Novel Treatment Options in Childhood Bone Diseases

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Keywords

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Abstract

Background: Several novel treatment options have recently become available in childhood bone diseases. The purpose of this article is to provide an update on some of the therapeutic agents used in the treatment of pediatric osteoporosis, X-linked hypophosphatemic rickets, and achondroplasia (ACH). **Summary:** Vitamin D3 and Ca supplementation remains the basis of childhood osteoporosis treatment. Bisphosphonate (BP) therapy is the main antiresorptive therapeutic option, while denosumab, a human monoclonal IgG2 antibody with high affinity and specificity for a primary regulator of bone resorption – RANKL, represents a possible alternative. Its potent inhibition of bone resorption and turnover process leads to continuous increase of bone mineral density throughout the treatment also in the pediatric population. With a half-life much shorter than BPs, its effects are rapidly reversible upon discontinuation. Safety and dosing concerns in children remain. Novel treatment options have

recently become available in two rare bone diseases. Burosumab, a monoclonal antibody against FGF-23, has been approved for the treatment of children with X-linked hypophosphatemic rickets older than 1 year. It presents an effective, more etiology-based treatment for rickets compared to conventional therapy, without the need for multiple daily oral phosphate supplementation. Its long-term efficacy and safety are currently being investigated. After years of anticipation, a novel treatment option for ACH has become available. C-type natriuretic peptide analog vosoritide effectively increases proportional growth and has a reasonable safety profile in children >2 years. Its effect on other features of the disease and the final height is yet to be determined. Several other treatment options for ACH exploring different therapeutic approaches are currently being investigated. **Key Messages:** Denosumab is effective in the treatment of childhood-onset osteoporosis; however, further studies are necessary to determine the optimal treatment protocol. Burosumab is more etiology-based and convenient in comparison to conventional treatment of X-linked hypophosphatemic rickets in children and adults. Vosoritide importantly changes the natural course of achondroplasia, at least in the short term.

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Pediatric Osteoporosis

Osteoporosis is a disease characterized by low bone mass and/or an alteration in bone microarchitecture predisposing to an increased risk of fracture. According to the current guidelines, diagnosis of osteoporosis in the pediatric population requires the presence of clinically significant fracture history together with low bone mineral content or density (Z -score ≤ -2.0 , adjusted for age, gender, and body size). Making the diagnosis remains challenging especially in patients with underlying bone fragility conditions [1, 2]. As 90% of bone mass is accrued in childhood and adolescent years which further influences the risk of fracture and osteoporosis throughout the life span, identification, and treatment of pediatric patients, who may benefit from pharmaceutical interventions is extremely important [3, 4].

The imbalance favoring osteoclast/bone-resorbing to osteoblast/bone-forming activity leads to poor bone health. Two major pathways, receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin and Wnt, play a key role in the bone remodeling process. They have been found altered not only in primary bone disorders but also in several other diseases in which bone health is also compromised, such as type 1 diabetes, alkaptonuria, hemophilia A, 21-hydroxylase deficiency, and Prader-Willi syndrome [5]. Primary osteoporosis in childhood is a rare entity, caused by primary bone diseases such as osteogenesis imperfecta, idiopathic juvenile osteoporosis, and osteoporosis-pseudo-glioma syndrome. Additionally, it is seen in connective tissue disorders and other conditions, such as homocystinuria, polyostotic fibrous dysplasia, hypophosphatasia, and Cole-Carpenter syndrome. The causes for secondary osteoporosis are numerous, including adverse effects of medication, immobilization, diseases associated with chronic inflammation, malnutrition, and endocrine disorders. With advances in medical care improving survival outcomes, its prevalence in the pediatric population has recently increased [6]. In addition, obesity in this age group is associated with compromised site-specific bone health and increased fracture risk [7].

