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Could Denosumab Support Bone Integrity in Sickle Cell Disease

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Abstract

Sickle cell anaemia is a congenital disease characterized by painful vaso-occlusive crises. It is associated with vitamin D deficiency, osteoporosis and recurrent attacks of micro-infarctions lead to bone osteonecrosis. The most common sites of osteonecrosis in sickle cell disease are the femoral and humeral heads which could lead to severe pain and extensive physical disability. Denosumab is a new human monoclonal antibody product; it is a receptor activator of nuclear factor kappa B ligand RANKL. That decreases osteoclastic bone restoration. It is Food and Drug Administration FDA approved for osteoporosis for women with high risk of fracture; and it is also being used for the treatment and prevention of bone loss in patients undergoing hormone ablation therapy for breast and prostate cancer. Denosumab is not restricted for sickle cell disease patients within its approved indications. It has less nephrotoxicity effect than the bisphosphonates which is a big advantage for sickle cell patients. It also used as an adjuvant agent to reduce metastatic bone pain in solid tumors. The extension of Denosumab use for sickle cell patients' osteoporosis and osteonecrosis deserve a randomized multi central trail aiming to improve bone integrity and possible reduction of the devastating pain in sickle cell disease patients.

Sickle Cell Disease (SCD)

Sickle cell disease (SCD) is the most common inherited blood disorder, with a worldwide distribution. Sickle cell hemoglobin is formed when the amino acid valine is substituted for glutamic acid at the sixth position of the β chain; this is the result of a point mutation in the gene coding for β globin synthesis [1]. The abnormally sickle shaped red blood cells are removed from circulation and destroyed in the reticuloendothelial system at increased rate, resulting in anemia. Sickled erythrocytes can cause ischemia and infarctions during the vaso-occlusive crises (VOC) [2]. The pathogenesis of VOC is complex, which involve activation and adhesion of white blood cells, platelets and endothelial cells [3]. This process can occur in any organ, it is particularly common in bone marrow infarcts [4]. The causes of the vulnerability of bone marrow to micro vascular occlusion are unclear; however it may be because of marrow hypercellularity which lead to impaired blood flow and regional hypoxia [5]. Bone integrity in SCD affected by vitamin D deficiency and bone vasculature abnormalities which could lead to osteopenia, osteoporosis and osteonecrosis [6,7]. The low level of vitamin D in SCD is associated with decrease in mineral acquisition by the bone [8], so the bone mineral density (BMD) is reduced in such patients. In a study a total of 65 SCD patients. It revealed 18.5% with normal BMD, 57% with osteopenia and 16 24.5% with osteoporosis, the overall, 53 patients (81.5%) had BMD below normal standards [9]. Normal bone vasculature is essential for skeletal development, modeling, remodeling, growth, and healing processes. Endothelium is an integral part of bone tissue expressing the physiological paracrine function via growth factors, chemokines release and interacting with several cellular lines. Alterations of the complexity between biochemical interactions, vasculature and bone cells may lead to various bone pathological and clinical manifestations [7]. The VOC in SCD is the prominent devastating phenomena; it causes impaired nourishment of critical structures in the big joints, lead to bony lesions with loss of trabeculae resulting in osteonecrosis and vertebral collapse [10]. The vaso-occlusive crises, also could affect the vertebrate and ribs [11]. Osteonecrosis was found in the epiphysis of almost 41% of adults with sickle cell disease [12-14]. Low whole body bone mineral content also found among the SCD more than the controls with normal hemoglobin. The participants in this study also found to have lower than normal vitamin D status [15].

Pain in SCD

Pain in SCD is the earliest, clinical manifestation and the major cause of hospitalization mainly by the painful vaso-occlusion crises [16]. Chronic pain occurs following recurrent crises, which leads to destruction of bones, joints and organs [17]. Most patients with osteonecrosis report a sudden onset of acute sever pain [18]. Vitmain D deficiency, osteopenia and osteoporosis could also cause pain in SCD patients [19-21]. In the meanwhile bisphosphonate, denosumab with vitamin D and calcium supplement are a major agents in treating low BMD due to osteopenia and osteoporosis in general population even including SCD patient because there is no restrictions in using such agents in SCD patients[22]. Denosumab and the several types bisphosphonate also used in bone metastasis in cancer patients as an adjuvant agents to reduce sever bone pain. Pamidronate disodium has shown to reduce the pain, hypercalcemia, and skeletal morbidity associated with breast cancer and multiple myeloma. Zoledronic acid has also been shown to relieve pain due to metastatic bone disease. Ibandronate another bisphosphonate, shown in a small trial to reduce

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pain in women with metastatic breast cancer. Older agents, including clodronate and sodium etidronate, appear to provide little or no analgesia [23]. As it is known in both SCD and cancer patients they have severe pain due to bone involvements.

Denosumab Role in Bone Integrity

Denosumab is a human monoclonal IgG2 antibody [24]. It is the newest bone antiresorptive agent, with a novel mechanism of action [25]. It is approved by FDA on 2010 for the treatment of osteoporosis in post menopausal women at high risk for fracture or for patients who have failed or are intolerant to other available osteoporosis therapies [26,27] also it was approved later for bone loss associated with hormone ablation therapy in prostate and breast cancer patients. The identification of RANK and RANK-L pathway in 1990 opened up the opportunity of developing this agents which would decreases osteoclastic bone resorption by inhibiting RANKL [28,29]. Binding of denosumab to RANKL inhibits its actions; consequently, so osteoclast recruitment, maturation and action are inhibited, and bone resorption slows [30]. It prevents the interaction of the receptor activator of nuclear factor kappa B ligand (RANK-L) with the receptor activator of nuclear factor kappa (RANK) and, thus, inhibits bone resorption [31]. Denosumab Recently approved also for unresectable giant cell tumor of bone in adults. It increase bone mass in patients at high risk for fracture including androgen deprivation therapy, prostate cancer, in breast cancer, and prevention of skeletal-related events in patients with bone metastases from solid tumors [32].

