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Review Article

Off-label uses of denosumab in metabolic bone diseases

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ABSTRACT

Denosumab (Dmab), a monoclonal antibody against the receptor activator of nuclear factor-κB (RANK) ligand (RANKL) which substantially suppresses osteoclast activity, has been approved for the treatment of common metabolic bone diseases, including postmenopausal osteoporosis, male osteoporosis, and glucocorticoid-induced osteoporosis, in which the pathway of the RANK/RANKL/osteoprotegerin is dysregulated. However, the imbalance of RANKL/RANK/osteoprotegerin is also implicated in the pathogenesis of several other rare metabolic bone diseases, including Juvenile Paget disease, fibrous dysplasia, Hajdu Cheney syndrome and Langerhans cell histiocytosis, thus rendering Dmab a potential treatment option for these diseases. Dmab has been also administered off-label in selected patients (e.g., with Paget's disease, osteogenesis imperfecta, aneurysmal bone cysts) due to contraindications or unresponsiveness to standard treatment, such as bisphosphonates. Moreover, Dmab was administered to improve hypercalcemia induced by various diseases, including primary hyperparathyroidism, tuberculosis and immobilization. The aim of this review is to summarize existing evidence on off-label uses of Dmab in metabolic bone diseases and provide opinion for or against its use, which should be always considered on an individual basis.

1. Introduction

Denosumab (Dmab) is a monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL) that prevents RANKL binding to its receptor (receptor activator of nuclear factor-κB [RANK]) on the surface of osteoclast precursors, thus preventing osteoclast differentiation, fusion and survival [1,2]. The effect of RANKL is endogenously counteracted by osteoprotegerin (OPG), a neutralizing decoy receptor. Imbalance of the RANKL/RANK/OPG system is implicated in the pathophysiology of many metabolic bone diseases [1]. Dmab was initially approved for the treatment of postmenopausal osteoporosis [2], but its approval has been extended to other bone diseases, whose pathogenesis is linked to RANKL/RANK/OPG imbalance, including male osteoporosis, glucocorticoid-induced osteoporosis, aromatase inhibitor-induced bone loss in women with breast cancer, androgen deprivation-induced bone loss in men with prostate cancer, skeletal-related events (bone pain and fractures) of multiple myeloma and bone metastases from solid tumors, giant cell tumor of bone and hypercalcemia of malignancy [3]. However, the imbalance of RANKL/RANK/OPG system is implicated in the pathogenesis of many more metabolic bone diseases, most of which are rare, thus rendering the setting of a randomized controlled trial (RCT) with Dmab practically impossible. Nonetheless, Dmab has been administered off-label in patients with some of these rare diseases, with favorable results in some cases. Thus, the evidence regarding Dmab effects on most of these conditions is limited to case reports or case series.

The aim of this review is to summarize existing evidence on off-label uses of Dmab in metabolic bone diseases. This may clarify and facilitate Dmab use for some of these diseases in clinical practice in selected individuals. Bone diseases associated with rheumatologic diseases and malignancies were not included.

2. Literature and clinical trial search

A computerized literature search was performed in PubMed. Search was not limited by publication time or language. Medical Subject Heading (MeSH) database was used as a terminological search filter. From the combination of terminological (MeSH terms) and methodological search filters, the following query was formatted: "((denosumab) NOT ((postmenopausal osteoporosis) OR (glucocorticoid

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Table 1
Main reports on off-label use of denosumab in metabolic bone diseases.[a]

Reference	Disease	Number of cases (n)	Treatment duration (mo)	Regimen	Main finding(s)	Additional information
Dmab administered mainly for BMD and/or BTM improvement and/or fracture risk reduction						
Schwarz, 2012 [5]	Paget's disease of bone	1	15	60 mg every 3–6 mo	Decrease in bone pain and BTM Decrease in scintigraphic activity	Coexistence of renal failure
Verma, 2016 [8]	Paget's disease of bone	1	6	120 mg every 1 mo	Decrease in GCT mass Asymptomatic at 15 mo of follow-up following GCT excision at 6 mo	Coexistence of GCT
Kostine, 2017 [6]	Paget's disease of bone	1	–	Single injection of 60 mg	Decrease in bone pain and BTM	Coexistence of renal failure Severe hypocalcemia
Tanaka, 2017 [9]	Paget's disease of bone	1	12	120 mg every 1 mo	Clinical improvement Decrease in GCT mass	Coexistence of GCT
Kuthiah, 2018 [7]	Paget's disease of bone	1	–	Single injection of 60 mg	Decrease in bone pain and BTM	Coexistence of renal failure
Grasemann, 2013 [11]	Juvenile Paget disease	1	3	0.5 mg/kg twice	Decrease in bone pain and BTM Improvement in audiologic tests	Severe hypocalcemia and sHPT
Polyzos, 2014 [12]	Juvenile Paget disease	2	24	30–60 mg every 2–6 mo	Decrease in bone pain Normalization of BTM No deterioration in retinopathy or hearing loss	Deterioration of cataract (one patient)
Boyce, 2012 [15]	Fibrous dysplasia	1	7	Monthly, starting at 1 mg/kg escalating by 0.25 mg/kg every 3 mo	Decrease in bone pain and BTM Decrease in femoral tumor expansion Femoral fracture at 7 mo	Hypophosphatemia and sHPT Rapid rebound of BTM and severe hypercalcemia upon Dmab discontinuation
Ganda, 2014 [18]	Fibrous dysplasia	2	8–20	60 mg every 4–9 mo	Decrease in bone pain Normalization of BTM	Transient asymptomatic hypocalcemia and/or hypophosphatemia and sHPT
Benhamou, 2014 [17]	Fibrous dysplasia	1	6	60 mg every 6 mo	Decrease in bone pain and BTM	
Eller-Vainicher, 2016 [19]	Fibrous dysplasia	1	25	60 mg every 2.5–3 mo	Decrease in bone pain Normalization of BTM	Gradual shortening of the pain-free interval between administrations Transient sHPT
Majoor, 2019 [20]	Fibrous dysplasia	12	12–19	60 mg every 3 or 6 mo	Decrease in pain Decrease in BTM	No patient developed hypocalcemia Skin rash in one patient
Yassin, 2014 [23]	Thalassemia major	30	12	60 mg every 6 mo	Increase in LS and FN BMD Decrease in BTM	
Voskaridou, 2018 [24]	Thalassemia major	32 on Dmab vs. 31 on placebo	12	60 mg every 6 mo	Reduce in pain Increase in LS and radius BMD Decrease in BTM	Randomized controlled trial
Chen, 2014 [34]	CKD/sHPT	12 on Dmab vs. 8 no treatment	–	Single injection of 60 mg	Increase in LS and FN BMD Decrease in bone pain Decrease in PTH levels Decrease in calcium$_*$phosphorus product	4 patients developed symptomatic hypocalcemia
Chen, 2015 [35]	CKD/sHPT	24 on treatment vs. 8 no treatment	–	Single injection of 60 mg plus calcitriol (2 μg/d) plus calcium carbonate (3 g/d) plus calcium diacylate (3.5 mEq/l)	Increase in LS and FN BMD Decrease in PTH Regression of parathyroid adenoma size	8 patients developed hypocalcemia
Hiramatsu, 2015 [31]	CKD	11	–	Single injection of 60 mg	Increase in LS and FN BMD	
Cheng, 2017 [30]	CKD	108	12	60 mg every 6 mo	Increase in FN BMD	
Festuccia, 2017 [29]	CKD	12	24	60 mg every 6 mo	No effect on quantitative ultrasound index Decrease in BTM	3 patients developed hypocalcemia
Takami, 2017 [32]	CKD	17 on Dmab vs. 20 no treatment	12	60 mg every 6 mo	Increase in radius BMD	Only men
Iseri, 2019 [33]	CKD	22 on Dmab vs. 24 on alendronate	12	60 mg every 6 mo vs. i.v. alendronate 900 μg every 4 weeks	Similar increase in LS, FN, radius BMD Similar decrease in BTM except for TRACP-5b (Dmab more effective)	Randomized Controlled Trial

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Table 1 (*continued*)

