hematology Association (EHA).

### Causes – Pathophysiology

TBD exhibits an extremely multifactorial etiology, something that complicates both the understanding of the development of the disorder, as well as its diagnosis and treatment. The purpose of this review is not to provide a detailed list and thorough description of those pathogenic pathways. Therefore, the etiology and pathogenesis of the bone disease will be described briefly, in order for the therapeutic approaches being implemented today to be better understood.

**a) Hyperplasia of the erythropoietic bone marrow.** The conditions of chronic hypoxia that prevail in the bodies of \(\beta T h\)-patients lead to an excessive expansion in the erythropoietic bone marrow. In the past, this mechanism resulted in marked deformation of bones rich in erythropoietic marrow, such as the cancellous bones of the skull, the vertebrae, as well as the bones of the pelvis\textsuperscript{5}. Today, the therapeutic protocols of frequent blood transfusions suppress the marrow sufficiently. However, a degree of increased activity continues to exist, leading to degeneration and thinning of the trabeculae, thinning of the cortex and, eventually, alterations of the normal bone architecture with degeneration of the bone quality\textsuperscript{5,15,22,23}.

**b) Genetic predisposition.** Genetic disorders that are diagnosed with increased frequency in the context of \(\beta T h\) have been considered responsible for modification of the genetic expression in a manner that favors the development of TBD in these patients. Polymorphisms of COLIA1 and COLIA2 genes (which affect the quality of collagen), polymorphisms such as BsmI and FokI (which affect the function of the vitamin-D receptor), polymorphisms affecting estrogen-receptors ER\(\alpha\) and ER\(\beta\) and calcitonin-receptor CALC-R, and even disorders in the sequencing of TGF-\(\beta1\), have been implicated\textsuperscript{8,5,7,18}.

**c) Reduced physical activity.** Often, \(\beta T h\)-patients do not exercise sufficiently, either due to serious co-morbidities or even due to overprotective parenting at younger ages\textsuperscript{14,19}.

**d) Hemosiderosis.** Excessive iron deposition in the bone tissue: i) exerts a direct toxic effect on osteoblasts reducing their number, ii) stimulates the secretion of Receptor Activator of Nuclear factor-kappaB Ligand (RANKL) and iii) inhibits the physiological mineralization of the osteoid\textsuperscript{6,24-28}. Furthermore, hemosiderosis exerts additional harmful effects on the skeleton through indirect mechanisms, affecting the functioning of other tissues and organs as discussed in detail below.

**e) Toxicity due to chelating agents.** Trials exist which prove the positive impact of chelating agents on bone metabolism due to a reduction in the iron overload\textsuperscript{9}. However, when these elements are improperly utilized, administered in high doses and/or without proper evaluation of the patients, this may lead to the development of several negative effects, such as pathological growth of the long
bones, platyspondyly, arthropathy, a disruption in normal functioning of the OPG/RANK/RANKL system in favor of osteoclasts, a reduction in the proliferation of osteoblasts and fibroblasts, as well as a lack in bone protective minerals and trace elements like calcium, phosphorus, zinc and vitamin-D5,24,29-34.

f) The OPG/RANK/RANKL system. A disruption in the normal balance of the ratio of the soluble fraction of RANKL to osteoprotegerin (OPG) has been observed in βTh, resulting in an increase in the sRANKL/OPG ratio and bone resorption. This has mainly to do with an overproduction of RANKL and, secondarily, with a possible slight reduction in OPG levels. In term of etiopathogenesis, hemosiderosis, chelating agents, hypogonadism and neurosecretory dysfunction of the growth hormone (GH) / insulin-like growth factor-1 (IGF-1) axis are implicated4,17,35.

(ii) Other cytokines and growth factors. Elevated levels of cytokines and growth factors that promote bone resorption are often detected in the sera of patients with βTh. Those molecules which present the greatest increase and have clearly been implicated in inducing bone complications in βTh are interleukins 1 and 6, sclerostin and the factors Dickkopf-1 and TNF-α5,36,37.

h) Endocrine and metabolic disorders. The endocrine glands are organs with extremely heightened sensitivity to the cytotoxic effects of iron overload. This fact leads many βTh-patients to develop a plethora of endocrine complications, which further affect their already disturbed bone metabolism.

(i) Hypogonadism is due to a malfunction of the gonadotrophic cells of the pituitary gland and/or the cells of the gonads (testes-ovaries). In related trials, it is reported that the complication is observed in 30-55% of patients of both sexes and often begins at a relatively young age5,38-42.

(ii) GH/IGF-1 axis disorder. This is due to a disorder of the somatotropic cells of the pituitary gland as well as possible concomitant hepatopathy. The incidence of the complication has not been firmly established, as most trials indicate that it usually develops in 7.9-15% of all patients, although higher rates of up to 32% have also been reported43-46.