Current preventive and therapeutic measures include adequate vitamin D and calcium intake, optimizing the management of the underlying conditions, and resolving risk factors associated with low BMD [6]. In order to prevent rickets and osteomalacia, the latest guidelines recommend vitamin D supplementation of 400 IU/day for infants up to 12 months of age and 600 IU/day for children and adolescents. Adequate dietary calcium intake to

prevent rickets in infants from birth to 6 months is 200 mg/day and 260 mg/day from 6 to 12 months of age [8]. Further on, recommended daily dietary calcium intake is 700 mg for children of 1–3 years, 1,000 mg for 4–8, and 1,300 mg for 9–18 [6]. Antiresorptive therapy is used in children with primary osteoporosis or in those with secondary osteoporosis whose risk factors are unlikely to be mitigated. Treatment with intravenous bisphosphonates (BPs) is currently the most widely used and there is growing evidence supporting their use in the pediatric population [6]. BPs in children are given intravenously and have a very long skeletal half-life and this limits their use in children. Therefore, other therapeutical options for the treatment of osteoporosis in children are being explored (Table 1).

Denosumab

Denosumab is a human monoclonal IgG2 antibody with high affinity and specificity for a primary regulator of bone resorption – RANKL, a transmembrane protein highly expressed in osteoblasts. RANKL promotes the differentiation of osteoclast precursors and activates mature osteoclasts by binding to the RANK receptor. Denosumab prevents the activation of the RANK receptor by binding to RANKL, which leads to impairment of osteoclast formation, function, and possibly survival [9]. It mimics the natural action of osteoprotegerin, an endogenous decoy receptor of RANKL, and by its binding prevents catabolic effects of RANK signaling pathway activation [10].

Denosumab's convenient subcutaneous application together with the rapid reversibility of its action in comparison to BP's long half-life, make it interesting for use in the pediatric population. Denosumab has more powerful inhibitory effects on bone resorption and turnover than BPs, increasing BMD at all skeletal sites, without changing bone microarchitecture and adversely affecting its mineralization [11, 12]. BMD increases progressively throughout denosumab use in contrast to BP where a plateau is reached after 2–3 years [13]. Additionally, it can be used in patients with renal function impairment, since it is thought to be cleared from the bloodstream through the reticuloendothelial system [14].

To date, the use of denosumab in the pediatric population is only approved for the treatment of giant cell tumors of the bone in skeletally mature adolescents, when the tumor is unresectable, requires morbid surgery, or in metastatic disease (approved by the Food And Drug Administration [FDA] and the European Medicines Agency [EMA]) [15, 16]. However, it is used off-label for the

Table 1. List of novel treatment approaches in selected bone disorders

Disease	Drug (brand name)MOA		Study phase	Dose
Osteoporosis	Denosumab (Prolia®, Xgeva®)	Monoclonal IgG2 anti-RANKL; blocks osteoclast maturation and bone turnover	EMA, FDA approved for the treatment of GCTB in skeletally mature children and adults	120 mg SC on days 1, 8, 15, and 28, and then every 4 weeks thereafter [16]
	Odanacatib	Cathepsin K inhibitor; reduces bone resorption	Phase III clinical trial in adults terminated early due to side effects, no clinical trials on pediatric population [43]	NA
XLH	Burosumab (Crysvita®)	Monoclonal IgG1 anti-FGF3; promotes phosphate reabsorption and increases serum concentrations of 1,25-dihydroxy cholecalciferol	EMA, FDA approved for treatment for children >1-year old	0.4 mg/kg SC every 2–4 weeks [56]
ACH	Vosoritide (Voxzogo®)	CNP analog; promotes endochondral bone formation	EMA, FDA approved	15 µg/kg SC daily [77]
	TransCon CNP	Prolonged-release CNP analog; promotes endochondral bone formation	Phase 2 clinical trial ongoing (NCT04085523)	NA

ACH, achondroplasia; CNP, C-type natriuretic peptide; EMA, European Medicines Agency; GCTB, giant cell tumors of the bone; FDA, Food And Drug Administration; FGF-3, fibroblast growth factor; MOA, mechanism of action; NA, not available; XLH, X-linked hypophosphatemia.

treatment of different pediatric skeletal disorders [17]. In contrast to adults, data on its use in the pediatric population are currently limited to case reports or small series. There are no studies available on the pharmacokinetics and pharmacodynamics in the pediatric population and no guidelines regarding optimal dosing or treatment duration in this age group [18]. In most studies, a protocol with applications of 0.5–1 mg/kg (with maximal dose of 60 mg) per 3 months is used; however, treatment dosage, intervals, and duration vary greatly in the published literature. Results of the studies show that the duration of denosumab action in children with the same bone disorder is variable [19].