Reference	Disease	Number of cases (n)	Treatment duration (mo)	Regimen	Main finding(s)	Additional information
Bonani, 2016 [41]	Kidney transplantation	46 on Dmab vs. 44 on placebo	12	60 mg every 6 mo	Increase in LS, FN and TH BMD Increase in volumetric BMD and cortical thickness at the distal tibia and radius in HR-pQCT No Dmab effect on graft rejection	Randomized controlled trial Higher rates of hypocalcemia and urinary tract infections with Dmab
Maehana, 2017 [43]	Kidney transplantation	4	12	60 mg every 6 mo	Increase in LS and FN BMD	
Brunova, 2018 [39]	Solid organ transplantation	63	20	60 mg every 6 mo	Increase in LS and FN BMD No effect on radius BMD	
Bonani, 2019 [40]	Kidney transplantation	23 on Dmab vs. 21 no treatment	12	60 mg every 6 mo	Increase in LS aBMD No significant effect on trabecular bone score	
Hoyer-Kuhn, 2014 [51]	Osteogenesis imperfecta type VI	4	24	1 mg/kg every 3 mo	Increase in LS BMD Rapid decrease in BTM Vertebrae reshape phenomenon Slight improvement in mobility	BTM returned to pre-treatment levels in 6–8 weeks after Dmab
Hoyer-Kuhn, 2016, [50]	Osteogenesis imperfecta type I, III, IV	10	12	1 mg/kg every 3 mo	Increase in LS BMD	Long bone Fx were observed in 4 patients during treatment
Uehara, 2017 [55]	Osteogenesis imperfecta type I	3	24	1 mg/kg every 3 mo	Increase in LS and TH BMD	
Kobayashi, 2018 [56]	Osteogenesis imperfecta type I	8	4–54	60 mg every 6 mo	Increase in LS and TH BMD Decrease in BTM	A Fx was observed in 1 patient during treatment
Trejo, 2018 [48]	Osteogenesis imperfecta type VI	4	12–42	1 mg/kg every 3 mo	Increase in LS BMD	Hypercalciuria and hypercalcemia 7–12 weeks after Dmab
Rehberg, 2019 [54]	Osteogenesis imperfecta type I, III, IV	8	12	1 mg/kg every 3 mo	Increase in aBMD and trabecular bone score	
Orsolini, 2017 [60]	Indolent systemic mastocytosis	4	12	60 mg every 6 mo	Increase in LS and FN BMD Decrease in BTM	
Sanchez Lopez, 2018 [61]	Systemic mastocytosis	1	24	60 mg every 6 mo	NA	Maxillar osteonecrosis
Uehara, 2018 [63]	Neurofibromatosis type 1	1	24	60 mg every 6 mo	Increase in LS and FN BMD Late decrease in BTM	A vertebral Fx was observed during treatment
Vazquez, 2015 [65]	Osteoradionecrosis	1	24	60 mg every 2–2.5 mo	Marked increase in BMD Improved independence and quality of life	
Uehara, 2018 [67]	Multiple-system atrophy	2	18 and 24	60 mg every 6 mo	Increase in LS and TH BMD	
Kumara, 2018 [70]	Duchenne muscular dystrophy	1	18	60 mg every 6 mo	Increase in LS BMD Decrease in BTM No effect on linear growth	Moderate hypocalcemia and sHPT
Gifre, 2016 & 2017 [73,74]	Spinal cord injury-associated bone loss	14 (15)	12	60 mg every 6 mo	Increase in LS, FN and TH BMD Decrease in BTM and sRANKL No effect on osteoprotegerin	
Jamieson, 2016 [77]	Anorexia nervosa	1	36	60 mg every 6 mo	Marked increase in LS, small increase in TH and reduction in FN BMD	No menses or weight gain during Dmab treatment
Lefever, 2018 [79]	Hypophosphatasia	2	NA	NA	Bilateral atypical femoral fractures in one patient	
Sanchez, 2016 [82]	PLO	2	12	60 mg every 6 mo	Case 1: Increase in volumetric BMD and thickness at radius and tibia in HR-pQCT Case 2: Increase in LS BMD	
Ijuin, 2017 [83]	PLO	1	–	Single injection of 60 mg	Increase in LS and FN BMD	
Dmab administered mainly to manage symptoms and lesions						
Adami, 2016 [86]	Hajdu Cheney syndrome	1	24	60 mg every 6 mo	Decrease in BTM Increase in LS and FN BMD	No effect on the progression of acroosteolysis

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Table 1 (*continued*)

Reference	Disease	Number of cases (n)	Treatment duration (mo)	Regimen	Main finding(s)	Additional information
Jerzakowski, 2017 [87]	Hajdu Cheney syndrome	1	8	60 mg every 6 mo	Decrease in metacarpal pain Increase in LS, but not FN BMD	No effect on the progression of acroosteolysis
Makras, 2017 [95]	Langerhans cell histiocytosis	2	6	120 mg every 2 mo	Pain relief Almost full remission of baseline lesions	A new lesion in one patient despite treatment
Bredell, 2018 [96]	Giant cell granuloma	5	12–15	120 mg every mo	Full clinical response	
Kurucu, 2018 [104]	ABC	9	6–14	70 mg/m^2 every week for the 1st month, then 70 mg/m^2 every month	Clinical improvement Radiological improvement in 7 patients	Disease progression in 1 patient Hypercalcemia in 2 patients after Dmab discontinuation Disease recurrence in 4 patients after Dmab discontinuation
Palmerini, 2018 [105]	ABC	9	3–55	120 mg every week for the 1st month, then 120 mg every month	Pain relief Radiological improvement	
Raux, 2019 [107]	ABC	5	4–23	70 mg/m^2 every month	Pain relief Improvement in neurological deficits (3 patients)	Mild hypocalcemia in 2 patients
Byberg, 2018 [120]	Melorheostosis	1	16	60 mg every 2 mo	Decrease in bone pain and BTM	Early pain relapse
Hallmer, 2018 [123]	Diffuse sclerosing osteomyelitis	2	20 and 12	Case 1: 120 mg every month for 3 months, then 120 mg in pain reccurence (5–6 mo); Case 2: 60 mg in pain reccurence (4 mo)	Complete pain resolution	
Otto, 2018 [122]	Diffuse sclerosing osteomyelitis	1	12	60 mg every 6 mo	Complete pain resolution	
Rolvien, 2017 [125]	Bone marrow edema	14	–	Single injection of 60 mg	Complete or partial resolution of lesions Decrease in pain	
Zaldibar Barinaga, 2019 [126]	Bone marrow edema	3	–	Single injection of 60 mg	Resolution of lesions	
Meiss, 2017 [129]	Perthes' disease	1	–	Single injection of 60 mg	Consolidation of the osteotomy and re-ossification	The results cannot be directly attributed to Dmab because of the subsequent osteotomy
Cai, 2018 [130]	Low back pain due to Modic changes	31 on Dmab vs. 35 on zoledronic acid vs. 37 on placebo	–	Single injection of 60 mg vs. single infusion of zoledronic acid 5 mg	Decrease in low back pain in Dmab and zoledronic acid compared to placebo in low back pain rating scale, but not in VAS	Randomized controlled trial
Nozawa, 2019 [132]	Gorham-Stout disease	1	–	Single injection of 120 mg plus sirolimus	No effect on the progression of the disease	
Matsumoto, 2019 [131]	Gorham-Stout disease	1	18	60 mg every 6 mo	Decrease in BTM No progression in the bone destruction	
Busch-Westbroek, 2018 [136]	Charcot neuropathic osteoarthropathy of the foot	11 on Dmab vs. 11 on standard treatment	–	Single injection of 60 mg	Shorter time to fracture resolution and on malalignment in Chopart-Lisfranc joint with Dmab vs. controls	
Dmab administered mainly to manage hypercalcemia						
Eller-Vainicher, 2018 [142]	pHPT	25 with pHPT vs. 25 with PMO	24	60 mg every 6 mo	Larger increase in LS and FN BMD in pHPT than PMO	2 patients in each group had an incident fracture
De Beus, 2012 [152]	Immobilization hypercalcemia	1	–	Single injection of 60 mg	Normalization of calcium for 2 months	Young adult with advanced renal insufficiency Transient hypocalcemia following Dmab administration
Booth, 2014 [151]	Immobilization hypercalcemia	1	–	Single injection of 60 mg	Normalization of calcium for 4 months	CKD stage 4

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Table 1 (*continued*)

Reference	Disease	Number of cases (n)	Treatment duration (mo)	Regimen	Main finding(s)	Additional information
Dahmani, 2017 [150]	Immobilization hypercalcemia	1	–	Single injection of 60 mg	Calcium fluctuating between upper normal limit and mild elevation for the next 3 weeks	End stage renal failure
Uehara, 2017 [149]	Immobilization hypercalcemia	1	–	Single injection of 60 mg	Normalization of calcium for 1 week	Hemodialysis patient
Torres-Ortiz, 2018 [153]	Tuberculosis-associated hypercalcemia	1	–	Single injection of 120 mg	Calcium normalized after one week	Significant hypocalcemia was developed (3rd-4th week)
Khoury, 2012 [157]	Myelofibrosis induced hypercalcemia	1	–	Single injection of 120 mg	Normalized serum calcium levels for 2 mo	

Abbreviations: aBMD, areal bone mineral density; ABC, aneurysmal bone cyst; BMD, bone mineral density; BP, bisphosphonate; BTM, bone turnover markers; CKD, chronic kidney disease; Dmab, denosumab; FN, femoral neck; Fx, fracture; GCT, giant cell tumor; HR-pQCT, high-resolution peripheral quantitative computed tomography; LS, lumbar spine; mo, month; NA, not available; pHPT, hyperparathyroidism; PLO, pregnancy and lactation-associated osteoporosis; PMO, postmenopausal osteoporosis; sHPT, secondary hyperparathyroidism; tHPT, tertiary hyperparathyroidism; TH, total hip; TRACP, tartrate resistant acid phosphatase; VAS, visual analog scale.

[a] For each specific disease, when there are studies lying over case reports in the pyramid of evidence-based medicine, case reports are not presented in this table.

induced osteoporosis) OR (aromatase inhibitor) OR (androgen deprivation) OR (multiple myeloma) OR (bone metastases))) NOT review [Publication Type]", which led to the initial retrieval of 970 articles (last update: August 14, 2019). The literature search was extended by "hand searching" in the "related citations" links of all included articles in PubMed (first 40 articles per included article, after sorting according to the relevance), and the references of all included articles.

