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# Developments in rare bone diseases and mineral disorders

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***Abstract*:** In the last decade, there have been a number of significant advances made in the field of rare bone diseases. In this review, we discuss the expansion of the classification system for osteogenesis imperfecta (OI) and the resultant increase in therapeutic options available for management of OI. Bisphosphonates remain the most widely used intervention for OI, although the effect on fracture rate reduction is equivocal. We review the other therapies showing promising results, including denosumab, teriparatide, sclerostin, transforming growth factor β inhibition and gene targeted approaches. X-linked hypophosphataemia (XLH) is the most common heritable form of osteomalacia and rickets caused by a mutation in the phosphate regulating endopeptidase gene resulting in elevated serum fibroblast growth factor 23 (FGF23) and decreased renal phosphate reabsorption. The traditional treatment is phosphate replacement. We discuss the development of a human anti-FGF23 antibody (KRN23) as a promising development in the treatment of XLH. The current management of primary hypoparathyroidism is replacement with calcium and active vitamin D. This can be associated with under or over replacement and its inherent complications. We review the use of recombinant parathyroid hormone (1–84), which can significantly reduce the requirements for calcium and vitamin D resulting in greater safety and quality of life for individuals with hypoparathyroidism. The use of receptor activator of nuclear factor κB ligand infusions in the treatment of a particular form of osteopetrosis and enzyme replacement therapy for hypophosphatasia are also discussed.

***Keywords:*** osteogenesis imperfecta, X-linked hypophosphataemia, primary hypoparathyroidism, osteopetrosis, hypophosphatasia

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## Introduction

Hereditary diseases affecting bone are heterogeneous in aetiology, in their onset and severity. The majority of these conditions individually are defined as 'rare', with less than 1 per 200,000 affected. There have been a number of significant advancements made in understanding the mechanisms underlying a variety of rare bone diseases. The aim of this review is to discuss the implications of new gene discovery in osteogenesis imperfecta (OI) and the novel therapeutic options for the treatment of X-linked hypophosphataemia (XLH), primary hypoparathyroidism, osteopetrosis and hypophosphatasia (HPP).

## Osteogenesis imperfecta

OI or 'brittle bone disease' is a clinically heterogeneous disorder of connective tissue. The features include low bone mass, increased bone fragility, bone deformity and growth deficiency. OI has a prevalence of 1 per 20,000 live births.[1]

### *Advances in the classification of OI*

The original classification by Sillence in 1979 described four subtypes determined by severity, phenotype and radiological findings.[2] Type I is classified as least severe, type II is perinatal lethal, type III is the most severe surviving form with type IV being of intermediate severity. The recent

evolution in genetics resulted in the discovery of several additional genes causative for OI.[3] The majority of these new mutations encode for proteins involved in the post-translational modification of collagen and genetic defects in osteoblast development. The identification of novel causative genes has greatly extended the understanding of cellular and biological pathways involved in OI pathogenesis.

There have been genetic, phenotypic and proposed functional classifications to incorporate the novel discovery of mutations causative for OI. As per the clinical classification, the newly discovered forms are merged into Sillence types I–IV by clinical severity with the addition of type V which has distinct radiographic features to the other types.[4] The concern with this classification is deemed to be a difficulty with giving accurate genetic counselling as disease may change in severity during a lifetime. The genetic classification expanded upon the original Sillence classification. It developed a new subtype for each defective gene.[5] A problem with this classification system is that it will be continually evolving as novel genes are discovered. Under a further functional classification system it is proposed that the subtype of OI be classified by the underlying mechanism of disease; therefore primary collagen structure and function would be grouped together, defects in ossification and mineralization would be grouped together and so on.[1] A brief description of the genetic subtypes, severity and characteristic clinical features are detailed in the Table 1.

