Challenges In Osteogenesis Imperfecta Care: Breaking The Barrier For A Promising Future

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The osteogenesis imperfecta (OI) remains one of the most challenging inherited skeletal disorders that manifests with recurrent fractures on minor stress, progressive deformities, chronic pain, and functional disabilities. The affected person can also have variable short stature, scoliosis, and extra-skeletal manifestations including blue sclera, sensory hearing loss, and dentinogenesis imperfecta.[1-3] In Pakistan, OI prevalence is similar to that of global estimates; about 1 in 10,000 to 20,000 births. The reliable national data are lacking due to frequent under-diagnosis or confusing with conditions like rickets and child abuse.[4] In contrast, high-income countries have centralized registries with the availability of genetic testing and multidisciplinary teams to manage the patients and improve their quality of life.

COL1A1 or COL1A2 gene are identified as the primary cause of classical OI. Autosomal mutation of this gene leads to reduction in type 1 collagen production and changes in the bone metabolism. As a result of this the bone becomes brittle and breaks more frequently. In recent studies, novel mutation G324C, in WNT1 gene variant was found in Pakistani families with autosomal recessive OI. This phenotype is aggressive in nature. It is reported in consanguineous marriages and mostly concentrated in the rural and low income population. Other recessive forms like WNT1, FKBP10, affect non-collagen genes in urban families with OI children.[4] WNT1 gene mutation was also identified in studies from Turkey and China.[5]

The cornerstone of OI treatment is targeted to reduce the frequency of recurrent fractures, prevent subsequent development of deformities and minimize functional disabilities. Bisphosphonate, an anti-resorptive disease modifying agent, is used as an adjunct to fracture stabilization with conservative and operative approaches. Bisphosphonates therapy improves bone mineral density, minimizes frequency of fractures, maintains vertebral height, improves quality of life and decreases functional disability.[2,6,7] However, these benefits diminish over period of time as the underlying problem of mutant collagen chains that hinder osteoblast activity continue and aberrant collagen production persists.

Denosumab, a monoclonal antibody that targets RANKL protein involved in bone resorption, has emerged as another disease modulating agent for OI. Denosumab slows down the calcium release from bones, thereby increases bone density and lessens the frequency of fractures.[8] Recently, setrusumab, an anti-slecrostin human monoclonal antibody, was introduced as another disease modifying agent that stimulates bone formation. However, a comparative study to find out the effectiveness of setrusumab with bisphosphonates revealed similar outcomes. Both the agents did not show a significant reduction in clinical fracture rate but achieved substantial improvement in spine bone density.[9,10] The hormonal therapies (growth hormone and teriparatide) are also tried, however, the results are still awaited.[2] Multiple gene based therapeutic trials are being conducted and reported in literature. This includes CRISPR/Cas9 editing, allele specific silencing, base editing, or prime editing of COL1A1 and COL1A2.[1,11] Stem cell therapy using stem cells derived from fetal liver is also reported in literature.[12] AGA2115, a novel humanized antibody to treat OI by increasing bone formation and decreasing bone resorption in adults and children with OI is under research.[13]

The fracture and deformity correction surgeries in OI face significant challenges. Treatment modalities included combination of conservative (immobilization, casting, bracing), surgical approaches like intramedullary nailing (IMN), adjuvant pharmacotherapies and physical rehabilitation protocols to maintain joint mobility and restore muscle strength. Over the years the fracture stabilization has moved from solid, static IMN to flexible and telescopic

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nails. The further innovation includes the use of Fassier-Duval telescopic nail with minimally invasive technique which is considered as a gold standard.[2,14,15] Moreover, the correction of angular deformities in OI with metaphyseal osteotomies and plating has been shifted to guided growth hemi-epiphysiodesis with staples. Guided growth technique by using tension band plates or 8-plates was popular about two decades ago. However, to overcome the high complication rates (cut through, implant failures and revision requirements), the novel fixation techniques of IMN combined with the plate and screw, provided encouraging successful outcome.[16]

In Pakistan due to delayed diagnosis, limited availability of the genetic tests, irregular drug supply, limited funding, less number of patients per institution, and lack of long-term data compromise the management of the patients as well research on the subject. The affected families endure a significant socioeconomic burden. This financial hardship leads to inadequate or incomplete treatments. Although there is no cure for OI, current treatments focus on improving bone structure by increasing bone mass, reducing frequency of fractures, improved pain management and quality of life of the affected individuals through a multidisciplinary approach. Establishing OI socio-rehabilitation centers and research at national level can go a long way to provide a holistic management strategy as well as education, awareness, genetic counseling, family support, psycho-social help and capacity building.

REFERENCES:

1. Schindeler A, Lee LR, O'Donohue AK, Ginn SL, Munns CF. Curative cell and gene therapy for osteogenesis imperfecta. J Bone Miner Res. 2022;37(5):826-36. doi: 10.1002/jbmr.4549.

