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Approach to the management of β thalassemia major associated osteoporosis - a long-standing relationship revisited

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Abstract. Adults with β- thalassemia major (β-TM) develop low BMD and fragility fractures at a higher incidence and at a younger age compared to the general population. The disease itself, including direct effects of anemia and iron overload toxicity on bone turnover, genetic susceptibility, thalassemia-related endocrinopathies and acquittance of suboptimal peak bone mass contribute to low bone mass and increased bone fragility frequently encountered among these patients. Current management of osteoporosis requires long-term treatment that can be provided by agents that reduce the risk of all osteoporotic fractures by modulating bone metabolism with different mechanisms of action. These include inhibitors of bone remodeling (e.g., bisphosphonates, denosumab) and stimulators of bone formation (e.g., PTHR1 agonists and sclerostin antibodies). Considering the unique characteristics of osteoporosis associated with β-TM and the clinical importance of balancing the risk/benefit of treatment in the long-term, appropriate use of these therapeutic approaches is essential for patient care. In this review we outline current literature on the use of anti-osteoporotic drugs in β-TM patients with osteoporosis focusing on data on the efficacy, safety, and duration of treatment. In addition, we propose a long-term management plan for β-TM -associated osteoporosis aiming at the optimal patient care for this special population. (www.actabiomedica.it)

Key words: Anemia, iron overload, bone cells, bisphosphonates, teriparatide, denosumab, fractures

Introduction

Osteoporosis associated with β-thalassemia major (β-TM) is a long-standing skeletal complication, that is increasingly recognized in the last decades due to the improved prognosis of β-TM patients and the subsequent prolongation of their lifespan. Low bone mass and increased risk of fractures even in patients with adequate transfusion and iron chelation therapy are related to a significant deterioration of quality of life and high morbidity (1,2). From a pathophysiological point of view, osteoporosis associated with β-TM shares common characteristics with postmenopausal osteoporosis but also displays some unique and distinct features related to the younger age of the patients, the chronic anemia and iron overload per se, and the

contribution of other associated endocrinopathies on bone modeling and remodeling (3). The prevalence of osteoporosis in well - treated β-TM patients varies from 13.6% to 50% (4-6) and is associated with increased fracture risk (up to 44%) (7-10), more frequently affecting upper extremities. Almost 20% of patients with β-TM and osteoporosis will experience a fragility fracture during their lifetime (8).

Current management of osteoporosis in the general population requires long-term treatment, using agents that reduce the risk of fractures at all sites by modulating bone remodeling with different mechanisms of action. These include inhibitors of bone remodeling (e.g., bisphosphonates, denosumab), stimulators of bone formation (e.g., PTHR1 agonists) as well as romosozumab, a dual action sclerostin inhibitor. The availability of these agents has led to novel paradigms of osteoporosis management, based on their sequential or combined use.

Consideration of the unique characteristics of osteoporosis associated with β-TM and balancing the long-term risk-benefit ratio of treatment for each individual, especially for younger patients, are essential to ensure appropriate use of these therapeutic approaches. In this review we outline current literature on the use of anti-osteoporotic drugs in β-TM patients with osteoporosis focusing on data on their efficacy, safety, and indicated duration of treatment. In addition, we propose a long-term management plan for β-TM associated osteoporosis aiming at the optimal patient care for this special population.

Pathophysiology of bone loss in β -thalassemia major

a. The impact of anemia and iron overload on bone remodeling

Chronic ineffective erythropoiesis expands bone marrow by significantly increasing (up to six-fold) the number of erythroid precursors (11) (Figure 1). Bone marrow expansion causes mechanical interruption of bone formation, resulting in cortical thinning, bone distortion, and increased fragility (7). The role of bone marrow expansion in β-TM associated bone loss could, therefore, explain why lumbar spine (LS), consisting mainly of trabecular bone, is more severely affected in these patients (12). Regular transfusion program suppresses bone marrow expansion, but even with optimal