Applications of denosumab in children and adolescents with osteogenesis imperfecta (receiving 1 mg/kg every 12 weeks up to 48 weeks) have been shown to effectively suppress osteoclastic activity and increase BMD. The side effects reported in these studies include asymptomatic rebound hypercalcemia in almost all the patients. Additionally, some participants developed hypercalciuria during treatment, and 1 patient developed nephrocalcinosis. Prolonging the interval between treatment applications resulted in a rapid decrease of acquired BMD in some patients [19, 20].

A recent case report observed clinical and radiological improvement in a pubertal boy with primary osteoporosis treated with denosumab (receiving 60 mg every 3

months for 30 months). As a side effect, transient hypercalcemia before applications in the second year of treatment was noted [21]. The improvement of BMD was also observed in treating childhood cancer survivors (receiving 1 mg/kg every 6 months until height-adjusted Z-scores of the BMD were >−1.5). A significant increase of BMD was observed after 1.5 years of treatment; however, 8 (40%) patients developed hypocalcemia, with 3 of them presenting with neurological symptoms. Hypercalcemia in this study was not observed [22].

Beneficial effects of denosumab use have also been reported in many small series/case reports in pediatric patients with osteoclast bone dysplasia, fibrous dysplasia, spinal aneurysmal bone cysts, Paget's disease, neuromuscular diseases, and in patients with Noonan syndrome with multiple giant cell lesions of the jaw [17, 23–28]. Different protocols for denosumab dosing and frequency of its application were used in each of the studies, nonetheless, all studies observed good clinical and/or radiological response to the treatment. Frequent disturbances in calcium metabolism were reported during the treatment and after its discontinuation, often requiring additional hospitalizations.

There are some potential risks for the use of denosumab in the pediatric population. Its potent bone turnover suppression could potentially affect the bone modeling process in the growing skeleton and compromise bone

shape and linear growth. Despite discouraging data in preclinical settings reporting inhibitory effects on linear growth and tooth eruption in rodents and primates, limited clinical studies have reported normal linear growth in children during denosumab treatment [17, 20]. Besides, in 2014, Wang et al. [29] provided histopathologic evidence that denosumab treatment did not appear to adversely affect the activity of growth plates in a growing child. No negative effects on fracture healing have been reported in preclinical studies as well as in scarce clinical studies in the adult and pediatric population, where fracture healing was analyzed [30]. The high incidence of hypercalcemia as a part of bone turnover rebound upon treatment discontinuation reported in the pediatric population presents another setback for its use [19, 21, 31–33]. This outcome could be attributed to the higher baseline bone turnover in children, related to their bone modeling process, and/or may also be the result of the mobilization of calcium from treatment-induced sclerotic transverse lines seen in metaphyses of fast-growing long bones in children treated with antiresorptive therapy [21, 33]. Prolonged, potent antiresorptive therapy (with BPs and denosumab) in adults is associated with rare complications such as osteonecrosis of the jaw and atypical femoral fractures [34, 35]. In October 2021, the first case of osteonecrosis of the jaw in a skeletally mature adolescent treated with denosumab for giant cell tumors of the bone as a part of a clinical phase 2 study was reported. Osteonecrosis in an adolescent was diagnosed after 3.6 years of treatment, receiving denosumab at a fixed dose of 120 mg on days 1, 8, 15, and 28, and then every 4 weeks, according to the study protocol. Moreover, in the same clinical study, a young adult presented with bilateral femoral cortical stress reaction after 4 years of treatment. All the studied patients (2 adolescents and 1 young adult) developed rebound hypercalcemia with acute kidney injury 5.5–7 months after treatment discontinuation [36]. To date, atypical femoral fractures have not been reported in the pediatric population.

Odanacatib

Odanacatib is a selective inhibitor of cathepsin K, lysosomal cysteine protease, which is highly expressed by the osteoclasts. Cathepsin K is a major protease responsible for the degradation of type 1 collagen, which constitutes approximately 90% of the bone organic matrix. Its inhibition results in slowing down the process of bone matrix resorption without substantially inhibiting bone formation [37].

