

## THERAPEUTICAL PERSPECTIVES IN OSTEOGENESIS IMPERFECTA

Dorina Stoicanescu<sup>1</sup>, Valerica Belengeanu<sup>1</sup>, Monica Stoian<sup>1</sup>, Otilia Marginean<sup>2</sup>, Calin Popoiu<sup>3</sup>,  
Maria Puiu<sup>1</sup>

<sup>1</sup>Medical Genetics Department, University of Medicine and Pharmacy “Victor Babes” Timisoara, Romania

<sup>2</sup>Pediatric Clinic I, University of Medicine and Pharmacy “Victor Babes” Timisoara, Romania

<sup>3</sup>Pediatric Surgery and Orthopedics Department, University of Medicine and Pharmacy “Victor Babes” Timisoara, Romania

### Abstract

Osteogenesis imperfecta is a genetic disease for which no cure is yet known. It is one of the most common skeletal dysplasias. It causes the osteoblasts to grow poorly, slowing the growth of children with the disease and causing their bones to break easily. The skeletal fragility is explained by the mutations in the genes for type I collagen, but the clinical range is wide and the relation between genotype and phenotype is complex. Some forms of osteogenesis imperfecta may cause severe disability and even death. Management of the disease includes focusing on preventing or minimizing deformities, and maximizing the individual's functional ability. With the more recent understanding of the molecular mechanisms of the disease, bone marrow transplantation is considered a potential future therapeutic modality. The young skeleton, normal or abnormal, is constantly changing, being formed and resorbed, modelled and remodelled. In theory blocking osteoclastic resorption or encouraging osteoblastic bone formation could produce useful increases in bone tissue even when the primary event is defective osteogenesis. Treatment with isolated allogeneic mesenchymal cells has the potential to enhance the therapeutic effects of conventional bone marrow transplantation in patients with genetic disorders affecting mesenchymal tissues. Thus, allogeneic mesenchymal cells offer feasible posttransplantation therapy for osteogenesis imperfecta.

**Key words:** osteogenesis imperfecta, therapy, bone marrow transplantation.

Osteogenesis imperfecta (OI) is a genetic bone disorder, leading to easily breaking of the bones, often from little or no apparent trauma. The disorder is characterized by failure of maturation and organization of collagen fibers. As collagen is an important protein in bone structure, this impairment causes weak or fragile bones. OI varies in severity from person to person, ranging from a mild type to a severe type, some forms may cause severe disability and even death. Other clinical features are short stature, scoliosis, blue sclerae, teeth defects (dentinogenesis imperfecta), hearing defects, ligamentous laxity, but muscle weakness, joint laxity and other skeletal malformations may also occur (1).

It is estimated that OI occurs in approximately 1 in 20,000 individuals; however, the mild form is underdiagnosed, and the actual prevalence may be higher. OI occurs with equal frequency among males and females and among different ethnic groups. Life expectancy varies depending on the severity of the disorder.

There are several types of OI, distinguished mostly by fracture frequency, severity and by some characteristic features (2). It is estimated that the vast majority (90 %) of OI is caused by a single dominant mutation in one of two type I collagen genes: COL1A1 or COL1A2. These genes provide instructions for making proteins that are used to create type I collagen, which is the most common protein in bone, skin and connective tissues. Type I collagen fibers are composed of a left-handed helix formed by intertwining of pro-alpha 1 and pro-alpha 2 chains. The COL1A gene on chromosome 17 encodes the pro-alpha 1 chain, and the COL2A gene on chromosome 2 encodes the pro-alpha 2 chain. Mutations in the loci that encode these chains cause the disease. Cartilage-associated protein (CRTAP) is a protein required for prolyl 3-hydroxylation. mutations of this gene cause excess posttranslational modification of collagen, and may be associated with syndromes resembling osteogenesis imperfecta, including recessive forms of lethal syndromes resembling the disorder (3). OI type VII is caused by recessive mutations in the CRTAP gene and type VIII by mutations of gene LEPRE1 (4).

**Type I** is the mildest form. Affected persons have bone fractures during childhood and adolescence often due to minor trauma, but during adulthood they have fewer fractures.

**Type II** is the most severe form. Infants with type II have shortarms and legs, bones that appear fractured before birth, narrow chest, fractured and misshapen ribs and underdeveloped lungs, unusually soft skull bones. Most infants are stillborn or die shortly after birth, usually from breathing failure.

