Review Article

Denosumab in pediatric bone disorders and the role of RANKL blockade: a narrative review

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Background and Objective: Denosumab is a valuable and safe therapy for skeletal disorders in adults and has received regulatory approval to treat osteoporosis and bone metastases. However, denosumab is not licensed for pediatric use due to a lack of high-quality prospective research on children. This study aimed to describe and discuss the benefits and disadvantages of denosumab in treating bone diseases in children and to summarize the current understanding of the role of denosumab therapy in children.

Methods: A narrative review was conducted using the literature retrieved from the PubMed, Embase, and Cochrane Library databases.

Key Content and Findings: In children with type 6 osteogenesis imperfecta (OI), juvenile Paget disease (JPD), and secondary osteoporosis who show poor response to bisphosphonate, the use of denosumab has been reported to improve osteoporosis and increase bone mineral density (BMD). Moreover, for those with relapse, progressive and refractory aneurysmal bone cyst (ABC), fibrous dysplasia (FD), giant cell tumor of bone (GCTB), and central giant cell granuloma (CGCG) lesions, denosumab can improve pain symptoms, control disease progression, and reduce serious adverse events. Although there have been sporadic reports of adverse events such as hypocalcemia during medication and rebound hypercalcemia after discontinuation, early prevention, monitoring, and timely intervention can prevent children from experiencing severe adverse events.

Conclusions: The published data indicate that denosumab has efficacy in alleviating disease in multiple refractory bone lesions in children.

Keywords: Denosumab; osteogenesis imperfecta (OI); fibrous dysplasia (FD); aneurysmal bone cyst (ABC); giant cell tumor of bone (GCTB)

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Introduction

Denosumab, a monoclonal antibody against receptor activator for nuclear factor kappa B ligand (RANKL), has recently seen widespread use in the treatment of adult osteoporosis and the prevention of bone-related events of bone metastases due to its ability to reduce bone turnover, increase bone density, and prevent the progression of certain bone neoplasms (1-4). However, the pharmacokinetics and pharmacodynamics of denosumab in children are not yet clearly known, and denosumab therapy in children is not currently licensed. Despite the scarcity of drugs available for refractory pediatric orthopedic-related diseases, including osteogenesis imperfecta (OI), fibrous dysplasia (FD), aneurysmal bone cyst (ABC), and secondary

Table 1 Literature search strategy for this review

Item	Specification
Date of search	December 3, 2021
Databases and other sources searched	PubMed, Embase, and Cochrane Library were searched. Important missed citations in the literature were searched for manually
Search terms used	Denosumab, child, adolescent, pediatric, giant cell tumor of bone, osteogenesis imperfecta, fibrous dysplasia, aneurysmal bone cyst
Timeframe	From the establishment of database to December 3, 2021
Inclusion and exclusion criteria	Inclusion criteria: studies of applying denosumab in children younger than 18 years old; in the English language; and including case and series reports, retrospective cohort studies, and prospective studies
	Exclusion criteria: lack of a detailed description of how to use denosumab and no data on effects or complications
Selection process	Daoxi Wang and Qianyu Shi conducted the selection independently and then worked cooperatively in the literature screening. When there was disagreement on a piece of literature, third experts (Tao Ji or Xueyang Tang) was consulted

osteoporosis, there are primarily literature reports of clinicians successfully treating skeletal system—immature children with denosumab, although these children also experienced some side effects that are rare in adults (5-8). These adverse effects included hypocalcemia, increased risk of infection when denosumab was applied in combination with steroids, and a serious adverse effect reported in adults—medication-related osteonecrosis of the jaw (MRONJ). To date, the effectiveness and safety of denosumab therapy in the field of pediatric orthopedic-related diseases is still under debate, particularly regarding standardized clinical practices and the prevention of bone turnover rebound after discontinuation in children (9-11). The aim of this review is thus to provide a historical perspective on applying denosumab in the management of refractory pediatric orthopedic diseases using the available data to encourage best practices. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-276/rc).

Methods

Literature to build this review was searched for and retrieved from the PubMed, EMBASE, and Cochrane Library databases. The specific literature search strategy is presented in *Table 1*. And literature search queries on PubMed was listed in Table S1.

Irrelevant studies were excluded through reading titles and abstracts. Those studies that recruited children who were under 18 years of age using denosumab for orthopedic disease were included, and those with unclear denosumab administration or missing treatment and follow-up data were excluded. The literature ultimately included in the review is listed in *Tables 2-5*.

Discussion

RANK/RANKL/osteoprotegerin (OPG) signaling pathway, childhood bone metabolism, and the history of denosumab

The human skeleton is an organ with a dynamic metabolism that is continuously remodeled throughout life to recover from minor bone fractures and to maintain mineral homeostasis in response to diverse environmental stimuli. Remodeling is a microscopic process achieved through the coordinated action of osteoclasts and osteoblasts. Old bone resorption in osteoclasts and new bone formation in osteoblasts are tightly coupled in time and space (34,35).

The growth of bone in children is a strictly controlled process of breaking bone remodeling homeostasis conditions. Linear bone growth occurs when bone formation exceeds bone resorption at the epiphyseal growth plate due to local bone mass growth. Bone thickening and enlargement occur in the remodeling process of the periosteum and bone marrow cavity (36,37). The vigorous osteogenesis process below the periosteum leads to an increase in bone mass and bone thickening, while the bone dissolution process in the bone marrow cavity leads to an increase in bone absorption and bone marrow cavity enlargement. As a result, the bone thickens, the marrow cavity enlarges, and the bone mass increases.