Although there may be an overlap in treatment targets in some conditions, retrieved diseases/conditions were grouped into three categories, according to the main target of Dmab administration: a) bone mineral density (BMD) and/or bone turnover markers (BTM) improvement and/or fracture risk reduction; b) management of symptoms (e.g., pain) and lesions; c) management of hypercalcemia. The main characteristics of the main reports retrieved are summarized in Table 1.

Additionally, we searched in the registries of clinical trials for ongoing clinical trials with Dmab administration in the conditions identified above. We used the tool provided by the World Health Organization (http://apps.who.int/trialsearch/), which provides the ability to search simultaneously in all large relevant databases worldwide, including, but not limited to ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, Japan Primary Registries Network.

2.1. Dmab administered mainly for BMD and/or BTM improvement and/or fracture risk reduction

2.1.1. Paget's disease of bone

Paget's disease of bone is reportedly the second most common bone disease, the first being osteoporosis. Bisphosphonates, and especially zoledronic acid, are the mainstay of its treatment [4]. Dmab has been administered in five patients with Paget's disease of bone, three with renal impairment, in whom bisphosphonates are contraindicated [5–7], and other two complicated with giant cell tumor, for which Dmab is regarded as standard treatment [8,9]. In patients with renal impairment, Dmab reduced bone pain and BTM without deteriorating renal function, but severe hypocalcemia was observed in one patient [6]. Notably, this patient had higher bone turnover [6] (compared with the one not experiencing hypocalcemia [5]) and was not compliant with calcium and vitamin D supplementation [6]. Higher Dmab dose was used in patients complicated with giant cell tumors leading to decrease in tumor mass and substantial clinical improvement [8,9]. Dmab should be considered in patients with Paget's disease of bone as alternative to bisphosphonate treatment; for example, when bisphosphonates are contraindicated (e.g., significant renal impairment) or when pagetic bone lesions are complicated with giant cell tumors. However, careful monitoring of calcium is needed, especially in patients with higher bone turnover.

2.1.2. Juvenile Paget disease

Juvenile Paget disease (JPD) is a rare disorder, mainly caused by mutations in the gene *TNFRSF11B,* encoding OPG [10]. Up to now, Dmab has been administered to five patients with JPD: an 8-year girl [11], two adults [12] and two more adults not yet published (Polyzos and Singhellakis). In adult patients with mild phenotype, Dmab (30–60 mg every 2–6 mo) was well tolerated and resulted in clinical and biochemical remission of the skeletal disease, without deterioration of hearing loss and retinopathy after a 2-year administration [12]. In the 8-year girl, who had severe phenotype, the administration of Dmab twice decreased bone pain and BTM more than previous pamidronate treatment, and improved audiological tests [11]. Nonetheless, severe hypocalcemia and secondary hyperparathyroidism (sHPT) occurred, which discouraged further Dmab use. Importantly, Dmab discontinuation resulted in acute deterioration in hearing [11]. Hypocalcemia was not observed in adult patients, presumably because bone turnover was lower when Dmab started [10]. One of the adults had also previously experienced severe hypocalcemia following zoledronic acid infusion,

Table 2
Registered clinical trials on Dmab in patients with metabolic bone diseases.

Disease/condition ID Registration date (DD/MM/YYYY)	Title	Design	Arms	Target sample size (n)	Duration (month)	Primary outcome
Dmab administered mainly for BMD or BTM improvement						
Fibrous dysplasia NCT03571191 18/06/2018	Denosumab Treatment for Fibrous Dysplasia	Single arm, open label, uncontrolled, phase 2	Dmab (120 mg every 1 mo)	14	6	Change in BTM
Thalassemia-induced osteoporosis NCT03040765 02/02/2017	Denosumab Versus Zoledronic Acid for Patients With Beta-Thalassemia Major-Induced Osteoporosis	RCT, open label, parallel assignment, phase 3	Dmab (60 mg every 6 mo) vs. zoledronic acid (single infusion of 5 mg)	40	12	Number of patients with ≥50% reduction in type-1 collagen carboxy telopeptide from the baseline
CKD-associated bone disease NCT02792413/EUCTR2016-000431-40 07/06/2016	Study Evaluating Denosumab on Bone and Vascular Metabolism in Osteoporotic Chronic Kidney Disease (HDENO)	RCT, triple blind, parallel assignment, multicenter, phase 4	Dmab (60 mg every 6 mo) vs. placebo	30	24	FN BMD change
Transplantation-associated bone disease NCT01377467 20/06/2011	Denosumab for Prevention of Osteoporosis in Renal Transplant Recipients (POSTOP)	RCT, open label, parallel assignment, phase 3	Dmab (60 mg every 6 mo) vs. placebo	90	12	LS BMD change
Transplantation-associated bone disease NCT03960554 16/04/2018	The Effects of 12-months of Denosumab on Bone Density in Prevalent Kidney Transplant Recipients (ProliaKTx)	RCT, double blind, parallel assignment, phase 2	Dmab (60 mg every 6 mo) vs. placebo	60	12	BMD change and change in bone strength measured by HR-pQCT imaging
Osteogenesis imperfecta NCT02352753/EUCTR2014-000184-40 02/02/2015	Multicenter, Single-arm Study to Evaluate Efficacy, Safety, & Pharmacokinetics of Denosumab in Children with OI	Single arm, open label, uncontrolled, multicenter, phase 3	Dmab (1 mg/kg up to a maximum of 60 mg every 6 mo)	153	36	LS BMD *Z*-score change
Osteogenesis imperfecta NCT03638128/EUCTR2018-000550-21 20/08/2018	Open-label Extension Denosumab Study in Children and Young Adults With Osteogenesis Imperfecta	Single arm, open label, uncontrolled, multicenter, phase 3	Dmab (60 mg every 6 mo)	150	18	Incidence of treatment-emergent adverse events
Systemic mastocytosis NCT03401060 17/01/2018	Interest of Denosumab Treatment in Osteoporosis Associated to Systemic Mastocytosis	RCT, triple blind, parallel assignment, multicenter, phase 3	Dmab (60 mg every 6 mo) vs. placebo	90	36	LS BMD change
Spinal cord injury-associated bone loss NCT01983475 14/11/2013	Denosumab Administration After Spinal Cord Injury	RCT, triple blind, parallel assignment, multicenter, phase 4	Dmab (60 mg every 6 mo) vs. placebo	24	18	Distal femur BMD change
Spinal cord injury-associated bone loss ACTRN12614000578606[a] 29/05/2014	The Effects of Denosumab (study medication) versus Placebo (Dummy medication) on Bone Density in People who have had a Spinal Cord Injury	RCT, double blind, parallel assignment, phase NA	Dmab (60 mg every 6 mo) vs. placebo	40	12	Total hip BMD change
Spinal cord injury-associated bone loss NCT03029442 24/01/2017	The Efficacy of Denosumab in Incomplete Patients Spinal Cord Injury	RCT, triple blind, parallel assignment, multicenter, phase 4	Dmab (120 mg every 6 mo) vs. placebo	32	18	Distal femur and proximal tibia areal BMD change
Anorexia nervosa NCT02567279[a] 02/10/2015	Impact of Denosumab in the Prevention of Bone Loss in Non-menopausal Women With Anorexia Nervosa (DIBLAN)	RCT, triple blind, parallel assignment, multicenter, phase 3	Dmab (60 mg every 6 mo) vs. placebo	84	12	LS BMD change
Anorexia nervosa NCT03292146 25/09/2017	Effects of Denosumab on Bone Mineral Density in Women With Anorexia Nervosa: A Pilot Study	RCT, double blind, parallel assignment, phase 1	Dmab (60 mg every 6 mo) vs. placebo	75	12	BMD change
Primary Hyperparathyroidism NCT01558115 20/03/2012	Denosumab in Primary Hyperparathyroidism	RCT, double blind, parallel assignment; phase 4	Dmab (60 mg every 6 mo; 24 mo) vs. placebo (12 mo)/Dmab (60 mg every 6 mo; 12 mo)	52	24	LS BMD change
Primary Hyperparathyroidism NCT03027557/EUCTR2016-001510-20 23/01/2017	Treatment of Primary Hyperparathyroidism With Denosumab and Cinacalcet (DENOCINA)	RCT, triple blind, parallel assignment, phase 3	Dmab (60 mg every 6 mo) vs. Dmab (60 mg every 6 mo) plus cinacalcet (30 mg daily) vs. placebo	46	12	BMD change
Dmab administered mainly to manage symptoms and lesions						
Langerhans cell histiocytosis NCT03270020 01/09/2017	Denosumab for the Treatment of Adult LCH	Single arm, open label, uncontrolled, phase 2	Dmab (120 mg every 2 mo)	12	6	Change in the activity status of the disease

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Table 2 (*continued*)