Denosumab versus bisphosphonate

There are many agents available for the treatment of bone integrity. Route and frequency of administration, adverse effects, and drug interactions should be taken into consideration when selecting therapy [33]. Denosumab treatment led to significantly greater reduction of bone turnover markers compared with alendronate therapy. Adverse events and laboratory values were similar for denosumab and alendronate treated subjects. Denosumab showed significantly larger gains in BMD and greater reduction in bone turnover compared with alendronate. The overall safety profile was similar for both treatments [34]. Denosumab has been used safely in renal failure so may be of particular benefit in this setting for the SCD patients because their kidneys are potentially in high risk of renal impairment because of the systemic micro-infarct [35,36]. RANKL inhibition prevents the fusion of monocytes-macrophages to become multi nucleated osteoclasts [37], whereas long-term bisphosphonate treatment has been associated with an increase in the number of osteoclasts, including giant, hyper nucleated [38]. Denosumab is the strongest bone protective agent, which has been demonstrated in an integrated analysis of 3 large head-to-head trials. Its unique mechanism of action allows administration to patients regardless of renal and hepatic functions [39]. Since denosumab specifically binds RANKL, it is less likely to affect the immune system or other regulatory system [40]. Denosumab does not have the potential for autoimmunization against the vital regulatory proteins and is characterized by a longer half-life, which permits less frequent dosing [41]. Each of these attributes makes denosumab a more attractive therapeutic agent than other forms of Osteoprogtegerin [42]. Denosumab significantly reduce the risk of Skeletal Related Events (SREs) compared with zoledronic acid. The improved efficacy with denosumab was observed as early as 6 months. The greater inhibition of osteoclast-induced bone resorption by Denosumab translates into improved clinical outcomes [43]. The availability of the monoclonal antibody denosumab, representing a new generation of bone targeted agents. Currently, in the oncology setting, the European Medicines Agency (EMA) has approved denosumab (60 mg subcutaneous every 6 months), while Zoledronic acid is the only bisphosphonate to provide statistically significant and durable reductions in the risk of SREs versus placebo in a randomized, controlled trial and to have received wide-spread regulatory approval [44].

Denosumab was superior to zoledronic acid in delaying or preventing SREs in patients with breast cancer, bone metastatis and was generally well tolerated with the convenience of a subcutaneous injection and no requirement for renal monitoring [43].

Side Effects

The most common adverse effects identified in initial studies of postmenopausal women include arthralgia, nasopharyngitis, back pain, headache, extremity pain, upper respiratory infection, constipation, urinary tract infection, and shoulder pain. Side effects such as sore throat and asymptomatic hypocalcemia have also been reported [45]. Malignancy has also been a concern with denosumab; however, current studies have not demonstrated a statistically significant increase in these events. Denosumab is contraindicated in patients with severe hypocalcemia. There is an increased risk of serious infections, including skin infections [33]. Osteonecrosis of the jaw has been observed in patients receiving denosumab, and all patients should receive an oral exam prior to therapy initiation and maintain good oral hygiene during therapy. Bone turn-over is significantly suppressed with denosumab, and all patients should be monitored for the consequences of bone suppression, such as Osteonecrosis of the Jaw, atypical fractures, and delayed fracture healing [46]. The Panel emphasized caution when considering denosumab treatment according to FDA-approvals it has as bisphosphonates a very long half- life, and should be used with extreme caution in women of childbearing age for concerns of teratogenicity, Patients with impaired immune systems or those on concomitant immunosuppressant agents may be at an increased risk and the benefits and risks of starting denosumab should be evaluated. Dermatologic reactions, such as rash, eczema, and dermatitis have been reported with denosumab [47]. Denosumab is bone antiresorptive agent as bisphosphonate drugs which could be helpful in delaying collapse of the femoral head in cancer patients with SREs and thus delaying the need for surgical intervention [48,49]. At the time being the long-term symptomatic treatment for osteonecrosis is ineffective and the big joints require surgery for pain relief and for functional improvement. In advanced osteonecrosis, the disease course will eventually require surgery. Patients with osteonecrosis related to SCD can be severely disabled where hip or shoulder arthroplasty remains the only surgical option for some of these patients [50], where the disease course will eventually require hip or shoulder arthroplasty [51].

Conclusion

No restrictions from the FDA to use Denosumab within the SCD patients. Denosumab showed high effectiveness in preserving bone integrity and helpful in delaying collapse of the femoral head. It has superior action in delaying or preventing skeletal-related events in

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patients with some metastatic cancers to bone and was generally well tolerated. The side effects are less toxic than bisphosphonates and the subcutaneous route of administration is more convents. We extrapolate our thought to the possibility of starting a multi-central randomized trial study for using denosumab in sickle cell patients to preserve bone integrity from progressing to bone fracture and it could also minimize the chronic devastating pain in SCD patients.

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