In the preclinical setting, cathepsin K inhibition resulted in reduced osteoclast-mediated bone resorption without decreasing osteoclast number or inhibiting other osteoclast functions. The process of bone formation was maintained or only transiently decreased. Its use was not found to affect the bone microarchitecture and an increase in spinal and lumbar BMD was reported in multiple animal models. In comparison to BPs and denosumab, the use of cathepsin K inhibitors has been shown to impair the bone formation process to a lesser degree [38–41]. Similar to denosumab, odanacatib action is rapidly reversible upon treatment discontinuation, returning accrued bone mass and density to pretreatment levels, accompanied by a small rebound of bone resorption markers [41]. Described characteristics together with its convenient oral application would make odanacatib an attractive therapy option for the pediatric population. Significant increases in BMD at all sites (lumbar, hip, and femoral), reduced risk of vertebral, non-vertebral, and hip fractures have been reported in postmenopausal women [42, 43]. However, its use in postmenopausal women was associated with a higher incidence of cardiovascular events (stroke and new-onset atrial fibrillation or flutter) and further development of odanacatib was discontinued by its manufacturer in September 2016 [43]. To date, the mechanism or possible relationship between inhibition of cathepsin K and an increased risk of cardiovascular events has not been elucidated.

X-Linked Hypophosphatemic Rickets

X-linked hypophosphatemia (XLH) is a rare hereditary metabolic disorder characterized by bone hypomineralization resulting in osteomalacia and skeletal deformities. It affects 1 in 20,000–25,000 children and is the most common amongst hereditary rickets disorders [44, 45]. It is caused by a mutation in the *PHEX* gene (*phosphate regulating endopeptidase homolog X-linked* gene), which encodes a transmembrane zinc-dependent endopeptidase that is involved in bone and dentin mineralization [44, 46]. Consequently, it decreases serum phosphate levels due to the increased urinary phosphate loss, up-regulation of FGF-23 (fibroblast growth factor 23) (FGF-23), and decreased active vitamin D3 levels [47]. In children, this results in short stature, deformations of the weight-bearing joints, rickets, dental complications, such as spontaneous dental abscess, fistulae, and motor development delay [48–50]. In adult patients, quality of life is considerably decreased by bone pain, early osteoarthritis,

stiffness, osteomalacic pseudofractures, and impaired mobility [50, 51].

Children with XLH are primarily managed by conventional medical treatment; supplementation with oral phosphate 20–60 mg/kg body weight daily (divided into several daily doses) and active vitamin D3 to improve intestinal absorption of phosphate and prevent secondary hyperparathyroidism [52, 53]. Conventional treatment is effective in treating XLH, however, it does not decrease FGF-23 levels [45]. Additionally, it is associated with secondary hyperparathyroidism, hypercalciuria, and nephrocalcinosis, which, if left untreated, leads to kidney damage and insufficiency [54]. Furthermore, compliance with this treatment regimen can be a serious issue in some patients [53].

Burosumab

Burosumab is the first etiologic treatment option that actively increases phosphate levels while also decreasing FGF-23 actions in XLH (Table 1) [49]. It is a monoclonal IgG1 antibody that suppresses the actions of FGF-23. FGF-23 is the key phosphaturic hormone and acts as a regulator of phosphate homeostasis [46]. It mediates its actions by binding to its cofactor alpha-Klotho and FGF-receptor 1 (FGFR1), through which it inhibits phosphate reabsorption in the kidney via downregulation of the sodium-dependent phosphate transporters (NaPi-2a and NaPi-2c) in proximal renal tubules [55]. Additionally, it suppresses renal 1 α -hydroxylase (CYP27B1) and activates 24-hydroxylase (CYP24A1), both of which contribute to lowering serum concentrations of 1,25-dihydroxy cholecalciferol and thus reduce intestinal uptake of phosphate [55]. The elimination of burosumab follows the endogenous immunoglobulin degradation pathway [56].

