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Review Article

Mesenchymal Stem Cells as a Therapeutic Treatment for Osteogenesis Imperfecta: Current Understanding Through Clinical Trials

Katherine E Gandy[1], Vincent S Gallicchio[1*]

[1]Department of Biological Sciences College of Science Clemson University Clemson, SC 29634, USA

***Correspondence author:** Vincent S Gallicchio, Department of Biological Sciences College of Science Clemson University Clemson, SC 29634, USA; E-mail: vsgall@clemson.edu

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Abstract

Osteogenesis Imperfecta (OI), also known as brittle bone disease, is a rare heterogeneous disorder with an incidence of 1 in 15,000 to 20,000 live births. Currently, OI has been associated with 19 different gene mutations, primarily affecting genes responsible for collagen type I production and resulting in clinical manifestations such as skeletal deformities and a disproportionate, short stature. OI also has associated extra-skeletal defects such as hearing loss, blue sclerae and cardio/respiratory defects. There are many types of OI, resulting in clinical severity from mild to severe based on clinical observations and genetic morphology of the patient. There is currently no cure for OI; however, bisphosphonates remain the only pharmacological off-label treatment for pediatric OI patients. This research paper examines different clinical trials that have occurred since 1999, assessing the use of mesenchymal stem cells as a method of treatment for skeletal defects in severe OI pediatric patients. Possible treatment mechanisms these clinical trials focus on are bone marrow derived mesenchymal stem cell transplants, allogeneic bone marrow derived mesenchymal stem cell engraftments, adeno-associated virus vectors for COL1A1 disruption and human first-trimester fetal blood or fetal liver mesenchymal stem cells. Through research on both adult MSCs and fetal/embryonic MSCs, they have proved to be a feasible, safe and effective therapy for pediatric patients with OI after prenatal and/or postnatal transplantations or infusions. Evidence on mesenchymal stem cells treatments has shown positive and promising benefits, suggesting a better understanding for elongating clinical benefits of long-term post-transplantation.

Keywords: Osteogenesis Imperfecta; Mesenchymal Stems Cells; Stem Cell Therapy; Allogeneic Bone Marrow Transplantation; Bone Marrow Derived Mesenchymal Stem Cells; Clinical Trials; Embryonic Mesenchymal Stem Cells; Pediatrics

Abbreviations

AAV: Adeno-Associated Virus; BLI: Bioluminescence; BM-MSCs: Bone Marrow Mesenchymal Stem Cells; BMT: Bone Marrow Transplant; BOOSTB4: Brittle Bones Before Birth; DXA: Dual-Energy X-Ray Absorptiometry; ELISA: Enzyme-Linked Immunosorbent Assay; FMSCs: Fetal Mesenchymal Stem Cells; FISH: Fluorescence In Situ Hybridization; HRQoL: Health-Related Quality of Life; HR-pQCT: High-Resolution Peripheral Quantitative Computed Tomography; hESCs: Human Embryonic Stem Cells; hfMSCs: Human Fetal Mesenchymal Stem Cells; GPLD1: Human Glycosylphosphatidylinositol-Specific Phospholipase D1; ITQOL: Infant Toddler Quality of Life; MSCs: Mesenchymal Stem Cells; NT: Nuclear Transfer; OI: Osteogenesis Imperfecta; PCR: Polymerase Chain Reaction

Introduction

Osteogenesis Imperfecta (OI), also known as brittle bone disease, is a rare heterogeneous disorder primarily caused by mutations in genes responsible for type 1 collagen production [1]. OI carries an incidence of 1 in 15,000 to 20,000 live births [2]. Currently, OI has been associated with 19 different gene mutations, resulting in clinical severity from mild to severe [3]. OI is phenotypically characterized by skeletal dysplasia through skeletal deformities and a disproportionate and short stature. OI affects other connective tissue functions, causing ecchymosis, hearing loss, joint hypermobility, dentinogenesis imperfecta, melanocytosis in the sclera and cardio/respiratory defects [4,5].

Pathophysiology of OI

The diseased phenotype of OI is caused by autosomal dominant variants of type I collagen genes, specifically COL1A1 and COL1A2 [6]. Mutations in COL1A1 and COL1A2 are common in approximately 85% of OI cases; however, some recessive, dominant and X-linked defects in encoding proteins for type 1 collagen and regulation of osteoblasts activity have been associated with OI (Fig. 1) [7].

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.

Figure 1: Registered genetic mutations associated with varied OI types [8].