The RANK/RANKL/OPG signaling pathway is

Table 2 Data on children and adolescents with osteogenesis imperfecta treated with denosumab reported in the literature

Study	Year	Patient age	Dose and interval of denosumab	Duration of treatment	Effect of treatment	Adverse events during treatment	Adverse events after treatment
Semler *et al.* (6)	2012	4 boys age 5–18 years (type 6)	1 mg/kg every 8–12 weeks	24 months	Increased BMD, improved pain	Mild hypocalcemia (1 patient)	Unknown
Hoyer-Kuhn *et al.* (12)	2014	4 boys age 5–18 years (type 6)	1 mg/kg every 8–12 weeks	24 months	Increased BMD, improved pain	Mild hypocalcemia (1 patient)	Unknown
Ward *et al.* (13)	2016	1 child age 2 years (type 6)	1 mg/kg every 4–12 weeks	12 months	Increased BMD, improved mobility, more osteoclasts formed	Severe hypercalcemia	None
Hoyer-Kuhn *et al.* (14)	2016	10 children age 5–11 years (types 1, 3, and 4)	1 mg/kg every 12 weeks	12 months	Increased BMD and increased height; bone pain did not change	Mild hypocalcemia (1 patient)	Mild hypercalcemia
Uehara *et al.* (15)	2017	1 child age 14 years	Every 6 months	24 months	Increased BMD	None	Unknown
Trejo *et al.* (16)	2018	4 children age 1.9–9 years (type 6)	1 mg per kg every 3 months	Mean 24 months	Increased BMD	Mild hypercalcemia and persistent hypercalciuria, nephrocalcinosis, rapid bone loss	None
Hoyer-Kuhn *et al.* (17)	2019	10 children, mean age 8.6 (6.16–12.13 years) (types 1, 3, and 4)	1 mg per kg every 20.3 weeks (depending on the individual urinary excretion course of deoxypyridinoline)	53.04 weeks (± SD 6.30)	Increased BMD	Arthralgia, muscle pain, symptomatic hypercalciuria	Symptomatic hypercalciuria

SD, standard deviation; BMD, bone mineral density.

Table 3 Data on children and adolescents with fibrous dysplasia treated with denosumab reported in the literature

Study	Year	Patient age	Dose and interval of Denosumab	Duration of treatment	Effect of treatment	Adverse events during treatment	Adverse events after treatment
Boyce *et al.* (7)	2012	9-year-old boy	1–1.5 mg/kg monthly	7 months	Decreased tumor expansion and pain	Mild hypophosphatemia	Severe hypercalcemia
Wang *et al.* (18)	2014	9-year-old boy	1–1.5 mg/kg monthly	7 months	Decreased tumor expansion and pain	Mild hypophosphatemia	Severe hypercalcemia
Majoor *et al.* (19)	2019	Median 8.8 years	Subcutaneous denosumab 60 mg at 3- or 6-month intervals	15.5 (range, 12–19) months	Reduction in bone pain	None	None
Raborn *et al.* (20)	2021	13-year-old girl	1 mg/kg every 4 weeks	3.5 years	Resolution of pain and progressive increase in extracranial bone density	None	Hypercalcemia, relapse

Table 4 Data on children and adolescents with aneurysmal bone cyst treated with denosumab reported in the literature

Study	Year	Patient's age	Dose and interval of denosumab	Duration of treatment	Effect of treatment	Adverse events during treatment	Adverse events after treatment
Lange *et al.* (21)	2013	8- and 11-year-old boys	70 mg/m^2 monthly	Ongoing	Cyst partial regression, improved pain	Mild hypocalcemia (1 patient)	Unknown
Pelle *et al.* (22)	2014	5-year-old boy	1.2–1.6 mg/kg monthly	12 months	Cyst regression, healed fracture, improved pain	None	Unknown
Fontenot *et al.* (23)	2018	13-year-old girl	Subcutaneous denosumab (120 mg) given every 4 weeks (with additional 120 mg SC doses on days 8 and 15 in cycle 1 only)	12 months	Pain improved, decreased tumor size	None	None
Raux *et al.* (24)	2019	Median age was 8 years (range, 7–17 years)	70 mg/m^2	A median of 12 months (range, 4–23 months)	Free of pain, and the neurological deficits in 3 patients had improve	Hypocalcemia	Hypercalcemia
Harcus *et al.* (25)	2020	1 child, 13 years old	Subcutaneous denosumab (70 mg/m^2) on a weekly–2 months–3 months–4 months–6 months		Pain free, new bone formation in the lesion	Calcification of the lower limb growth plates	Rebound hypercalcemia
Fadavi *et al.* (26)	2021	1 child, 13 years old	120 mg every 4 weeks	12 months	Neurologic symptoms fully recovered	None	None

an important bone metabolic pathway that has been widely studied over the past 20 years (38,39). RANKL is a transmembrane protein expressed on the surface of bone tissue cells and T lymphocytes and is involved in the mature differentiation of osteoclasts. RANK, which is highly expressed in osteoblasts and osteocytes, is the receptor protein of RANKL. When RANK and RANKL combine, osteoclast activation and differentiation are induced, promoting bone absorption and bone turnover, decreasing bone mineral density (BMD), and potentially even inducing osteolytic lesions. OPG is a transmembrane protein produced by bone marrow stromal cells that can bind to the RANKL-RANK complex to inhibit the activity of osteoclasts. RANK/RANKL/OPG are the centers of the hub and enable the skeleton to establish and maintain bone strength (*Figure 1*).

Denosumab is a subcutaneously administered, wholly human-derived, highly specific monoclonal antibody against RANKL. It binds RANKL with high affinity and specificity, initiating a metabolic process similar to that induced by OPG that inhibits osteoclast activation and differentiation, reduces bone resorption, and indirectly increases BMD (40). Denosumab was approved by the U.S. Food and Drug Administration (FDA) in 2010 as Prolia, initially listed alongside bisphosphonates as a first-line treatment for postmenopausal osteoporosis. Denosumab was launched in November 2010 under the name Xgeva for the treatment of skeletal problems in patients with solid tumors with bone metastases. In 2013, the FDA approved denosumab for the treatment of adult and skeletally mature adolescent patients with giant cell tumors of the bone (GCTBs) that cannot be resected or for which resections would result in significant morbidity. Indications were also extended to multiple myeloma and hypercalcemia just a few years later (41,42). A growing amount of literature supports the efficacy of denosumab as an inhibitor of bone resorption, with reports suggesting that common side effects in adults include hypocalcemia, muscle and joint pain in the extremities, rare cases of osteonecrosis of the jaw, and atypical femoral fractures (43-45).

