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Denosumab is effective in the treatment of bone marrow oedema syndrome

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ABSTRACT

Bone marrow oedema (BMO) syndrome describes a painful condition with increase of interstitial fluid within bone and is often lately diagnosed due to unspecific symptoms. The underlying causes are diverse while it is widely assumed that in cases of BMO local bone resorption is increased. Denosumab, a human monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand (RANKL) inhibits osteoclastic bone resorption and is commonly administered in the treatment of osteoporosis. Besides one previous case report, its clinical effectiveness in the treatment of bone marrow oedema has not been elucidated. We treated 14 patients with primary (idiopathic) bone marrow oedema of the lower extremity with single dose denosumab application. Mean time between onset of pain and therapy was 155 days. MRI scans were performed for initial diagnosis, and 6–12 weeks after denosumab injection. Vitamin D and calcium homeostasis were strived to be balanced before initiation of therapy. Furthermore bone status was analysed using Dual-energy X-ray absorptiometry (DXA) and extended bone turnover serum markers. After 6–12 weeks, BMO dissolved partly or completely in 93%, while a complete recovery was observed in 50% of the individuals. Visual analogue scale (VAS) evaluation revealed a significant decrease in pain level. Furthermore, bone turnover decreased significantly after treatment. No adverse reactions were reported. In conclusion, our retrospective analysis shows that denosumab is highly effective in the treatment of bone marrow oedema and therefore represents an alternative treatment option.

Introduction

Bone marrow oedema (BMO) syndrome describes a state of increased fluid in the bone accompanied by unspecific joint pain [1]. While various conditions including vitamin D deficiency, osteoarthritis, rheumatoid arthritis, fractures and tumours may lead to bone marrow oedema seen in magnetic resonance imaging (MRI), it is also considered an isolated finding (primary, idiopathic) [2]. The pathophysiology of BMO is poorly understood and thought to be multifactorial. Histological findings suggest abnormal vascularity and increased focal bone turnover [3]. It is still not clear whether BMO syndrome represents an early stage of avascular necrosis or a transient disease itself [4]. The lack of osteonecrosis in histological analyses of BMO specimens, as well as marked increases of bone turnover in these patients suggest an own entity [5].

BMO most commonly affects middle aged patients and weight-bearing joints [6]. However, no large adequate epidemiological studies are available so far. The correct diagnosis is often delayed due to unspecific symptoms and the inability to assign symptoms to BMO, since BMO is not commonly known and often a diagnosis of exclusion. Only in MRI, bone marrow oedema can be diagnosed, and an early diagnosis has been found essential regarding the therapeutic success [7]. The main risk of BMO is the progression towards osteonecrosis and joint destruction [8].

Intravenous bisphosphonates, prostacyclin treatment as well as extracorporeal shock wave therapy showed reduction of bone marrow oedema [6,9–11]. Furthermore, intravenous bisphosphonates have been found to be effective in the treatment of BMO in professional athletes [7]. A positive therapeutic effect of denosumab has only been shown in a single case of bone marrow oedema of the knee [12]. However, there has been no study to comparatively demonstrate the outcome of denosumab treatment

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in bone marrow oedema in all three major weight-bearing joints. Hence, in this study we aimed to address the success rate of this anti-resorptive drug.

Methods

This retrospective study (level of evidence 3) included 14 symptomatic patients with atraumatic bone marrow oedema (BMO) syndrome. All major causes of secondary bone marrow oedema were excluded. The affected skeletal sites were femoral head (n = 8), distal femur (=5) and metatarsus (n = 1). All patients were treated with 20′000 IE vitamin D weekly prior to the denosumab (Prolia®) application. The injection consisted of a single dose of subcutaneous denosumab 60 mg. Informed consent for the off-label use was obtained from each patient and alternative treatment options were explained precisely.

MRI scans were performed at least twice: (1) In order to diagnose BMO and (2) 6–12 weeks after the denosumab treatment. Evaluated MRI sequences were short-tau inversion recovery (STIR) when available or fat-saturated (FS), proton density (PD)-weighted images. Bone marrow oedema development was classified in MRI images as completely dissolved ("Recovery"), partly dissolved ("Reduction"), constant or worsened. A visual analogue scale (VAS) to measure pain was performed at initial consultation and after therapy.

In the context of osteological diagnostics laboratory tests for bone turnover were performed and bone mineral density (BMD) was determined for each patient using dual-energy X-ray absorptiometry (DXA) bone densitometry (Lunar iDXA; GE Healthcare; Madison, WI, USA) in the lumbar spine and proximal femur. Laboratory tests included calcium, 25-hydroxyvitamin D_3 (25-OH-D_3), parathyroid hormone (PTH), osteocalcin, bone specific alkaline phosphatase (BAP), and deoxypyridinoline (DPD) cross links per creatinine in the urine.

