Clinical Pediatric Endocrinology

Vol.34 / No.3
July 2025
pp 152–161

Review

Osteogenesis imperfecta: pathogenesis, classification, and treatment

Kosei Hasegawa[1]
[1]*Department of Pediatrics, Okayama University Hospital, Okayama, Japan*

Highlights

- Alteration in the genes related to the type I collagen production causes OI.
- Bisphosphonate is the mainstream treatment for OI.
- Excessive TGFβ signaling and ER stress are the pathogenesis of OI.

Abstract. Osteogenesis imperfecta (OI) is a congenital skeletal disorder characterized by varying degrees of bone fragility and deformities. Extraskeletal manifestations, such as blue sclera, dentinogenesis imperfecta, growth disturbance, hearing impairment, and muscle weakness, occasionally accompany OI. Many genes have been identified as causative of OI, such as the type I collagen gene and genes involved in the folding, processing, and crosslinking of type I collagen molecules, osteoblast differentiation, and bone mineralization. According to the discovery of the causative gene of OI, nosology and classifications have also been revised and the "dyadic approach" based nomenclature according to the severity and each causative gene of OI was recently adopted. Intravenous or oral bisphosphonates have been administered to treat bone fragility in children with OI and a reduction in the frequency of bone fractures has been reported. However, despite the increase of bone mineral density, evidence of bone fracture prevention is limited. Recently, excessive transforming growth factor β signaling pathway and excessive endoplasmic reticulum stress have been reported as the pathogenesis of OI, and treatment strategies based on these pathogeneses have been developed. This review summarizes the molecular basis, transition of nosology and classification, status of bisphosphonate therapy, and development of treatment strategies.

Key words: fracture, child, bisphosphonate, classification, treatment

Received: January 18, 2025 Accepted: March 20, 2025 Advanced Epub: March 31, 2025
Corresponding author: Kosei Hasegawa, M.D., Ph.D., Department of Pediatrics, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
E-mail: haseyan@md.okayama-u.ac.jp

Introduction

Osteogenesis imperfecta (OI) is a congenital skeletal disorder characterized by varying degrees of skeletal fragility and bone deformities. Extraskeletal manifestations include dentinogenesis imperfecta (DI), blue sclera (BSc), hearing impairment, growth disturbances, and muscle weakness. OI is a genetically heterogeneous disorder caused by pathogenic variants of type I collagen genes (*COL1A1* and *COL1A2*) and genes involved in collagen folding, processing, crosslinking of type I collagen molecules, osteoblast differentiation, and bone mineralization. The frequency of OI is approximately 1/15,000–20,000, and the modes of inheritance thereof include autosomal dominant, autosomal recessive, and X-linked recessive inheritance. Diagnosis is based on clinical symptoms, family history, and radiological examination, including bone survey by radiography, measurement of bone mineral density (BMD) by dual X-ray absorptiometry (DXA), and molecular diagnosis.

Intravenous bisphosphonate infusion, including cyclic pamidronate (PAM) infusion (1) and oral bisphosphonate administration (2, 3), have been used for the treatment of bone fragility in children with OI. However, there are still many concerns regarding bisphosphonate therapy, such as the limited evidence of bone fracture reduction, excessive suppression of bone resorption (bisphosphonate-induced osteopetrosis) (4) and atypical femur fracture (5), and the risk of medication-related osteonecrosis of the jaw (MRONJ), although MRONJ has not been reported in children with OI (6, 7).

Treatment strategies based on the pathogenesis of OI have been developed to resolve these problems. We, therefore, aimed to review and summarize the genetic causes of OI, transitions in nosology and classification, bisphosphonate therapy, and new treatment strategies for OI.

Type I collagen production and pathogenesis of OI

Type I collagen is an extracellular matrix expressed in various tissues, such as bone, skin, and tendons. Type I collagen procollagen is formed as a heterotrimer, and consists of two α1 chains and one α2 chain, which are coded by the *COL1A1* and *COL1A2* genes, respectively, and are assembled from the C-terminus to the N-terminus (**Fig. 1**). In the endoplasmic reticulum (ER), prolyl 4-hydroxylase and lysyl hydroxylase cause posttranslational modifications of proline and lysine residues of procollagen, respectively, for protein folding. Specific hydroxylation of proline 986 in the α1 chain by the prolyl 3-hydroxylation complex, consisting of prolyl 3-hydroxylase1 (P3H1), cartilage-associated protein (CRTAP), and peptidylprolyl isomerase B (PPIB), is also an important process for protein folding (8–11). The ER chaperone heat shock protein 47 and FKBP65, encoded by the *SERPINH1* and *FKBP10* genes, respectively, stabilize the triple helix and prevent procollagen aggregation during trafficking to the Golgi (12, 13). KDELR2 stimulates intracellular recycling of ER-resident proteins (14). The triple helical domain in both the α1 and α2 chains consists of multiple repeats of glycine–X (proline is predominant)–Y (hydroxyproline is predominant). Procollagen is secreted from cells, and N- and C-terminal propeptides are enzymatically cleaved from procollagen by a disintegrin and metalloproteinase with thrombospondin motifs 2 (ADAMTS-2) and BMP1 (bone morphogenetic protein 1)/tolloid-like proteinases, respectively. Cleaved N- and C-terminal propeptides are used as the bone formation markers, aminoterminal propeptides of type I collagen (PINP) and carboxyterminal propeptides of type I collagen (PICP), respectively. Lysyl oxidases connect mature type I collagen molecules by pyridinoline crosslinking, and form type I collagen fibers embedded in the extracellular matrix by secreted protein acidic and rich in cysteine (SPARC), which is a matricellular glycoprotein that binds to the extracellular matrix (15).