Denosumab is a far more potent inhibitor of bone resorption than are bisphosphonates, which work by binding

Table 5 Data on children and adolescents with giant cell tumor of bone treated with denosumab reported in the literature

Study	Year	Patient age	Dose and interval of denosumab	Duration of treatment	Effect of treatment	Adverse events during treatment	Adverse events after treatment
Chawla *et al.* (27)	2013	10 children ≥12 years old	120 mg monthly	Ongoing	Decreased tumor size, improved pain	None	Unknown
Karras *et al.* (28)	2013	10-year-old girl	120 mg monthly	24 months	Decreased tumor size, improved pain	Mild hypocalcemia and hypophosphatemia	Severe hypercalcemia
Gossai *et al.* (29)	2015	10-year-old girl	120 mg monthly	24 months	Decreased tumor size, improved pain	Mild hypocalcemia and hypophosphatemia	Severe hypercalcemia
Setsu *et al.* (30)	2016	10-year-old boy	120 mg monthly	14 months	Decreased tumor size, improved pain	None	Severe hypercalcemia
Kobayashi *et al.* (31)	2015	10-year-old boy	120 mg monthly	14 months	Decreased tumor size, improved pain	None	Severe hypercalcemia
Uday *et al.* (9)	2018	14-year-old girl and 15-year-old boy	120 mg subcutaneously on days 1, 8, 15, and 28, and then every 4 weeks	1.3 years	Unknown	Unknown	Osteonecrosis of the jaw rebounded hypercalcemia, acute kidney injury
Sydlik *et al.* (32)	2020	6–17 years old	60 mg on days 1, 8, 15, and 28 and then once a month	7–17 months	Decreased tumor size	Unknown	Tumor relapse, hypercalcemia
Reddy *et al.* (33)	2021	14-year-old and 16-year-old	120 mg subcutaneously once weekly for 3 weeks during the first cycle then once every 4 weeks with plans to complete a total of 26 cycles	14/26 (26 months)	Reduction in tumor size	Mild hypocalcemia	None

to hydroxyapatite and inhibiting osteoclast activity (46). Denosumab has an advantage over bisphosphonates, exhibiting better compliance, comfort, and ease of use by patients and requiring only subcutaneous injection. Denosumab therapy was generally well tolerated in multiple large trials, with no significant increase in adverse event incidence compared with that with placebo or bisphosphonates (47). However, because denosumab inhibits bone turnover with a shorter half-life than do bisphosphonates, the effect is completely reversible after withdrawal.

Thus far, the effects of denosumab on the growing skeleton have not been well described, the pharmacokinetics and pharmacodynamics of denosumab in children are not yet fully understood, and there is no consensus for standardized clinical practices in children. Moreover, scattered reports have revealed mixed results on the use of denosumab for various conditions in children (*Figure 2*). Controversies regarding denosumab use in children mainly concern its safety, specifically the optimal dose in individual children, dose frequency, therapy duration, impact on children's epiphyseal development, and the means to preventing post-discontinuation rebound (6,12).

OI

OI was the first disease for which an attempt to treat pediatric patients with denosumab was reported, as OI is the most common primary osteoporosis in children. Patients with OI are routinely treated with bisphosphonates, but type

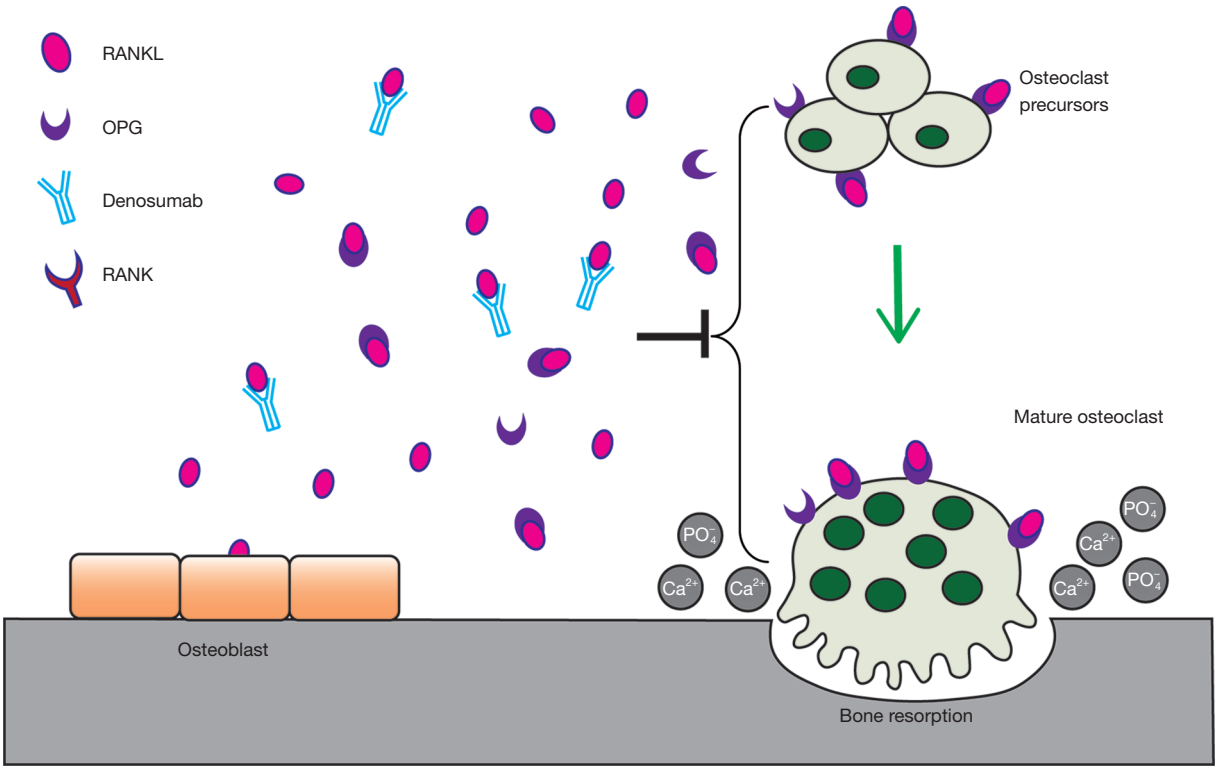

Figure 1 Regulation of osteoclast-mediated bone resorption. RANKL, receptor activator for nuclear factor kappa B ligand; OPG, osteoprotegerin; RANK, receptor activator for nuclear factor kappa B.