### *Importance of novel genetic classification for the patient*

While there is a lack of consensus as to how to incorporate the newly discovered genes for OI into a clinically useful system, there is no doubt that their identification has provided crucial information. These discoveries allow for accurate genetic counselling and development of screening programmes in dedicated centres for the management of this increasingly complex disorder. In addition, these novel gene discoveries facilitate investigations into common pathways involved in OI.

### *Current therapeutics in OI*

At present, bisphosphonates are the mainstay of treatment. Bisphosphonates bind to hydroxyapatite and are taken up by osteoclasts where they exert their antiresorptive effect. The rationale for bisphosphonate use in OI is to increase bone volume (albeit of reduced quality) and that this increased density will make bone more fracture resistant. There have been multiple studies in both children and adults demonstrating an improvement in bone mineral density (BMD), particularly at the lumbar spine with bisphosphonate treatment. Bone histology obtained from 45 children with OI treated with cyclical bisphosphonates revealed an increase in cortical thickness from baseline (pre-treatment) of 88%, an increase in cancellous bone volume of 46% and a higher trabecular number.[6] In a large study by Bishop and colleagues,[7] risedronate increased BMD at the lumbar spine in 94 children with OI assigned to treatment *versus* placebo (16.3% *versus* 7.6%, $p < 0.0001$).

In the adult population with OI, a randomized, double-blind, placebo-controlled 3-year study of alendronate showed an increase in BMD at the lumbar spine (10.1% *versus* 7.1%, $p < 0.0001$) and a higher BMD at the hip (3.3% gain *versus* a decrease of 0.3%).[8] A study at our centre of individuals with OI attending a metabolic bone clinic demonstrated that bisphosphonate therapy was associated with a 15.1% increase in BMD at the lumbar spine and a normalization of bone turnover markers.[9]

The method of administration of bisphosphonate, intravenous *versus* oral therapy, may have an effect. In a study by Shapiro and colleagues, intravenous pamidronate but no oral agents increased BMD and decreased fracture rate in type III and IV OI but not in the milder type I.[10] Zoledronic acid is more commonly used than pamidronate largely because it is a more potent antiresorptive with a lower frequency of infusion. A recent retrospective review detailed the adverse effects associated with intravenous bisphosphonate administration with a variety of rare bone diseases. They were hypophosphatemia (25.2%), followed by acute phase reaction (19.1%) and hypocalcaemia (16.4%). Renal impairment (<35 ml/min) is an absolute contradiction to bisphosphonate use which can limit its administration.[11]

Despite the significant improvement in BMD, a proven reduction in fracture rate in OI has been difficult to demonstrate.[7,12] Meta-analyses have concluded that failure to demonstrate reduced fracture rate is secondary to insufficiently powered randomized control trials.[13] There are also concerns regarding long-term use of bisphosphonates, particularly given their half life and their utilization in children. The use of bisphosphonates in

**Table 1.** Novel gene subtypes of osteogenesis imperfecta. Adapted from Forlino and Marini.[1]

| Type | Inheritance | Mutation | Protein | Disease mechanism | Skeletal phenotype | Associated features |
|---|---|---|---|---|---|---|
| I | AD | COL1A/2 | Collagen type 1, α1/2 | Collagen synthesis/ processing | Mild–moderate | DI, blue sclera, deafness |
| II | AD | | | | Lethal | Pulmonary hypoplasia |
| III | AD | | | | Severe | |
| IV | AD | | | | Moderate | DI, basilar invagination |
| V | AD | IFITM5 | Interferon-induced transmembrane protein 5 | Mineralization defect | Moderate | Hyperplastic callous formation |
| VI | AR | SEPINF1 | Pigment epithelium-derived factor | Mineralization defect | Moderate–severe | 'Fish scale' pattern on iliac crest biopsies |
| VII | AR | CRTAP | Cartilage-associated protein | Collagen modification | Severe–lethal | Similar to IV, rhizomelia |
| VIII | AR | LEPRE1 | Leucine proline-enriched proteoglycan 1/prolyl 3-hydroxylase 1 | Collagen modification | Severe–lethal | Platyspondyly, scoliosis |
| IX | AR | PPIB | Peptidylprolyl isomerase B/cyclophilin B | Collagen modification | Severe | Short stature |
| X | AR | SERPINH1 | Serpin peptidase inhibitor | Chaperone defect collagen folding | Severe | Nephrolithiasis |
| XI | AR | FKBP10 | FK506 binding protein 65 | Chaperone defect collagen folding | Moderate–severe | Congenital contractures |
| XII | AR | SP7 | Transcription factor 7 | Osteoblast development | Moderate | Midface hypoplasia |
| XIII | AR | BMP1 | Bone morphogenic protein 1 | Collagen synthesis/ processing | Mild–severe | Umbilical hernia |
| XIV | AR | TNEM38B | Transmembrane protein 38 B | Collagen modification | Severe | |
| XV | AR | WNT1 | Wingless-type member 1 | Osteoblast development | Moderate–severe | Neurological deficits |
| XVI | AR | CREB3L1 | CAMP responsive element binding | Osteoblast development | Severe | |