Table 1 summarizes the types and causative genes of OI registered in OMIM (https://omim.org). Approximately 90% of OI cases are caused by the heterozygous pathogenic variants in *COL1A1* and *COL1A2*, which encode α1 and α2 chains of type I collagen molecules, respectively (16). There is a clear genotype–phenotype correlation between the type of variant in the type I collagen gene and OI severity. Nonsense, frameshift, and splice site variants, which cause early mRNA termination, reduce the expression of type I collagen. These variants are called "quantitative defects," and tend to lead to mild clinical phenotype type 1 OI. In contrast, alteration of glycine in glycine-X–Y repeats in α1 and α2 chains to other amino acids, called "qualitative defects," which affect the structure of type I collagen molecules and tend to result in severe clinical phenotype-like types 2, 3, and 4 OI (17–22). Type 5 OI is characterized by excessive callus formation after bone fracture, ossification of the interosseous membrane, and the absence of DI or BSc. Type 5 OI is caused by the specific c.-14C>T heterozygous variant of the *IFITM5* gene (23, 24). The *IFITM5* gene encodes bone-restricted IFITM-like (BRIL) protein, which activates the transcription of *SERPINF1*, and *SERPINF1* encodes pigmented epithelium-derived factor (PEDF), which is an antiangiogenic factor (25–28). Other than type I collagen genes, various genes relating to prolyl 3-hydroxylation complex components (*P3H1* (10), *CRTAP* (8, 9), and *PPIB* (11)), osteoblast differentiation (*SP7* (29), *TMEM38B* (30), *WNT1* (31), *CREB3L1* (32), *SPARC* (33), and *MBTPS2* (34)), bone mineralization (*IFITM5* (23, 24) and *SERPINF1* (35)), and collagen processing and crosslinking (*SERPINH*1 (36), *FKBP10* (37, 38), *PLOD2* (39), and *BMP1* (40)) have been found by the development of next generation sequencing. Recently, a biallelic pathogenic variant of plekstrin homology-like domain family B member 1 (*PHLDB1*) was reported to result in mild OI (41), which was registered as type

doi: 10.1297/cpe.2025-0009

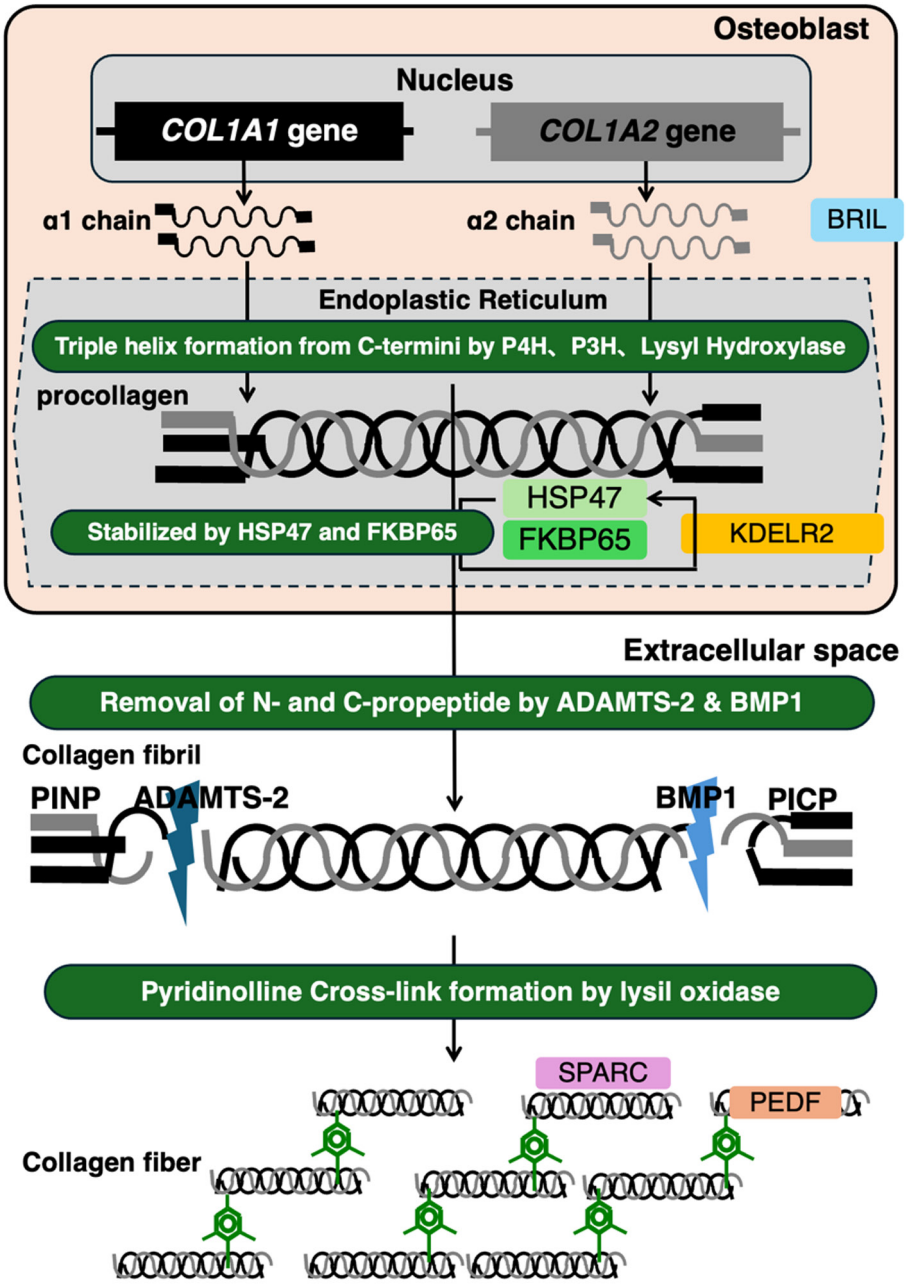

Fig. 1. Mechanisms of the type I collagen synthesis. BRIL activates the transcription of *SERPINF1* gene which encodes PEDF. BRIL and PEDF affected bone mineralization. KDELR2 stimulates intracellular recycling of ER-resident proteins such as HSP47 and FKBP65. SPARC binds the collagen to extracellular matrix. ADAMTS-2, a disintegrin and metalloproteinase with thrombospondin motifs 2; BRIL, bone-restricted Ifitm-like; BMP1, bone morphogenetic protein; FKBP65, 65-kDa FK506-binding protein; HSP47, heat shock protein 47; KDELR2, KDEL endoplasmic reticulum protein retention receptor 2; P3H, Prolyl 3-hydroxylase; P4H, prolyl 4-hydroxylase; PEDF, pigment epithelium-derived factor; PICP, carboxyterminal propeptides of type I collagen; PINP, aminoterminal propeptides of type I collagen; SPARC, secreted protein acidic and rich in cysteine.

XXIII OI in OMIM. *PHLDB1* is involved in multiple phosphorylation processes.