Disease/condition ID Registration date (DD/MM/YYYY)	Title	Design	Arms	Target sample size (n)	Duration (month)	Primary outcome
Bone marrow edema NCT01734824 28/11/2012	Treatment of Atraumatic Bone Marrow Edema With Denosumab and Teriparatide vs Placebo	RCT, single blind, parallel assignment, phase 2	Dmab (single injection of 60 mg) vs. teriparatide (20 μg daily; 3 mo) vs. placebo	90	3	Reduction or resolution of bone marrow edema
Charcot neuropathic osteoarthropathy ACTRN12617000937314 21/06/2017	Novel treatment of acute Charcot foot using the medication denosumab combined with immobilization	RCT, open label, no placebo, parallel assignment, phase 2	Dmab (60 mg every 6 mo) plus immobilization vs. immobilization	40	12	1) Foot improvement as assessed by calcaneal quantitative ultrasound parameters; 2) Time to normalization of foot temperature
Periprosthetic osteolysis NCT02299817/EUCTR2013-004940-48 24/11/2014	Denosumab for Treating Periprosthetic Osteolysis	RCT, double blind, parallel assignment, phase 2	Dmab (60 mg every 6 mo) vs. placebo	20	30	Change in the volume of the osteolytic lesion
CKD-associated bone disease ISRCTN92563400 01/11/2018	Changes in cardiovascular calcification after denosumab in dialysis patients with secondary hyperparathyroidism and low bone mass	Nonrandomized, open-label, parallel assignment, phase 2	Dmab (60 mg every 6 mo) vs. conventional treatment	21	6	Changes in coronary and abdomen aorta calcifications assessed by helical computed axial tomography

Abbreviations: BMD, bone mineral density; BTM, bone turnover markers; CKD, chronic kidney disease; Dmab, denosumab; FN, femoral neck; HR-pQCT; high resolution peripheral quantitative computed tomography; LCH, Langerhans cell histiocytosis; LS, lumbar spine; NA, not available; OI, osteogenesis imperfecta; RCT, randomized controlled trial.

[a] Terminated due to difficulty in recruitment.

starting at a much higher bone turnover rate [13]. Therefore, hypocalcemia does not seem to be drug specific, but associated with the bone turnover. Based on this consideration, Dmab may be initiated at a lower dose in patients with high BTM and subsequently be increased at the standard dose when BTM are normalized [10]; however, the validity of this speculation, the specific initial dose and the cut-offs for BTM remain to be showed by future research.

2.1.3. Fibrous dysplasia

Fibrous dysplasia is a rare skeletal disorder, caused by somatic activating mutations of the a-subunit of the Gs stimulatory protein, leading to dysregulated proliferation of bone marrow stromal cells (BMSCs) [14]. It is characterized by the replacement of normal bone and bone marrow by fibro-osseous tissue, resulting in pain, deformity and fractures [15]. The combination of fibrous dysplasia with one or more extraskeletal manifestations is termed McCune-Albright syndrome [15]. By using immunohistochemistry, RANKL expression was observed in cases of fibrous dysplasia [15,16]. Furthermore, a 16-fold and a 12-fold increase in serum RANKL and RANKL/OPG ratio, respectively, were reported in patients with fibrous dysplasia compared to apparently healthy controls, and RANKL levels were positively associated with the disease severity [14]. High RANKL levels were released in BMSCs cultures of fibrous dysplasia, whereas being undetectable in cultures of controls. Notably, BMSCs-induced osteoclastogenesis was prevented by Dmab addition [14], thus rendering Dmab a potential therapeutic target for fibrous dysplasia. Dmab has been administered in patients with fibrous dysplasia, resulting in reduction in pain, BTM and tumor growth rate, which were more prominent than those achieved with bisphosphonates in the past [15,17–19]. Hypocalcemia and/or hypophosphatemia and sHPT are common [15,18,19], being mild in most cases. In the largest to-date case series (n = 12), 10 patients reported improvement in pain, six of whom experienced complete pain remission [20]. All patients had been previously treated with bisphosphonates for a median time of 8.8 years. Notably, a sustained reduction in BTM was observed when Dmab 60 mg was administered every three, but not every six months [20]. Upon Dmab discontinuation, rapid BTM rebound and severe hypercalcemia have been observed in a patient [15]. BTM rebound may occur in < 6 months after Dmab injection in patients with higher disease activity [18,19]. The above imply the necessity of shorter than 6 months dosing intervals, similarly to other high bone turnover diseases, such as JPD [13]. A clinical trial testing Dmab in patients with fibrous dysplasia is ongoing (NCT03571191; Table 2).

2.1.4. Thalassemia bone disease

Thalassemia bone disease is a state of increased bone resorption, currently treated with bisphosphonates besides other disease-specific interventions (normalization of hemoglobin levels, adequate hormone replacement and effective iron chelation) [21].

RANKL levels have been found increased in patients with thalassemia [22]. In an uncontrolled trial in regularly transfused adults with thalassemia, Dmab for 12 months decreased BTM and increased both lumbar spine (LS) and femoral neck (FN) BMD [23]. More importantly, in an 1-year phase 2 RCT in patients with thalassemia major bone disease, Dmab reduced bone pain, decreased BTM and increased LS and radius BMD compared with placebo, and was well tolerated [24]. A phase 3 clinical trial comparing Dmab with zoledronic acid in patients with thalassemia-induced bone disease is ongoing (NCT03040765; Table 2).

2.1.5. Chronic kidney disease-associated bone disease

Low-energy fractures comprise a significant cause of morbidity and mortality in patients with chronic kidney disease (CKD) [25]. Although low BMD cannot differentiate the different types of renal osteodystrophy, it can predict fractures in patients with CKD stages 3–5 [26]. However, care must be taken to correctly identify and treat other forms of renal bone disease before initiating anti-osteoporosis treatment,

especially anti-osteoclastic agents [25].

The use of Dmab in patients with CKD has several advantages over bisphosphonates. First, there is no need for dose adjustment according to renal function [27], while there is no concern about nephrotoxicity or bone retention during long-term use. Regarding efficacy, in a secondary analysis from the FREEDOM trial, similar efficacy of Dmab treatment for 36 months was reported in women with different stages of CKD in terms of BMD increase and fracture risk reduction [28]; however, it should be noted that women with end-stage (stage 5) CKD were not included in this study. Regarding safety, including changes in renal function, no particular differences were observed between patients on Dmab or placebo.

Data regarding the effect of Dmab on BMD, mineral homeostasis and BTM in patients with end-stage renal disease (ESRD) are limited and are derived mostly, but not exclusively, from observational studies (Table 1) [29–32]. A recent 12-month RCT compared the effect of Dmab vs. i.v. alendronate (900 μg/4 weeks) on LS BMD in 46 patients on hemodialysis. Both treatments similarly increased LS BMD [33]. Regarding the effects on sHPT in patients undergoing dialysis, Dmab might be an effective treatment option by reducing calcium and phosphate efflux from bone and widening the therapeutic window for high dose vitamin D and calcium supplementation. Specifically, in an open-label prospective study, a single Dmab injection in patients with ESRD on dialysis and severe sHPT, decreased PTH, calcium*phosphorus product, reduced bone pain and increased BMD [34]. Four patients developed symptomatic hypocalcemia [34]. In a subsequent study with 24 patients on dialysis and severe sHPT (PTH > 800 pg/ml), the same group reported that Dmab along with high calcitriol, calcium carbonate and calcium diacylate resulted in regression of the size of parathyroid glands only in patients with high bone turnover, while it increased in 8 controls [35]. Notably, 33% of the patients developed hypocalcemia and 4% respiratory infections. These data indicate that Dmab might be a valuable treatment option to improve bone strength in patients with ESRD, especially those with high bone turnover. However, close monitoring and adequate calcium and calcitriol supplementation is important to prevent hypocalcemia [34–37], which might occur early (within 7–21 days) following Dmab injection and may be severe, requiring hospitalization in some cases. There are also two ongoing clinical trials with Dmab in patients with CKD-associated bone disease, the first aiming to study changes in FN BMD (NCT02792413/EUCTR2016-000431-40) and the second in vascular calcifications (ISRCTN92563400; Table 2).

2.1.6. Organ transplantation-associated bone disease

Both underlying disease and immunosuppression, especially glucocorticoid use, that follows successful organ transplantation cause bone loss and increase the fracture risk. Bone disease may differ depending on the organ that fails and may need different diagnostic and therapeutic approach [38].

In a pooled solid organ (kidney and pancreas, only kidney, and only liver) transplant population, Dmab treatment for approximately 20 months (mean) resulted in increase in LS and FN BMD [39]. In a post-hoc analysis of the same study, Dmab had a non-significant trend towards increase in trabecular bone score [40]. In an RCT in kidney transplant recipients, Dmab increased BMD at all sites that were comparable to those reported in postmenopausal women with osteoporosis and other patient groups [41]. Besides, areal BMD (aBMD), volumetric BMD and estimated bone strength at the tibia were also improved [41,42]. Similar effects of Dmab on BMD have been reported in a small retrospective study in Japanese patients [43]. BMD improvement has also been reported with combination of Dmab and calcitriol in a kidney transplant recipient with severe bone loss due to therapy-resistant sHPT [44]. Increased incidence of asymptomatic transient hypocalcemia and increased risk for urinary tract infections, mainly cystitis, have been reported in kidney transplant recipients treated with Dmab compared with placebo [41]. Sporadic cases of persistent hypocalcaemia with a dramatic increase in PTH have also been reported [45]. The risk of acute hypocalcaemia following Dmab was also reported in heart and lung transplant recipients [46]. Hypocalcaemia was associated with lower baseline mean estimated glomerular filtration rate, i.e. worst renal function, in these patients [46]. The effectiveness of Dmab on liver, heart or lung transplants has not been extensively studied with the exception of the pooled population reported above [39]. No adverse effect of Dmab on graft function has been reported. There are also two ongoing clinical trials aiming to study Dmab efficacy in patients with renal transplantation-associated bone disease (NCT01377467 and NCT03960554; Table 2).