AD, autosomal dominant; AR, autosomal recessive.

the treatment of osteoporosis has been associated with osteonecrosis of the jaw (ONJ) and cumulative micro damage resulting in atypical femoral fractures. A retrospective review of imaging from a large cohort of 176 bisphosphonate-treated patients with OI examined the location of femoral fractures. The incidence of subtrochanteric femoral fractures in this group was compared with a pre-bisphosphonate historical control group. There was a higher incidence of overall fractures in the untreated group ($n$ = 34 fractures to 26 patients) but the femoral fractures that occurred were more widespread in distribution along the femoral shaft as opposed to those on bisphosphonate therapy (16 femoral fractures, all but two were in the subtrochanteric region).[14] A more recent study, however, looked at 127 femoral fractures sustained by 24 patients with OI; 50% of

these fractures occurred in bisphosphonate-naïve patients, 35% during bisphosphonate treatment and 16% after treatment discontinuation. The pattern distribution of the fractures was similar across all three groups. The incidence of atypical femoral fracture did not correlate with bisphosphonate use but rather severity of underlying disease (with a higher incidence in OI types III and IV *versus* type I).[15] In relation to ONJ, a review of five studies conducted in children and adolescents with OI ($n = 439$) who received intravenous bisphosphonates (mean duration of treatment 4.6–6.8 years) did not reveal an episode of ONJ.[16]

### Advances in therapeutics in OI

Despite the significant gains in BMD, the equivocal fracture rate reduction has prompted study into alternative agents to bisphosphonates.

Denosumab is one such alternative agent. It is a human immunoglobulin G2 (IgG2) antibody that binds RANKL (receptor activator of nuclear factor κB ligand) to its receptor. By inhibiting this interaction, denosumab is a potent antiresorptive. There is no long-term accumulation of denosumab, which makes it an attractive alternative to bisphosphonate therapy. A particular study of children ($n = 4$) with type VI OI demonstrated improved benefit in terms of mobility and BMD. Type VI OI is typically associated with a poor response to bisphosphonate therapy primarily due to the lack of bisphosphonate binding to poorly mineralized bone. No significant adverse events were reported in this study, but larger longer-term studies are required.[17] A further study of denosumab in OI demonstrated a significant increase in lumber spine BMD percentage change after 48 weeks of treatment in 10 patients (children aged 5–11 years).[18]

Teriparatide, a parathyroid hormone (PTH) analogue, is an anabolic agent stimulating bone formation. It is approved for use in postmenopausal women, men and glucocorticoid-induced osteoporosis. PTH stimulates bone remodelling, bone formation more so than bone resorption and has been shown to reduce the incidence of both vertebral and nonvertebral fractures. A randomized, prospective, placebo-controlled trial in adults ($n = 79$) with OI was conducted with teriparatide; after 18 months of treatment there was an increase in BMD at the lumbar spine (6.1% *versus* 1% change from baseline, $p < 0.05$) and at the hip (2.6% *versus* –2.4%, $p < 0.0001$). There was a differential treatment response in patients with a quantitative collagen deficiency with the beneficial effect on BMD being more significant in the milder forms of OI (type I) than in the more severe forms (III, IV). There was no difference, however, in fracture rate between the two cohorts and longer studies are required to establish fracture prevention with teriparatide in an OI cohort.[19]