Type 1 collagen is a necessary and crucial protein as its primary responsibilities are to form the organic matrix of bone and provide structural integrity for bone materialization. Also, type 1 collagen is an essential component to regulate osteoblasts, osteoclasts and osteocytes, which are important cellular components for forming, breaking and maturing bone [9]. Type 1 collagen is composed of two alpha-1 chains and one alpha-2 chain, creating a heterotrimer that consists of a triple helical domain with uninterrupted repeats of glycine-X-Y tripeptides. In OI, the most common mutations leading to the diseased phenotype are missense substitutions of a glycine residue in the Gly-X-Y region, resulting in a COL1A1 or COL1A2 variant. The second most common mutation is a nonsense/frameshift or splicing variation, resulting in a non-functional or degraded COL1A1 or COL1A2 allele [10]. Studies show that when the COL1A2 mutation is present, osteogenic differentiation, maturation and osteoclastogenesis are inhibited. OI defective osteoblasts exhibit upregulated oxidative cell stress [11] due to mitochondrial dysfunction and overproduction of reactive oxygen species [12], as well as autophagy pathways. An extracellular accumulation of defective type 1 collagen fibers results in the activation of the TGF-β pathway leading to inflammatory responses. In

combination with defective osteoblasts and defective type 1 collagen, bone fragility increases due to a destabilization in bone turnover [11].

Current Treatments for OI

OI is characterized by skeletal and extra-skeletal defects, affecting different connective tissues and important senses, such as hearing. There is currently no cure for the disease and no FDA approved treatments. Symptomatic treatments for OI provide management of bone fragility, skeletal abnormalities and other defects, requiring a multidisciplinary approach to provide relief of symptoms. Occupational therapy, orthopedic surgery, physical therapy, dental surgery and medications aid in providing strength and stability of the skeletal deformities' present [13]. Specialties such as nutrition, aid in supporting bone health and vitamin and nutrient levels to increase efficacy and decrease reactions to bisphosphonates, which is one of the only medications shown to have a positive impact on patients with OI [14]. Bisphosphonates are an orally or intravenously off-label prescribed medication intended to reduce the risk of fractures in patients with OI, as studies have shown positive association with an increase in bone mineral density and bisphosphonates [15]. However, confirmative data on fracture protection by bisphosphonates is still minimal [16]. Studies are still ongoing to determine the capacity of how bisphosphonates treat patients with OI but currently they are the principal pharmacological treatment for pediatric OI patients [15]. Investigational therapies and treatments such as growth hormone therapy, anti-resorptive treatments, osteo-anabolic therapies, TGF-β inhibition and stem cell therapies are being clinically tested, focusing on correcting the genetic, protein and hormonal defects of OI that occur cellularly in the body [14].

Discussion

MSCs as a Potential Therapeutic Treatment for OI

MSCs or stromal cells, are multipotent stem cells that can be isolated from multiple tissues, such as bone marrow, adipose tissue, umbilical cord and endometrial polyps [17]. Stem cell therapies, specifically MSCs, have been focused on in clinical trials to correct molecular defects of OI. Researchers show interest in MSCs in clinical trials as a potential treatment for OI, as they exhibit the capacity to migrate to sites of damage, have immuno-modulary properties and can differentiate into multiple lineages [18]. MSCs can differentiate into osteocytes, adipocytes and chondrocytes [19]. MSCs are considered non-immunogeneic and have properties to increase the efficacy of an individual's immune system. Studies of MSCs have clinically shown to be safe in clinical use and improve clinical outcome, migrate to fracture and growth sites in bone and have a therapeutic effect resulting from possible paracrine mechanisms [18].

Studies have shown MSCs to be effective in OI treatment; however, there are disadvantages to this treatment. As MSCs are typically isolated from an individual, there are ethical concerns and restrictions, as well as concerns of invasiveness. Bone marrow derived MSCs are typically acquired from an invasive bone marrow aspirate but are the most common source of MSCs for clinical trials. MSCs can be isolated from locations, such as dental pulps and adipose tissue, involving a less invasive procedure. However, the number of cells available are questioned based on the location. Placenta-derived MSCs can be isolated from the individual during a pregnancy without harming the fetus, eliminating ethical concerns and have shown to harvest and proliferate in higher numbers and rates *in-vitro*. These MSCs can eliminate ethical concerns that fetal MSCs and umbilical cord MSCs express. Another disadvantage of MSCs was found in several reports of being directly or indirectly involved in cancer, as well as worsening bacterial infections, resulting from MSCs anti-inflammatory properties. Also, the environment and culture conditions of MSCs must be specific to prevent degradation and limiting therapeutic effects, as cryopreserved MSCs have been shown to limit therapeutic aid [18].