(iii) Diabetes mellitus in βTh usually begins as a kind of type-2 diabetes in the second decade of life or later. This occurs at a rate of 7-11%, while prediabetes is seen with much greater frequency47,48.

(iv) Hypothyroidism. Thyroid function disorders occur in approximately 10-15% of βTh-patients and are related almost entirely to the presence of subclinical or clinical hypothyroidism due to damage to the cells of the thyroid and/or the thyrotroph cells of the pituitary gland49,50.

(v) Hypoparathyroidism affects 13.5-14.6% of patients and can lead to severe hypocalcemia, hypercalciuria and inadequate production of active vitamin-D50,51.

(vi) Vitamin deficiencies. Beta-thalassemia often co-exists with liver dysfunction, impaired kidney function, and malabsorption due to hemosiderosis of the gastrointestinal tract. Combined with the effects of chelating agents, the above conditions have been deemed responsible for the very common vitamins D and C deficiencies seen in βTh-patients. Indicatively, values of 250HD <20 ng/ml have been described at a rate of greater than 42%, and between 20-29 ng/ml in 30% of American patients, mainly of Asian and Caucasian descent5,24,29-52.

(vii) Metal homeostasis disturbance: In approximately 30% of adult patients hypercalciumia develops, often complicated by nephrolithiasis, which is estimated to be present in up to 18% of patients23. Indeed, these percentages seem to increase more when the population being studied pertains to adult patients treated with the chelating agent deferasirox in moderate and high doses. The pathogenesis of the disorder is multi-factorial (chronic hypoxia, frequent blood transfusions, iron toxicity in the kidneys, chelation, hypoparathyroidism etc)31,32,55-58. Hyperphosphaturia has also been reported in βTh, but at lower rates. It has been associated with chelation regimens, while it is also feasible that hemosiderosis itself may be a predisposing factor in its development, since the intravenous administration of iron seems to promote the development of phosphaturia by increasing fibroblast growth factor-23 FGF-23 in the serum16,59,60. In addition to the above, albuminuria and hyperuricosuria are also observed more often in βTh than in the general population. Hypocalcemia represents yet another manifestation that seems to develop more frequently in the patients and is due mainly to hypoparathyroidism. Finally, low levels of other minerals have been observed in the blood, such as magnesium, copper and zinc, a condition which is attributed to both the action of chelation as well as malabsorption in the gastrointestinal tract5,29,61.

A contemporary therapeutic approach

As the development of TBD is attributed to numerous causes and disorders, methodical and comprehensive treatment should ideally be directed towards all the factors that affect the skeleton in βTh. Nowadays, it has become clear that any treatment intervention must begin promptly and continually be adjusted depending on changes in the clinical history of each patient over time. The therapeutic approach to TBD includes the following levels of preventive and curative measures, which should ideally be combined.

A. General measures and Lifestyle

In βTh, the degree of maintenance -or even improvement- in bone mass is remarkable when patients adopt a healthy lifestyle and follow appropriate instructions as regards exercise, nutrition, and behaviors which improve bone metabolism. These general measures include5,61-63: (1) The daily adequate intake of dairy products in quantities that
fall within the guidelines aimed at the normal population. A mild exposure of a portion of the skin to the sun for approximately 20 minutes daily is also recommended. (2) Restricting the excessive consumption of salt, caffeine, protein and carbonated soft-drinks which are known, in large quantities, to increase calcium excretion in the urine. (3) Restricting alcohol consumption and smoking cessation. In addition to the other complications that these habits can cause, they negatively affect bone health by disrupting the normal functioning of bone cells and the metabolism of calcium53,64-67. (4) Adopting an individualized exercise regimen -in consultation with the hematologist and the cardiologist- in order to promote bone formation. Ideally, the exercise must be carried out for at least 30 minutes daily, five days per week. The benefits of exercise in TBD are unquestionable since, in addition to the direct impact on bone metabolism, exercise improves cardiovascular functioning as well as the endocrinological and metabolic profile of patients, which in turn affect bone health4,5,17.

**B. Treatment of hematological disease and its complications**

I. Programs of regular blood transfusions for the purpose of maintaining hemoglobin levels greater than 9-10.5 g/L in βTh-patients have now been adopted by all transfusion centers worldwide. In addition to the cardiovascular and hematologic benefits gained in this manner, it is especially beneficial to bone health as well; hypoxia stops to exist and the erythropoietic marrow stops being stimulated and expanding4,5,8.