Transition of classifications and nosology of OI

The nosology and classification of OI has been repeatedly revised based on the discovery of new clinical phenotypes and causative genes. In "A Nomenclature for constitutional (intrinsic) diseases of bones," the first published nomenclature of skeletal disorders in 1971, which was developed at the meeting of the European Society of Pediatric Radiology held in Paris in 1969, OI was initially classified as "congenita" or "tarda" (**Table 2**) (42, 43). In 1979, Sillence *et al*. published a clinical system that classified patients with OI into

doi: 10.1297/cpe.2025-0009

Table 1. Types of OI and causative genes registered in OMIM

Type	Phenotype OMIM number	Gene/Locus	Protein	Gene/Locus OMIM number	Location	Inheritance
I	# 166200	*COL1A1*	Collagen α1 (I)	*120150	17q21.33	AD
II	# 166210	*COL1A1*	Collagen α1 (I)	*120150	17q21.33	
		COL1A2	Collagen α2 (I)	*120160	7q21.3	
III	# 259420	*COL1A1*	Collagen α1 (I)	*120150	17q21.33	
		COL1A2	Collagen α2 (I)	*120160	7q21.3	
IV	# 166220	*COL1A1*	Collagen α1 (I)	*120150	17q21.33	
		COL1A2	Collagen α2 (I)	*120160	7q21.3	
V	# 610967	*IFITM5*	BRIL	*614757	11p15.5	
VI	# 613982	*SERPINF1*	PEDF	*172860	17p13.3	AR
VII	# 610682	*CRTAP*	CRTAP	*605497	3p22.3	
VIII	# 610915	*P3H1*	P3H1	*610339	1p34.2	
IX	# 259440	*PPIB*	CyPB	*123841	15q22.31	
X	# 613848	*SERPINH1*	HSP47	*600943	11q13.5	
XI	# 610968	*FKBP10*	FKBP65	*607063	17q21.2	
XII	# 613849	*SP7*	OSTERIX	*606633	12q13.13	
XIII	# 614856	*BMP1*	BMP1	*112264	8p21.3	
XIV	# 615066	*TMEM38B*	TRIC-B	*611236	9q31.2	
XV	# 615220	*WNT1*	WNT1	*164820	12q13.12	
XVI	# 616229	*CREB3L1*	OASIS	*616215	11p11.2	
XVII	# 616507	*SPARC*	SPARC	*182120	5q33.1	
XVIII	# 617952	*TENT5A*	FAM46A	*611357	6q14.1	
XIX	# 301014	*MBTPS2*	S2P	*300294	Xp22.12	XLR
XX	# 618644	*MESD*	MESD	*607783	15q25.1	AR
XXI	# 619131	*KDELR2*	KDEL receptor 2	*609024	7p22.1	
XXII	# 619795	*CCDC134*	CCDC134	*619795	22q13.2	
XXIII	# 620639	*PHLDB1*	PHLDB1	*612834	11q23.3	

AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.

four groups (I, II, III, and IV) according to the severity of skeletal manifestations, mode of inheritance, and the presence of BSc and DI (44, 45). This classification became the basic framework for later OI classifications, including the revisions in 1991 after the meeting of the International Working Group on Bone Dysplasia in Bad Honnef in Deutschland (46) and in Los Angeles, CA in 1997 (47). In a 2001 revision developed by the International Working Group on the Classification of Constitutional Disorders of Bone in Oxford in 2011, clinically distinctive type V OI was established, and the term "nomenclature" was replaced by "nosology" (48). In the 2006 revision, which was developed in 2005 at a meeting of the International Skeletal Dysplasia Society (ISDS) established in1999 to cope with the complexity of skeletal dysplasias and to revise the nosology and classification, the types of OI were changed from Roman to Arabic numerals (49). In the 2010 revision, OI was classified into five groups (1–5) by the members of the Nosology Workshop of ISDS meeting held in Boston in 2009 (50), and this classification was adopted in the 2015 (51) and 2019 revisions (52). The classifications in these revisions by ISDS were based on clinical phenotype, in contrast to the OMIM classification based on genotype. However, the 2023 revision published after the ISDS meeting in 2022 in Lausanne, adopted the "dyadic approach" based "nosology" (53), not "classification", according to the clinical characteristics (modified Sillence classification) and each causative gene, such as "Osteogenesis imperfecta, non-deforming (Sillence type 1), and COL1A1-related" (Supplementary Table) (54).

Bisphosphonate therapy for bone fragility of OI

Bone fragility is a main clinical symptom of OI, treated with various drugs, such as high-dose vitamin D and calcitonin; however, a significant increase in BMD may not be attained and bone fracture not sufficiently suppressed (55–57). In 1998, Glorieux *et al.* reported that cyclic PAM infusion increased BMD and reduced bone fractures in patients with severe OI (1). We also previously analyzed the effect of cyclic PAM infusion in infants with types 1, 3, and 4 OI; cyclic PAM infusion increased lumbar BMD and tended to improve compression of the lumbar spine (58). Bisphosphonate infusion, including cyclic PAM infusion, increases BMD in children with OI (59–61). Besides PAM, where usage for OI is covered by health insurance in Japan, zoledronate (ZOL), a third-generation bisphosphonate, shows high and long acting anti-resorptive activity in the treatment of OI (62–64). However, there is limited evidence of a reduction in bone fracture frequency (65). This applies to treatment with oral bisphosphonates

doi: 10.1297/cpe.2025-0009

Table 2. Transition of nosology and classification of OI between 1970 to 2023

Year	Nosology and classification	
1970	Osteogenesis imperfecta congenita (Vrolik, Porak-Durante)	Osteogenesis imperfecta tarda (Lobstein)
1977	Osteogenesis imperfecta congenita (several forms)	Osteogenesis imperfecta tarda (several forms)
1979	**Sillence Classification**	
	I (Congenita tarda) II (Congenita(always))	III (Congenita (tarda)) IV (Congenita tarda)
1991	Osteogenesis Imperfecta (several types)	
1997	Osteogenesis imperfecta I (without opalescent teeth) Osteogenesis imperfecta I (with opalescent teeth) Osteogenesis imperfecta II	Osteogenesis imperfecta III Osteogenesis imperfecta IV (without opalescent teeth) Osteogenesis imperfecta IV (with opalescent teeth)
2001	Osteogenesis imperfecta I (normal teeth) Osteogenesis imperfecta I (opalescent teeth) Osteogenesis imperfecta II Osteogenesis imperfecta III	Osteogenesis imperfecta IV (normal teeth) Osteogenesis imperfecta IV (opalescent teeth) Osteogenesis imperfecta V Osteogenesis imperfecta VI
2006	Osteogenesis imperfecta type 1 Osteogenesis imperfecta type 2 Osteogenesis imperfecta type 3 Osteogenesis imperfecta, recessive, unlinked to COL1A1 and COL1A2	Osteogenesis imperfecta type 4 Osteogenesis imperfecta type 5 Osteogenesis imperfecta type 6 Osteogenesis imperfecta type 7 (so-called “rhizomelic form”)
2010 & 2015	Osteogenesis imperfecta, non-deforming form (OI type 1) Osteogenesis imperfecta, perinatal lethal form (OI type 2) Osteogenesis imperfecta, progressively deforming type (OI type 3)	Osteogenesis imperfecta, moderate form (OI type 4) Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5)
2019	Osteogenesis imperfecta, nondeforming with persistently blue sclerae (OI type 1) Osteogenesis imperfecta, perinatal lethal form (OI type 2) Osteogenesis imperfecta, progressively deforming type (OI type 3)	Osteogenesis imperfecta, moderate form (OI type 4) Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus (OI type 5)
2023	Nomenclature by “dyadic approach” (Shown in supplemental table)	