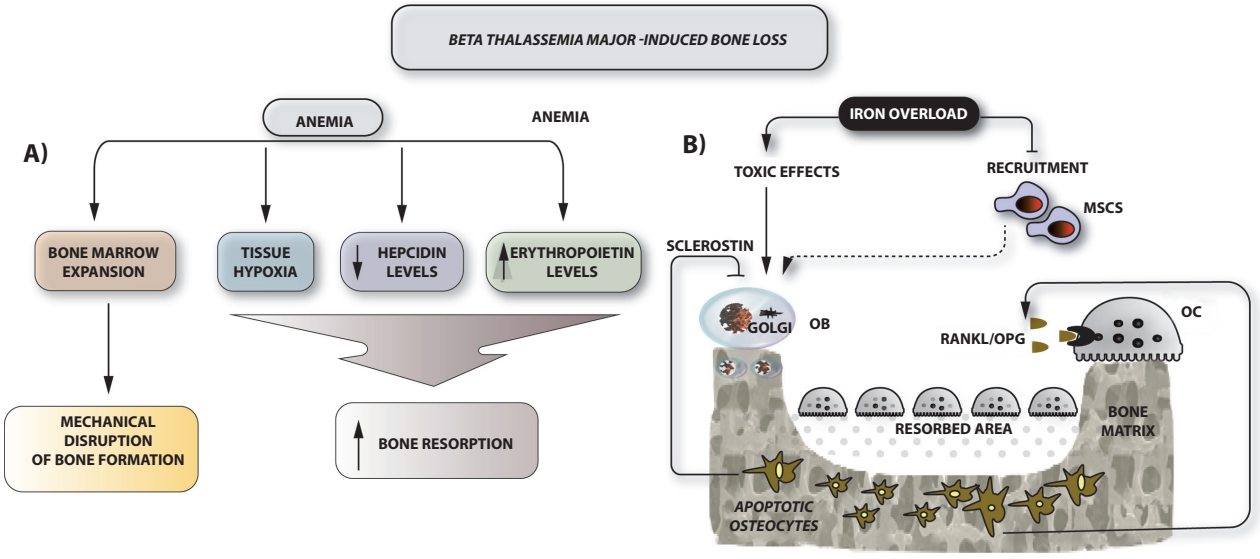

Figure 1. Underlying mechanisms of anemia and iron-overload induced bone loss in β-thalassemia major.

Legend: OB = osteoblast; OC = osteoclast; MSCs = mesenchymal stem cells; OPG = osteoprotegerin; RANKL = Receptor Activator of Nuclear Factor κBLigand.

transfusion erythroid activity cannot be completely restored (13).

Tissue hypoxia, increased erythropoietin and reduced hepcidin, which is a major regulator of iron homeostasis, are all associated with defective erythropoiesis and exert direct unfavorable effects on the skeleton by increasing bone resorption (14-17) (Figure 1).

Tissue toxicity due to iron overload is the major complication of chronic transfusion therapy in β-TM leading to liver disease, cardiac dysfunction, and endocrine dysregulations. Regarding the skeleton, several lines of evidence have demonstrated direct detrimental effects of iron overload on bone cells. Iron directly disrupts bone formation (17) through toxic effects on osteoblasts (18,19) and decreased recruitment of mesenchymal stem cells on the osteoblastic lineage (20), while on the other hand, it enhances bone resorption through increased intracellular oxidative stress in osteoclasts (16,21-23) (Figure 1). Additionally, recent evidence from *in vivo* and *in vitro* experiments suggests that free iron also exerts direct toxic effects on the osteocytes, which are the key regulators of bone remodeling. Hepcidin - /- mice, representing an iron overload experimental model, display low bone mass with alterations of bone microarchitecture (17). The main cause of reduced bone mass in this mouse model was the increased number of apoptotic osteocytes due to increased oxidative stress, while reducing iron overload and oxidative stress with deferoxamine and N-actyl-L-cysteine, respectively, reduces bone loss by preventing osteocyte apoptosis (24). Osteocyte apoptosis, in turn leads to increased expression of sclerostin and activation of RANKL/OPG signaling, thereby decreasing bone formation and enchasing bone resorption (22,24) (Figure 1). Taking all the above data together, osteocytes appear to be the main bone cell type affected by iron overload, orchestrating bone loss and at the same time compromising bone strength.

b. Other Contributing factors.