In early 2018, burosumab was approved by the EMA and the FDA for XLH in children aged 1 year or older until the cessation of linear growth [56, 57]. Before starting burosumab treatment, supplementation with phosphate and active vitamin D should be stopped. In children, it is given subcutaneously every 2 weeks, which is much more convenient and should result in improved compliance compared to multiple daily doses of phosphate and vitamin D3. The recommended starting dose of burosumab is 0.4 mg/kg body weight every 2 weeks [53, 58]. In several phase 2 open-label trials in children with XLH, burosumab improved phosphate homeostasis with normalization of phosphaturia and significantly reduced rickets severity score (RSS) [52, 59]. It decreased pain score and improved mobility function in a recent phase 3 study [53, 60]. In another phase 3 study (study identifier

NCT02915705) burosumab treatment was superior to conventional therapy regarding growth velocity and disease progression determined by RSS [49]. An interesting point of view on burosumab efficacy was reported by Brenner et al. [61] using bioelectrical impedance analysis they determined improved body composition (increased fat-free mass) after 6 and 12 months of burosumab treatment. The effectiveness and safety of very early use of burosumab in children less than 1 year are currently being studied (study identifier NCT04188964).

Adverse events were more frequently reported in patients treated with burosumab compared to the conventional treatment [49]. However, it is generally well-tolerated and adverse events are mild and transient [53]. The most common side effects are local reactions at the site of injection (such as itching, pain, erythema, or bruising), cough, headache, fever, arthralgias, diarrhea, constipation, and nausea [52]. Possible increased risk for dental caries and dental abscess in children needs further evaluation [62]. Pathologic tissue calcification was one of the feared potential severe adverse events of burosumab treatment. Transient hypercalcemia was however rare, nephrocalcinosis due to calciuria under treatment with burosumab was not reported and transient hypercalcemia with pathological cardiac calcifications was described in one adult patient [49, 54]. The long-term safety of burosumab is being longitudinally studied in XLH patients of all ages (study identifier NCT03651505).

Achondroplasia

Achondroplasia (ACH) is the most common form of skeletal dysplasia characterized by disproportionate rhizomelic short stature, hypoplasia of the midface, and macrocephaly. Numerous orthopedic and neurological complications are associated with the disease [63]. Recently, comprehensive meta-analyses estimated its worldwide prevalence of 4.6 per 100,000 births. Large regional variations have been reported with the highest ACH prevalence in North Africa and the Middle East [64]. Prevalence in Europe has been estimated to be 3.62–3.72 per 100,000 births [64, 65].

ACH is caused by a gain-of-function mutation in the FGFR3 gene, a member of the tyrosine kinase receptor family [66]. The mutation is spontaneous in 80% of cases. ACH is inherited in an autosomal dominant manner and is characterized by full penetration, meaning that all individuals with the mutation have ACH. Excessive FGFR3 activation results in downstream activation of multiple

intracellular signaling pathways, leading to intensified inhibition of cartilage tissue formation at the level of chondrocyte proliferation (via STAT1), hypertrophy, differentiation, and synthesis of the extracellular matrix (via Erk-MAPK signaling pathway) [67]. The latter pathway has also been shown to be involved in premature synchondrosis closure and increased bone formation, leading to skeletal abnormalities (spinal canal stenosis, foramen magnum stenosis, and cranial base hypoplasia) which cause neurological problems in patients with ACH [68].

Therapy options for ACH are limited. Active follow-up and symptomatic treatment of the complications present the forefront of patient management. Growth hormone supplementation has not shown promising results and is not viewed as a standard treatment for ACH. The progress in the understanding of ACH pathogenesis has led to the development of many potential therapeutic strategies for modulating excessive FGFR3 activation (Table 1). Approaches are varied and include inhibiting the tyrosine kinase activity of FGFR3 (infigratinib), producing artificial FGFR3 as a decoy for FGF ligand (re-cifercept), inhibition of FGFR3 downstream signaling pathways (meclizine, C-type natriuretic peptide [CNP] analogs), modulation of growth via natriuretic peptide receptor 2 (NPR2) receptor (CNP analogs) and use of aptamers or monoclonal antibodies to prevent binding of FGF to its receptor (aptamer RBM-007, vofatamab). The investigations into analogs of CNP, especially vosoritide, are currently the most advanced [69].