such as alendronate and risedronate; therefore, evidence of bone fracture prevention remains controversial (2, 3, 66–68).

Bone strength, which prevents fractures, is defined as 70% BMD and 30% bone quality (69). Bone quality is defined by bone microstructure, bone turnover, microfractures, and bone tissue calcification. Trabecular bone score (TBS), which is calculated using the images of DXA, quantifies the bone microstructure (70). Bisphosphonate treatment affects TBS differently according to the clinical severity of OI (71), and the relationship between TBS and bone fractures differs according to the genotype of the type I collagen gene (72). BMD and bone quality should be assessed, and the treatment protocol should be stratified according to the severity of OI to reduce bone fractures effectively. However, currently, there are no methods to assess bone quality in clinical settings. Therefore, further research on treatment protocols using bisphosphonates that are suitable for bone fracture prevention according to the severity of OI is necessary.

Novel therapeutic strategy for children with OI

Recent studies have focused on novel treatment strategies, other than bisphosphonates, for bone fragility in children with OI. Sclerostin is an inhibitor of Wnt signaling, which stimulates bone formation. Loss of function variants in the *SOST* gene, which codes for sclerostin, cause sclerosteosis, which shows high BMD (73, 74). Anti-sclerostin antibodies are currently used in adult patients with osteoporosis who are at high risk of bone fractures. Sclerostin antibody injections in various types of OI model mice show various results according to the age, sex, and types of OI model mice, such as Brtl/+ (75, 76), CRTap(-/-) (77), Col1a1(Jrt)/+ (78–80), and oim/oim (81, 82). Romosozumab and setrusumab are currently undergoing phase 3 clinical trials for children with OI (NCT05972551, NCT05768854, and NCT05768854; see ClinicalTrials.gov, https://clinicaltrials.gov).

Denosumab is an antibody against receptor activator of the NF-κB ligand (RANKL), which expresses in osteoblasts and stimulates differentiation and maturation of osteoclasts (83). Denosumab suppresses

doi: 10.1297/cpe.2025-0009

bone resorption and is currently used to treat adult patients with osteoporosis, bone erosion caused by rheumatoid arthritis, giant cell tumors of the bone, bone lesions caused by multiple myeloma, and metastasis of solid tumors. Clinical trials have also been conducted in children and young adults with OI. However, the phase 3 (NCT03638128/NCT02352753) study was terminated because of safety concerns regarding high levels of calcium, and no other clinical trials have been registered on the ClinicalTrial.gov website.

Teriparatide (TPD), 1-34 parathyroid hormone, is used for the treatment of adult osteoporosis patients because of its bone anabolic effects by intermittent administration, and some clinical trials of TPD used to treat adult OI patients have been reported. Gatti *et al*. also reported that 18-months of TPD treatment increased BMD in postmenopausal women with OI who were previously treated with neridronate, and that this increase is lower than those seen in postmenopausal women or patients with senile osteoporosis (84). Orwoll *et al*. reported that TPD therapy significantly increased BMD and estimated bone strength in adults with mild forms of OI (NCT00131469) (85). However, this effect is reduced in severe forms of OI. Another multicenter, randomized, double-blind study shows that TPD treatment increased areal BMD compared to a neridronate treatment in 98 adult patients with type 1 OI; however, a high fracture rate was reported in both groups (86). Currently, a randomized controlled trial of therapy with 2 years TPD treatment following a single infusion of ZOL is underway (Treatment of Osteogenesis imperfecta with Parathyroid Hormone and Zoledronic Acid [TOPaZ]; NCT03735537).

Excessive TGFβ signaling has been observed in OI mouse models and in patients with OI, focused as a new pathophysiology of OI (87, 88). TGFβ signaling suppresses osteoblast differentiation and mineralization. Various doses and frequencies of the anti-TGFβ antibody have been administrated to mouse models of OI and the effects on bone turnover, bone geometry, and BMD are different according to the treatment protocol and the types of models (89, 90). Phase 1 clinical trials using fresolimumab, a human IgG4 monoclonal antibody that neutralizes TGFβ, have been conducted on adult patients with OI (NCT03064074) (88). Fresolimumab (1 mg/kg and 4 mg/kg) was administered to eight patients with types III, IV, and VIII OI (accompanying LEPRE1 pathogenic variants). In the 1 mg/kg group, bone turnover was stimulated, and areal BMD (aBMD) of the lumbar spine increased in two patients with type IV OI, in contrast to patients with type III or IV OI, whose BMD decreased or remained unchanged after 180 days, respectively. In the 4 mg/kg group, bone turnover was suppressed compared to that in the 1 mg/kg group, and the increase in BMD in the type IV OI group was smaller than that in the 1 mg/kg group. The decrease in the lumbar spine aBMD in patients with type III OI was greater than that in the 1 mg/kg group. Another phase 1 study was conducted using SAR439459, which is a different anti TGFβ antibody (NCT05231668). However, the study was terminated prematurely at the sponsor's discretion.

Another novel pathophysiology of OI involves excessive ER stress (91). Abnormal collagen produced by pathogenic variants of OI-related genes accumulates in the ER and causes excessive stress, leading to osteoblast dysfunction and bone fragility. Several drugs have been developed to reduce this stress. 4-Phenlbutyric acid (4-PBA) is a chemical chaperone that has been experimentally proven to reduce ER stress in fibroblasts from patients with OI (92), and ameliorate osteogenesis in induced pluripotent stem cell (iPSCs)-derived osteoblasts (93, 94). The administration of 4-PBA improves bone phenotypes and reduces late bone fractures in Aga2 OI model mice (95). In contrast, in α2(I)-G610C OI models, 4-PBA treatment did not improve bone fragility, although stagnated differentiation of hypertrophic chondrocyte-to-osteoblast growth was improved (96).