### Therapies in development for OI

The newer agents in development phases for OI include antibodies to sclerostin and transforming growth factor β (TGFβ). In animal studies, sclerostin antibody is a candidate anabolic treatment that stimulates bone formation and increases bone mass, an essential restorative factor in OI. A study of the mouse model of OI reported promising results with romosozumab in the milder forms of OI.[20] In human studies in osteoporosis, the recently published FRAME study administered the sclerostin antibody romosozumab for a period of 1 year, which resulted in a reduction in the incidence of vertebral fractures and clinical osteoporosis.[21] However, the clinical availability of romosozumab has been delayed pending further cardiovascular safety data. Anti TGFβ therapy may prove to be beneficial as a treatment for OI in reducing osteoblast signalling and bone resorption.[22] A phase I study is currently testing the safety profile of fresolimumab, an antibody that targets TGFβ in moderate to advanced OI disease [ClinicalTrials.gov identifier: NCT03064074].

In severe OI, damage begins in early fetal life and may lead to perinatal lethality. Mesenchymal stem cells (MSCs) are multipotent cells that can be induced to differentiate into osteoblasts. MSCs typically have a low immunogenic profile and are not rejected during allogenic transplantation. Infusion of MSC with osteoblast potential have resulted in improvements in skeletal phenotype in a mouse model of OI.[23] Prenatal MSC transplantation has been used in the fetus to prevent early fractures.[24] Gene manipulation may offer a future potential therapeutic option for OI. Gene silencing with small interfering RNAs has also been possible in human bone derived cells.[25]

In summary, the expanded classification system allows for improved counselling of patients with regard to the natural history of their OI, and should facilitate individualized, tailored therapeu-

tic approaches based on the underlying pathophysiology of the individual's OI.

## X-linked hypophosphataemia

X-linked hypophosphataemia (XLH) is a rare disorder caused by an inactivating mutation in the phosphate regulating endopeptidase (PHEX) gene. The estimated incidence is 1 per 20,000 live births. This mutation affects the metabolism of fibroblast growth factor 23 (FGF23), a factor which is secreted from osteocytes. FGF23 inhibits renal phosphate reabsorption *via* reduction in the number and activation of sodium phosphate (Na Pi) cotransporters in the apical membrane of the proximal renal tubule. FGF23 also alters vitamin D metabolism, resulting in low or inappropriately normal 1,25 OH vitamin D levels. This results in hypophosphataemia, phosphaturia and resultant osteomalacia. The typical phenotype observed in childhood is that of lower extremity 'bowing' and shortened stature. In adulthood, the primary symptom is arthralgia.

The goals of medical management of XLH are to improve osteomalacia and rachitic deformities, maximizing growth in affected children. The traditional medical treatment for XLH has been phosphate supplementation and the use of activated vitamin D analogues. Phosphate supplementation can be limited by gastrointestinal adverse effects. In addition, oral phosphate replacement can result in hypocalcaemia which can increase PTH secretion resulting in secondary and, if sustained, tertiary hyperparathyroidism.[26] This can result in nephrocalcinosis.