(i) Genetic background

Genetic factors seem to play an important, although not yet fully clarified, role in the development of low bone mass in patients with β-TM (25) (7). Polymorphisms at the Sp1 site of collagen type Ia1 (COLIA 1) gene that encodes type I collagen (the major protein of bone matrix), and in the vitamin D receptor (VDR) gene are well-known determinants of bone mass in the general population (26). The polymorphism at the Sp1 site of COLIA 1 has been related to severe osteoporosis at the LS and total hip (TH) in male β-TM patients (27), suggesting a role in identifying individuals at high risk of osteoporosis and fractures (28). Other studies, however, did not confirm this association (29). VDR gene polymorphisms in single nucleotide, such as BsmI G > A, located at the intron 8, was also significantly correlated with low bone mass in β-TM patients (30), as well as with favorable response to treatment with alendronate (29).

(ii) Suboptimal peak bone mass

Patients with β-TM are often characterized by suboptimal bone accrual during childhood and adolescence (8). Disorders of puberty development significantly impair adequate bone mineralization and achievement of peak bone mass (31). In addition to gonadal status, increased bone turnover and lower weight are independent predictors of low bone mass in people with β-TM at the age of 20, preventing them from attaining optimal peak bone mass (8).

(iii) Hypogonadism

Early onset hypogonadism, mainly the hypogonadotrophic form, and to a lesser extent due to gonadal failure, is highly prevalent in β-TM patients and is caused by excess iron deposition in the anterior pituitary and the gonads, respectively (32). Several studies have confirmed that hypogonadism, a well-known cause of low bone mass in the general population, is also associated with osteoporosis in patients with β-TM (33,34).

(iv) GH-IGF-1 axis

Patients with β-TM are characterized by significant alterations in growth hormone (GH) / insulin growth factor 1 (IGF-1) axis, with the majority of them having low circulating levels of IGF-1 and IGF-binding protein 3 (IGFBP-3) (12). Low serum IGF-1

concentrations are mainly attributed to GH insensitivity (through iron deposition to liver and chronic hepatitis), but are also to some extent caused by impaired GH secretion (12),(35). IGF-1, through its anabolic effects and stimulation of osteoblasts' function, plays a crucial role in bone formation during childhood and bone maintenance during adulthood (36). As a result, IGF-1 deficiency leads to decreased bone formation and ultimately bone loss (7). Several studies have demonstrated a significant positive correlation between BMD of the LS and serum concentrations of IGF-1 and IGFBP-3 (1),(7). Individuals with β-TM and low IGF-1 have significantly lower BMD of the LS compared to those with normal IGF-1 values (37).

(v) Vitamin D deficiency

Low vitamin D levels are very common in patients with β-TM due to several contributing factors (8), including impaired 25-hydroxylation of vitamin D due to liver hemosiderosis, intestinal malabsorption of vitamin D, defective skin synthesis due to jaundice, and limited exposure to sunlight (12). Vitamin D is essential for calcium homeostasis and bone mineralization. However, there are conflicting data regarding the association of low vitamin D levels with osteoporosis in β-TM (25), and the extent to which suboptimal vitamin D levels contribute to low BMD remains unclear.

(vi) Iron chelators

Deferoxamine (DFX), the most widely used parenteral iron chelator, exerts a direct negative effect on osteoblasts by inhibiting proliferation and differentiation of osteoblast precursors, and ultimately reducing collagen formation. In high doses, it also enhances osteoblast apoptosis (1,7). DFX use in childhood may induce dysplastic bone changes in the long bones, associated with short stature and characteristic radiological features (38).

Deferasirox, an oral iron-chelating agent, may reversibly increase serum creatinine levels and is linked to elevated levels of renal tubular markers, indicative of tubulopathy (25). Deferasirox, at therapeutic doses, has also been associated with an almost 4-fold increase in urine calcium to creatinine ratio and hypercalciuria in a dose-dependent manner (39). There is also evidence that treatment with deferasirox in β-TM patients carries a high risk for nephrolithiasis, while male patients with kidney stones have a higher likelihood for reduced BMD of femoral neck and fractures (40). The most likely explanation for this observation is that deferasirox-related hypercalciuria leads to bone loss through increased bone resorption in an attempt to maintain normocalcemia, although the exact underlying mechanisms warrant further research (25,39).