**Type III** also has relatively severe signs and symptoms. Infants have very soft and fragile bones that may begin to fracture before birth or in early infancy. Bone abnormalities tend to get worse over time, being considered a progressive form.

**Type IV** is the most variable form OI. Symptoms of OI type IV can range from mild to severe. Scleras are normal.

**Type V** has severity similar to that of type IV disease but with a predisposition to hyperplastic callus formation.

**Type VI** is clinically similar to types II and IV, but it has distinctive histology.

**Type VII** is clinically similar to osteogenesis imperfecta types II and IV but with rhizomelia as a distinctive feature.

**Type VIII** is associated with protein leprecan.

Precise typing is often difficult. Severity ranges from mild forms to lethal forms in the perinatal period. In addition, several syndromes resemble OI, with congenital bone fragility in association with other distinctive clinical or histologic features. In severe cases, prenatal screening ultrasonography performed during the second trimester may show bowing of long bones, fractures, limb shortening, and decreased skull echogenicity. Lethal OI cannot be diagnosed with certainty in utero (5).

Osteogenesis imperfecta is often inherited from an affected parent. Most types are inherited in an autosomal dominant pattern. The diagnosis is made on the basis of family history, clinical presentation, bone density measurements (6), X-ray findings that include fractures that are at different stages of healing, an unexpected skull bone pattern called Wormian bones and bones in the spine called "codfish vertebrae." Laboratory testing may include either biochemical testing involving studying collagens or DNA-based sequencing of COL1A1 and COL1A2. DNA sequencing of COL1A1 and COL1A2 is used to identify the type I collagen gene mutation responsible for the altered collagen protein. Normal biochemical and molecular testing in a child with OI warrants additional testing of less common collagen genes (CRTAP and LEPRE1) responsible for the rare recessive forms of OI. 25-30 % of cases occur as a result of new mutations.

Osteogenesis imperfecta is a genetic disease for which no cure is yet known. Treatment requires a coordinated multidisciplinary team approach, and consists of physical therapy, surgical interventions, medications, and in some cases, experimental therapies (7, 8). Osteogenesis imperfecta treatment is typically focused on preventing or controlling symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Treatment involves supportive therapy to decrease the number of fractures and disabilities, help with independent living and maintain overall health. Medical and surgical care are completed by physical and occupational therapies that will help improving the ability to move, to prevent fractures and to increase muscle strength (9).

A newer treatment with medication called biophosphonates is being used to help with bone formation and to decrease the need for surgery (10). A surgical procedure called "rodding" is frequently considered for individuals with OI. This osteogenesis treatment involves inserting metal rods through the length of the long bones to

strengthen them and prevent or correct deformities (11). Patients are encouraged to exercise as much as possible to promote muscle and bone strength, which can help prevent fractures. Swimming and water therapy are common exercise choices for people with osteogenesis imperfecta, as water allows independent movement with little risk of fracture. For those who are able, walking is excellent exercise. Children and adults with osteogenesis imperfecta will also benefit from maintaining a healthy weight. To date, no drug or vitamin therapy regimen has been effective as a treatment for this disorder. Research scientists continue to make progress with these issues.

Osteogenesis imperfecta causes the osteoblasts to grow poorly, which slows the growth of children with the disease and causes their bones to bend and break easily. In previous research studies it was found that children treated with bone marrow transplant began to grow faster, had more minerals in their bones, and broke their bones less often than before the bone marrow transplant (12). Several months after the bone marrow transplant however, body growth once again began to slow down (13). Chamberlain et al. designed a gene construct that targets exon 1 of the gene for collagen type I $\alpha$ 1 (COL1A1), which encodes one of the two collagen subunits. They predicted that, on insertion, the construct would both inactivate COL1A1 and confer resistance to the antibiotic neomycin. To insert the gene construct efficiently they used an adenoassociated virus as a vector, which, unlike adenoviruses, is integrated into chromosomal sites.