There are advantages and disadvantages to hESCs in comparison to adult stem cells. In the case of hfMSCs, they are nonimmunogenic and phenotypically like adult MSCs, however, they have the capacity of higher proliferation and are genetically characterized with longer telomeres, allowing them to differentiate into bone, skeletal muscle and oligodendrocytes more readily. From these observations, hfMSCs are suggested to have greater utility in cellular therapy compared to adult MSCs. As hESCs have the possibility of invoking immune rejection and adult stem cells can be difficult to analyze, MSCs have the capacity to prevent adverse reactions and rejection due to their anti-inflammatory and immunosuppressive characteristics [20].

Clinical Methodology for OI Diagnosis

In 1979, Australian physician David Sillence introduced the first classification system for OI, known as the "Sillence

classification". The Sillence classification included four types of OIs, types I-IV, basing the diagnosis of each type on clinical findings with radiological subclassifications for OI type II and mode of inheritance, specifically heterogeneity. Later, the Sillence criteria were used to determine severity and clinical differences, as it was discovered that all OI types exhibited heterozygous type I collagen mutations. However, some lethal or severe OI types do not exhibit a collagen type I mutation, which led to the expansion of the Sillence classification to include seven OI types, their documented mutation, mode of inheritance and clinical severity (Fig. 2) [21].

Type	Clinical severity	Typical features	Associated mutations[a]	Inheritance
I	Mild non-deforming	Normal height or mild short stature; blue sclera; no DI	Premature stop codon in *COL1A1*	AD
II	Perinatal lethal	Multiple rib and long bone fractures at birth; marked deformities; broad long bones; low density of skull bones on x rays; dark sclera	Glycine substitutions in *COL1A1* or *COL1A2*	AD Rarely AR[b]
III	Severely deforming	Very short; triangular face; severe scoliosis; grayish sclera; DI	Glycine substitutions in *COL1A1* or *COL1A2*	AD
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; grayish or white sclera; DI	Glycine substitutions in *COL1A1* or *COL1A2*	AD
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no DI	Unknown	AD
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fishscale pattern of bone lamellation; white sclera; no DI	Unknown	AR
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no DI	Hypomorphic expression of *CRTAP*	AR

DI, dentinogenesis imperfecta; AD, autosomal dominance; AR, autosomal recessivity; *COL1A1* and *COL1A2*, genes encoding type I collagen.
[a] The associated collagen mutations may or may not be detectable in a given patient.
[b] Association with null mutations in *CRTAP* or *P3H1* (see text for details).

Figure 2: Expanded classification for OI including clinical severity listed for each type of OI, along with typical clinical manifestations associated with the OI type and their known or unknown mutation and inheritance [22].

Many clinical trials focus on OI types I-IV, as they involve a COL1A1 or COL1A2 variant. During diagnosis, the specific OI type is identified through clinical manifestations such as fractures, dentinogenesis imperfecta and adult age hearing loss, as well as genetic testing.

After clinical and genetic results, clinicians can classify the OI type, ultimately understanding the severity of the patient's OI. OI type I is known as classic non-deforming OI with blue sclerae and OI type II is known as perinatally lethal OI [23]. OI type II is clinically the most lethal type of OI, as abnormalities typically begin to show during the second trimester of pregnancy, resulting in early death of the child [24]. OI type III is known as progressively deforming OI and OI type IV is characterized as a common variable OI with normal sclerae [23].

OI can be diagnosed during the prenatal period, at birth or during early childhood as clinical manifestations, such as fractures, appear, as well as with genetic testing and family history [7]. The diagnosis of OI also comes from radiography imaging. The two most used imaging techniques used are Conventional Radiography and DXA. DXA can assess bone mineral density; however, there are limitations to the technology when characterizing bone fragility. To assess and characterize bone fragility, evidence is toward HR-pQCT as an improved technology to overcome the DXA's limitations [25].

Nonembryonic/Adult Mesenchymal Stem Cells Clinical Trials

1999 Clinical Trial: BM-MSC Transplantability and Therapeutic Effects

A preclinical study determined BM-MSCs experience a homing capacity, as the transplanted mesenchymal cells migrated and became incorporated into the bone and muscle of recipient animals. This discovery led researchers to believe BMT could correct a wide range of inherited and acquired disorders, such as OI. However, information regarding BM-MSCs was understood through animal models, so the capability of engraftment transplantation of MSCs in allogeneic hosts from human bone marrow and their differentiation and function *in-vivo* was unidentified. Ultimately, an animal model of OI showed a small improvement regarding its mutated phenotype after a MSC engraftment [26].