II. Regular transfusions unfortunately lead to excessive iron deposition in the tissues, the cytotoxic effect of which is responsible for the development of serious to fatal complications in multiple organs70-71. As early as the 1970’s, chelating agents have provided a solution to this problem, with the introduction of the subcutaneously administered chelating factor deferoxamine. From 1990’s onwards, two other orally administered agents have been introduced, deferiprone and deferasirox, so that now, depending on the particularities of each patient, a completely individualized chelation regimen can be implemented, entirely eliminating -in the majority of patients- unnecessary iron from tissues70-72. The removal of excess iron from the skeleton itself has an extremely favorable effect on bone health. In addition, successful chelation leads to improvement in the functioning of the endocrine glands and adequate production of hormones that have a positive effect on bone metabolism. Trials and case reports exist from recent years pertaining even to full reversal of endocrine disorders such as hypothyroidism, hypoparathyroidism, hypogonadism and diabetes mellitus73,74. The above observations have also been confirmed by a recent study that came to light in 2014, conducted by Casale M. et al, who studied the positive effects of deferasirox on the endocrine glands and bone. Among other things, they confirmed a significant improvement in the BMD of the spine during administration of the drug (p<0.001), a trend of improvement in the BMD of the hip (p=0.2), as well as a reduction in the percentage of patients with osteoporosis of the lumbar spine. In addition, they documented that these bone effects were independent of the effects of any anti-osteoporosis treatment and were due exclusively to successful long-term chelation75. On the other hand, as already noted, the excessive or incorrect use of chelating agents may significantly worsen bone metabolism and BMD. On the basis of the above, proper and individualized use of chelating preparations following assessment of: a) the clinical history of each patient, b) serum ferritin levels and c) measurements of tissue-iron, using newer specialized MRI-techniques, is the strategy proposed today, initially to improve and then to maintain, both the skeleton as well as the whole body of βTh-patients in the best possible condition5,24,29-32.

III. Prevention and treatment of other co-morbidities of patients with βTh also constitute a key factor, which is favorable to their skeletal health. Complications such as heart failure and severe liver dysfunction represent difficult-to-control entities which, in addition to being able to become life-threatening, have an adverse effect on the skeleton. Monitoring of patients by a cardiologist and a hepatologist is deemed necessary4,5. Furthermore, almost all the hormonal deficiencies gradually lead to major bone damage. Therefore, successful regulation of these endocrine disorders is extremely beneficial in TBD, among other things. Special mention should be made of the most common endocrine complication found in beta-thalassemia, hypogonadism. It has been established that hypogonadism and its treatment through appropriate hormone replacement therapy (HRT), have a significant impact on BMD and the incidence of fractures in the general population76. Similar trials in βTh-patients have demonstrated the benefits of HRT in improving bone mass, even though there are still no clear data on the effect on the frequency of fractures79. Yet another characteristic of TBD is that βTh-sufferers with hypogonadism, although greatly benefited by the administration of HRT, fail to improve, as regards BMD, to the same extent as non-thalassemic patients with hypogonadism receiving the same treatment39,76. Furthermore, the gonadal hormones must be used with special caution in βTh; due to the hepatic, cardiac and vascular disorders, the safer transdermally administered forms of androgen and estrogen are preferable to the oral or intramuscular forms77. Also, the dosage of these hormones should be the lowest possible for each patient, so as to ensure a positive impact on the bones while minimizing the risk of further complications. Finally, the indications for, and length of, therapy must also be carefully assessed and periodically adjusted, as these vary by age, the presence
of thrombophilia, splenectomy, diabetes and various other pathological states. As regards the inadequate functioning of the GH/IGF-1 axis, we should mention that the effects of administering the recombinant-GH in adult populations of βTh-patients have not been studied thus far at the TBD level and, consequently, the hormone must be administered only on the basis of the indications it has in childhood.

C. Management of hypercalciuria

As previously mentioned, hypercalciuria occurs in about one-third of βTh-patients. In order to control this disorder, the implementation of dietary measures that reduce the excretion of calcium in the urine (see above) and pertain to good hydration is initially recommended. Especially as regards the intake of calcium, this should not be entirely restricted, but must range between 800-1000 mg of calcium daily, preferably with food, and evenly distributed with meals. Without calcium supplementation bone health is bound to worsen significantly while, in addition, a mechanism is triggered for the development of hyperoxaluria and the formation of oxalate stones. At the same time, the intake of vitamin-D should also not be limited, but should be ingested at a sufficient dose to maintain 25OHD levels at the lower end of the normal range.

When the above measures are not sufficient and the hypercalciuria persists, it is recommended to commence treatment with thiazide diuretics (TZD). In clinical practice, hydrochlorothiazide and bendroflumethiazide are used today, administered as monotherapy or in combination with potassium-sparing diuretics. In general, as regards TZD, it is recommended that these be administered only when absolutely indicated, and in the lowest possible doses. Beta-thalassemia patients often maintain normal or borderline-low arterial blood pressure readings, and the risk of developing hypotension is significant. Also, it is necessary to evaluate sodium and potassium levels after the first 2-3 weeks of starting the medication, as the likelihood of hyponatremia and hypokalemia is not negligible. It should also be noted that when hypercalciuria co-exists with significant bone disease, the initial administration of TZD is recommended since, even if the hypercalciuria is regulated through dietary measures, the bone disease is not bound to improve. Finally, if bisphosphonates or denosumab are administered as an anti-osteoporosis therapy in a patient with hypercalciuria who also suffers from severe TBD, the hypercalciuria is also expected to improve to a certain extent.