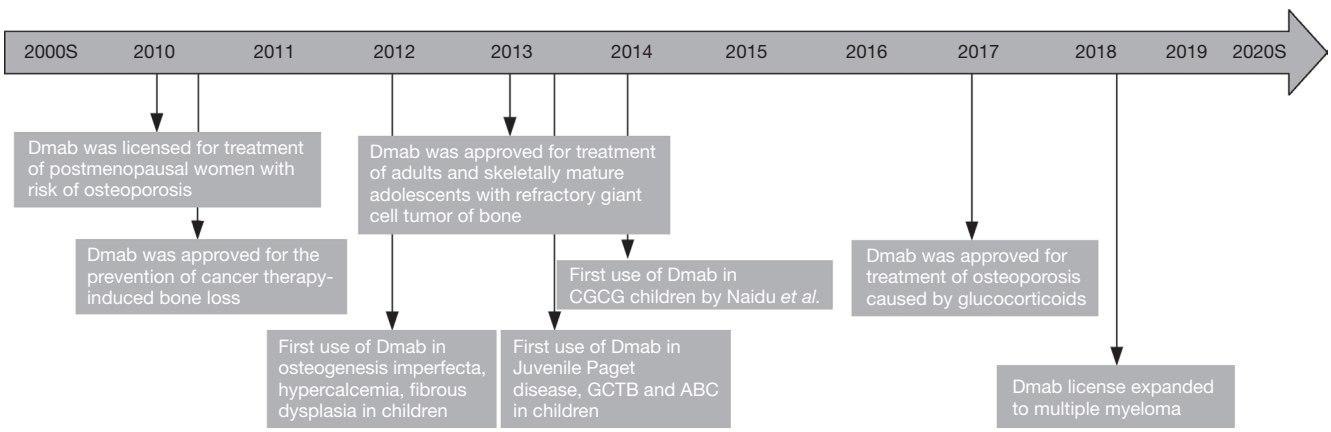

Figure 2 Timeline of key events in the development denosumab for the management of bone health in adults and children. CGCG, central giant cell granuloma; GCTB, giant cell tumor of bone; ABC, aneurysmal bone cyst; Dmab, denosumab.

6 OI has a poor therapeutic response to bisphosphonates. Type 6 OI is an autosomal recessive form caused by the *SERPINF1* (Serpin family F member 1) mutation. There is experimental evidence suggesting that functional deficiency in SERPINF1 activates osteoclasts through the RANK/RANKL pathway (48). Based on preliminary study and due to the lack of available drugs for use in children, denosumab was first used by Semler *et al.* to treat 4 children with type

6 OI whose disease was refractory to bisphosphonates (6). The approach they used was to inject denosumab subcutaneously every 3 months (1 mg/kg BW) with an initial 12-week interval, and no serious side effects were found. A rapid decline in bone resorption was detected after each denosumab dose, and bone resorption returned to pretreatment levels at approximately 6 weeks, so the dose interval was adjusted to approximately 10 weeks. During the treatment period, no serious uncomfortable reactions were observed in the 4 children, improved osteoporosis and increased BMD became apparent, and only 1 instance of asymptomatic hypocalcemia was noted.

In another report, a boy with type 6 OI was treated with denosumab (1 mg/kg every 3 months) and received conventional calcium supplements during treatment. No hypercalcemia or hypocalcemia occurred. However, persistent bone fractures were found after 12 months of initial treatment. After that, subsequent denosumab treatment led to a rise in BMD. Interestingly, 2 biopsies in the denosumab treatment period demonstrated an increase in the number of osteoclasts compared to the pretreatment level (13).

After encouraging preliminary data were reported, additional studies have been conducted on the treatment of OI in children. In 2016, a prospective study involving 10 children with OI treated with denosumab was published. The authors evaluated the safety and efficacy of denosumab for the treatment of different types of OI by which denosumab's dose interval varied from 3 to 12 months (1 mg/kg BW) (14). All the children studied could safely tolerate denosumab therapy; only 1 child with asymptomatic hypocalcemia was observed during the therapy period, and coincidentally, mild asymptomatic hypercalcemia was observed in several patients prior to the fourth dose of denosumab. Uehara *et al.* reported a similar result in their 2017 study (15). These trials confirmed the efficacy of denosumab in OI, with an increase in bone BMD observed during treatment, although pain symptoms and activity did not improve. These findings also raise further questions, and the optimal dose and appropriate dose interval of denosumab based on the metabolic characteristics of children warrant further research and confirmation.

In 2018, Trejo *et al.* evaluated the use of denosumab in 4 children with type 6 OI using the most classical treatment strategy (1 mg per kg body mass every 3 months) (16). Hypercalcemia occurred in all 4 children during the treatment period. In 2 children aged 3.9 and 4.6 years, respectively, hypercalcemia occurred between 7 and 12 weeks after the most recent injection of denosumab. BMD declines rapidly when the dose interval is increased up to 6 months for clinical reasons. Another study found that the inhibition of absorption by denosumab appeared to last only 6 to 8 weeks, so shortening the dose interval from the initial 12 weeks to a minimum 10-week interval may prevent hypercalcemia (12). However, 1 patient in this study developed hypercalcemia only 7 weeks after injection of denosumab. The authors raised two critical issues: whether the denosumab dose interval should be shorter in children than in adults and whether denosumab along with bisphosphonates can be used to treat OI to prevent discontinuation turnover rebound (16).

A recent study in 2019 on denosumab for OI in children sought to determine the optimal dose and interval for denosumab in children to address questions raised by previous authors. The investigators administered denosumab at a dose of 1 mg/kg body weight to 10 pediatric patients with OI and, for the first time, used urinary deoxypyridinoline (DPD) levels as a marker to assess osteoclastic activity and to personalize the interval of denosumab injection. When the level of DPD/creatinine (CREA) prior to injection of denosumab was increased, a second dose of denosumab was administered (17). All 10 children tolerated denosumab therapy, and only a few patients reported muscle and joint pain during the treatment period, with these cases all being relieved without intervention. In their study, symptomatic hypercalciuria was observed 12 months after drug withdrawal, and renal function was assessed and found not to be impaired. Finally, the denosumab interval was delayed from 12 to 20.3 weeks. The increase in bone mass and BMD during the trial was significantly higher during the follow-up period, proving its efficacy in treating OI. Constant bone growth assessment throughout the 2-year observation period showed that bone growth in pediatric patients was not affected. This study demonstrates the possibility and necessity of individualized treatment strategies based on urinary bone resorption marker levels.