A clinical trial conducted in Memphis, Tennessee at the St. Jude Children's Research Hospital in 1999 included three children diagnosed with type III severe deforming OI, noting patients 1 and 3 had a COL1A1 mutation, patient 2 had a COL1A2 mutation and patient 3 had three intramedullary rods. The patients underwent myeloablative conditioning before an intravenous infusion of unmanipulated bone marrow donor cells. The donors were determined through HLA-identical or single-antigen-mismatched siblings. Osteoblasts were cultured from new bone biopsy specimens and concluding, with the use of flow cytometric analysis, no contamination of lymphohematopoietic cells. FISH was used to detect the amount of donor cells present in the patient after transplantation, which was determined to be 1.5% to 2.0% [26].

Fluorescence microscopy was used to examine bone histology before and after the BMT from the trabecular bone of the iliac wing. Researchers found that after the transplantation, there was improved bone histology when looking at the organization, size and numbers of osteoblasts, osteocytes and lacunae. Also, they specifically looked at the pattern of tetracycling labeling before and after transplantation to determine bone formation and mineralization. Ultimately, they observed improved bone formation and mineralization through the linear formation of single and double tetracycline labeling [26].

Important clinical manifestations investigated during the trial were bone fractures and growth velocity. DXA was used to determine the change in total body bone mineral content and all fractures were clinically determined by clinical assessment and full skeletal radiography.

After transplantation, the patients experienced increased linear velocity growth and improvements in bone fractures. Patients 1 and 2 did not experience any toxicity reactions over the course of the transplantation. However, patient 3 experienced toxicity in the forms of sepsis, pulmonary insufficiency and bifrontal hygroma development [26].

Ultimately, the researchers were able to determine that transplantation of mesenchymal progenitor cells in bone marrow has the capacity to migrate to bone in pediatric patients with OI. This migration was responsible for the rise of osteoblasts, leading to increased bone structure and function. Only 1.5-2.0% of donor mesenchymal cells were present after 3-5 months after transplantation, showing low levels of mesenchymal progenitor cell engraftment can be sufficient to convert a severe OI phenotype into a less severe one. This observation could also be independent of donor osteoblasts and instead induced by the allogeneic BMT. The patients experienced improvements in bone histology, total body bone mineral content, bone fractures and body length growth. The improvement in bone density was attributed to the improved ratio of normal to mutated collagen, leading to increased mineralization. Lastly, they concluded that the therapeutic effects of a BMT for OI would be dependent on the quantity and ability of mesenchymal progenitor cells in an infusion, as well as the safety and easiness of clinical protocols [26].

2002 Clinical Trial: Allogeneic BM-MSCs engraftment and growth stimulation in OI pediatric patients

Many preclinical studies have suggested that unmanipulated bone marrow contains mixtures of mesenchymal progenitors, some expressing an unrestricted capacity for differentiation and some that commit to differentiation in one or two lineages. With understanding differentiation and advances in MSC isolation, expansion and characterization, researchers have studied the possibility of using human MSCs as a cell-based therapy for mesenchymal tissue genetic disorders. But, for isolated allogeneic MSCs, their capacity for engraftment and their clinical benefits to patients remained unknown [27].

A study performed in 2002 at the St. Jude Children's Research Hospital in Memphis, Tennessee by the same researchers as the 1999 trial mentioned previously, focused on the idea of using isolated MSCs without bone marrow ablative conditioning as an

additional therapy to prolong the clinical benefits, such as growth rate, after transplantation. The clinical trial included six patients with OI who previously participated in a clinical trial focusing on allogeneic BMT for severe OI pediatric patients. Two retroviral vector supernatants were prepared using PG13 producer cell lines, which were LNc8 and G1PLII. LNc8 encodes the neomycin phosphotransferase gene (neoR) and its expression is a result of retroviral long terminal repeats.

G1PLII is responsible for encoding no expressing β-galactosidase (β-gal) and neoR sequences
that have an ATG → CTG mutation present. After bone marrow was harvested from the original marrow donor of the patient, the cells were divided into two fractions: one which was minimally cultured cells and infused into the patient and another, which was expanded over three passages and infused into the patient. The patients each received two infusions that lasted approximately 10-15 minutes and the dosage was determined by the number of available cells after the *ex-vivo* expansion. However, the target dose was based on body weight. The target dose for the first infusion was 1×10^6 cells/kg and the second infusion target dose was 5×10^6 cells/kg [27].

The researchers focused their trial using transduction efficiency assay, osteogenic induction assay, analysis of donor MSC engraftment, immune responses, evaluation of growth before and after engraftment and using DXA to measure total body bone mineral content [27].