D. Vitamins and minerals

Just as in the general population, so too with beta-thalassemia, adequate vitamin-D levels and adequate calcium intake significantly contribute to maintaining and improving bone health and preventing the development of osteomalacia. In βTh-patients, 25OHD levels are very often lower than normal, thus requiring laboratory testing every 6-12 months and exogenous supplementation when indicated. Although sufficient data do not exist to determine the ideal 25OHD levels in βTh, recent trials have demonstrated positive non-linear correlation between the concentrations of 25OHD and BMD (Z-Score), with a plateau at concentrations of 25OHD above 15 ng/ml. These levels are therefore considered to be at minimum necessary in order for the BMD not to deteriorate. In other trials, medical correction is recommended for levels below 20 ng/ml, with a proposed dose of vitamin-D3 of 2,000 IU p.o daily for a period of 8 weeks, and laboratory re-evaluation for possible continuation of administration. In order to maintain satisfactory levels, a daily intake of 800-1,000 IU of vitamin-D2 or D3 is recommended, especially in regions with decreased sunlight. Regimens with 50,000 IU of vitamin-D2 orally administered weekly or monthly have also been implemented for correction of deficiencies or maintenance of satisfactory levels respectively. Based on the above, in general, the recommended daily intake of vitamin-D does not seem to vary significantly from what is recommended for each age group in the healthy population. But, in βTh we must be more cautious, mainly due to the frequent hypercalciuria that is identified in patients. For the same reason, it is desirable for the level of 25OHD to be at approximately 30 ng/ml and not to exceed this by too much. It should be noted finally that, from all the relevant preparations, cholecalciferol should generally be preferred, while on the background of developing complications from other organs (hyperparathyroidism, liver dysfunction, kidney disorders) careful use of the more specific vitamin-D metabolites such as alfacalcidol and calcitriol may be required.

As regards calcium intake, the treating physician must decide, again guided by the pathophysiology and co-morbidity of βTh. In general, patients should be encouraged to receive sufficient quantities of the mineral, according to the guidelines for the healthy population and mainly through meals, both because of the hypercalciuria as well as the potential coexistence of injury to the endothelium of the vessels due to iron deposits. If, however, the calcium must be administered through supplementation, low doses are preferable, or splitting of higher doses in 2-3 individual doses over a 24-hour period, in addition to the foregoing, for optimal absorption by the gastrointestinal tract. Although there is no official contraindication for the administration of calcium through supplements, even today some researchers point to a possible correlation of its administration with cardiovascular events. At the same time, many other trials have failed to demonstrate any such correlation. Furthermore, in βTh-patients deficiencies in other minerals, such as magnesium, zinc and copper are also observed. There is causal speculation pertaining to the involvement of malabsorption from the gastrointestinal tract and/or of the action of chelating agents. Consequently, both periodic hematological testing and correction of low mineral levels are deemed absolutely essential. The role of magnesium...
in bone metabolism is fundamental. Zinc is another mineral that significantly affects bone health. Indeed, correction of zinc deficits has been shown to contribute significantly to improvement in BMD, but also to the metabolism of glucose in βTh-patients. Therefore, although no specific instructions exist to date for determining the ideal daily dose and frequency of administration of the above supplements, physicians should be encouraged to monitor their patients periodically and to take action whenever low levels are identified. Finally, it is recommended that vitamin-C be taken in sufficient quantities, through food or even with additional supplements, if a lack is identified.