(vii) Cytokine network

Cytokines, such as IL-1α (interleukin-1 α), IL-6, and TNF-α (tumor necrosis factor-α), have been correlated with markers of bone resorption in patients with β-TM, suggesting that these cytokines may enhance bone resorption and lead to bone loss (12,41).

(viii) Nutritional status and lack of physical activity

Patients with β-TM may have a degree of undernutrition, partially explained by their increased resting metabolic rate along with anemia and increased cardiac output (1). Low body weight and zinc deficiency, which is relatively common in these patients due to increased urinary zinc excretion, are also associated with β-TM associated osteoporosis (7). Additionally, patients with β-TM often have limited physical activity either due to disease complications or due to ill-founded beliefs around their lifestyle. Since regular muscle activity is of paramount importance to maintain bone mass, physical exercise on a regular basis (7) can have a positive impact on bone health in these patients.

Efficacy and safety of anti-osteoporotic drugs in β-TM associated osteoporosis

a) Bisphosphonates

Bisphosphonates (BPs) are the most widely used drugs for the prevention and treatment of bone loss irrespective of the underlying disease (42), and this is also the case for β-TM (1,3,43,44).

(i) Efficacy

Oral alendronate (45,46), IV neridronate (47), clodronate (48), pamidronate (46,49,50) and zoledronate (51-54), and IM clodronate (45) have been tested against placebo or no therapy in randomized clinical trials (RCTs) and prospective observational studies evaluating patients with β-TM associated osteoporosis. In general, BPs use in this setting resulted in a significant reduction in bone turnover markers (BTM), accompanied by improved BMD at all skeletal sites compared to baseline and placebo (43,55) with the exception perhaps of clodronate, which reduced BTM but did not improve BMD (45,48). Interestingly, BMD gains were comparable or even greater than those reported with the same agents in postmenopausal osteoporosis (55). Reduction of back pain has also been reported with neridronate (47) and zoledronate (52).

However, due to the small sample size, the short duration and the very low incidence of fragility fractures in studies with BPs use in β-TM associated osteoporosis, their antifracture efficacy has not been proven (55). Positive effect on bone quality has been reported in a small, non-randomized histomorphometry study, in which IV pamidronate was given in a dose of 1mg/kg monthly for 3 years (50).

Alendronate is the only oral BP tested in β-TM patients with osteoporosis. In an RCT directly comparing alendronate 10mg daily with IM clodronate 100mg every 10 days, alendronate performed better in terms of BMD increases (45). In contrast, in another RCT, IV monthly administration of pamidronate 90mg resulted in higher BMD increases at both the LS and femoral neck (FN) compared to oral alendronate 70 mg weekly (46).

Although direct comparison among studies is not appropriate, zoledronate seems to be the most efficacious BP in terms of BMD increases in β-TM associated osteoporosis (43,55). The regimens that were used were 4mg every 3 (51,52) or 6 months (52), resulting in a cumulative dose much higher than the dose administered for postmenopausal osteoporosis (5mg yearly). The 3-monthy regimen resulted in higher reductions in BTM and significantly higher increases at the LS BMD with borderline higher increases at the FN BMD compared to the 6-monthly regimen (52). Importantly, BMD at the LS, the FN and the radius continued to increase up to 24 months after discontinuation of 1-year zoledronate treatment in both the 3-monthly and the 6-monthly regimen (53).

(ii) Safety

The duration of BP treatment in β-TM associated osteoporosis in the currently published studies does not exceed 3 years, thus the safety of their administration for longer periods in such patients remains unknown. For the given treatment periods BPs were generally well-tolerated, and the type as well as the frequency of reported adverse events where as expected, consisting of mild upper gastrointestinal toxicity (alendronate) (45), acute phase reaction (IV BPs) (47,51,52), and local pain at the site of injection (IM BPs) (45). However, given the young age of β-TM patients and the frequently ensuing necessity for longer-term BP administration, there are concerns regarding their long-term safety and their reproductive safety (56), while their anti-fracture efficacy and their effects on morbidity and mortality remain currently unknown. It has been proposed that BPs should be discontinued in women who intend to conceive and be reinstituted after delivery, if indicated (57).