### *Advances in therapeutics for XLH*

Although XLH is caused by an increase in serum levels of FGF23, PTH also plays a role through an independent effect on the tubular threshold for phosphate reabsorption. An alternative to phosphate and calcitriol treatment therefore is the calcimimetic cinacalcet. Calcimimetics increase the sensitivity of the calcium sensing receptor to extracellular calcium, thus reducing PTH secretion. Cinacalcet has been successfully used in the treatment of secondary hyperparathyroidism in chronic renal disease.[27] Cinacalcet increases plasma phosphate levels in FGF23-mediated tumour-induced osteomalacia, thereby facilitating a reduction in phosphate and vitamin D supplementation.[28] Alon and colleagues studied the effect of cinacalcet in children with XLH. A single cinacalcet dose in combination with phosphate supplementation reduced both PTH and calcium levels and increased phosphate levels compared with traditional replacement therapy.[29] Case reports also demonstrated similar findings in adolescents and adults affected by XLH.[30,31] Cinacalcet offers an alternative to phosphate therapy in those who cannot tolerate supplementation.[32]

As a result of improved understanding of the pathophysiology of XLH, a novel antibody which inhibits the biologic activity of FGF23 is being clinically trialled in humans with XLH. The development of KRN23 (burosumab, Ultragenyx [California, USA]), a recombinant human IgG monoclonal antibody that binds to FGF23 is an exciting advance in the field. In a PHEX-deficient mouse model, a single injection of this antibody increased the expression levels of the Na Pi cotransporter and 1$\alpha$ hydroxylase, the enzyme responsive for converting 25 hydroxylase to the active form of vitamin D. Sustained use resulted in reversal of the bone deformities in the PHEX-deficient mouse model.[29] Carpenter and colleagues recently reported on the use of KRN23 in adults. In 38 individuals with XLH it was found that KRN23 increased the renal tubular threshold for phosphate reabsorption, resulting in increased serum phosphate and 1,25 OH D levels. Individuals studied did not develop negative effects such as nephrocalcinosis, hypercalcaemia or an elevated PTH.[33]

In individuals with XLH, treatment options now extend beyond the use of phosphate and vitamin D supplementation to include cinacalcet and the monoclonal antibody to FGF23: KRN23.

## Hypoparathyroidism

Hypoparathyroidism results from a deficiency in PTH. PTH regulates calcium homeostasis through the mobilization of calcium from the skeleton and the absorption of calcium from the intestine *via* calcitriol. PTH also increases calcium reabsorption through the thick ascending limb of the nephron and facilitates the excretion of phosphate.

The estimated prevalence in the US is 60,000–80,000 affected individuals. The vast majority (75%) of hypoparathyroidism is secondary to surgical excision. Clinical manifestations are dependent upon the acuteness of the change in calcium

level and the absolute calcium value. Classical presentation is with neuromuscular irritability and perioral paraesthesia. Cerebral hypocalcaemia can be associated with seizures and myoclonic jerking. The cardiac complications include QT prolongation and cardiomyopathy. Typically BMD is increased as there is a reduction in bone turnover. Impaired renal function is common and dependent on age, duration of disease, level of calcium and the presence of hypercalciuria.

### *Current therapeutic options for hypoparathyroidism*

Conventional treatment uses oral active vitamin D (calcitriol or alphacalcidol) given once or twice daily and oral calcium prescribed several times daily to achieve a low-normal calcium level. The difficulty with managing hypoparathyroidism is in attaining the balance between a desirable calcium level and avoiding over replacement, which can result in nephrocalcinosis, nephrolithiasis and ultimately renal failure. Replacement of the deficient hormone is an attractive option.

### *Advances in therapeutics for hypoparathyroidism*

Human PTH [teriparatide (1–34)] has been used safely and effectively in both children and adults with postsurgical hypoparathyroidism. In a 3-year study of 12 children, teriparatide reduced calcium and vitamin D requirements compared with conventional treatment.[34] Due to its short half life, delivery of PTH (1–34) continuously *via* an insulin pump had the closest physiological replacement profile for hypoparathyroidism.[35] Teriparatide is not currently approved for the clinical management of hypoparathyroidism.