For statistical analyses of the pre- and post-interventional data including laboratory results and pain levels on the VAS, a paired *t*-test was performed using SPSS 22 (IBM, Armonk, New York, USA). A p-value < 0.05 was considered statistical significant. This retrospective analysis was evaluated according to the rules of the local ethics committee of the University Medical Center Hamburg-Eppendorf, Germany.

Results

From 14 patients included in this study, all patients were diagnosed with symptomatic BMO. Mean age of the included individuals was 49 years (18–79 years). According to DXA measurements, four patients were diagnosed with osteoporosis (T-score < -2.5), while six were found to have osteopenia in the femoral neck or spine (T-score between -1 and -2.5), and four a bone mineral density within the reference range. Mean time between onset of pain to denosumab treatment was 5.2 ± 4.3 months (155 days). In all patients calcium levels were within the reference range at initial consultation, while 25-OH-D3 >30 μg/l was present in 10/14 patients and >20 μg/l in 12/14 patients before denosumab treatment (Table 1).

In five individuals DPD cross-links were elevated indicating increased bone resorption. Besides the normalization of calcium homeostasis by vitamin D treatment, denosumab was the only bone specific medication given to our patients. Only one case (*Case 14*, foot) had received a previous ibandronate treatment, while two patients (*Case 7, 8*, hip) underwent additional core decompression right after denosumab administration due to a subchondral demarcation seen in MRI, and one patient (*Case 10*, knee) underwent additional knee arthroscopy due to a diagnosed meniscus tear.

6-12 weeks after denosumab treatment the bone marrow oedema resolved completely in 7/14 (50%) patients and was reduced in additional 6 patients, while it remained constant in only one patient (*Case 10*) and worsened in no case. This indicates an overall treatment success of 93% and a treatment success of 78.5% not including the patients with additional core decompression. In the hip, bone marrow oedema was successfully treated in both old and young patients (*Case 4, 6*; Fig. 1a and b), while we could detect a reduction of BMO in cases with denosumab application plus core decompression (*Case 7*, Fig. 1c). In the knee, BMO of the lateral femur condyle was treated successfully (*Case 12*; Fig. 2a). Moreover, one patient (*Case 9*) suffering from spontaneous osteonecrosis of the knee (SONK/Morbus Ahlback/medial condyle) accompanied by bone marrow oedema showed equal improvement of BMO in MRI (Fig. 2b). Although we could only include one patient with BMO of the foot, this young patient recovered completely from the oedema in the cuboid and metatarsus even after unsuccessful ibandronate treatment in the past (Fig. 3).

Overall, VAS score decreased significantly between initial presentation and post-intervention (Fig. 4a). Furthermore, bone turnover in terms of DPD cross links (bone resorption, Fig. 4b), as well as BAP and Osteocalcin (both bone formation, Fig. 4c and d) decreased significantly. Mean calcium level did decrease during therapy, but no deviation below reference range was noted. 25-OH-D_3 levels further increased from 30.9 μg/l to 39.9 μg/l along the denosumab treatment period. The treatment was well tolerated in all 14 patients with no side effects.

Table 1
Individual data for each patient at initial presentation.

Subject	Sex M/F	Age years	Location of BMO	Time until Therapy months	25-OH-D3 μg/l	PTH ng/l	DPD nmol/mmol	BAP μg/l	Osteocalcin μg/l	BMO Development	Previous Treatment
1	M	48	Femoral Head	2	12.7	82	4	29.3	15.1	Reduction	/
2	F	66	Femoral Head	8	32.6	34.4	10	14.4	26.1	Reduction	/
3	M	41	Femoral Head	3	31.5	79.5	5	15.1	18	Recovery	/
4	M	70	Femoral Head	3	19	86	7	9.5	17.9	Recovery	/
5	F	61	Femoral Head	9	26.7	48.6	5	11.9	15.4	Recovery	/
6	F	18	Femoral Head	3	37.1	36.7	4	15.9	31	Recovery	/
7	F	20	Femoral Head	5	36.9	28	6	17.5	15.1	Reduction	Core Decompression
8	F	32	Femoral Head	4	46.7	57	9	19	30.6	Reduction	Core Decompression
9	M	70	Knee	4	26	89.3	4	11.8	16.5	Reduction	Arthroscopy
10	M	43	Knee	6	18.1	69.7	3	13.9	17.4	Constant	/
11	M	57	Knee	3	42.2	72.8	6	18.9	19.4	Recovery	/
12	F	79	Knee	1.5	38.7	36	14	12.6	23.1	Reduction	/
13	M	54	Knee	3	32.4	59.6	5	11.2	17.6	Recovery	/
14	M	29	Metatarsus	18	32.9	28.3	3	13.8	17.3	Recovery	Ibandronate