E. Anti-osteoporosis medication

(i) CALCITONIN. Calcitonin is one of the most well studied anti-osteoporosis drugs that have been administered to βTh-patients. It was widely used during earlier years without, however, leading to truly remarkable results. Nevertheless, it seemed to restrict bone loss to a certain extent, while its contribution to the reduction of bone pain due to microfractures was also significant. In subsequent years, with the advent of bisphosphonates, the use of calcitonin was practically abandoned. Nevertheless, it has been concluded, judging by the final increase in BMD, that the most effective category is that of the intravenously administered amino-bisphosphonates, represented by zoledronic acid (ZA), pamidronate, and neridronate (Table 1). Administration of these specific preparations has led to increases in BMD of up to 50% in the lumbar spine, and up to 40% in other locations of the skeleton. Out of the substances administered orally, the most favorable therapeutic results are observed with alendronate. Unfortunately, in most of these trials, the number of participants was quite small, their heterogeneity really great (in terms of age, gender, chelation regimen and co-morbidity) and the time they were followed was brief. What has become clear thus far is that, in βTh-patients greater resistance develops to BPs than that which occurs at least in postmenopausal osteoporosis. To a certain extent, the multifactorial etiopathogenesis of the TBD is definitely responsible for this. For this reason, it has been proposed by many experts that in βTh-individuals, BPs be administered at higher doses than the conventional ones used. With the exception of alendronate, which seems to increase BMD to a sufficient extent at the usual oral dose of 70 mg/week, more aggressive protocols than the “classic” ones have been tested in terms of intravenously administered amino-bisphosphonates. In particular, ZA -probably the most effective bisphosphonate for TBD- has shown greater efficacy at doses of 4 mg/3months and 1 mg/3months, and especially during the first year of administration, with a significant reduction of biochemical bone turnover markers (BTMs), but also with improvement in musculoskeletal pain when this was assessed through the use of special questionnaires. Pamidronate has been administered in monthly doses of 15, 30, 60 mg and 1 mg/Kg for a total of 1 to 3 years, also with satisfactory results as regards increasing BMD in the spine and hip, and a reduction in BTMs. More recently, the intravenous administration of neridronate has also yielded satisfactory results in increasing BMD and reducing pain while, finally, it is noted that both intravenous and intramuscular administration of clodronate has proven practically ineffective.

It should be noted that, as regards the use of BSPs in TBD, no significant adverse effects have been described in the relevant trials published, at the dosages and intervals that have been utilized to date. However, the potential risk of atypical hip fractures or osteonecrosis of the jaw with long-term use of these drugs -due to a reduction in bone remodeling- has not yet been sufficiently investigated. Moreover, though a causal relationship cannot be proven, two reported cases of the development of atypical hip fractures in βTh-patients who had previously received BSPs have already been published. Furthermore, in 2014, three cases were announced of βTh-patients who had previously taken p.o bisphosphonates, presenting with osteonecrosis of the jaw diagnosed at stage zero. Therefore, the administration of BSPs must be evaluated individually for each patient and must be determined very carefully. Since there are no formal specific guidelines, neither as regards the suggested length of administration nor the dosage regimens, many researchers believe that the most logical approach is for BSPs to initially be administered on the basis of the thoroughly tested standards pertaining to postmenopausal osteoporosis: 5 years for oral and 3 years for i.v. BSPs (with the safest dose being ZA in 5 mg/year), and for the results be re-assessed at regular intervals. Unfortunately, evaluation data on the effect of BSPs in preventing fractures in TBD, have not yet been published. The main reasons for this include the small number of participants and the short monitoring period in the trials carried out to date. Finally, since the anti-osteoporosis drugs are administered at significantly younger ages in TBD than in the general population, further individualized data will need to be taken into account as regards their use in each patient such as, for example, family planning, as BSPs remain in the body for long periods of time, and we are unfamiliar with the effects that they may have on the pregnancy and fetus.

(ii) BISPHONONATES. Bisphosphonates (BSPs) are potent inhibitors of the bone resorption, drastically reducing the induction, proliferation, differentiation and the lifespan of osteoclasts. Over the past two decades, many trials have been published on the subject of assessing the behavior and the effectiveness of the various types of BSPs on the TBD. Out of these, it has been concluded, judging by the final increase in BMD, that the most effective category is that of the intravenously administered amino-bisphosphonates, represented by zoledronic acid (ZA), pamidronate, and neridronate (Table 1). Administration of these specific preparations has led to increases in BMD of up to 50% in the lumbar spine, and up to 40% in other locations of the skeleton. Out of the substances administered orally, the most favorable therapeutic results are observed with alendronate. Unfortunately, in most of these trials, the number of participants was quite small, their heterogeneity really great (in terms of age, gender, chelation regimen and co-morbidity) and the time they were followed was brief. What has become clear thus far is that, in βTh-patients greater resistance develops to BPs than that which occurs at least in postmenopausal osteoporosis. To a certain extent, the multifactorial etiopathogenesis of the TBD is definitely responsible for this. For this reason, it has been proposed by many experts that in βTh-individuals, BPs be administered at higher doses than the conventional ones used. With the exception of alendronate, which seems to increase BMD to a sufficient extent at the usual oral dose of 70 mg/week, more aggressive protocols than the “classic” ones have been tested in terms of intravenously administered amino-bisphosphonates. In particular, ZA -probably the most effective bisphosphonate for TBD- has shown greater efficacy at doses of 4 mg/3months and 1 mg/3months, and especially during the first year of administration, with a significant reduction of biochemical bone turnover markers (BTMs), but also with improvement in musculoskeletal pain when this was assessed through the use of special questionnaires. Pamidronate has been administered in monthly doses of 15, 30, 60 mg and 1 mg/Kg for a total of 1 to 3 years, also with satisfactory results as regards increasing BMD in the spine and hip, and a reduction in BTMs. More recently, the intravenous administration of neridronate has also yielded satisfactory results in increasing BMD and reducing pain while, finally, it is noted that both intravenous and intramuscular administration of clodronate has proven practically ineffective.