The full length form of recombinant PTH (rhPTH) (1–84) (Natpara, New Jersey, USA) was approved by the US Food and Drug Administration (FDA) in 2015 for the management of hypoparathyroidism inadequately controlled by conventional therapy. A prospective 4-year study of PTH (1–84) in 27 patients with hypoparathyroidism demonstrated a reduction in calcium replacement by 37% and a reduction in active vitamin D by 45%. Total calcium levels remained the same and femoral neck BMD remained stable.[36] A longer 6-year study of a larger cohort ($n$ = 33) using recombinant human PTH (rhPTH) (1–84) 100 μg on alternative days reduced calcium requirement by 53% and active vitamin D requirement by 67% (with 48% completely off active vitamin D).[37] The REPLACE study was a randomized, double-blind, placebo-controlled study of 134 adults across eight countries using once daily rhPTH (1–84) *versus* placebo. Individuals were recruited if they had a diagnosis of hypoparathyroidism for at least 18 months. rhPTH was administered at a dose of 50 μg (uptitrated to 75 μg and 100 μg to achieve endpoint) for a period of 24 weeks. The primary endpoint was a reduction in calcium replacement by over 50% or on 500 mg of oral calcium per day and a reduction in active vitamin D by over 50% or on less than 0.25 μg of calcitriol or less than 0.5 μg of alphacalcidol per day. The endpoint was achieved in 53% of the rhPTH group compared with 2% of the placebo group. This study demonstrated that long-term rhPTH therapy is associated with a significant reduction in supplementation with good tolerability.[38] The REPEAT study was an extension of REPLACE to assess long-term efficacy and safety of rhPTH. Twenty-four patients were enrolled for a period of 24 weeks ($n$ = 16 previously treated with rhPTH and $n$ = 8 rhPTH treatment naïve). At week 24, 75% achieved the primary endpoint as per the REPLACE study protocol. There was a reduction in urinary calcium and an increase in bone turnover markers. There were no serious adverse events recorded.[39]

The phase III REPLACE study was recently published. This study looked at additional relevant results from the original REPLACE study, particularly phosphate homeostasis in 124 patients with hypoparathyroidism. This is of relevance given that active vitamin D does not replace the phosphaturic effect of PTH.[40] This study again demonstrated that after 24 weeks of treatment with rhPTH (1–84) normocalcaemia was achieved despite a reduction in active vitamin D and oral calcium. In addition, rhPTH (1–84) reduced phosphate levels.

The management of hypoparathyroidism is complex. Renal complications are often underestimated. Frequent monitoring and clinical visits are integral and this can be costly and inconvenient to the patient. The approval of rhPTH by the FDA and pending approval by the European Medicines Agency should play a significant role in improving care for individuals with hypoparathyroidism.

## Osteopetrosis

Osteopetrosis is a disease caused by an impairment in osteoclasts. This impairment results in

excessive bone mass but a deterioration in bone quality resulting in atraumatic fractures. The inheritance pattern is predominantly autosomal with recessive and dominant forms. There are two types of dominant forms (AD01, AD02). The dominant forms result in a milder phenotype. The prevalence of AD02 or 'marble bone disease' is 1 per 20,000 live births.[41] The recessive forms of osteopetrosis are associated with a severe phenotype and are generally lethal in infancy or childhood. The *combined* prevalence of the recessive forms is 1 per 250,000 live births.[42] The recessive form is characterized by brittle bones, radiologically long bones with funnel-like extremities and narrowed medullary cavities.[42] The reduced medullary cavity results in haematological failure with anaemia, leukopenia and susceptibility to infection. Visual loss is also a frequent occurrence secondary to nerve compression. Biochemical analysis typically reveals hypocalcaemia, an elevated alkaline phosphatase and reduced bone resorption markers. To date, there are six known causative genetic mutations for the recessive form of osteopetrosis. Two of these gene mutations code for RANKL or its receptor. The RANK/RANKL pathway is implicated in osteoclast formation. There is interest in this specific pathway in the discovery of potential therapeutic options, particularly given that this specific mutation type cannot be treated with the currently available curative therapy.