Rapamycin, an mTOR inhibitor, reduces ER stress, and treatment partially improves osteogenesis of iPSCs from patients with OI (97). Rapamycin also improves trabecular bone parameters in α2(I)-G610C OI model mice; however, bone fragility was not rescued, and longitudinal and transverse growth of long bones is suppressed (98). No clinical trials on 4-PBA or rapamycin have been registered at ClinicalTrials.gov.

Conclusion

Recent advances in the molecular basis, classification, and treatment of OI have been summarized. Further research on effective treatments for the prevention of bone fractures and complications is mandatory. Also, there remains many problems in transition from childhood to adult; scarceness of 1) disease educational program for patients from adolescent to adult, 2) stratified treatment strategies according to the broad disease severities of OI, 3) follow-up strategies of complications in adult, 4) doctors and multidisciplinary team with sufficient knowledge and follow-up experiences of adult patients with OI. Therefore, patient-centered strategies for seamless transition of treatment and follow-up from childhood to adulthood by multidisciplinary team with sufficient experiences and knowledges need to be developed.

Conflict of interests: Kosei Hasegawa has no financial support or relationships that may pose conflicts of interest for this review.

Acknowledgments

I would like to thank the patients at Okayama University Hospital, as well as my colleagues at the Okayama University Hospital and related hospitals.

doi: 10.1297/cpe.2025-0009

References

1. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 1998;339: 947–52. [Medline]
2. Ward LM, Rauch F, Whyte MP, D'Astous J, Gates PE, Grogan D, *et al*. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. J Clin Endocrinol Metab 2011;96: 355–64. [Medline]
3. Bishop N, Adami S, Ahmed SF, Antón J, Arundel P, Burren CP, *et al*. Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial. Lancet 2013;382: 1424–32. [Medline]
4. Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S. Bisphosphonate-induced osteopetrosis. N Engl J Med 2003;349: 457–63. [Medline] [CrossRef]
5. Vuorimies I, Mäyränpää MK, Valta H, Kröger H, Toiviainen-Salo S, Mäkitie O. Bisphosphonate treatment and the characteristics of femoral fractures in children with osteogenesis imperfecta. J Clin Endocrinol Metab 2017;102: 1333–9. [Medline] [CrossRef]
6. Contaldo M, Luzzi V, Ierardo G, Raimondo E, Boccellino M, Ferati K, *et al*. Bisphosphonate-related osteonecrosis of the jaws and dental surgery procedures in children and young people with osteogenesis imperfecta: A systematic review. J Stomatol Oral Maxillofac Surg 2020;121: 556–62. [Medline] [CrossRef]
7. Lasky S, Moshal T, Shakoori P, Roohani I, Jolibois M, Youn S, *et al*. The risk of medication-related osteonecrosis of the jaw in children: guidance for antiresorptive use in pediatric patients. J Oral Maxillofac Surg 2024;82: 1285–94. [Medline] [CrossRef]
8. Barnes AM, Chang W, Morello R, Cabral WA, Weis M, Eyre DR, *et al*. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. N Engl J Med 2006;355: 2757–64. [Medline] [CrossRef]
9. Morello R, Bertin TK, Chen Y, Hicks J, Tonachini L, Monticone M, *et al*. CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. Cell 2006;127: 291–304. [Medline] [CrossRef]
10. Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S, *et al*. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. Nat Genet 2007;39: 359–65. [Medline] [CrossRef]
11. van Dijk FS, Nesbitt IM, Zwikstra EH, Nikkels PG, Piersma SR, Fratantoni SA, *et al*. PPIB mutations cause severe osteogenesis imperfecta. Am J Hum Genet 2009;85: 521–7. [Medline] [CrossRef]
12. Ishida Y, Kubota H, Yamamoto A, Kitamura A, Bächinger HP, Nagata K. Type I collagen in Hsp47-null cells is aggregated in endoplasmic reticulum and deficient in N-propeptide processing and fibrillogenesis. Mol Biol Cell 2006;17: 2346–55. [Medline] [CrossRef]
13. Ishikawa Y, Vranka J, Wirz J, Nagata K, Bächinger HP. The rough endoplasmic reticulum-resident FK506-binding protein FKBP65 is a molecular chaperone that interacts with collagens. J Biol Chem 2008;283: 31584–90. [Medline] [CrossRef]
14. van Dijk FS, Semler O, Etich J, Köhler A, Jimenez-Estrada JA, Bravenboer N, *et al*. Interaction between KDELR2 and HSP47 as a key determinant in osteogenesis imperfecta caused by bi-allelic variants in KDELR2. Am J Hum Genet 2020;107: 989–99. [Medline] [CrossRef]
15. Mayer U, Aumailley M, Mann K, Timpl R, Engel J. Calcium-dependent binding of basement membrane protein BM-40 (osteonectin, SPARC) to basement membrane collagen type IV. Eur J Biochem 1991;198: 141–50. [Medline] [CrossRef]
16. Sykes B, Ogilvie D, Wordsworth P, Wallis G, Mathew C, Beighton P, *et al*. Consistent linkage of dominantly inherited osteogenesis imperfecta to the type I collagen loci: COL1A1 and COL1A2. Am J Hum Genet 1990;46: 293–307. [Medline]
17. Stephen J, Shukla A, Dalal A, Girisha KM, Shah H, Gupta N, *et al*. Mutation spectrum of COL1A1 and COL1A2 genes in Indian patients with osteogenesis imperfecta. Am J Med Genet A 2014;164A: 1482–9. [Medline] [CrossRef]
18. Higuchi Y, Hasegawa K, Futagawa N, Yamashita M, Tanaka H, Tsukahara H. Genetic analysis in Japanese patients with osteogenesis imperfecta: Genotype and phenotype spectra in 96 probands. Mol Genet Genomic Med 2021;9: e1675. [Medline] [CrossRef]
19. Garibaldi N, Besio R, Dalgleish R, Villani S, Barnes AM, Marini JC, *et al*. Dissecting the phenotypic variability of osteogenesis imperfecta. Dis Model Mech 2022;15: dmm049398. [Medline] [CrossRef]
20. Storoni S, Verdonk SJE, Zhytnik L, Pals G, Treurniet S, Elting MW, *et al*. From genetics to clinical implications: a study of 675 Dutch osteogenesis imperfecta patients. Biomolecules 2023;13: 281. [Medline] [CrossRef]
21. Holtz AP, Souza LT, Ribeiro EM, Acosta AX, Lago RMRS, Simoni G, *et al*. Genetic analysis of osteogenesis imperfecta in a large Brazilian cohort. Bone 2023;169: 116683. [Medline] [CrossRef]
22. Tüysüz B, Elkanova L, Uludağ Alkaya D, Güleç Ç, Toksoy G, Güneş N, *et al*. Osteogenesis imperfecta in 140 Turkish families: Molecular spectrum and, comparison of long-term clinical outcome of those with COL1A1/A2 and biallelic variants. Bone 2022;155: 116293. [Medline] [CrossRef]
23. Cho TJ, Lee KE, Lee SK, Song SJ, Kim KJ, Jeon D, *et al*. A single recurrent mutation in the 5′-UTR of IFITM5 causes osteogenesis imperfecta type V. Am J Hum Genet 2012;91: 343–8. [Medline] [CrossRef]
24. Semler O, Garbes L, Keupp K, Swan D, Zimmermann K, Becker J, *et al*. A mutation in the 5′-UTR of IFITM5 creates an in-frame start codon and causes autosomal-dominant osteogenesis imperfecta type V with hyperplastic callus. Am J Hum Genet 2012;91: 349–57. [Medline] [CrossRef]
25. Li F, Song N, Tombran-Tink J, Niyibizi C. Pigment epithelium-derived factor enhances differentiation and mineral deposition of human mesenchymal stem cells. Stem Cells 2013;31: 2714–23. [Medline] [CrossRef]
26. Farber CR, Reich A, Barnes AM, Becerra P, Rauch F, Cabral WA, *et al*. A novel IFITM5 mutation in severe atypical osteogenesis imperfecta type VI impairs osteoblast production of pigment epithelium-derived factor. J Bone Miner Res 2014;29: 1402–11. [Medline] [CrossRef]
27. Gattu AK, Swenson ES, Iwakiri Y, Samuel VT, Troiano N, Berry R, *et al*. Determination of mesenchymal stem cell fate