An important finding observed from the trial was the location of gene-marked allogeneic BM-MSCs. With minimally cultured cells, the PCR observed signals of G1PLII in the bone and skin in patient 2 and in the bone and stroma in patient 4. With expanded cells, the G1PLII vector was observed in the stroma, bone, skin and stroma and bone and stroma in patients 1, 3 and 5.

As the gene marked cells were found in skin biopsies from two patients, the researchers suggested that the infused MSC populations contained pluripotent stem cells that have the capacity to differentiate into mesenchymal progenitors or ectodermal pathways. This differentiation allows the ability of skin fibroblasts to be formed after these progenitors crossed the embryonic germ layer barriers [27].

None of the biopsies contained traces of the LNc8 vector, suggesting an immune recognition of MSCs with expressed neoR marker genes. As G1PLII was present in five out of six patients, this suggests that since the G1PLII-transduced cells did not express foreign antigens, there would be no cytotoxic T lymphocyte response against the cells *in-vitro*. However, this led to the conclusion to determine and screen for neoR specific cytotoxic T lymphocyte populations, as there were no LNc8-transduced cells present in any of the patients [27].

Similarly to their previous trial in 1999, the researchers determined that an engraftment of MSCs can occur at low levels to produce effective clinical benefits, as the donor-derived osteoblasts did not exceed 1%. However, the researchers determined that the mechanisms which control linear growth and bone mineralization are distinct from each other, as they did not observe an increase in total body bone mineral content three months after transfusion, while they saw a major improvement in bone mineralization. This led them to believe there is a beneficial effect in total body bone mineral content that is from whole transplanted marrow that is not present in isolated MSC infusions [27].

Ultimately, the researchers concluded that allogeneic MSCs are feasible and safe to administer to severe OI pediatric patients, as they can differentiate to osteoblasts, extend clinical benefits of BMTs and can engraft in defective bone. To maximize clinical benefits, more research must be done to prolong differentiation and proliferation of cells through cell-based treatments. The researchers determined a disadvantage associated with allogeneic MSC transplantation as there were limited therapeutic effects, such as poor mineral content increase and low levels in engraftment. Possibilities of using immature mesenchymal progenitors or true pluripotent stem cells to replace marrow stromal cells should be studied [27].

2004 Clinical Trial: Adeno-associated virus vectors for COL1A1 gene disruption in MSCs
A clinical trial performed in 2004 focused on using gene targeting to disrupt dominant-negative mutant COL1A1 genes in MSCs in patients with OI by using AAV vectors. Their previous understanding was that to perform a successful genetic treatment on a dominant-negative mutant protein, it would require complete elimination through mutant mRNA degradation or disruption of the mutated gene. So, in their proposed treatment, they were focusing on converting the mutant COL1A1 gene into a null

form to lessen the severity of symptoms with the OI type. The researchers determined the point mutations associated with COL1A1 in the MSC lines in two patients with severe OI and infected the mutated cells with an AAV vector, for gene targeting, labeled as AAV-COLe1INpA. This virus vector inserts an internal ribosome entry site, neomycin phosphotransferase gene and a polyadenylation signal, ultimately disrupting exon 1 on the chromosome the COL1A1 gene is present on [28].

The researchers focused their procedures on different characteristics of MSCs that would be important or necessary for an individual with severe OI. They looked at the disruption of the mutated allele and the expression of wild-type collagen polypeptides, allele preference and collagen stability and structure. Also, they focused on making sure gene-targeted cells protected their ability to form bone *in-vivo*, as that is an important concept for treatment in OI patients. Lastly, they also studied the capacity of MSCs to differentiate into different lineages, such as adipocyte formation [28].

Through their research, they found that gene-targeted autologous MSCs have the capacity to avoid problems that allogeneic BMTs are associated with, such as toxicity, poor engraftment of MSCs and lack of donors. The researchers found that since they did not use a mutation-specific AAV vector, possibly designing a pair of vectors that could disrupt both COL1A1 and COL1A2 mutations could be a treatment for severe OI patients. A disadvantage found was that AAV vectors can target both mutant and wild-type alleles. However, from their research, they determined this isn't a complete disadvantage and shouldn't eliminate this technique as a treatment, as a partial correction of the mutated cells can lead to clinical improvement. They saw that cells do not interfere with other individual cells during collagen production, so mutated and wild-type collagen in different cells will not disrupt each other. Also, they saw there was a genetic mosaic in severe OI patients that is not severely affected through genetic changes, so it is possible that not all the mutated cells need to be corrected. Lastly, they suggested that cells with wild-type collagen could have a growth advantage, which could lead to a larger ratio of wild-type collagen expressing cells compared to mutated cells. Another disadvantage present from their researcher was the immunogenicity towards the foreign neo gene; however, it could be corrected by neo cassette excision after selection or by using selective marker alternatives [28].