2. Chaugule S, Constantinou CK, John AA, Micha D, Eekhoff M, Gravallese E, et al. Comprehensive review of osteogenesis imperfecta: current treatments and future innovations. Hum Gene Ther. 2025;36(5-6):597-617. doi: 10.1089/hum.2024.191.

3. Hayat S, Mayan AR, Khan MW, Hayat QJ. Blue sclera to brittle bones: a rare case of osteogenesis imperfecta with dentinogenesis imperfecta and nephrocalcinosis. J Investig Med High Impact Case Rep. 2025;13: 23247096251334237. doi: 10.1177/ 23247096251334237.

4. Kausar M, Siddiqi S, Yaqoob M, Mansoor S, Makitie O, Mir A, et al. Novel mutation G324C in WNT1 mapped in a large Pakistani family with severe recessively inherited osteogenesis imperfecta. J Biomed Sci. 2018;25(1):82. doi: 10.1186/s12929-018-0481-x.

5. Liu Y, Song L, Ma D, Lv F, Xu X, Wang J, et al. Genotype-phenotype analysis of a rare type of osteogenesis imperfecta in four Chinese families with WNT1 mutations. Clin Chim Acta. 2016;461:172-80. doi: 10.1016/j.cca. 2016.07.012.

6. Devogelaer JP. Clinical use of bisphosphonates. Curr Opin Rheumatol. 1996;8(4):384-91. doi: 10.1097/00002281-199607000-00018.

7. Riaz M, Hafeez S, Ibrahim MN, Khoso ZA, Laghari TM, Raza SJ. Safety and efficacy of zoledronic acid in children with osteogenesis imperfecta. J Coll Physicians Surg Pak. 2022;32(9):1165-9. doi: 10.29271/jcpsp. 2022.09.1165.

8. Semler O, Netzer C, Hoyer-Kuhn H, Becker J, Eysel P, Schoenau E. First use of the RANKL antibody denosumab in osteogenesis imperfecta type VI. J Musculoskelet Neuronal Interact. 2012;12(3):183-8.

9. Ultragenyx receives breakthrough therapy designation for setrusumab (UX143) in osteogenesis imperfecta. News release. Ultragenyx. October 7, 2024. [Internet] Available from URL https://www.globenewswire.com/en/newsrelease/2024/10/07/2958870/20739/en/Ultragenyx-Receives-Breakthrough-TherapyDesignation-for-Setrusumab-UX143-in-Osteogenesis-Imperfecta.html. Accessed in February 2026.

10. Ultragenyz and Mereo BioPharma announce new phase 2 data from phase 2/3 Orbit study demonstrating sustained reductions in fracture rates following treatment with setrusumab (ux143) in patients with osteogenesis imperfecta (OI). News release. Ultragenyx. June 11, 2024. [Internet} Available from URL https://ir.ultragenyx.com/ news-releases/news-release-details/ultragenyx-andmereo-biopharma-announce-new-phase-2-data-phase. Accessed in February 2026.

11. Jung H, Rim YA, Park N, Nam Y, Ju JH. Restoration of osteogenesis by CRISPR/Cas9 genome editing of the mutated COL1A1gene in osteogenesis imperfecta. J Clin Med. 2021;10(14):3141. doi: 10.3390/jcm10143141.

12. Sagar RL, Åström E, Chitty LS, Crowe B, David AL, DeVile C, et al. An exploratory open-label multicentre phase I/II trial evaluating the safety and efficacy of postnatal or prenatal and postnatal administration of allogeneic expanded fetal mesenchymal stem cells for the treatment of severe osteogenesis imperfecta in infants and fetuses: the BOOSTB4 trial protocol. BMJ Open. 2024;14(6):e079767. doi: 10.1136/bmjopen-2023-079767.

13. Brown K. A phase 2, multi-center, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of AGA2115 in adults with type I, III, or IV osteogenesis imperfecta (OI). 2026-01-11. Angitia Incorporated Limited. [Internet] Available from URL https://clinicaltrials.gov/study/NCT07062588. Accessed in February 2026.

14. Zhang W, Lu X, Yang N, Zhu X, Hu H. Extendable intramedullary nailing in a child with osteogenesis imperfecta of bilateral femoral fractures: a case report. Front Surg. 2026;12:1454192. doi: 10.3389/fsurg.2025.1454192.

15. Ahmad S, Khan L, Bashir MF, Ahmad S, Javed S, Aziz A. Outcome of shish kabab osteotomies fixed with sign nail in osteogenesis imperfecta. our experience at Ghurki Trust Teaching Hospital, Lahore, Pakistan. Esculapio. 2017;13(1):44-9.

16. Emet A, Yilmaz ET, Danisman M, Aksoy C, Yilmaz G. Fixation techniques in lower extremity correction osteotomies and fractures in mild-to-severe osteogenesis imperfecta patients: evaluation of the results and complications. J Orthop Surg Res. 2023;18(1):437. doi: 10.1186/s13018-023-03917-z.

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