The results obtained with mesenchymal stem cells from two patients with osteogenesis imperfecta were extremely encouraging. In 31 to 90 % of the cells that became resistant to neomycin, the gene construct had inserted itself into either the wild-type or the mutated COL1A1 allele. In all cultures of the neomycin-resistant cells, most signs of the dominant negative protein defect were corrected — apparently because the cells in which the mutated allele was inactivated began to produce an adequate amount of wild-type collagen. Most important, the quality of bone synthesized by the altered mesenchymal stem cells was improved (14). Adult stem cells offer the potential to treat many diseases through a combination of ex vivo genetic manipulation and autologous transplantation. Mesenchymal stem cells, also referred to as marrow stromal cells are adult stem cells that can be isolated as proliferating, adherent cells from bones. Mesenchymal stem cells can differentiate into multiple cell types present in several tissues, including bone, fat, cartilage, and muscle, making them ideal candidates for a variety of cell-based therapies (15). The present findings suggest that long-term cultured bone marrow stromal cells from osteogenesis imperfecta (OI) animals have the potential to traffic through the circulatory system, home to bone, form bone and continue to express exogenous genes. These findings open the possibility of using these cells as vehicles to deliver normal genes to bone as an alternative approach for the treatment of some forms of OI and certain other bone acquired and genetic diseases.

**References**

1. Plotkin H, Primorac D, Rowe D. Osteogenesis imperfecta. In: Glorieux F, Pettifor J, Juppner J, eds. *Pediatric Bone: Biology and Disease*. 2003:443-71.
2. Venturi G, Tedeschi E, Mottes M, Valli M, Camilot M, Viglio S, Antoniazzi F, Tato L. Osteogenesis imperfecta: clinical, biochemical and molecular findings. *Clin Genet*. 2006 Aug;70(2):131-9
3. Plotkin H. Syndromes with brittle bones, hyperostotic bone disease and fibrous dysplasia of bone. In: Lifshitz F, ed. *Pediatric Endocrinology*. 5<sup>th</sup> ed. 2006.
4. Roughley PJ, Rauch F, Glorieux FH. Osteogenesis imperfecta--clinical and molecular diversity. *Eur Cell Mater*. 2003 Jun 30;5:41-7;
5. Plotkin H, Primorac D, Rowe D. Osteogenesis imperfecta. In: Glorieux F, Pettifor J, Juppner J, eds. *Pediatric Bone: Biology and Disease*. 2003:443-71.
6. Huang, RP, Ambrose, CG, Sullivan, E, Haynes, RJ. Functional significance of bone density measurements in children with osteogenesis imperfecta. *J Bone Joint Surg Am* 2006; 88:1324.
7. Antoniazzi, F, Mottes, M, Fraschini, P, et al. Osteogenesis imperfecta: practical treatment guidelines. *Paediatr Drugs* 2000; 2:465.
8. Rauch, F, Glorieux, FH. Osteogenesis imperfecta. *Lancet* 2004; 363:1377.
9. Vallo, A, Rodriguez-Leyva, F, Rodriguez Soriano, J. Osteogenesis imperfecta: anthropometric, skeletal and mineral metabolic effects of long-term intravenous pamidronate therapy. *Acta Paediatr* 2006; 95:332.
10. Rauch, F, Glorieux, FH. Bisphosphonate treatment in osteogenesis imperfecta: which drug, for whom, for how long? *Ann Med* 2005; 37:295.
11. Zeitlin, L, Fassier, F, Glorieux, FH. Modern approach to children with osteogenesis imperfecta. *J Pediatr Orthop B* 2003; 12:77.
12. Prockop, DJ. Targeting gene therapy for osteogenesis imperfecta. *N Engl J Med* 2004; 350:2302.
13. E M Horwitz, D J Prockop, P L Gordon, W W Koo, L A Fitzpatrick, M D Neel, M E McCarville, P J Orchard, R E Pyeritz, M K Brenner. Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. *Science*. 2004 Feb 20;303(5661):1198-201 14976317
14. Chamberlain, JR, Schwarze, U, Wang, PR, et al. Gene targeting in stem cells from individuals with osteogenesis imperfecta. *Science* 2004; 303:1198
15. S L Gerson. Mesenchymal stem cells: no longer second class marrow citizens. *Clin Orthop*. 2002 Aug;(401):6-16.

---

---

Correspondence to:

Dorina Stoicanescu,  
Medical Genetics Department,  
University of Medicine and Pharmacy "Victor Babes",  
P-ta E. Murgu Nr. 2,  
Timisoara,  
Tel: 0256-204476  
E-mail: dstoicanescu@yahoo.com