Ultimately, the researchers found that gene targeting was possible in nonembryonic MSCs through effective COL1A1 disruption. Since this is possible in nonembryonic MSCs, the ethical and clinical limitations, such as immune rejection and teratoma formation, that are found with embryonic MSCs are prevented. With the differentiation capacity of MSCs and the ability of AAV vectors to introduce genetic modifications at multiple chromosomal loci, it is suggested that autologous, gene-targeted MSCs could be a possible treatment for severe OI patients, as well as for other diseases [28].

2021 Clinical Trial: Phase I TERCELOI clinical trial on pro-osteogenic paracrine response and MSCs in pediatric OI patients

A phase I clinical trial performed in 2021 aimed to determine the efficacy and safety of administering multiple reiterative infusions of MSCs into two non-immunocompromised pediatric patients with severe and moderate OI during a 2.5-year period. However, the mechanism of action of MSCs beneficial effects was unknown, leading the researchers to study and determine the paracrine therapeutic effect of MSCs. The TERCELOI clinical trial was the first clinical trial to determine the effects of serial MSC infusions, as well as the mechanism of action of MSC therapy in OI patients. The clinical trial consisted of five total MSC infusions, one each five to six months, using same-donor allogeneic MSCs determined from nonmutated HLA-identical or histocompatibility in both pediatric patients. Each infusion was measured to be 4×10^6 MSCs/kg. Similarly to other trials, the researchers measured bone mineral density, specifically in spinal lumbar L1 to L4, by a whole-body scanner DXA [3].

Before, during and after each MSC infusion, sera were collected from each patient and used for the detection of GLPD1 by using a human GLPD1 ELISA kit. Also, from the sera collections, the researchers performed antibody array assay to observe the expression of more than 1000 human serum proteins and look at protein intensities using a RayBio Label-based (L-Series) Human Antibody Array 1000 kit (AAH-BLG-1000) and an Axon GenePix laser scanner. The sera samples collected from both patients were used to extract miRNAs and look at 21 circulating miRNAs that express the capacity for bone quality and musculoskeletal diseases, using a OstemoiR test [3].

An important screening mechanism the researchers used was the HRQoL measurement to evaluate clinical outcomes and a PedsQL questionnaire to gauge the children's physical, emotional, social and scholastic state with their OI disorder, as struggling with chronic pain can elicit a negative impact on an individual's quality of life. They observed that patient 1, who has the more severe OI phenotype, had lower HRQoL measurements than patient 2, who had a moderate OI phenotype. However, after the

start of cell therapy and throughout the clinical trial, both patients observed improvements in their quality of life, specifically in psychological support which was the highest parameter improvement for both patients. Interestingly, the expression of GPLD1 was associated with the patients HRQoL measurements. In mouse embryos, GPLD1 was observed to be associated with developing bone, while GLPD1 has also been documented as a possible therapeutic treatment for individuals of an older age, as it can provide similar benefits as exercise can. These understandings led the researchers to determine a comparison between GPLD1 and patient HRQoL measurements, discovering improvements in bone parameters and HRQoL, especially in patient 1 immediately after the first two infusions, but leveled off after four months. Both parents and patients were able to detect a noticeable difference in the number of bone fractures and bone durable improvements after infusions, improving the patients HRQoL measurements and boosting the bravery and self-esteem of each patient to participate in new activities and games [3].

The primary purpose of the clinical was to determine the safety and feasibility of serial MSC infusions, irrespectively from bisphosphonate treatments and without immunosuppressive treatment, while gaining knowledge about the paracrine mechanism induced by infused MSCs in pediatric OI patients. The researchers were able to discover a systematic pro-oncogenic response in OI patients from the MSC therapy, as serum levels elevated in the therapeutic molecule and increases in GPLD1 levels were present early on after infusions. Through their discoveries and data during the trial, it is suggested that the efficiency of the paracrine response that is initiated by MSCs is dependent on the OI severity, such as patient 1 experienced a more noticeable reduction in fractures after treatments and in findings of sera composition, miRNAs modulation and increase TNAP activity. Along with this suggestion, the researchers found that osteoporosis-related miRNAs in patient 1 basal serum were overexpressed, likely due to the more severe OI phenotype. Ultimately, they determined continuous cell therapy can restore upregulation of these miRNAs, as they can have a cumulative and gradual improvement on the severe OI phenotype. Another finding in relation to a paracrine response was the potential shift in MSC osteogenic lineage in the cultured serum and the enhancement of TNAP activity in the cells, resulting in early osteogenesis and improved mineralization of OI MSCs. At the conclusion of the research, they suggested that repeated long-term infusions would be required to maintain the clinical benefits that histocompatibility MSCs have on OI patients, especially in severe OI types. Also, they determined the OI microenvironment was extremely important in their findings, as MSC osteogenic potential has the capacity to be enhanced by serum after cell therapy and future research should prompt interest in severe microenvironments, such as severe OI [3].