Three cases (2 females, 1 male) of osteonecrosis of the jaw have been reported with alendronate 70 mg weekly administered for 3.5-4 years (58). One patient had received pamidronate 60 mg/month for 2 years prior to alendronate. All 3 patients had been subjected to tooth extraction, a well-known predisposing factor for osteonecrosis of the jaw development (59). There is only one published case of atypical femoral fracture, in a 36-old male with β-TM treated with zoledronate for 3 years but being off-treatment for 1 year before the event (60).

BPs did not influence iron status or hemoglobin levels, supporting their safety from a hematological point of view (55).

b) Denosumab

Increased RANKL/ OPG ratio is one of the key mechanisms of bone loss in β-TM (61). In specific,

the RANKL/OPG ratio remains at high levels despite the effective management of low hemoglobin levels and hormonal disorders, thereby enhancing the activity of osteoclasts and consequently favoring bone loss (62,63). Along these lines, denosumab (Dmab), a human monoclonal antibody binding RANKL, appears to be a rational treatment approach.

(i) Efficacy

In the first single arm study evaluating Dmab in β-TM associated osteoporosis, 30 relatively young patients (age range: 17-32 years) received the usual 60mg SC 6-monthly dose over a period of 1 year (64). Along with a considerable reduction in bone resorption markers, noticeable increases at the LS and FN BMD (9% and 6%, respectively) were observed. A phase III, randomized, comparative, parallel assignment, open label clinical study is currently undergoing by the same research group, aiming to compare Dmab (60 mg every 6 months SC) and zoledronate (5mg annually IV) in 40 adult patients (20 within each arm) (65). In addition, a randomized placebo-controlled phase 2b study evaluated 63 patients (age range: 34 – 78 years; 32 received Dmab and 31 placebo) over a period of one year (66). BMD increased more at the LS and radius, but not at the FN, in the Dmab treated patients. Additionally, in contrast with placebo, Dmab reduced both formation and resorption BTM along with sRANKL and sRANKL/OPG ratio (66). In a post hoc analysis of this study, Dmab reduced noggin levels compared to placebo (67). As noggin inhibits bone morphogenetic proteins leading to decreased bone formation, the lower noggin levels could represent an additional mechanism by which Dmab increases BMD in this group of patients.

(ii) Safety

Available data regarding the safety profile of Dmab in patients with β-TM associated osteoporosis is reassuring, although both the number of patients and the duration of treatment are limited and probably inadequate to draw definite conclusions. Most of the adverse events were mild and concerned gastrointestinal problems (nausea, abdominal pain, diarrhea), headache and fever, while hypocalcemia was observed in less than 10% (64,66). Interestingly, pain at the back and extremities was reported by only 13% of the patients in the single arm study (64) while in the placebo-controlled trial a significant reduction of bone pain was observed in the Dmab group (66). Special attention should be given to the susceptibility to upper respiratory system and gastrointestinal infections; increased incidence of these infections has been reported in patients treated with Dmab for postmenopausal and male osteoporosis (68), and β-TM patients are already more prone to these events due to disease-dependent factors such as splenectomy, heart disease, and other comorbidities (44).

Finally, Dmab discontinuation is an issue of concern, as a "rebound" phenomenon in bone remodeling resulting in substantial BMD loss is expected, especially in those who have been treated for long periods, and a subsequent anti-resorptive treatment is not given (69). Considering the results from studies in postmenopausal osteoporosis and the data from BPs studies among β-TM patients, sequential administration of zoledronate, and possibly alendronate, is expected to mitigate BMD losses following Dmab discontinuation, especially among β-TM patients treated for up to 2.5 - 3 years with Dmab (70,71).

c) Osteoanabolic Treatment

a) Teriparatide

Teriparatide (TPTD) is the most widely used osteoanabolic agent, approved worldwide for the management of postmenopausal, male, and glucocorticoid-induced osteoporosis in adults. In addition, TPTD is used off-label in several other inherited and secondary conditions associated with bone fragility, with favorable results, at least in terms of increased BMD (72-74). Osteoanabolic agents have superior antifracture efficacy compared with BPs, especially in patients at high fracture risk, and recent evidence suggest that osteoanabolic treatment preceding antiresorptive agents results in higher BMD gains (75). While the pathophysiology of bone fragility in β-TM is multifactorial, defective osteoblast function, is a well

-established contributor of bone loss in these patients. TPTD, increases bone formation by direct actions on osteoblast precursors and mature osteoblasts, on bone lining cells and on the Wnt- pathway on osteoblasts and osteocytes, by suppressing sclerostin and by Wnt-ligand independent mechanisms (76).