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(iii) DENOSUMAB. One of the key-mechanisms of the pathogenesis of the TBD is the increased sRANKL/OPG ratio, resulting in excessive heightening of the osteoclasts function. It has even been noted that,
| AUTHOR YEAR | STUDY DESIGN | INTERVENTION | Duration (months) | Number & Sex of participants | Age (years) |
|-------------|--------------|--------------|-------------------|-----------------------------|-------------|
| Morabito et al, 2002 | Randomized, parallel arm, placebo-controlled | Alendronate 10 mg/d (A) vs IM Clodronate 100 mg/10d (B) vs placebo (C) | 24 | 25 6M/19F | 26.6 ± 7.1 |
| Results: (A) ↑ 2.8% LS BMD, ↑ 15.64% FN BMD All Sign. vs placebo, (B) ⇔ LS and FN BMD vs placebo and baseline |
| Pennisi et al, 2003 | Randomized, controlled | Clodronate 300 mg/3w vs Cal+Vit.D | 24 | 30 30M | 27.44 ± 3.28 |
| Results: ⇔ LS and FN BMD T-Score NS vs baseline / p<0.01 vs Cal+Vit. D |
| Voskaridou et al, 2003 | Non-randomized, non-controlled, parallel arm | Pamidronate 30 mg/m (A) vs Pamidronate 60 mg/m (B) | 12 | 26 6M/20F | 35.5 |
| Results: (A) and (B) ↑ LS BMD Z-Score / ⇔ FN and Forearm BMD Z-Score vs baseline |
| Gilfillan et al, 2006 | Randomized, double-blind, placebo-controlled | ZA 4 mg/3m vs placebo | 24 | 23 17M/6F | (ZA) 27.8 (18.2-40.4) (pl) 27.7 (18.9-43.7) |
| Results: ↑ 10.2% LS BMD / ↑ 5.2% FN BMD / ↑ 6% Tot.Hip BMD / ↑ 4.6% Tot.BMD - All Sign. vs placebo |
| Voskaridou et al, 2006 | Randomized, parallel arm, placebo-controlled | ZA 4 mg/6m (A) vs ZA 4 mg/3m (B) vs placebo (C) | 12 | 66 22M/44F | (A) 44.1 ± 11.7 (B) 42.6 ± 10.7 (C) 44.9 ± 10.7 |
| Results: (A) ↑ 5.8% LS BMD, ↑ 4.8% FN BMD NS vs placebo, (B) ↑ 15.2% LS BMD, ↑ 11.3% FN BMD Sign. vs placebo |
| Otrock et al, 2006 | Open label, non-randomized, controlled | ZA 4 mg/3m (A) vs ZA 4 mg/6m (B) vs placebo (C) | 12 | 28 18M/10F | (A) 22.72 ± 5.85 (B) 19.10 ± 4.07 |
| Results: (A) ↑ LS and FN and Tot.Hip BMD Z-Score vs baseline, (B) ⇔ LS and FN and Tot.Hip BMD Z-Score vs baseline |
| Perifanis et al, 2007 | Single arm, non-controlled | ZA 1 mg/3m vs placebo | 12 | 29 13M/16F | 27.2 ± 7.3 |
| Results: ↑ LS BMD T-Score vs baseline |
| Skordis et al, 2008 | Randomized, parallel arm, non-controlled | Alendronate 70 mg/w (A) vs Pamidronate 90 mg/m (B) | 24 | 53 22M/31F | (A) 33.3 (20-47) (B) 34.4 (25-50) |
| Results: (A) ⇔ LS and FN BMD Z-Score vs baseline, (B) ↑ LS and FN BMD Z-Score vs baseline |
| Patiroglu et al, 2008 | Single arm, non-controlled | Pamidronate 15 mg/3m | 12 | 23 11M/12F | 7-14 |
| Results: ↑ FN BMD Z-Score vs baseline |
| Leung et al, 2009 | Non-randomized, parallel arm, controlled | Pamidronate (A) vs Cal+Alfacalcidol (B) vs Observation (C) | 36 | 39 16M/23F | (A) 18.9 (17.5-22.4) (B) 22.2 (19.0-27.8) (C) 17.7 (16.3-21.3) |
| Results (Z-Scores): (A) ↑ LS & FN BMD vs baseline, (B) ⇔ LS & FN BMD vs baseline, (C) ⇔ LS & ∆ FN BMD vs baseline |
| Chatterjee et al, 2012 | Non-randomized, controlled | Pamidronate 1 mg/Kg/m (A) vs observation (B) | 36 | 34 18M/16F | 17-43 |
| Results: (A) ↑ LS and Tot.Hip BMD Z-Score vs baseline, (B) ⇔LS and Tot.Hip BMD Z-Score vs baseline |
| Shirani et al, 2012 | Single arm, Non-controlled | Aledronate 10 mg/d | 12 | 120 57M/69F | 33 (20-50) |
| Results: ↑ LS and FN BMD T-Score vs baseline |
| Forni et al, 2012 | Randomized, open-label, controlled | Neridronate 100 mg/90d vs Cal+Vit.D | 12 | 118 51M/67F | 32.8 ± 8.1 |
| Results: ↑ LS and FN and Tot. Hip BMD vs Cal+Vit. D |
despite the successful efforts in normalizing hemoglobin levels, appropriate HRT and substitution with thyroxine or GH, satisfactory control of diabetes and effective chelation, the sRANKL/OPG ratio continues to remain at pathologically high levels.\textsuperscript{39,113,114} Denosumab, a monoclonal anti-RANKL antibody that inhibits the binding of RANKL to RANK, would theoretically significantly correct this specific abnormality and would drastically reduce bone resorption\textsuperscript{115}. The first non-controlled study on the effect of denosumab in TBD was published in 2014, with very encouraging results indeed\textsuperscript{116}. In that trial, 30 patients with TBD aged 17 to 32, received the drug subcutaneously at the usual dose of 60 mg/6months and, after 12 months, changes in BMD were evaluated, as were BTMs. A significant improvement in BMD of the femoral neck of 6.0%, an even greater improvement in the lumbar spine of 9.2%, and a considerable reduction of bone resorption markers were observed. Side effects were mild and mostly pertained to pain in the spine and the extremities (12%), as well as the presence of nausea (10%). The development of hypocalcemia in 7% of patients was mild and asymptomatic. Of course, the frequent presence of hypoparathyroidism and renal disorders in βTh requires attention to this specific matter.