Fetal/Embryonic MSC Clinical Trials

2008 Clinical Trial: Human first-trimester fetal blood MSCs intrauterine transplantation in homozygous OI affected oim mice

For prenatal OI, the only option is termination of pregnancy, as there is no treatment focusing on the collagen defect associated with OI, resulting in recurrent fractures before or after birth, short stature and premature respiratory death from kyphoscoliosis [29].

In 2008, studies had previously focused on nonembryonic MSCs and their clinical benefits from allogeneic whole BMT or from BM-MSCs. However, an anecdotal report of an attempted cell therapy rescue on a fetal OI patient by transplanted fetal liver MSCs showed evidence of progress in childhood but was ultimately confounded using bisphosphonates with other treatment options. The researchers of the 2008 clinical trial focused their research on the effect of bone pathology in homozygous oim mice by transplanting human first-trimester fetal blood MSCs in utero [29].

From their research, they saw similar clinical benefits compared to adult MSCs, such as decreased fractures at 4, 8 and 12 weeks after transplantation, increased tibial bone growth parameters and improved femoral cortical thickness at 4, 8 and 12 weeks of age. With the use of BLI and photo emission quantification, donor cells were present in bone, ribs, spine and other various organs up to 12 weeks after birth, confirming the presence of donor cells in organs from all three embryonic germ layers up more prevalently in the first week of birth compared to 12 weeks after birth. However, the donor retention was higher in the skeleton compared to other extra-skeletal organs, such as lungs, heart, liver, spleen, kidney and skin. In terms of location, donor cells were observed in areas of active bone formation, remodeling and healed fracture sites and human osteopontin was present within the bone matrix, below the growth plate and in the primary spongiosa, signaling that donor cells contribute to bone formation in intact bones.

Due to human-specific markers, the researchers determined that donor cells remained as progenitor cells in the bone marrow but expressed an osteoblast phenotype, as they were present in large quantities in the bone but not the bone marrow. Also,

hydroxyproline, a non-essential collagen amino acid that is responsible for collagen synthesis and triple-helical conformation stability levels were decreased in oim mice expressing the COL1A1 mutant allele, as it contains a higher level of hydroxyproline, suggesting that producing COL1A2 chains can alter the imbalance and reduce collagen type I oim homotrimers [29,30].

Advantages of FMSCs were found through this research in comparison to adult MSCs. Similarly, the donor cells present in the MSC transplantation in bone were 5%, suggesting a low engraftment of donor cells can improve the OI phenotype. An advantage found was that within the fetal environment, FMSCs have the capacity to be less committed to a lineage, less immunogenic and grow at a faster rate in comparison to adult MSCs. Also, they may be able to express an adhesion molecule profile that can engraft long term after pregnancy, as well as default as an osteogenic progenitor *in-vivo* and *in-vitro*. Lastly, the clinical effects associated with intrauterine transplantation of MSCs were like evidence of postnatal bisphosphonate therapy. As they saw earlier, treatment led to a reduced fracture frequency and decrease in growth plate height [29].

Ultimately, the researchers determined that FMSC transplantation in utero has the capacity to provide additional benefits such as decreased growth plate height and increased limb length. They determined that using hfMSCs were safe and feasible to transplant into prenatal patients with OI, making it a possible treatment option for pregnancies affected by OI [29].

2013 Clinical Trial: Fetal MSC transplantation during pre- and postnatal periods in pediatric OI patients

A clinical trial in 2014 focused on hfMSCs transplantation during pre- and postnatal periods of two patients affected by OI, specifically type III and IV. These researchers reported earlier on prenatal hfMSCs transplants; however, they noticed clinical benefits began to plateau at certain postnatal periods for each patient, resulting in a postnatal transplantation of same donor hfMSCs to elongate benefits. The MSCs were collected and isolated from two male fetal livers, at 10 weeks' gestation for patient A and at 7 weeks and 3 for patient B. They performed ELISA to detect antibodies against FBS and conducted genotyping, determining patient A and B had a COL1A2 mutation. They conducted immune response assays and FISH on specimens collected before and after postnatal transplantation [31].