by pigment epithelium-derived factor (PEDF) results in increased adiposity and reduced bone mineral content. FASEB J 2013;27: 4384–94. [Medline] [CrossRef]
28. Moffatt P, Gaumond MH, Salois P, Sellin K, Bessette MC, Godin E, *et al*. Bril: a novel bone-specific modulator of mineralization. J Bone Miner Res 2008;23: 1497–508. [Medline] [CrossRef]
29. Lapunzina P, Aglan M, Temtamy S, Caparrós-Martín JA, Valencia M, Letón R, *et al*. Identification of a frameshift mutation in Osterix in a patient with recessive osteogenesis imperfecta. Am J Hum Genet 2010;87: 110–4. [Medline] [CrossRef]
30. Shaheen R, Alazami AM, Alshammari MJ, Faqeih E, Alhashmi N, Mousa N, *et al*. Study of autosomal recessive osteogenesis imperfecta in Arabia reveals a novel locus defined by TMEM38B mutation. J Med Genet 2012;49: 630–5. [Medline] [CrossRef]
31. Fahiminiya S, Majewski J, Mort J, Moffatt P, Glorieux FH, Rauch F. Mutations in WNT1 are a cause of osteogenesis imperfecta. J Med Genet 2013;50: 345–8. [Medline] [CrossRef]
32. Keller RB, Tran TT, Pyott SM, Pepin MG, Savarirayan R, McGillivray G, *et al*. Monoallelic and biallelic CREB3L1 variant causes mild and severe osteogenesis imperfecta, respectively. Genet Med 2018;20: 411–9. [Medline] [CrossRef]
33. Mendoza-Londono R, Fahiminiya S, Majewski J, Tétreault M, Nadaf J, Kannu P, *et al*. Care4Rare Canada Consortium. Recessive osteogenesis imperfecta caused by missense mutations in SPARC. Am J Hum Genet 2015;96: 979–85. [Medline] [CrossRef]
34. Lindert U, Cabral WA, Ausavarat S, Tongkobpetch S, Ludin K, Barnes AM, *et al*. MBTPS2 mutations cause defective regulated intramembrane proteolysis in X-linked osteogenesis imperfecta. Nat Commun 2016;7: 11920. [Medline] [CrossRef]
35. Homan EP, Rauch F, Grafe I, Lietman C, Doll JA, Dawson B, *et al*. Mutations in SERPINF1 cause osteogenesis imperfecta type VI. J Bone Miner Res 2011;26: 2798–803. [Medline] [CrossRef]
36. Christiansen HE, Schwarze U, Pyott SM, AlSwaid A, Al Balwi M, Alrasheed S, *et al*. Homozygosity for a missense mutation in SERPINH1, which encodes the collagen chaperone protein HSP47, results in severe recessive osteogenesis imperfecta. Am J Hum Genet 2010;86: 389–98. [Medline] [CrossRef]
37. Kelley BP, Malfait F, Bonafe L, Baldridge D, Homan E, Symoens S, *et al*. Mutations in FKBP10 cause recessive osteogenesis imperfecta and Bruck syndrome. J Bone Miner Res 2011;26: 666–72. [Medline] [CrossRef]
38. Shaheen R, Al-Owain M, Faqeih E, Al-Hashmi N, Awaji A, Al-Zayed Z, *et al*. Mutations in FKBP10 cause both Bruck syndrome and isolated osteogenesis imperfecta in humans. Am J Med Genet A 2011;155A: 1448–52. [Medline] [CrossRef]
39. Puig-Hervás MT, Temtamy S, Aglan M, Valencia M, Martínez-Glez V, Ballesta-Martínez MJ, *et al*. Mutations in PLOD2 cause autosomal-recessive connective tissue disorders within the Bruck syndrome--osteogenesis imperfecta phenotypic spectrum. Hum Mutat 2012;33: 1444–9. [Medline] [CrossRef]
40. Martínez-Glez V, Valencia M, Caparrós-Martín JA, Aglan M, Temtamy S, Tenorio J, *et al*. Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. Hum Mutat 2012;33: 343–50. [Medline] [CrossRef]
41. Tuysuz B, Uludag Alkaya D, Geyik F, Alaylıoğlu M, Kasap B, Kurugoğlu S, *et al*. Biallelic frameshift variants in *PHLDB1* cause mild-type osteogenesis imperfecta with regressive spondylometaphyseal changes. J Med Genet 2023;60: 819–26. [Medline] [CrossRef]
42. Nomenclature for constitutional (intrinsic) diseases of bones. Pediatrics 1971;47: 431–4. [Medline] [CrossRef]
43. International nomenclature of constitutional diseases of bone. Revision, May, 1977. Ann Radiol (Paris) 1978;21: 253–8. [Medline]
44. Sillence DO, Rimoin DL. Classification of osteogenesis imperfect. Lancet 1978;1: 1041–2. [Medline] [CrossRef]
45. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979;16: 101–16. [Medline] [CrossRef]
46. Spranger J. The International Working Group on Constitutional Diseases of Bone. International classification of osteochondrodysplasias. Eur J Pediatr 1992;151: 407–15. [Medline] [CrossRef]
47. Lachman RS. International nomenclature and classification of the osteochondrodysplasias (1997). Pediatr Radiol 1998;28: 737–44. [Medline] [CrossRef]
48. Hall CM. International nosology and classification of constitutional disorders of bone (2001). Am J Med Genet 2002;113: 65–77. [Medline] [CrossRef]
49. Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A 2007;143A: 1–18. [Medline] [CrossRef]
50. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, *et al*. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A 2011;155A: 943–68. [Medline] [CrossRef]
51. Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, *et al*. Nosology and classification of genetic skeletal disorders: 2015 revision. Am J Med Genet A 2015;167A: 2869–92. [Medline] [CrossRef]
52. Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Mundlos S, *et al*. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A 2019;179: 2393–419. [Medline] [CrossRef]
53. Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, *et al*. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet 2021;108: 8–15. [Medline] [CrossRef]
54. Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, *et al*. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A 2023;191: 1164–209. [Medline] [CrossRef]
55. Castells S, Colbert C, Chakrabarti C, Bachtell RS, Kassner EG, Yasumura S. Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. J Pediatr 1979;95: 807–11. [Medline] [CrossRef]
56. Rebelo I, da Silva LP, Blanco JC, Monteiro ME, Ferreira NC. Effects of synthetic salmon calcitonin therapy in children with osteogenesis imperfecta. J Int Med Res 1989;17: 401–5. [Medline] [CrossRef]