2.1.7. Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a rare, inherited disorder characterized by reduced bone mass, increased bone fragility, skeletal deformities, and short stature [47]. Most cases are due to mutations in the two genes encoding collagen type-1, *COL1A1* and *COL1A2*, although mutations in several other genes involved in collagen processing, post-translational modification and crosslinking of type 1 collagen have been implicated in the pathogenesis of the disease [47]. From a pathogenetic point of view, antiresorptives are not the optimal approach for OI, since they could not restore the collagen defects. However, given the lack of a specific treatment restoring the collagen defects, bisphosphonates are currently the standard pharmacotherapy for patients with severe OI, despite concerns about their long-term safety and effectiveness [47,48].

Dmab has been administered in small, mostly pediatric, populations with OI. Patients included in all studies had been pretreated with bisphosphonates. The regimen used in children with OI in all studies was 1 mg/kg every three months [48–52]. Especially in case of mutations in the *SERPINF1* gene, which encodes pigment epithelium-derived factor (PEDF), Dmab seems to be a treatment closer to the pathogenetic defect, because experimental evidence suggests that loss of functional *SERPINF1* leads to activation of osteoclasts through the RANK/RANKL pathway [53]. Indeed, in four children with a mutation in *SERPINF1* causing OI type VI, who had poor response to bisphosphonates, treatment with Dmab for up to 33 weeks was well tolerated and rapidly decreased BTM, which, however, returned to pre-treatment levels 6–8 weeks after each injection [49]. The decrease in bone resorption markers was more pronounced than the decrease achieved with previous bisphosphonates use. In the 2-year extension of the above study, aBMD and *Z*-score at the LS gradually increased [51]. A slight improvement in mobility was also observed. More importantly, spine morphology revealed a stabilization or improvement of the vertebral shape with radiographic evidence of a re-shape phenomenon. However, the antiresorptive effect of Dmab injection seemed to last only 6 to 8 weeks, which prompted the investigators to decrease the interval between Dmab injections from the original 12 weeks to a 'minimum 10-week' interval [51]. This has been also proposed for other metabolic bone diseases, such as JPD [12]. Later on, other investigators also suggested that the effect of Dmab is of shorter duration in children with OI type VI than in adults with osteoporosis [52]. Furthermore, hypercalciuria and hypercalcemia 7–12 weeks after Dmab injection have been reported in another case series of children with the same type of OI treated with Dmab [48]. In the latest case series, when the interval between Dmab injections was increased to six months, LS BMD z-scores decreased rapidly [48]. In another study, children with OI type I, III or IV caused by mutations in *COL1A1* and *COL1A2*, treated with Dmab every three months, increased LS aBMD and *Z*-score at 48 weeks without significant changes in motor function, walking performance, spine morphometry or bone pain [50]. Four patients experienced long bone fractures during the study [50]. Likewise, in another pediatric series, increase in aBMD and trabecular bone score was higher after Dmab than previous bisphosphonate use [54]. In an adult case series, Dmab treatment every six months resulted in increase in LS and hip BMD with scarce fragility fractures or adverse events [55,56]. There are also two ongoing clinical trials with Dmab in patients with OI

(NCT02352753/EUCTR2014-000184-40 and NCT03638128/EUCTR2018-000550-21; Table 2).

2.1.8. Mastocytosis

Mastocytosis is an uncommon disease involving abnormal proliferation of neoplastic mast cells and infiltration of several organs, with a specific predilection for skin and bone marrow [57]. Indolent systemic mastocytosis is the most frequent variant with bone manifestations being the dominant clinical feature, characterized by bone pain, reduced bone mass, low energy fractures, and both osteosclerotic and osteolytic lesions [58,59]. In a recent small case series, Dmab was administered for 12 months in 4 postmenopausal female patients with established osteoporosis and a previous history of bisphosphonate treatment [60]. BMD increased along with a profound decrease in BTM in all patients. Notably, tryptase levels also decreased, implying a potential effect of Dmab on the activity of the disease [60]. Nonetheless, another case of systematic mastocytosis, treated with Dmab for two years because of esophagitis due to previous bisphosphonate use, experienced maxillar osteonecrosis [61]. A clinical trial testing Dmab in patients with systemic mastocytosis is ongoing (NCT03401060; Table 2).

2.1.9. Neurofibromatosis

Neurofibromatosis type 1 (NF1) is a multisystem disease caused by either inherited or sporadic mutations of the *NF1* gene. Apart from the neurofibromas and other tumors manifested in this disease, skeletal dysplasia and low bone mass are common clinical features [62]. Dmab was administered for a period of 2 years in a 58-year female patient with a history of osteoporosis, fragility fractures and previous alendronate treatment. BMD increased and BTM were eventually decreased at the end of the treatment period, despite the lack of a response during the first year of treatment and an incident vertebral fracture while on Dmab [63].

2.1.10. Osteoradionecrosis

Osteoradionecrosis is a serious complication of radiotherapy applied for cancer, which appears approximately one year after irradiation and can result in bone pain and pathological fractures [64]. In one case report, Dmab 60 mg every 2–2.5 months for 2 years significantly improved BMD, as well as the independence and quality of life of a 14-year male patient with multiple low energy fractures, considerable pain and marked functional impairment [65].

2.1.11. Multiple system atrophy

Multiple system atrophy results from central nervous system cell loss and/or dysfunction linked to aggregates of α-synuclein [66]. The disease lacks specific treatment and has poor prognosis. Symptoms include cerebellar ataxia, parkinsonism, and autonomic dysfunction. In two male patients, aged 54 and 68 years, with multiple system atrophy and established osteoporosis [67], Dmab substantially improved LS and hip BMD, while no adverse effects were reported.

2.1.12. Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked inherited disorder resulting from mutations in the dystrophin gene [68]. DMD is associated with an increased risk of low-energy fractures, due to the adverse effects of glucocorticoid therapy and the progressive muscle weakness leading eventually to loss of ambulation. Bisphosphonates were shown to increase BMD in patients with DMD [69]. Dmab was administered in a 13-year boy with a history of bilateral femoral neck fractures [70]. At 12 months, LS BMD was increased, while a moderate decrease in calcium and phosphate levels and sHPT were observed, partly owing to inability to swallow calcium and vitamin D supplements. BTM decreased after each Dmab injection. His linear growth was not affected [70]. Despite, these favorable results, more data are needed on Dmab in DMD or other inherited myopathies.

2.1.13. Spinal cord injury- associated bone loss

Spinal cord injury-associated bone loss is characterized by rapid deterioration of bone strength below the level of the lesion, at a rate of 4% and 2% per month at sites rich in trabecular and cortical bone, respectively, clearly exceeding other states of rapid bone loss, such as long-term bed rest (0.1% per week) or space flight (0.25% per week) [71]. Reduction in BMD seems to stabilize after 12–24 months, but it might continue, albeit at a slower rate, afterwards. It is reported that up to 81% of patients with complete spinal cord injury eventually develop osteoporosis. Bisphosphonates, especially zoledronic acid, might retard bone loss, when administered in the acute phase, while there are inconsistent results regarding their effectiveness in the chronic phase [71]. In a study in veterans with spinal cord injury-associated bone loss (n = 2675), Dmab was administered in 14 of them (0.5%), but its efficacy was not reported [72]. Dmab was administered for 12 months in 14 men with spinal cord injury-associated bone loss [73]. Dmab was well tolerated and led to substantial reduction in BTM and significant increases in LS, FN and total hip BMD. Although nine patients developed 29 urinary tract infections, their rate did not differ to that prior to Dmab administration. In a later report of almost the same group, substantial reduction in serum RANKL following Dmab was observed, with 10 patients having undetectable levels [74]. Furthermore, changes in RANKL were correlated with changes in total hip BMD. Dmab had no effect on serum OPG. These promising results should be confirmed in adequately controlled trials. There are two ongoing clinical trials with Dmab in patients with spinal cord injury-associated bone loss (NCT01983475 and NCT03029442); another clinical trial was early terminated because of low recruitment rate (ACTRN12614000578606; Table 2).

2.1.14. Anorexia nervosa

The complications of bone disease and low-energy fractures are a continuing source of concern for patients with anorexia nervosa and their clinicians [75]. There is currently no treatment specifically approved for bone disease in anorexia nervosa. Patients with anorexia nervosa have been reported to have increased circulating RANKL levels and a reduced OPG/RANKL ratio [76]. In a 29-year-old woman with low bone mass and a low-energy calcaneal trauma, a 3-year Dmab administration resulted in a marked increase in LS BMD by 14.8%, but a small increase in total hip (1.4%) and a 5.7% decrease in FN BMD [77]. A clinical trial administering Dmab in patients with anorexia nervosa is ongoing (NCT03292146) while another one was early terminated due to difficulty in the recruitment of patients (NCT02567279; Table 2).