The positive results of this trial have prompted the same researchers to launch, in 2017, a new randomized, open labeled, parallel assignment, interventional clinical phase-III trial to compare denosumab with ZA. A total of 10 patients were recruited in each group, and the initial results for changes in BMD and BTMs are expected to be announced in 2018. Finally, at the 22\textsuperscript{nd} annual Congress of the European Hematology Association (EHA), which took place in Madrid in 2017, the initial results of the single-site, clinical trial by Voskaridou et al. were announced, which pertained to the administration of denosumab in 31 βTh-patients, at a dose of 60 mg/6months for one year, compared with the administration of a placebo in 30 other βTh-patients. The results after the first two doses of the drug, here too revealed significant increases in the BMD in the denosumab group, both in the lumbar spine (6.02 ± 5.30%) and the femoral neck, clearly superior to the placebo, and an excellent safety profile, with no significant side effects (Voskaridou E. et al. Denosumab increases BMD in patients with thalassemia-major and osteoporosis: Results of a randomized, placebo-controlled, double-blind, phase-2B Clinical Trial - EHA22, June 2017 / Unpublished data).

One observation that should be emphasized at this point is that, among the side effects of denosumab, a possible mild increase in the likelihood of the development of certain infections is mentioned, such as upper respiratory tract, urinary, skin and ear infections\textsuperscript{117}. Since βTh-patients represent a group with a mildly increased susceptibility to infections\textsuperscript{118,119} and often have a positive history for splenectomy, heart disease, and various co-morbidities, this observation should always be assessed by their treating physicians, without of course necessarily precluding the use of denosumab for TBD. Moreover, in the trials to date, there are no reports of a causal relationship between the drug and the development of infections in βTh-individuals.

(iv) TERIPARATIDE. Teriparatide is currently the only anabolic drug marketed for the treatment of osteoporosis. Nonetheless, its use in TBD has not yet been sufficiently studied, although it represents a tempting choice since very low BMD values are often observed in βTh-patients. Moreover, osteoblasts and bone formation are significantly affected in this hematologic disease\textsuperscript{91}. On the other hand, due to its mechanism of action, the question remains as to whether or not this can significantly worsen any possible concomitant hypercalciuria. In addition, in quite a few transfused patients, foci of severe extramedullary hematopoiisis develop, which lead to serious pressure phenomena in the spine and require the implementation of radiotherapy. In these cases, the use of teriparatide is contraindicated\textsuperscript{16}. To date, only three case reports have been published on the use of this drug in a corresponding number of βTh-patients with serious TBD and pathological fractures, and the truth is that, in all three, the results were very encouraging, with notable increases in BMD in the lumbar spine, the femoral neck and the total hip, at 12 and 18 months\textsuperscript{120-122}. Of course, more data are clearly required to substantiate both the efficacy and safety of teriparatide for its generalized use in severe TBD.