 doi: 10.1297/cpe.2025-0009

57. Plante L, Veilleux LN, Glorieux FH, Weiler H, Rauch F. Effect of high-dose vitamin D supplementation on bone density in youth with osteogenesis imperfecta: A randomized controlled trial. Bone 2016;86: 36–42. [Medline] [CrossRef]
58. Hasegawa K, Inoue M, Seino Y, Morishima T, Tanaka H. Growth of infants with osteogenesis imperfecta treated with bisphosphonate. Pediatr Int 2009;51: 54–8. [Medline] [CrossRef]
59. Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M, *et al*. Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res 2003;18: 126–30. [Medline] [CrossRef]
60. Letocha AD, Cintas HL, Troendle JF, Reynolds JC, Cann CE, Chernoff EJ, *et al*. Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. J Bone Miner Res 2005;20: 977–86. [Medline] [CrossRef]
61. Gatti D, Antoniazzi F, Prizzi R, Braga V, Rossini M, Tatò L, *et al*. Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. J Bone Miner Res 2005;20: 758–63. [Medline] [CrossRef]
62. George S, Weber DR, Kaplan P, Hummel K, Monk HM, Levine MA. Short-term safety of zoledronic acid in young patients with bone disorders: an extensive institutional experience. J Clin Endocrinol Metab 2015;100: 4163–71. [Medline] [CrossRef]
63. Kumar C, Panigrahi I, Somasekhara Aradhya A, Meena BL, Khandelwal N. Zoledronate for Osteogenesis imperfecta: evaluation of safety profile in children. J Pediatr Endocrinol Metab 2016;29: 947–52. [Medline] [CrossRef]
64. Tsimicalis A, Boitor M, Ferland CE, Rauch F, Le May S, Carrier JI, *et al*. Pain and quality of life of children and adolescents with osteogenesis imperfecta over a bisphosphonate treatment cycle. Eur J Pediatr 2018;177: 891–902. [Medline] [CrossRef]
65. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev 2016;10: CD005088. [Medline]
66. Bishop N, Harrison R, Ahmed F, Shaw N, Eastell R, Campbell M, *et al*. A randomized, controlled dose-ranging study of risedronate in children with moderate and severe osteogenesis imperfecta. J Bone Miner Res 2010;25: 32–40. [Medline] [CrossRef]
67. Sakkers R, Kok D, Engelbert R, van Dongen A, Jansen M, Pruijs H, *et al*. Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. Lancet 2004;363: 1427–31. [Medline] [CrossRef]
68. Rauch F, Munns CF, Land C, Cheung M, Glorieux FH. Risedronate in the treatment of mild pediatric osteogenesis imperfecta: a randomized placebo-controlled study. J Bone Miner Res 2009;24: 1282–9. [Medline] [CrossRef]
69. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285: 785–95. [Medline] [CrossRef]
70. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. Bone 2008;42: 775–87. [Medline] [CrossRef]
71. Futagawa N, Hasegawa K, Miyahara H, Tanaka H, Tsukahara H. Trabecular bone scores in children with osteogenesis imperfecta respond differently to bisphosphonate treatment depending on disease severity. Front Pediatr 2024;12: 1500023. [Medline] [CrossRef]
72. Ohata Y, Kitaoka T, Ishimi T, Yamada C, Nakano Y, Yamamoto K, *et al*. Association of trabecular bone score and bone mineral apparent density with the severity of bone fragility in children and adolescents with osteogenesis imperfecta: A cross-sectional study. PLoS One 2023;18: e0290812. [Medline] [CrossRef]
73. Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M, *et al*. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet 2001;10: 537–43. [Medline] [CrossRef]
74. Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, *et al*. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet 2001;68: 577–89. [Medline] [CrossRef]
75. Sinder BP, Eddy MM, Ominsky MS, Caird MS, Marini JC, Kozloff KM. Sclerostin antibody improves skeletal parameters in a Brtl/+ mouse model of osteogenesis imperfecta. J Bone Miner Res 2013;28: 73–80. [Medline] [CrossRef]
76. Sinder BP, White LE, Salemi JD, Ominsky MS, Caird MS, Marini JC, *et al*. Adult Brtl/+ mouse model of osteogenesis imperfecta demonstrates anabolic response to sclerostin antibody treatment with increased bone mass and strength. Osteoporos Int 2014;25: 2097–107. [Medline] [CrossRef]
77. Grafe I, Alexander S, Yang T, Lietman C, Homan EP, Munivez E, *et al*. Sclerostin antibody treatment improves the bone phenotype of Crtap(-/-) mice, a model of recessive osteogenesis imperfecta. J Bone Miner Res 2016;31: 1030–40. [Medline] [CrossRef]
78. Roschger A, Roschger P, Keplingter P, Klaushofer K, Abdullah S, Kneissel M, *et al*. Effect of sclerostin antibody treatment in a mouse model of severe osteogenesis imperfecta. Bone 2014;66: 182–8. [Medline] [CrossRef]
79. Sinder BP, Salemi JD, Ominsky MS, Caird MS, Marini JC, Kozloff KM. Rapidly growing Brtl/+ mouse model of osteogenesis imperfecta improves bone mass and strength with sclerostin antibody treatment. Bone 2015;71: 115–23. [Medline] [CrossRef]
80. Sinder BP, Lloyd WR, Salemi JD, Marini JC, Caird MS, Morris MD, *et al*. Effect of anti-sclerostin therapy and osteogenesis imperfecta on tissue-level properties in growing and adult mice while controlling for tissue age. Bone 2016;84: 222–9. [Medline] [CrossRef]
81. Cardinal M, Tys J, Roels T, Lafont S, Ominsky MS, Devogelaer JP, *et al*. Sclerostin antibody reduces long bone fractures in the oim/oim model of osteogenesis imperfecta. Bone 2019;124: 137–47. [Medline] [CrossRef]
82. Cardinal M, Chretien A, Roels T, Lafont S, Ominsky MS, Devogelaer JP, *et al*. Gender-related impact of sclerostin antibody on bone in the osteogenesis imperfecta mouse. Front Genet 2021;12: 705505. [Medline] [CrossRef]