2.1.15. Hypophosphatasia

Hypophosphatasia (HPP) is a rare metabolic bone disorder, characterized by low circulating alkaline phosphatase (ALP) levels and bone, muscle, dental and systemic manifestations, owing to mutations in the ALP gene (*ALPL*) [78]. Asfotase alfa is an enzyme replacement therapy developed to treat HPP [78]. However, its administration is limited by its high cost. Dmab has been administered in two patients with HPP, in whom osteoporosis was initially misdiagnosed [79]. Dmab treatment resulted in bilateral atypical femoral fractures in one of the patients [79]. Based on this observation and in line with the pathogenesis of the disease featuring low bone turnover, Dmab is not recommended in patients with HPP. Generally, the use of antiresorptives, including Dmab, should be more cautiously weighted in women with low ALP, because it could mask hypophosphatasia or other low bone turnover diseases, in which the use of antiresorptives might deteriorate bone strength by further reducing the turnover rate.

2.1.16. Pregnancy and lactation-associated osteoporosis

Pregnancy and lactation associated osteoporosis (PLO) is a rare condition, usually presenting with multiple vertebral fractures during the last trimester of the pregnancy or in the early postpartum period [80]. Given its poorly elucidated pathophysiology, the management of

PLO remains empirical. Adequate calcium and vitamin D intake along with discontinuation of breastfeeding are advocated by most experts. Although these measures result in BMD improvement in most cases, treatment with antiresorptive or osteoanabolic medications may be necessary. Several case reports and a few case series indicate that treatment with bisphosphonates or teriparatide results in BMD increase [80]; however, the necessity of such treatments in PLO is uncertain given the lack of RCTs comparing these medications with standard management (adequate calcium and vitamin D intake). Evidence regarding Dmab administration in PLO cases is limited. In a retrospective case series, Dmab was administered after delivery in five of 14 women with PLO [81], but its efficacy and safety were not reported. There are also three cases of PLO treated with Dmab. The first case refers to a woman with four vertebral fractures managed with kyphoplasty during her first pregnancy [82]. She was treated with Dmab for one year. There was substantial improvement in trabecular volume and thickness at the radius and tibia. The second case received Dmab after 1-year treatment with strontium ranelate, leading to increase in LS BMD [82]. Another woman, with three vertebral fractures after delivery, received Dmab following a six-month course with weekly teriparatide [83]. Treatment with Dmab led to additional increase in LS and FN BMD. There are some important issues that need to be considered before using Dmab in PLO or generally in premenopausal women. First, as pregnancy progresses, higher transport of monoclonal antibodies, like Dmab, to the fetus is expected. Second, it remains largely unknown whether Dmab is excreted in human milk, although animal data suggest that RANKL inhibition might impair lactation. More importantly, Dmab discontinuation, after treatment for a relatively short period in women with PLO, may increase the risk of multiple vertebral fractures, as shown in women with postmenopausal osteoporosis [84]. Considering the above, the use of Dmab should be avoided in women with PLO.

2.2. Dmab administered mainly to manage symptoms and lesions

2.2.1. Hajdu Cheney syndrome

Hajdu Cheney syndrome (HCS) is a rare genetic autosomal dominant disorder characterized by severe osteoporosis, acroosteolysis and craniofacial dysmorphism. Extraskeletal manifestations have been also reported, such as polycystic kidney disease, neurological complications, cardiovascular defects and splenomegaly [85]. HCS is associated with *NOTCH2* gain-of-function mutations. Bone loss has been attributed to increased osteoclastogenesis and bone resorption due to enhanced RANKL expression [85], thus rendering Dmab a rational therapeutic approach. Dmab has been administered in two patients with HCS, in whom rapid reduction of C-terminal telopeptide (CTX) and improvement in BMD were observed [86,87]. However, Dmab did not prevent the progression of acroosteolysis of the hands. Given the potential pathogenetic association of HCS with RANKL, Dmab treatment warrants further investigation in patients with HCS.

2.2.2. Langerhans cell histiocytosis

Langerhans Cell Histiocytosis (LCH) is a rare disease of unknown etiology with variable clinical course exhibiting both neoplastic and inflammatory features and characterized by the accumulation and/or proliferation of specific dendritic cells resembling normal epidermal Langerhans cells (LCs) [88,89]. LCH is more often encountered in children, whereas it is more rare in adults [90,91]. There is a wide spectrum of clinical manifestations of LCH, since almost every tissue can be involved with or without associated dysfunction. The majority and diversity of clinical manifestations in LCH are attributed to immunological dysfunction resulting from LC derived cytokine secretion both at the lesional and systemic level [92,93]. In a recent study [94], RANKL was found to be abundantly expressed in cells within diverse LCH lesions from adult patients, especially in inflammatory infiltrates, a finding in line with a previously reported high OPG and low RANKL levels in the serum of patients with or without bone involvement [93]. Based on these findings, Dmab was administered as a rational therapeutic strategy in a bimonthly treatment schedule, in four doses of 120 mg, in two young female patients with bone and lung involvement [95]. Pain relief was observed soon after treatment initiation and an almost full remission of the initial bone and lung lesions were observed, although a new lesion appeared in one patient. Based on the above findings, a phase 2 clinical trial administering Dmab in patients with LCH has been launched (NCT03270020; Table 2).

2.2.3. Giant cell granuloma

Giant cell granuloma (GCG) is a rare benign disease that involves a bone destructive lesion consisting mainly of giant cells [96]. These lesions can be intraosseous, central or peripheral, and often present as oral tumors [97]. Although aggressive surgery can cure the disease in some cases, the resulting morbidity is usually high, owing to cosmetic and functional problems. Intralesional corticosteroid administration is empirically used [98,99], however, a definite pharmacological treatment is lacking. In a recent retrospective series, five patients with large jaw GCG were given Dmab for a period of 25 to 49 months, in a similar protocol with that of the malignant counterpart, namely the giant cell tumor [96]. In specific, with the exception of a dose-adapted protocol for the adolescent patient, the rest four adults received 12–15 monthly doses of Dmab 120 mg. Patients exhibited a full clinical response after one-year of treatment, except from an initially non-compliant patient, who, however, responded after treatment restarting [96]. Dmab may be considered as an alternative therapeutic option, at least for the management of recurrent, disfiguring and resistant to other treatment options central and peripheral GCG [96,98–103]. A treatment length of at least 12 months is recommended [96], which however needs verification.

2.2.4. Aneurysmal bone cysts

Aneurysmal bone cysts (ABC) are benign tumors, accounting for up to 15% of all bone tumors [104–106]. They usually present in childhood or early adulthood as expansile lesions, located at the metaphysis of long bones (67%), the spine (15%) and the pelvis (9%), and can be locally aggressive. ABC are either primary tumors (70%), usually associated with chromosomal rearrangements resulting in the upregulation of *USP6* gene, or secondary to another primary tumor, such as osteoblastoma, giant cell tumor of bone, chondroblastoma, fibrous dysplasia or low-grade osteosarcoma [106]. Treatment options include en bloc resection, excision with or without use of local adjuvants, sclerotherapy, embolization, radionuclide ablation and radiotherapy, while non-invasive interventions consist of potent inhibitors of osteoclast activity, such as i.v. bisphosphonates and Dmab. In tissue specimens from ABC, increased RANKL and RANK expression in the fibroblast-like stromal cells and osteoclastic multinucleated giant cells, respectively, were demonstrated [16,106]. Since RANKL/RANK activation may contribute to the aggressive osteolytic behavior of ABC, Dmab use is justified. Data regarding the effect of Dmab on ABC refer to case series and case reports. The largest case series involved nine patients each [104,105]. One of them included patients aged 14–42 years who were administered 3–61 Dmab injections [105]. All symptomatic patients experienced pain relief and radiographic improvement on follow-up computerized tomography (CT) and most of them improvement on magnetic resonance imaging. There were no significant side effects [105]. The second series included patients aged 5–18 years who were administered 9–17 Dmab injections [104]. All patients experienced clinical improvement within 3 months of treatment initiation. Radiographic improvement was observed in 7 patients, while disease progressed in 1 patient. Five months after Dmab discontinuation, severe rebound hypercalcemia requiring hospitalization was observed in two patients, and four patients had clinical and/or radiological recurrence requiring retreatment with Dmab (n = 1) or surgical intervention (n = 3). In another pediatric case series (n = 5), pain remission was observed in all patients and improvement in neurological deficit in

three of them [107]. Importantly, imaging studies revealed central remineralisation and cortical reconstitution [107]. Likewise, several case reports [106,108–118], totally including 16 patients, report favorable clinical and radiological results following Dmab treatment in cases refractory to conventional treatment. In general, Dmab was well tolerated. Hypocalcemia was reported in one case [113]. Nevertheless, the effect of Dmab on linear growth has not been formally evaluated, which should be considered in patients whose linear growth is not completed. More studies are warranted to verify these results and determine the indications and the optimal duration of treatment.

2.2.5. Melorheostosis

Melorheostosis is a rare sclerosing bone dysplasia, characterized by a "flowing" hyperostosis of the cortex of tubular bones. Melorheostosis is an uncommon manifestation of Buschke-Ollendorff syndrome, and could be presented alone or in association with osteopoikilosis [119]. Dmab administration in a woman with melorheostosis, reduced BTM and bone pain more than previous treatment with zoledronic acid [120]. However, the pain relapsed at approximately 1.5 month after the first Dmab injection, thus requiring bimonthly injections [120]. Dmab could be considered in melorheostosis, especially in patients unresponsive to bisphosphonate treatment or in whom bisphosphonates are contraindicated.