(v) STRONTIUM RANELATE. In terms of the effectiveness of strontium ranelate in TBD, only one randomized controlled trial was conducted, with relatively positive results, as an increase in BMD was observed -mainly in the spine- as well as normalization of BTMs, a reduction in sclerostin levels in the serum, and a reduction in musculoskeletal pain\textsuperscript{123}. Nevertheless, the drug practically ceased to represent a treatment option for TBD from the moment that new data arose pertaining to the safety of its administration, which were related to an increased risk of cardiovascular complications\textsuperscript{124}. These situations render it dangerous in practice for a patient-population with an increased prevalence of a variety of cardiovascular and thrombophilic problems. In any case, strontium ranelate is no longer available, as its manufacturers decided to cease supply of the drug treatment in August 2017.

(vi) NEW THERAPEUTIC AGENTS

\textbf{Antibodies against sclerostin.} Romosozumab is a monoclonal antibody that selectively binds to sclerostin and inhibits its action. It belongs to the anabolic drugs, as its administration significantly increases bone formation, and through this mechanism dramatically improves, in trials to date, the BMD in the spine and hip\textsuperscript{125}. Although its action in TBD has not yet been examined, scientific interest in its potential efficacy is
great, as significantly higher levels of sclerostin have been found in the serum of βTh-patients compared to the general population\textsuperscript{16,126,127}. Of course, the relatively recent reports of potentially increased incidence of cardiovascular episodes in clinical phase-III trials (“ARCH” and “BRIDGE”), draw attention for a potential future use of the drug in TBD. Activin-A Inhibitors. Activins are members of the transforming growth factor-β (TGF-β) superfamily and carry out multiple biological actions in several tissues. Activin-A is a protein that is expressed particularly in the bones and it has been observed to be increased in the sera of patients with osteoporosis. In humans, it has been documented to promote osteoclastogenesis and differentiation of osteoclasts, while simultaneously inhibits differentiation and the action of osteoblasts\textsuperscript{128,129}. Based on these observations, agents have been developed which inhibit the effects of activin-A on the skeleton and are expected to improve bone status in individuals with osteoporosis. The implementation of this type of treatment in TBD has garnered great interest in recent years since, apart from the action of these drugs on the bone metabolism, a simultaneous significant increase in hemoglobin levels was identified in the preclinical trials on experimental animal models\textsuperscript{130-132}. The action on the hematopoietic tissue is carried out in the final stages of differentiation of red blood cells, correcting -to a certain extent- the ineffective erythropoiesis that occurs in βTh. In this manner, the need for transfusions, hyperplasia of the hemopoietic marrow, and hemosiderosis are reduced and quality of life is improved. On the level of clinical trials in βTh-patients, two separate molecules of activin-A inhibitors have already been administered, sotatercept and luspatercept, with very good results in terms of hematological data, but also with only mild side effects\textsuperscript{133-135}. At this stage, research continues only with luspatercept, for which is underway, since 2016, an international multicenter randomized, double-blind phase-III trial (“BELIEVE Clinical Trial) with a three years duration, with the participation of 300 βTh-patients. Of these, 200 receive the medicinal agent at varying doses subcutaneously every 3 weeks and the remaining 100 have been randomized in the placebo group. The first results are expected to be announced in 2018, and these will focus primarily on the hematologic data. However, some parameters which pertain to the effects of the drug on the bone metabolism, will also be tested\textsuperscript{136}.

Conclusion

βTh is a serious hematologic disorder with many accompanying complications, part of which is the early development of a particular type of bone disease with a multifactorial etiopathology. The treating physician is initially called upon to implement the necessary preventative measures in order to limit the unfavorable development of skeletal problems and secondly, if required, to create a completely specialized and individualized treatment plan for each patient. Maintaining sufficient levels of hemoglobin, effective chelation, the most effective possible treatment of co-morbidities, proper nutrition, adequate calcium intake, correction of deficits of other minerals such as magnesium and zinc, strengthening of vitamin-D stores, management of hypercalciuria and appropriate exercise, now represent the cornerstones of a comprehensive preventive and therapeutic approach, even before the use of anti-osteoporosis drugs. Of course, with the most serious forms of TBD, the implementation of a more specialized medication regimen is strongly recommended. In such cases, the administration of BSPs was, until a few years ago, the only option for which numerous officially published data existed. Although BSPs still remain by far the most adequately studied medications in TBD, in recent years, more and more trials are coming to light on the use of new agents as well, with very promising results. Of these, very important information has been announced about denosumab, pertaining to satisfactory increases in BMD after 12 months of administration. The role of teriparadise should also be explored further. Finally, newer substances that are being developed, such as romosozumab and luspatercept, pique the interest and optimism of both doctors and patients. As the data to date are deemed to be encouraging and optimistic on the whole, the therapeutic approach of these patients is expected to be more multidimensional in the very near future.

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