The above studies are summarized in *Table 2* and indicate that denosumab might represent a valid alternative approach to treating OI in children. Further studies need to be carried out to determine the safety and standardized clinical practices of denosumab in children. The level of DPD/CREA is an example of good practices for monitoring medication safety.

FD and McCune-Albright syndrome (MAS)

FD is a rare disorder of the skeletal system caused by

mutations in the alpha subunit of the Gs stimulator protein (Gsα), which activates the cyclic adenosine phosphate (cAMP) regulatory protein. Because normal bone and marrow are replaced by fibrous bone tissue, clinical manifestations vary widely and can include dysfunction, deformity, and pain. FD may be associated with skin hyperpigmentation and endocrine hyperfunction, including hyperthyroidism, precocious puberty, excess growth hormone, and Cushing syndrome. FD combined with one or more extraosseous manifestations is defined as MAS (49).

Because of the wide range of FD lesions, it is difficult to completely cure the disease. At present, the treatment goal for FD is mainly to control disease progression and prevent bone and severe osteoarticular deformities. Surgical treatment is performed only in cases of acute bone fracture or severe osteoarticular malformations. At present, the mainstream treatment drug is bisphosphonates, which can effectively relieve the pain caused by FD; however, preliminary evidence indicates that they cannot alleviate the progression of the disease (50,51).

It has been speculate that bisphosphonates' lack of effect in this regard is due to its action requiring the binding to the mineralized matrix, which is greatly reduced in FD tissues (19,52). Recent research has revealed that skeletal neoplasm development depends on RANKL and cAMP/protein kinase A. A growing number of studies have reported that the inhibition of RANKL by denosumab is effective against GCTB, and a preliminary study of FD and ABC demonstrated that they shared a similar pathogenic lesion with GCTB.

Based upon these data and research, denosumab was first used to treat FD in a child with a rapidly expanding FD lesion by Boyce *et al.* in 2012 (7). They applied denosumab in a 9-year-old boy who was diagnosed with MAS due to extensive skeletal FD, hyperthyroidism, and skin pigmentation abnormalities. He was first treated with bisphosphonates for 1 year, but the pain was not relieved, and the lesion continued to progress. After denosumab (1–1.5 mg/kg every 1 month) was injected for 7 months, the rate of progression slowed, and the pain improved. However, acute rebound hypercalcemia occurred 2 months after drug withdrawal and was relieved by treatment with bisphosphonates and calcitonin.

After the first satisfactory result of treatment of a child with FD was reported, additional groups reported their experience of using denosumab in children with FD. In the studies of Wang *et al.* (18), Majoor *et al.*, (19) and Raborn *et al.* (20), the safety and efficacy of denosumab in children with FD exhibited good results. These studies confirmed the effectiveness of denosumab in the treatment of FD, in alleviating disease progression, and in relieving pain. No serious adverse events were observed during the denosumab therapy period. Both Wang *et al.* and Raborn *et al.* reported there to be severe hypercalcemia after drug withdrawal, while Raborn *et al.* noticed a tendency of tumor relapse after drug withdrawal. Another unexpected benefit was reported by Wang *et al.*, who found that denosumab treatment seemed to not affect the growth or development of the epiphyseal plates in the children.

A recent study on a mouse model of FD revealed that treatment with an anti-RANKL antibody prevented the formation of new lesions and promoted skeletal stem cell differentiation into functional osteoblasts, resulting in mineralized lamellar bone formation (50). This result showed that compared with bisphosphonates, which require binding to the mineralized matrix to impact osteoclasts, denosumab is a promising treatment because it does not require matrix incorporation and can directly target ectopic osteoclasts.

Data on children with FD reported in the literature using denosumab are summarized in *Table 3*. The FD patient follow-up in these data is relatively short, and the longest period with follow-up data was 3.5 years. Most treated children were still in an immature skeleton condition. Consequently, the long-term safety and efficacy of FD treatment are still unknown. Furthermore, since effective management of refractory FD requires long-term treatment, it is unclear whether continuous denosumab treatment will affect the growth and development of children's epiphyses. To reduce the effect of long-term denosumab on bone development, intermittent medication may work, but intermittent treatment leads to the problem of rebound bone turnover and an increased risk of neoplasm relapse. To solve these problems, prospective trials of denosumab in the treatment of FD in children and its withdrawal rebound trial (NCT03571191) are underway.

Aneurysmal bone cyst

ABC, which accounts for approximately 5% of benign bone tumors, is a locally destructive benign bone tumor, with 90% of cases occurring in young people under the age of 20 years and 25% of these being secondary ABCs that may form within preexisting benign or malignant bone tumors, including GCTB and FD (53,54). Recent studies have found translocation or gene fusions of the *USP6* gene

on chromosome 17p.3 in 75% of primary ABCs, pointing to the true oncological etiology and representing the molecular confirmation ABC (55,56).

The most common body location of ABC is the long diaphysis and posterior spine, but other sites may also be involved. The chief complaint is pain and swelling in the affected area, and pathological fractures may sometimes be observed. A relatively well-defined lytic "dilatative" lesion can be seen on plain radiographs and may rupture from the periosteum and have a soapy appearance (57,58).

The mainstream treatment for ABC is curettage with various local adjuvants, such as application of a high-speed burr, argon beam, phenol, etc. The incorporation of new adjuvants in treatment has significantly reduced the recurrence rates (7–12.5%) compared to those with curettage alone (59%), with intralesional doxycycline being particularly effective (59). ABC accounts for 15% of primary spinal tumors, of which 20% to 30% occur in the sacrum, and surgical resection carries high risk of life-threatening bleeding and damage to nerves or adjacent visceral organs and leads to disability and relapse. Treatment of ABCs in their critical locations remains a tremendous challenge (60).

A previous study revealed that the pathogenesis of ABC is similar to that of GCTB. The activation of RANK-RANKL signaling is crucial to the development and progression of ABC, and tumor spindle cells in ABC express high levels of RANKL, leading to osteoclast-like giant cell activation and osteolysis (22). Due to the histopathological similarities between GCTB and ABC, off-label denosumab therapy has been used in children with ABC.