2.2.6. Diffuse sclerosing osteomyelitis

Diffuse sclerosing osteomyelitis (DSO) of the mandible is a rare disease, characterized by severe recurrent pain, swelling, and trismus [121]. Treatment options include non-steroidal anti-inflammatory drugs, antibiotics, corticosteroids and surgical procedures, while several reports describe favorable results with i.v. bisphosphonates [121]. Data regarding Dmab administration in DSO cases are limited in 3 patients [122,123]. A 64-year woman with a 5-year history of DSO, previously treated with i.v. ibandronate, received Dmab after disease recurrence [122]. Almost complete resolution of pain within 10 days, which was accompanied by decreased tracer uptake on bone scintigraphy were reported. Repeat administration of Dmab after 6 months, due to recurrence of symptoms, led again to rapid pain resolution [122]. Likewise, another two patients with DSO showed rapid pain resolution after Dmab administration [123] and Dmab was successfully repeated when the pain recurred after 4–6 months [123]. These favorable results of Dmab in patients with DSO should be well judged against a potential higher risk of osteonecrosis of the jaw in these patients.

2.2.7. Bone marrow edema syndrome

Idiopathic bone marrow edema (BME) syndrome is characterized by severe joint pain. It mainly affects the weight-bearing joints of middle-aged individuals. Few histological studies report that the lesions are characterized by fibrosis, lymphocytic infiltration, increased vascularization, reduced mineralization and high bone turnover [124]. BME syndrome may progress to osteonecrosis and eventually joint destruction, although some authors advocate that BME syndrome is a self-limited disease. Several, mostly uncontrolled studies, indicate that bisphosphonates reduce pain and might improve the functional outcome [124]. In a retrospective series, Dmab was administered in 14 patients with idiopathic BME syndrome approximately 5 months after the pain onset [125]. After 6–12 weeks, patients reported pain relief, while complete resolution of BME lesions was observed in 50% of the patients and partial resolution in another 42%, thus exhibiting a favorable response in 13 cases. Likewise, favorable results were reported in another series of three men [126] and a third retrospective series, in which Dmab was administered in three of 34 patients with BME, two of whom showed favorable results [127]. Given that the lack of control group in studies with a disease that is often self-limited is an important limitation, further studies with appropriate control groups are required to better evaluate the effect of Dmab on BME syndrome. Importantly, there is an ongoing controlled clinical trial with Dmab in patients with BME (NCT01734824; Table 2).

2.2.8. Perthes' disease

Perthes' disease (also known as Legg-Calvé–Perthes' disease) is a disorder of unknown etiology, starting at childhood, induced by the disruption of blood flow to the femoral head, which results to increased bone resorption and delayed bone formation, and subsequent femoral head deformity [128]. Bisphosphonates have been previously used with conflicting results. A single Dmab dose of 60 mg was administered in a 9-year boy with an early stage (Ia) Perthes' disease, following by varus osteotomy 8 months later [129]. Consolidation of the osteotomy and 90% re-ossification were observed at 6 and 24 months post-operatively, respectively. The patient had no pain and normal hip motion [129]. The authors suggested that this favorable outcome was unlikely to be solely attributed to surgery, thus a possible positive effect of Dmab in the course of disease could be implied, especially if given at an early phase.

2.2.9. Low back pain and Modic changes

Chronic low back pain is a common and disabling problem. No specific pathologies are present in > 85% of people with low back pain; however, a subset of patients presents with Modic changes, which includes three types of vertebral endplate bone abnormalities [130]. In an RCT comparing the 6-month effect of Dmab vs. zoledronic acid vs. placebo on low back pain due to Modic changes, both Dmab and zoledronic acid reduced low back pain compared to placebo according to the low back pain rating scale, but not according to the Visual Analog Scale (VAS) [130]. In post-hoc analyses, Dmab reduced VAS in subpopulations of the study, e.g., participants with milder disc degeneration and non-neuropathic pain, and those with type 1 Modic changes.

2.2.10. Gorham-Stout disease

Gorham-Stout disease (GSD) is a rare disorder of unknown pathogenesis. It is a form of lymphangiomatosis characterized by diffuse lymphatic vessel proliferation accompanied by increased osteoclastic activity, which leads to progressive and massive bone destruction [131]. Bisphosphonates have been used in some patients resulting in stabilization of bone destruction [131]. Dmab was used in a 72-year woman with GSD presenting with progressive osteolysis of both shoulders. An early decline (at 3 months) in BTM and stabilization of bone destruction were reported [131]. On the contrary, neither bisphosphonates nor Dmab added to sirolimus (a mammalian target of rapamycin [mTOR] inhibitor, acting as an anti-angiogenic medication) managed to cease the progression of osteolysis in another patient with more severe GSD, who finally died from skull base osteomyelitis [132]. Dmab was also administered in a 29-year man with GSD and mandibular involvement, but the treatment outcome is unknown [133]. Although secure conclusions could not be drawn, it has been hypothesized that treatment may be more effective, if it starts at the early disease stages [132].

2.2.11. Charcot neuropathic osteoarthropathy

Charcot neuropathic osteoarthropathy is a rare but severe disorder of bones and joints in weight-bearing skeletal structures. It exclusively occurs in patients with neuropathy, thus most cases are currently observed in patients with diabetic neuropathy [134]. The most common location of the disease are the feet ("Charcot foot") [134]. Since RANKL has been reported upregulated in Charcot neuropathic osteoarthropathy [135], Dmab seems to be a reasonable therapeutic approach. A single Dmab administration in 11 patients with "Charcot foot" lead to favorable clinical outcomes compared with historical controls having received standard treatment, including shorter time to fracture resolution [136]. There is an ongoing clinical trial with Dmab in patients with Charcot neuropathic osteoarthropathy (ACTRN12617000937314; Table 2).

2.2.12. Periprosthetic osteolysis

Total joint arthroplasty (TJA) is increasingly utilized, partly owing to the aging population. Late periprosthetic bone loss leading to aseptic loosening is the main reason for TJA revision [137]. RANKL-mediated periprosthetic bone loss has been implicated in the pathogenesis of TJA [138]. Bisphosphonates have not provided favorable results [138]. In a rat study, alendronate failed to produce favorable effects, whereas administration of OPG-Fc, a molecule that binds to RANKL and blocks its action, similarly to Dmab, prevented the development of osteolytic lesions [139]. Based on this observation a 3-year RCT (NCT02299817/EUCTR2013-004940-48; Table 2) is currently testing the efficacy of Dmab in reducing wear-induced osteolysis [140], expressed as change in volume of the osteolytic lesion (measured by 3D-CT in cm^3), around uncemented acetabular implants used in total hip arthroplasty, performed between 7 and 20 years before inclusion.

2.3. Dmab administered mainly to manage hypercalcemia

2.3.1. Hyperparathyroidism

Bone disease in hyperparathyroidism (HPT) is a condition of high bone turnover with increased bone resorption that overpasses bone formation. In primary HPT (pHPT) the cortical bone is predominantly affected, while trabecular bone is relatively preserved. However, fracture risk is increased at all skeletal sites [141]. Parathyroidectomy represents the treatment of choice, with antiresorptives, mainly bisphosphonates, as alternatives to manage bone disease and hypercalcemia [141]. Parathyroid hormone (PTH) stimulates osteoclastic bone resorption through increased RANKL production [141]. In a small retrospective study, pHPT patients treated with Dmab for 24 months achieved larger BMD increases in the LS and FN compared to patients with postmenopausal osteoporosis [142]. Additionally, in patients with pHPT, Dmab lowers calcium levels and could be used to treat resistant hypercalcemia [143]. Dmab was also successfully used in a patient with pHPT, CKD and medullary nephrocalsinosis to reduce severe hypercalcemia before parathyroidectomy [144], and as palliative treatment in a patient with parathyroid carcinoma and parathyrotoxicosis [145]. A case of Dmab-induced hypophosphatemia in a patient with normocalcemic pHPT highlights the importance of adequate calcium and vitamin D supplementation to avoid excessive PTH increase and hyperphosphaturia following Dmab [146]. Of note, prolonged hypocalcaemia has been reported in two patients with CKD and tertiary HPT (tHPT) following a single Dmab dose [147]. The effect of Dmab in the setting of sHPT is discussed above in the section of CKD. There are two ongoing clinical trials with Dmab in patients with pHPT, aiming to study its efficacy on BMD rather than on hypercalcemia (NCT01558115 and NCT03027557/EUCTR2016-001510-20; Table 2).

2.3.2. Immobilization hypercalcemia

Immobilization hypercalcemia results from an imbalance of bone remodeling favoring bone resorption over bone formation, while renal insufficiency, if present, is a risk factor of this rare condition [148,149]. Given that RANKL is a key factor of osteoclastogenesis, Dmab seems to be a rational option in controlling hypercalcemia due to increased osteoclastic function. A single injection of Dmab 60 mg rapidly decreased immobilization-induced hypercalcemia in 4 case reports with CKD [149–152]. In three of them, previous short-term bisphosphonate treatment (alendronate [149] or pamidronate [150,152]) had failed to control hypercalcemia, while decreased calcium levels were evident after Dmab for a follow up period ranging between 1 week [149] and four months [151] (Table 1).