(i) Efficacy

Information regarding the use of TPTD in patients with β-TM associated osteoporosis is limited to one retrospective case series (77) and single case reports (78,79). Gagliardi et al. (77) recently published the largest, so far, case series of 11 patients with β-TM and established osteoporosis (6 males and 5 females, mean age 45 ± 4.38 years) treated with TPTD for a mean duration of 18.7 ± 7.0 months (6 patients completed the 24 months TPTD treatment). Sixty-four percent of the patients were previously treated with BPs. The authors reported substantial improvements in BMD at the LS (19% and 22%) and at the TH (13% and 14.2%), at 12 and 24 months, respectively. Serum osteocalcin levels increased by 225% at the first year of treatment and remained above baseline (+54%) by the end of the second year. No fractures occurred during treatment, while the pain visual analogue scale did not change. Trotta et al. (78) described a case of a 43-year-old woman with multiple vertebral fractures while on alendronate, in whom treatment with TPTD for 18 months resulted in substantial increase of both LS and TH BMD, and no new fractures. Tournis et al. (79) also reported the efficacy of two courses of TPTD (18 months and 12 months) in a male patient with β-TM and multiple vertebral fractures while on alendronate. During the first 6 months of TPTD BMD at the TH decreased, followed by significant increase (9.3% and 9.8% at the FN and TH, respectively) at 18 months. Serum levels of the bone formation marker procollagen type I N-terminal propeptide (P1NP) continued to increase by the 18th month (+340%), while levels of the bone resorption marker β-C-terminal telopeptide (CTX) peaked at 12 months (+600%) and then dropped at 18 months. A second 12-month course of TPTD, after another 4 years with alendronate was then decided due to an insufficiency fracture of the left ischiopubic ramus and resulted in further BMD increases (10% and 5.3% at the FN and TH respectively). Bone turnover markers did not change during this second course (79).

Discontinuation of TPTD is followed by progressive loss of BMD (80), while subsequent treatment with BPs or Dmab results in further BMD gains (71,81,82). Although there are no such data in patients with β-TM, sequential treatment with antiresorptive agents should be applied. The FDA recently removed the 2-year in lifetime treatment limitation for TPTD in patients who remain at high risk for fracture. Thus, some β-TM patients may benefit from a longer duration or a second course TPTD treatment (83).

There are no data concerning combination therapy of TPTD with antiresorptive agents (i.e., zoledronate and Dmab) in patients with β-TM, although favorable results have been reported in postmenopausal osteoporosis (81,84).

(ii) Safety

In the study by Gagliardi et al (77) 45% of the patient's cohort reported side effects, including bone pain (5/11), muscle pain (4/11) and fever (1/10), while 3 patients discontinued therapy. Interestingly, the frequency of these side effects was higher compared to the pivotal TPTD trial (85), but the size of the study was small (77). There was no association between Hb levels, chelation regimen or iron status and bone pain (77). In the authors' personal experience these symptoms are commonly encountered in patients with β-TM, especially bone pain and chills. Concerning calcium homeostasis, TPTD treatment may worsen hypercalciuria, that is already observed in up to one-third of patients with β-TM (3). In the pivotal TPTD trial (85), 24h urinary calcium levels increased by 30 mg, although the incidence of hypercalciuria (> 300 mg/24h) per se, did not change. However, in cases with concomitant hypoparathyroidism, TPTD may have a neutral effect on renal calcium excretion. Close monitoring and proper treatment adjustment is required, especially in patients with kidney stones (up to 18.1%) (25) and/or under deferasirox therapy, that is known to increase urinary calcium excretion.

b) Other osteoanabolic agents

Up to date there are no studies evaluating the efficacy of the PTHrp analogue abaloparatide or the sclerostin inhibitor romosozumab in β-TM patients.