Alhumaid *et al.* summarized the most current clinical experiences of denosumab-treated ABC and found that denosumab therapy could offer therapeutic clinical and radiological benefits in patients with ABC, particularly those patients with locally advanced, recurrent, or inoperable disease. Although the study was mainly limited to adults, it still can serve as a useful reference and guide for the treatment of children (61).

In 2013, Lange *et al.* were the first to apply denosumab in children with ABC (21). The 2 treated children had recurrent and refractory ABC lesions in the fifth cervical vertebra. Considering the special position, high potential for side effects, and risks of various treatment methods, Lange *et al.* finally chose individualized denosumab for trial treatment. The efficacy of denosumab in children with ABC was demonstrated and yielded good clinical results with improved pain and radiological short-term response with partial regression of the cyst. During the treatment period, only 1 child reported mild hypocalcemia, and no other serious adverse reactions occurred. Because the drug continues to be used, the adverse effects after discontinuation are unknown.

In 2014, Pelle *et al.* reported a 5-year-old male patient with a large and locally aggressive ABC involving the sacrum. The patient received 10 doses of denosumab, and symptoms were relieved, with complete remission of lower genitourinary symptoms and no radiological signs of recurrence (22).

In 2018, Fontenot *et al.* reported a 13-year-old female patient with a history of recurrent ABC involving the distal fibula (long bone). The patient received preoperative denosumab for 1 year (120 mg given every 4 weeks with additional 120-mg subcutaneous doses on days 8 and 15 in cycle 1) followed by intralesional curettage with high-speed burring and cement augmentation (23). In 2019, Raux *et al.* reported 5 cases of children with ABC, with an average age of 8 years, which was the highest number of cases reported in children thus far (24). The main lesion positions were the lumbosacral vertebrae and femoral neck. Denosumab was administered to treat these inoperable or refractory ABCs provided clinical and radiological improvements, with further tumor progression after denosumab discontinuation occurring in only 1 of the 5 patients. Hypocalcemia occurred in 2 patients, whereas hypercalcemia occurred in 2 patients. These data suggest a possible elevated risk of rebound hypercalcemia when denosumab therapy is prolonged. Dunnion *et al.* reported dense sclerotic metaphyseal bands caused by denosumab therapy in a 12-year-old girl with ABC, indicating the need to be aware of its alarming effects on the growing skeleton (62). Fadavi *et al.* reported a challenging case, a 13-year-old boy with cervical ABC progression to quadriparesis. He experienced significant regression after the first dose of denosumab, and after 12 courses, neurological symptoms recovered completely (26).

The efficacy of denosumab in ABC therapy has been confirmed by the above-mentioned literature (the data are shown in *Table 4*). However, different pathological situations, different treatment strategies and dose intervals, and various performance side effects were demonstrated. Adverse reactions include gastrointestinal discomfort, hypocalcemia, and calcification of the lower limb growth plates. Hypercalcemia after drug withdrawal was reported in 4 studies. The dosage varied from 1.2–1.6 mg/kg to 70 and 120 mg, with intervals including 1 week, 2 weeks, 4 weeks, and 6 months. Therefore, further information is needed

to determine the optimal dose, dose interval, and therapy duration in children who are skeletally immature. The literature also suggests that appropriate monitoring is required once denosumab use has been initiated and during the drug withdrawal process. It is recommended that blood calcium concentration is monitored every 2 months and that parents are educated on the common clinical manifestations of hypercalcemia to detect and prevent adverse reactions in advance (25).

Giant cell tumor of bone (GCTB)

GCTB is a locally invasive osteoclast stromal tumor. At present, the challenge in the treatment of GCTB is to reduce the recurrence rate, and it is critically necessary to find an effective adjuvant therapy for refractory GCTB when it is located in particularly difficult sites, such as the spine, pelvis, or facial bones, when resection could result in severe morbidity (63-65).

Denosumab is approved by the US Food and Drug Administration (FDA) for treatment of patients whose GCTB cannot be surgically removed. Denosumab can be used in adults and bone-matured adolescents, while a growing number of studies support denosumab as a valid therapeutic approach for GCTB in adults and skeletally mature adolescents (27-29,32,66).

When denosumab is used to treat GCTB, tumor recurrence after drug withdrawal can be disappointing. Research data indicate there to be a regression of the therapeutic effect, and up to 26% of individuals exhibit disease progression after withdrawal. Basic studies have shown that denosumab mainly acts on osteoclastic megakaryocytes in bone tissue but has no effect on mesenchymal cell proliferation and cannot completely prevent the progression of the disease. Other alternative strategies and new therapies need to be studied concerning this mechanism (67,68).

The incidence of GCTB is low in children. Primarily, studies have reported that in GCTB occurring in children before epiphyseal maturity, there is a higher incidence of multicenter lesions of the vertebrae (27,69). There are limited drugs and strategies for treating refractory GCTB. The use of denosumab for GCTB therapy in children was first reported by Karras *et al.* in 2013 (28). The researchers administered denosumab to adolescents over the age of 12 at the recommended adult dose of 120 mg per month to halt the progression of lesions, and there were no reported serious adverse reactions.

Furthermore, other groups have reported the successful application of denosumab in the treatment of GCTB in children, including Gossai *et al.* (29), Kobayashi *et al.* (31), and Setsu *et al.* (30). Kobayashi *et al.* reported a case in whom sclerosing bands were present in almost all radiographs of the metaphysis. However, the patient showed no signs of growth retardation at the last follow-up.

In 2021, Reddy *et al.* reported their experience with denosumab in 2 children with GCTB and pulmonary metastasis, achieving satisfactory results (33). During the denosumab treatment period, a reduction in the size of the primary lesions and lung metastatic lesions was observed, and pain was relieved. However, both patients developed mild hypocalcemia.

All these data (in *Table 5*) support denosumab as an effective treatment in children which can reduce pain and alleviate lesion progression. In contrast to adults, children frequently develop acute rebound of bone metabolism with severe and life-threatening hypercalcemia several months after discontinuation, often requiring hospitalization and bisphosphonate treatment. This finding represents a serious safety issue that is rarely reported in adults and appears to be primarily associated with pediatric patients. It has been speculated that the basal bone metabolic rate of children is higher than that of skeletally mature adults. Bone metabolism tends to rebound rapidly after drug withdrawal, resulting in increased bone absorption and elevated blood calcium levels. Although Uday *et al.* reported the first case of rare jaw osteonecrosis in a young patient with GCTB treated with denosumab. If jaw symptoms occur the drug should be stopped (9).