2.3.3. Tuberculosis-associated hypercalcemia

A patient with tuberculosis-associated hypercalcemia and acute kidney failure has been treated with Dmab [153]. In granulomatous diseases, such as tuberculosis, hypercalcemia develops as a result of 1,25-$(OH)_2$-Vitamin D overproduction within the granulomatous tissue [154]. Glucocorticoids are the mainstay of treatment for hypercalcemia of granulomatous diseases [154]. Dmab was administered as the initial pharmaceutical calcium-lowering intervention. Calcium levels were normalized after one week, but significant hypocalcemia developed between the 3rd and 4th week after Dmab administration [153], which further underlines the need for close monitoring of calcium levels among patients with impaired renal function receiving Dmab [155].

2.3.4. Myelofibrosis

Myelofibrosis is a myeloproliferative neoplastic disorder characterized by clonal proliferation of mutated stem cells and secondary inflammation that lead to bone marrow fibrosis [156]. Hypercalcemia is a rare complication of myelofibrosis with a few case reports in the literature [157–159]. A 62-year female with an abrupt presentation of hypercalcemia resistant to pamidronate and calcitonin treatment, was treated with a single Dmab injection of 120 mg [157]. She remained normocalcemic for the next two months, while i.v. treatment with zoledronic acid was required 3 months after Dmab administration.

3. Closing remarks and future directions

Dmab has been used off-label in several metabolic bone diseases, which are summarized in Table 1. For some of them, Dmab use seems to be a pathogenetically rational option, since the RANK/RANKL/OPG axis participates in the pathogenesis of specific diseases, e.g., JPD, fibrous dysplasia, HCS, LCH. In other cases, Dmab was administered to selected patients (e.g., with Paget's disease, OI, aneurysmal bone cysts) due to renal impairment, since other treatment options (e.g., bisphosphonates) may affect renal function and/or their levels may be affected by renal impairment [27]. Other patients received Dmab due to contraindication or unresponsiveness to standard treatment. Moreover, Dmab has been administered to improve hypercalcemia, induced by various diseases, including pHPT, tuberculosis and immobilization; especially in pHPT, Dmab was selected as palliative treatment in patients unable to undergo parathyroidectomy or as a temporary measure to reduce calcium levels until parathyroidectomy.

Many diseases in which Dmab has been used off-label are rare. In this regard, it is unlikely to perform RCTs even in a multicentre basis, due to the difficulty to recruit an adequate number of patients and the lack of interest by pharmaceutical industry [160]. Therefore, the management of these diseases is usually based on evidence lying low in the pyramid of evidence-based medicine or expert opinion. For the less rare diseases e.g., CKD and transplantation-associated bone loss, RCTs with adequate samples could be performed, and for some of these conditions such RCTs have already been initiated, as summarized in Table 2. For these, less rare diseases, it would be more prudent to wait for more data from RCTs, until deciding whether Dmab could be used or not.

In its reported off-label use, Dmab was generally well tolerated without major adverse events. A common adverse event is hypocalcemia, most commonly seen in patients with CKD and sHPT (Table 1). However, hypocalcemia may develop in any disease, mainly in those with a high bone turnover, like JPD. Based on these observations, is seems rational that calcium intake should be optimal and vitamin D levels are repleted before Dmab administration. Specifically for patients with CKD or kidney transplant recipients, calcitriol rather than vitamin D_3 (cholecalciferol) is required [35]. Importantly, in cases of high bone turnover, a lower initiating Dmab dose may be considered to minimize the risk of hypocalcemia and sHPT, and when BTM decrease, then Dmab dose may be gradually increased [10]. If hypocalcemia occurs, standard guidelines on its management should be followed, as described in detail elsewhere [161]. Briefly, in cases of symptomatic hypocalcemia or calcium levels < 1.9 mmol/l (< 7.6 mg/dl), hospitalization may be required, during which calcium gluconate should be intravenously administered: it is typically recommended to start with 10 ml dextrose solution of 10% calcium gluconate over 10 min,

followed by calcium gluconate infusion (rate should be adjusted every 4 h according to serum calcium measurement). Vitamin D analogues (calcitriol or alfacalcidol) per os should be also administered (initial dose 0.5–1.0 μg/d, respectively; adjustment every 4–7 d). In milder cases of hypocalcemia, calcium carbonate intake (1–3 g/d) and cholecalciferol (50,000 IU/week) are recommended [161]. In some cases (e.g., renal impairment) calcitriol instead of cholecalciferol is required.

As aforementioned, there are considerations regarding Dmab use not only in women with PLO, but generally in pregnancy and lactation. Furthermore, until more data are available, Dmab discontinuation should be followed by a bisphosphonate to minimize the risk of multiple vertebral fractures observed in a minority of postmenopausal patients following Dmab discontinuation [155].

In some diseases, a better response to treatment might be expected if Dmab is administered early in their course, when the skeletal and potential extraskeletal complications are not established, thus preventing skeletal and extraskeletal malformations. Nevertheless, the safety of Dmab in childhood/adolescence has not yet been established and there is consideration for its effect on linear growth [10]. Therefore, an individualized approach is needed to carefully weigh the advantages and disadvantages of Dmab in the specific child/adolescent before its administration.

Other important, yet unresolved, issues are the duration of Dmab treatment and discontinuation of Dmab. Dmab has proved its efficacy and safety for up to 10 years; its lifelong use raises concerns, while its discontinuation has been associated with multiple vertebral fractures in a minority of patients [84,162,163]. The use of potent bisphosphonates, e.g. zoledronic acid, following Dmab discontinuation may prevent the observed bone loss, at least in women with postmenopausal osteoporosis [164], but it still remains a controversial issue [165]. Until conclusive data are available, the duration of treatment with Dmab as well as potential treatment alternatives after Dmab discontinuation should be considered in an individual basis before Dmab initiation.

Considering the above, we made suggestions on Dmab use for each reported disease (Table 3). These suggestions are based on the pathophysiology of each disease and existing data, thus reflecting our opinion rather than evidence-based decisions. Many questions remain to be answered regarding off-label use of Dmab in metabolic bone diseases, including its long-term effectiveness and safety, its optimal regimen in each condition, as well as the ideal way of its discontinuation. Until then, the off-label use of Dmab should be carefully considered on an individual basis.

Table 3
Expert opinion on off-label denosumab use in metabolic bone diseases based on current evidence and the pathogenesis of each disease.

Disease	Suggestion based on preliminary results (Yes; Yes in specific conditions; No; Neither yes or not)[a]	Specific conditions to be considered
Dmab administered mainly for BMD and/or BTM improvement and/or fracture risk reduction		
Paget's disease of bone	Yes in specific conditions	Renal impairment; BP contraindication; giant cell tumor co-existence
Juvenile Paget disease	Yes	
Fibrous dysplasia	Yes	
Thalassemia bone disease	Yes	
CKD-associated bone disease	Yes in specific conditions	sHPT
Organ transplantation-associated bone disease	Yes in specific conditions	Renal impairment; contraindication or unresponsiveness to other treatment options
Osteogenesis imperfecta	Neither yes or not	Possible use: Cases with mutations in the *SERPINF1* gene; renal impairment; BP contraindication; unresponsiveness to BP
Mastocytosis	Neither yes or not	
Neurofibromatosis	Neither yes or not	
Osteoradionecrosis	Neither yes or not	
Multiple system atrophy	Neither yes or not	
Duchenne muscular dystrophy	Neither yes or not	
Spinal cord injury-associated bone loss	Neither yes or not	
Anorexia Nervosa	Neither yes or not	
Hypophosphatasia	No	
Pregnancy and lactation-associated osteoporosis	No	
Dmab administered mainly to manage symptoms and lesions		
Hajdu Cheney syndrome	Yes	
Langerhans cell histiocytosis	Yes	
Giant cell granuloma	Yes in specific conditions	Lesions recurrent, disfiguring and resistant to other treatment options
Aneurysmal bone cysts	Yes in specific conditions	Renal impairment; contraindication or unresponsiveness to other treatment options
Melorheostosis	Neither yes or not	Possible use: BP contraindication; unresponsiveness to BP
Diffuse sclerosing osteomyelitis	Neither yes or not	
Bone marrow edema syndrome	Neither yes or not	
Perthes' disease	Neither yes or not	
Low Back Pain and Modic Changes	Neither yes or not	
Gorham-Stout disease	Neither yes or not	
Charcot neuropathic osteoarthropathy	Neither yes or not	
Periprosthetic osteolysis	Human data still unpublished	
Dmab administered mainly to manage hypercalcemia		
Hyperparathyroidism	Yes in specific conditions	Renal impairment; resistant hypercalcemia; hypercalcemia before PTx; patients unable to undergo PTx (palliative treatment)
Immobilization hypercalcemia	Yes	
Tuberculosis-associated hypercalcemia	Yes in specific conditions	Renal impairment
Myelofibrosis	Neither yes or not	

Abbreviations: BMD, bone mineral density; BP, bisphosphonate; BTM, bone turnover markers; CKD, chronic kidney disease; Dmab, denosumab; PTx, parathyroidectomy; sHPT, secondary hyperparathyroidism.

[a] Recommendations based on evidence lying low at the evidence-based pyramid.

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