Authors' proposal on the management of bone fragility in β thalassemia major induced osteoporosis

According to the 2021 guidelines for the management of transfusion-dependent thalassemia by the Thalassemia International Federation (TIF) (86), assessment of BMD by dual-energy X-ray absorptiometry (DXA) should be performed every 24 months after the age of 10 years, accompanied by vertebral fracture assessment. In addition, annual assessment of bone health should include measurement of serum calcium, phosphate, alkaline phosphatase, 25 (OH) vitamin D, PTH (parathyroid hormone), and, ideally, one marker of bone formation, and one marker of bone resorption. Preventive measures are of paramount importance, including sufficient blood transfusions, optimal iron chelation, regular physical activity, adequate calcium and vitamin D intake, and hormone replacement therapy in cases of hypogonadism. In addition, specific anti-osteoporotic treatment with currently available anti-resorptive and osteoanabolic agents should be initiated in patients with very low BMD values, progressive significant BMD loss and/or fragility fractures (69). As osteoporosis is a chronic disease requiring long-term management, special consideration should be given in younger β-TM patients with low bone mass. None of the currently available anti-osteoporotic agents has proven efficacy and safety beyond 10 years of treatment, whereas the osteoanabolic agent teriparatide is administered for only 2 years. Additionally, all these agents are contraindicated or should be administered with great caution in women who are pregnant or even of childbearing potential.

The up-to-date experience with pharmacological agents in the management of β- TM-associated osteoporosis includes almost all commercially available anti osteoporotic agents, except for selective estrogen receptor modulators (SERMS) and the novel osteoanabolic agents, abaloparatide and romosozumab. Since most of the osteoporotic β-TM patients are premenopausal women or men, SERMs are not indicated. Currently there are no data available for the efficacy and safety of romosozumab and abaloparatide, in β-TM associated osteoporosis.

Indications for specific anti-osteoporotic treatment should be carefully balanced against the need for lifelong treatment, and the possible adverse effects of long-term BPs or the rebound phenomenon seen after denosumab discontinuation (69,70,87,88).

Based on data from postmenopausal women and men with osteoporosis, an initial 1 to 3-year course of zoledronate or up to 5 years oral BPs would be a relatively safe approach for osteoporotic patients with β-TM. Alternatively, a 3 to 5 years course of Dmab is also an option. Two years treatment with TPTD could be considered in cases of severe osteoporosis with fractures and should always be followed by a course of oral BPs of 1-2 years or one course of iv. administered zoledronate (Figure 2). Similarly, Dmab should be followed by treatment with BPs in order to prevent rapid BMD loss and the rebound in vertebral fracture risk (71,89). In this case, patients treated with Dmab for less than 2.5 years should be sequentially treated with 1-2 years of oral BPs or 1-2 years of zoledronate 5mg given annually. Patients with longer duration of Dmab treatment (>2.5 years) may require zoledronate infusion at 6 months intervals depending on BTM values or BMD changes (71).

After the initial treatment course and during follow–up, absence of new or worsening osteoporotic fractures and stability of BMD values, even in the osteoporotic/ osteopenic range, should be reassuring for premenopausal women and younger men with β-TM associated osteoporosis. On the contrary, progressive BMD decrease and/or new fragility fractures is an indication for re-initiating treatment (55). Transitioning from an antiresorptive to an osteoanabolic agent is considered less effective than the opposite (90) as BMD increase is more modest and delayed, but should be considered in cases of treatment failure (91). Transitioning from one antiresorptive agent to another given at larger intervals (e.g., from oral BPs to IV zoledronate) or considered more potent (e.g., from