Central giant cell granuloma (CGCG)

CGCG is a bony destruction with multinucleated giant cells, which usually occurs only in the mandible and rarely occurs in the maxilla. It usually grows slowly with local cortical expansion without pain symptoms. Sometimes it can demonstrate invasive lesions with rapid growth and pain. Its incidence rate is about 1.1 per million, with a higher prevalence in children and adolescents, as well as in females (70). The first-line treatment is surgical excision or curettage, which is associated with higher of dentition loss, mastication and cosmetic defects, sensory loss, and up to 70% recurrence (64). Therefore, for CGCG that is difficult to treat surgically with a good cosmetic result or that recurs after surgery, a drug-based comprehensive treatment regimen should be initiated.

In the early stages of treatment, there were some reports of denosumab therapy in adult patients with CGCG. After successful results were obtained in adults, reports of denosumab treatment in children gradually began to emerge (71-73).

In 2014, Naidu *et al.* were first to report a trial of denosumab in children with CGCG (8). In another retrospective study of denosumab treatment that followed up the child for 75 months, the treatment was found to be generally safe. However, the patient relapsed and developed rebound hypercalcemia 14 months after discontinuation (74).

The largest group of children studied with CGCG treated using denosumab was reported in Texas Children's Hospital in 2021 (75,76). In this study, 6 children aged 5 to 12 years were followed up for an average of 20 months. After loading doses on days 1, 8, and 15 of cycle 1, patients received a dose of 70 mg/m^2 (maximum 120 mg) every 4 weeks, and generally received 12 doses until treatment ended. Favorable response, symptom relief, lesion reduction, and improved BMD were observed in all denosumab-treated patients. Moreover, 4 patients developed mild hypocalcemia, and 3 patients developed rebound hypercalcemia and acute kidney injury, which occurred 5 months after drug withdrawal. No rebound hypercalcemia was observed in any child after drug reduction via descending dosage. In addition, the bone age for all patients remained normal.

Secondary osteoporosis and other rare diseases

Other cases reported in children include those with osteopetrosis, hypercalcemia (5,10), juvenile Paget disease (JPD) (77), and secondary osteoporosis in children (78,79). Secondary osteoporosis in children mainly includes disuse osteoporosis and glucocorticoid-related osteoporosis.

Shroff *et al.* reported that 2 children (3 and 12 years old) with functional-loss mutations in the *TNFRSF11A* gene encoding RANK underwent hematopoietic stem cell transplantation, resulting in strong osteoclast activation and refractory hypercalcemia. In both patients, denosumab led to rapid normalization of serum calcium levels (5). JPD is an abnormal and rare genetic disorder of rapid bone remodeling in infants or individuals in early childhood. Symptoms extend beyond the bone and can include hearing loss and retinopathy. Bisphosphonates were the first recommended drug. However, several clinical trials have confirmed that while bisphosphonates can relieve bone lesion progression in JPD, they cannot alleviate extraosseous progression, which may include hearing and vision impairment. Grasemann *et al.* reported an unexpected improvement in hearing test results in an 8-year-old girl with severe JPD treated with denosumab, in addition to the alleviation of bone damage. However, serious hypercalcemia occurred post-discontinuation in JPD, which suggests careful consideration is needed for the application of this treatment approach (77).

Anastasilakis *et al.* reported the treatment of children with severe primary osteoporosis with denosumab and indicated denosumab to be highly effective, with remarkable clinical and radiological responses. Transient hypercalcemia occurred but was probably due to amplification of the effect of growth spurts and puberty on bone remodeling by the transient, short-term discontinuation of the drug (80).

Common causes of secondary osteoporosis include immobility, inflammatory conditions treated with steroids, Duchenne muscular dystrophy (DMD) and other myopathies, leukemia, and other cancers. Huang *et al.*'s preliminary study found denosumab to be an effective treatment for low BMD in childhood cancer survivors, although hypocalcemia occurred in 40% of patients (81). Scheinberg *et al.* reported their experience in treating disuse osteoporosis caused by cerebral palsy with denosumab (78). Additionally, Kumaki *et al.* described the first experience of denosumab treatment for glucocorticoid-induced osteoporosis in a patient with DMD (82), with the BMD increasing to some extent.

Treatment strategy and safety of denosumab in children

The above-mentioned studies demonstrated that denosumab is a promising treatment for bone disorders in children and represents a valid alternative therapeutic approach to improve pediatric bone health. A summary of the studies reporting the use of denosumab in children and adolescents in is presented in *Table 6*.

To date, serious side effects, such as osteonecrosis of the jaw and asymptomatic femoral fracture, have rarely been reported in children. However, there are still several concerns about pediatric clinical use that deserve further discussion and investigation.

Denosumab is a powerful anti-resorption agent, and early preclinical studies in rodents and primates have shown that it can significantly inhibit bone growth and tooth eruption (83). Denosumab has a significant advantage over bisphosphonates due to the reversibility of its

Table 6 Summary of denosumab treatment in children and adolescents in the literature

Disease	Dose and interval of denosumab	Preparation before start denosumab	Supplements in therapy	Monitoring in therapy	Dose modifications	Monitoring after end of therapy
ABC GCTB CGCG	<45 kg 70 mg/m^2 every month; ≥45 kg 120 mg every month	Treat and prevent oral diseases; correct hypocalcemia and vitamin D deficiency	Calcium 500 mg/day, vitamin D 400 IU/day	Serum calcium ≥2 mmol/L and ≤2.9 mmol/L	Hold denosumab when serum calcium <2 mmol/L or if denosumab-related grade 3 or 4 adverse events occur	Monitoring calcium >6 months, if symptomatic hypercalcemia is observed, decrease doses every 3 months
FD	1–1.5 mg/kg every month					
OI	1 mg/kg every 3 months					

ABC, aneurysmal bone cyst; GCTB, giant cell tumor of bone; CGCG, central giant cell granuloma; FD, fibrous dysplasia; OI, osteogenesis imperfecta.

effect. Moreover, bisphosphonates need to bind to bone hydroxyapatite, which results in a longer half-life of bone, so their effect lasts longer. In the published data, denosumab has been shown to affect radiographic changes in the bone epiphysis, and while sclerotic epiphyseal bands may appear, they tend to fade with time (31,62). Although clinical data are limited, there are many reports of continued bone growth after denosumab use (18,84). Wang *et al.* examined the effects of denosumab treatment and discontinuation on skeletal growth plates in children. In a 9-year-old boy with FD who received denosumab for 7 months, imaging and histological analysis of the growth plates of the limbs showed that although sclerotic bands developed near the growth plate during the treatment, the sclerosing bands gradually dissolved after treatment, and the epiphyseal growth continued during and after treatment (18). Similar results were found in children treated with bisphosphonates, but there was no significant clinical significance for bone growth (18,85). Although limited by a small sample size, Wang *et al.* directly demonstrates that denosumab has no significant adverse effects on bone growth in children.