Vosoritide

Vosoritide is a recombinant CNP analog. Endogenous CNP and its action on the growth plate through NPR-B are recognized as one of the important regulating mechanisms of longitudinal bone growth. Coupled with NPR-B, CNP antagonizes downstream FGFR3 signaling by inhibiting the Erk-MAPK signaling pathway at the level of Raf. This leads to chondrocyte proliferation, differentiation and increases the extracellular matrix synthesis [70]. CNP-targeted overexpression in the cartilage or its continuous delivery by intravenous infusion has shown normalization of the impaired bone growth in mouse models with ACH [70, 71]. Endogenous CNP has a short half-life of 2–3 min, as it is rapidly degraded by neutral endopeptidase [72]. Vosoritide is more resistant to the action of neutral endopeptidase and has an extended half-life of approximately 15–20 min [73].

Preclinical studies in healthy mice and cynomolgus monkeys have shown the efficacy of daily subcutaneous vosoritide applications on endochondral bone growth

stimulation without causing significant changes in bone quality parameters [74]. In August 2021, results of the extension phase 3 clinical trial in children with ACH aged between 5 and 18, receiving vosoritide 15 µg/kg once daily in subcutaneous injection, were published. An increase in annualized growth velocity was observed, with 3.52 cm of height gain over a 2-year treatment period in comparison to untreated patients. In addition, improvement in the proportionality of body segments and no acceleration of the bone maturation process (determined by bone age assessment) was observed [75]. No serious adverse effects were reported; however, mild adverse effects such as reactions at the injection site occurred in up to 73% of patients, and in 23% mild, transient, in majority asymptomatic hypotension was observed after vosoritide application [76]. Due to the possibility of transient hypotension after treatment administration, current recommendations include hydration 30 min before vosoritide injection [77]. Vosoritide was approved by both EMA and FDA for the treatment of ACH in children from the age of 2 years until their growth plates are closed [78, 79]. Vosoritide's effect on final adult height and prevention of neurological and orthopedic complications requiring surgical interventions is yet to be established. Current ongoing trials investigating its safety and efficacy in infants, young children, and those at risk of requiring cervical-medullary decompression surgery, will provide further insights into treatment effects on growth, proportionality, and other medical complications of ACH [80].

TransCon CNP

TransCon CNP is an investigational prodrug of CNP designed for the treatment of ACH in children. In TransCon CNP, CNP is conjugated via a cleavable linker to a polyethylene glycol carrier molecule that prolongs CNP's half-life to 90 h. This prolongation is achieved by increased resistance to the action of neutral endopeptidase and minimizing renal clearance. The cleavage process results in slow, sustained CNP release, leading to continuous exposure of CNP at the growth plate. Its long half-life also allows convenient weekly subcutaneous administrations [81].

Recent preclinical data in healthy cynomolgus monkeys showed that treatment with TransCon CNP subcutaneously once per week resulted in significant growth increases in body, tail, and long bones compared to controls. An increase in height was also more pronounced in comparison to the animals receiving a daily dose of CNP analog with the same amino acid sequence as vosoritide (5% vs. 3%, respectively), and no significant changes in

bone quality were observed with both treatments. Moreover, sustained CNP release resulted in lower systemic CNP peak levels and has not been associated with adverse cardiovascular effects in monkeys treated with repeated weekly doses up to 100 µg/kg [81]. The safe cardiovascular profile has also been recently confirmed in the first human clinical trial in healthy adult males receiving single doses of TransCon CNP up to 150 µg/kg [82]. Phase 2 of the TransCon CNP clinical trial to assess its safety, tolerability, and effect on annual growth velocity started in June 2020 is still ongoing. TransCon CNP will be administered subcutaneously once per week for 52 weeks in children with ACH aged 2–10 years (study identifier NCT04085523).

Conclusion

Several novel treatment options for childhood bone disorders were presented (Table 1). The common denominators of these treatments are novel, efficient, pos-

sibly more etiology-based, and convenient treatment schemes. Long-term efficiency and safety will, however, need to be established.

Conflict of Interest Statement

Lecture fees were received from Kyowa Kirin, Pfizer, and Novo Nordisk by P.K. M.K. and S.J. have no conflicts of interest to declare.

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Author Contributions

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