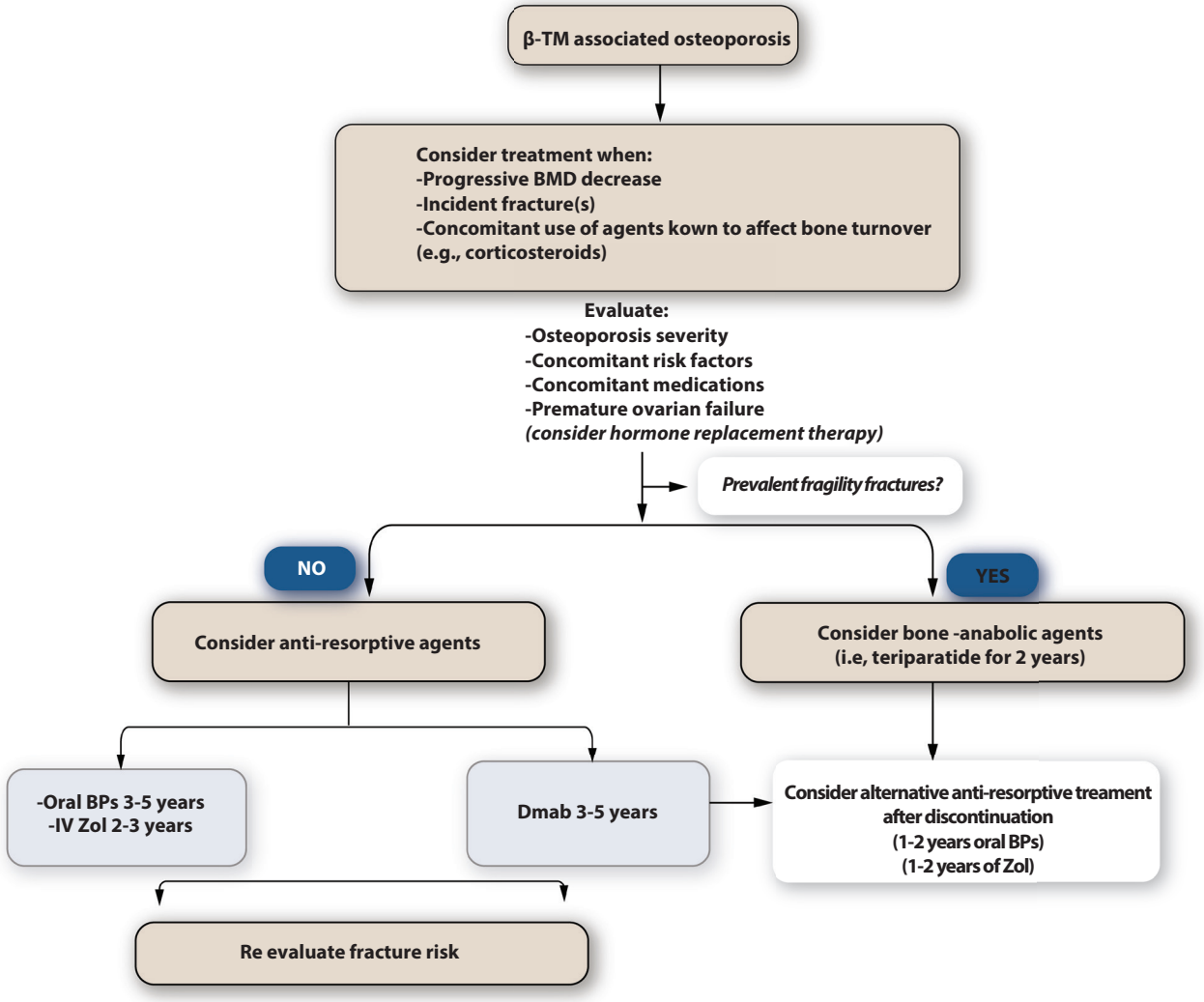

Figure 2. A proposed treatment plan of the use of anti-osteoporotic drugs in β -Thalassemia major associated osteoporosis.
Legend: β-TM = β -Thalassemia major; BMD = bone mineral density; BPs = bisphosphonates; Zol = zoledronate; Dmab = denosumab.

oral BPs to Dmab) could also be considered (90). Combined administration of anti-osteoporotic agents, mainly TPTD with Dmab or zoledronate have shown a clear advantage over TPTD monotherapy in patients with severe postmenopausal osteoporosis, but such combinations have not been tested in β-TM osteoporotic patients.

Nevertheless, the "treat to target" concept applied to date for postmenopausal osteoporosis is probably also valid for β-TM osteoporotic patients, suggesting that treatment decisions should be made targeting either stability in BMD or maintenance of low fracture risk (92). Concepts such as long-term treatment and drug-holiday, however, should be evaluated from a different point of view in these patients who have unique demographic (younger age) and pathophysiological (iron toxicity and anemia) characteristics of bone loss. A tailored treatment plan based on the patient's disease profile, needs, and preferences is what should be currently recommended among patients with β-TM associated osteoporosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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