Previous case reports have mentioned the minor adverse reactions observed during the denosumab treatment period, including occasional asymptomatic hypocalcemia and hypophosphoremia, mild gastrointestinal reactions, self-relieving muscle and joint pain, and urinary calcium detection, which do negate its validity as a therapeutic approach. Safety concerns related to rebound bone turnover and hypercalcemia after discontinuation are currently the main concerns regarding the safe use of denosumab in children. Hypercalcemia after discontinuation of denosumab therapy in adults is rarely reported, but the incidence in children is significantly higher. Some authors speculate that the main cause of hypercalcemia in children is the basal bone metabolic rate being higher than that in adults (24,30). The stronger the inhibition of bone metabolism during treatment is, the higher the rebound after drug withdrawal.

High blood calcium levels could occur as early as 7 to 8 weeks after discontinuation, and some reported instances occurred 20 weeks after discontinuation. This kind of hypercalcemia can require hospitalization for pain control and/or hydration and correction of hypercalcemia; fortunately, patients can quickly recover through bisphosphonate treatment. A multifactorial analysis of thoracic vertebral fractures after drug discontinuation suggested bisphosphonates to be a protective factor against fracture after drug discontinuation. This finding provides a direction for denosumab discontinuation strategies, as discontinuation therapy with bisphosphonate can be routinely used to prevent hypercalcemia (32,86).

The pharmacodynamic effects of drugs in children are mainly affected by two factors: (I) levels of RANK/RANKL/OPG activity due to increased bone turnover related to the child's bone growth rate and (II) body weight and surface area (87).

Therefore, the optimal denosumab dose and interval for children and how to regulate the duration of denosumab therapy through monitoring bone metabolic markers in blood or urine are the most urgent problems to be solved. Hoyer-Kuhn *et al.* (17) reported that by flexibly adjusting the injection interval of denosumab based on the content of the urinary metabolite DPD/CREA and extending the injection interval from 8 to 20 weeks, they could achieve the best efficacy results with no hypercalcemia, thus providing a good reference for the adjustment of denosumab administration. To prevent the occurrence of hypercalcemia, it is necessary to closely monitor the fluctuation of bone metabolic marker levels and maintain a stable state of bone metabolism in children requiring lifelong medication or young patients with a high metabolic

rate in bone. Children who are about to cease denosumab therapy may need to reduce the dose gradually to achieve a stable balance of blood electrolytes. Therefore, the dose and interval of denosumab administration, the monitoring and adjustment strategy during drug use, the withdrawal strategy, and the monitoring strategy post-discontinuation need to be holistically considered.

In the short term, it is of great significance to strengthen the monitoring of markers of bone metabolism, strengthen the monitoring of blood marker cutoffs, and educate patients and their parents on the common symptoms of hypercalcemia for the early detection and prevention of hypercalcemia.

The main disadvantage of denosumab is that its effect on bone turnover and inhibitory effect on bone lesions are reversible. Some primary bone neoplasms will recur after discontinuation of denosumab therapy, which has been reported for GCTB. Therefore, long-term drug safety tests should be considered for patients who relapse after drug withdrawal. In addition, how to inhibit the continued proliferation of bone tumor stromal cells in bone neoplasms is another area worth further study.

Limitations and future directions

Some limitations to this review should be noted. Fist, all of the literatures gathered were comprised of case reports and retrospective studies, which lacked controlled research groups and prospective design, and the research samples were mixed with adults. The studies were greatly affected by various biasing factors. Therefore, the level of evidence-based evidence was not high, and any conclusions drawn from them should be carefully scrutinized. Additional clinical trial models are warranted regarding the optimal dose and discontinuation time of denosumab in children, and indeed, several are already underway. We look forward to the completion of valuable research in the future to better inform the safe use of denosumab in children.

Conclusions

Refractory benign bone lesions in children include a wide range of bone diseases; due to their unfavorable location and their inability to be surgically resected, they seriously affect the quality of life of children. Thus far, there is no approved effective and safe treatment strategy.

Denosumab, which has been approved for the treatment of bone disease in adults, has demonstrated a potential role in alleviating disease in multiple refractory bone lesions in children according to the published data.

Previous reports of denosumab in children showed that it was relatively safe, and no serious complications were observed. Hypocalcemia during the medication period could be prevented by calcium supplementation. Rebound hypercalcemia after discontinuation can be effectively controlled by close monitoring and bisphosphonate intervention. Again, no adverse effects on bone growth or development have been observed with denosumab therapy in children. Although it is currently used off-label, ongoing high-quality pediatric denosumab studies may achieve further advances.

Finally, denosumab needs to be used with caution in children with refractory benign bone lesions. A comprehensive assessment should be initiated before its use, including monitoring the development status of bones and teeth. During the therapy period, close monitoring of bone turnover markers to prevent safety issues related to bone turnover rebound and mineral homeostasis is necessary.

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Supplementary

Table S1 Literature search queries on PubMed

Search#	Query
1	Denosumab
2	Child*
3	Adolescen*
4	Pediatric*
5	1 AND (2 OR 3 OR 4)
6	Giant cell tumor of bone
7	Osteogenesis imperfecta
8	Fibrous dysplasia
9	Aneurysmal bone cyst
10	Central giant cell granuloma
11	1 AND (6 OR 7 OR 8 OR 9 OR 10)
12	5 OR 11

https://dx.doi.org/XXXXXXX