doi: 10.1297/cpe.2025-0009

83. Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, *et al*. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19: 1059–66. [Medline] [CrossRef]
84. Gatti D, Rossini M, Viapiana O, Povino MR, Liuzza S, Fracassi E, *et al*. Teriparatide treatment in adult patients with osteogenesis imperfecta type I. Calcif Tissue Int 2013;93: 448–52. [Medline] [CrossRef]
85. Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C, *et al*. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J Clin Invest 2014;124: 491–8. [Medline] [CrossRef]
86. Leali PT, Balsano M, Maestretti G, Brusoni M, Amorese V, Ciurlia E, *et al*. Efficacy of teriparatide *vs* neridronate in adults with osteogenesis imperfecta type I: a prospective randomized international clinical study. Clin Cases Miner Bone Metab 2017;14: 153–6. [Medline] [CrossRef]
87. Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, *et al*. Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta. Nat Med 2014;20: 670–5. [Medline] [CrossRef]
88. Song IW, Nagamani SC, Nguyen D, Grafe I, Sutton VR, Gannon FH, *et al*. Targeting TGF-β for treatment of osteogenesis imperfecta. J Clin Invest 2022;132: e152571. [Medline] [CrossRef]
89. Greene B, Russo RJ, Dwyer S, Malley K, Roberts E, Serrielo J, *et al*. Inhibition of TGF-β increases bone volume and strength in a mouse model of osteogenesis imperfecta. JBMR Plus 2021;5: e10530. [Medline] [CrossRef]
90. Tauer JT, Abdullah S, Rauch F. Effect of anti-TGF-β treatment in a mouse model of severe osteogenesis imperfecta. J Bone Miner Res 2019;34: 207–14. [Medline] [CrossRef]
91. Lisse TS, Thiele F, Fuchs H, Hans W, Przemeck GK, Abe K, *et al*. ER stress-mediated apoptosis in a new mouse model of osteogenesis imperfecta. PLoS Genet 2008;4: e7. [Medline] [CrossRef]
92. Besio R, Iula G, Garibaldi N, Cipolla L, Sabbioneda S, Biggiogera M, *et al*. 4-PBA ameliorates cellular homeostasis in fibroblasts from osteogenesis imperfecta patients by enhancing autophagy and stimulating protein secretion. Biochim Biophys Acta Mol Basis Dis 2018;1864(5 Pt A): 1642–52. [Medline] [CrossRef]
93. Takeyari S, Kubota T, Ohata Y, Fujiwara M, Kitaoka T, Taga Y, *et al*. 4-Phenylbutyric acid enhances the mineralization of osteogenesis imperfecta iPSC-derived osteoblasts. J Biol Chem 2021;296: 100027. [Medline] [CrossRef]
94. Duangchan T, Tawonsawatruk T, Angsanuntsukh C, Trachoo O, Hongeng S, Kitiyanant N, *et al*. Amelioration of osteogenesis in iPSC-derived mesenchymal stem cells from osteogenesis imperfecta patients by endoplasmic reticulum stress inhibitor. Life Sci 2021;278: 119628. [Medline] [CrossRef]
95. Duran I, Zieba J, Csukasi F, Martin JH, Wachtell D, Barad M, *et al*. 4-PBA treatment improves bone phenotypes in the aga2 mouse model of osteogenesis imperfecta. J Bone Miner Res 2022;37: 675–86. [Medline] [CrossRef]
96. Scheiber AL, Wilkinson KJ, Suzuki A, Enomoto-Iwamoto M, Kaito T, Cheah KS, *et al*. 4PBA reduces growth deficiency in osteogenesis imperfecta by enhancing transition of hypertrophic chondrocytes to osteoblasts. JCI Insight 2022;7: e149636. [Medline] [CrossRef]
97. Kawai S, Yoshitomi H, Sunaga J, Alev C, Nagata S, Nishio M, *et al*. In vitro bone-like nodules generated from patient-derived iPSCs recapitulate pathological bone phenotypes. Nat Biomed Eng 2019;3: 558–70. [Medline] [CrossRef]
98. Bateman JF, Sampurno L, Maurizi A, Lamandé SR, Sims NA, Cheng TL, *et al*. Effect of rapamycin on bone mass and strength in the α2(I)-G610C mouse model of osteogenesis imperfecta. J Cell Mol Med 2019;23: 1735–45. [Medline] [CrossRef]

doi: 10.1297/cpe.2025-0009