### *Current therapeutic options in osteopetrosis*

Haemopoeitic stem cell transplant (HSCT) is effective in restoring normal bone resorption and haematopoesis in severe autosomal recessive osteopetrosis.[43] However, HSCT is associated with many potential adverse effects, including acute rejection, graft *versus* host disease and veno-occlusive events. Interferon γ can be used with good effect on haematological recovery but it is not curative and is seen as a 'bridge' to definitive HSCT therapy.[44] There is currently no treatment available for the dominant forms. The success of HSCT is dependent on human leukocyte antigen matching and host compatibility. HSCT cannot be used to treat recessive forms caused by mutations in the RANK pathway; for these reasons, there is interest in alternative therapeutic options.

### *Advances in therapeutics for osteopetrosis*

RANKL deficiency can potentially be treated with an infusion of recombinant soluble RANKL. The systemic administration of recombinant soluble RANKL in animal models for a period of 1 month resulted in observed beneficial effects on bone and bone marrow. However, treatment remains a challenge as an overproduction of cytokines and lethality secondary to respiratory failure was noted during the study period. This was dose dependent; skeletal monitoring and dose taper were deemed necessary to prevent this complication.[45]

## Hypophosphatasia

HPP is a rare disorder caused by mutations in the gene ALPL which encodes tissue nonspecific alkaline phosphatase. The function of this enzyme is to prompt appropriate mineralization at an appropriate time in skeletal tissue. Severe HPP occurs in 3.3 per million live births. The occurrence of milder forms of the disorder is estimated at 1 per 7000 live births. HPP is classified by age at presentation. The phenotype is usually classified into six forms dependent on the age at onset and the severity of clinical features: perinatal, benign prenatal, infantile, childhood, adult and odonto (relating to dental issues alone).[46,47] Infants with the disorder present with failure to thrive and respiratory distress. Biochemical abnormalities include a low serum alkaline phosphatase (hypophosphataemia), hypercalcaemia, hypercalciuria and resultant nephrocalcinosis. Craniosynotosis and seizure activity is a relatively frequent feature. In childhood the disorder presents with loss of primary dentition, low bone mass, poorly healing fractures and rachictic-like bone. In adulthood the findings are more subtle but include osteoporosis, recurrent fractures and crystal arthropathy.

To date the management of pain, respiratory symptoms and seizures is supportive. The management of hypercalcaemia is also supportive, primarily with adequate hydration. Bisphosphonates are contraindicated as they will exacerbate symptoms, being a chemical analogue of the mineralization inhibitor pyrophosphate that accumulates in HPP.

### *Advances in therapeutics in HPP*

Enzyme replacement therapy using bone-targeted recombinant alkaline phosphatase (asfotase α) has been shown to be transformative in the treatment of HPP and represents the most recent successful therapeutic intervention for this rare disorder.

An ongoing multicentre open-label study demonstrated that asfotase α treatment is associated with improved mineralization of the skeleton, improved respiratory function and overall improved survival in patients with infantile and perinatal HPP.[48]

A further prospective Japanese study of both infants and adults with HPP also demonstrated skeletal and respiratory benefits with few adverse effects.[49] The adverse effects reported were hypocalcaemia, as the mineralization process requires calcium deposition in bone, and hyperphosphataemia, which may aggravate ectopic calcification. Biochemical monitoring and restriction of phosphorus use are recommended.

## Conclusion

To summarize, in this review, we have detailed the advancements in the therapeutic options available for the management of osteopetrosis, XLH, hypoparathyroidism and HPP. We have also detailed the expanding classification system and its clinical applicability in OI. Over the past decade significant strides have been made in our understanding of the genetic and molecular pathways involved in the pathogenesis of rare bone diseases. As a result, our diagnostic capability and our ability to provide accurate genetic counselling have been greatly facilitated. The comprehension of pathogenic molecular pathways is essential for drug design and there is much interest in gene manipulation therapy to provide curative options for these often lethal disorders.

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