Patient A experienced osteogenic differentiation of donor cells, post prenatal transplantation, at 9 months of age, had linear growth for weight and height and documented three fractures but no complications or pain during the first two years of life. However, between two years to 8 years and two months of age, the patient experienced increased fractures in the long bones, skull, vertebrae and clavicle, as well as the development of scoliosis. Patient A underwent a rod replacement procedure at the age of 6 years and 1 month and after bone, bone marrow, muscle and skin biopsies were examined. There were no signs of MSC donor cells detected by XY FISH or SRY by PCR. From these histological and clinical observations, patient A underwent a postnatal transplantation of hfMSCs from the same prenatal transplantation donor. During the two years after this transplantation, the patient did not document any new fractures and was able to walk without difficulty. After analysis of bone 9 months after the postnatal transplantation and at age 8 years and 11 months, low levels of donor cell engraftment, specifically 0.003%, were observed by Y-chromosomal FISH [31].

Patient B underwent an allogenic prenatal transplantation at 31 weeks of gestation, after the identification of fractures and healing bones at 26 weeks of gestation. During the next 7 weeks of gestation until the child was delivered, no new fractures were documented. However, after quantitative PCR of the umbilical cord and its blood, as well as the placenta, there were no observations of Y-chromosome signals from MSC donor cells. The patient also showed poor mineralization in the lumbar spine, but many healed fractures, at birth, prompting the child to begin bisphosphonate therapy at one month of age. Over the next 12 months, the child did not grow according to her centile lines, which led to the performance of a postnatal intravenous infusion of hfMSCs at age 19 months and 11 days. Clinical observations showed improved growth velocity and the ability to walk shortly after the transplantation [31].

In the clinical trial, patient C was documented; a boy born at 38 weeks of gestation with extreme and harsh clinical signs of OI, prompting the patient to begin calcium/D3 and zoledronic acid treatment at 6 days of age. The patient was diagnosed with severe OI, specifically type II or III, with a dominant COL1A2 mutation. Patient C received a second dose of zoledronate (0.025 mg/kg) at 12 weeks of age and underwent an examination of bone mineral density of the lumbar spine by DXA, showing improved bone density. Unfortunately, the patient succumbed through respiratory failure secondary to pneumonia a week later after hospital readmittance at 19 weeks of age [31].

The primary goal of this clinical trial was to determine the efficacy of postnatal hfMSC transplantations, after a previous prenatal hfMSC transplantation and its effects on elongating clinical benefits. The researchers focused on long-term follow ups, specifically 3-10 years after prenatal transplantation and 2-2.5 years after postnatal transplantation, as short term follow ups had been previously reported about OI. They focused on patient response to infused donor cells, observing no evidence of immune responses or acute or chronic toxicity, suggesting allogeneic hfMSCs are safe for use in prenatal settings. An important measurement observed during the trial was the engraftment rate of donor cells in the bone. Regarding patient A, they documented a donor cell engraftment rate in bone as 7.4% after prenatal transplantation, but 0.003% after postnatal transplantation. They suggested different possible reasons for this observation, such as fetal circulation and specific cellular adhesion molecules on hfMSCs. In terms of fetal circulation, a prenatal infusion of hfMSCs bypasses the pulmonary vasculature into the patent foramen-ovale, which enhances the engraftment downstream of the arterial tree, unlike during postnatal periods, the infusion of hfMSCs is trapped and is redistributed to the body. Also, they suggested that there are more homing capabilities of hfMSCs during prenatal periods compared to postnatal periods, as the specific cellular adhesion molecules on the hfMSCs may regulate more of the homing process to fetal bones. Ultimately, they determined that prenatal transplantation followed by postnatal transplantations was safe and effective for OI pediatric patients. For future research, it is important to refine the appropriate stem cell type selection and its preparation to sustain therapeutic benefits, most likely requiring a multi-transplantation strategy to optimize skeletal growth and development during fetal and childhood years [31].

2024 Clinical Trial: BOOSTB4 open-label multicenter phase I/II trial on prenatal and postnatal administration of allogeneic expanded fMSCs in severe OI patients

The BOOSTB4 trial is an open-label, exploratory, multicenter, phase I/II trial to assess the efficacy and safety of administering repetitive postnatal or prenatal and postnatal intravenous MSCs in pediatric patients with severe OI, becoming the first trial to assess this concept.

Originally, 30 patients, 15 infants and 15 fetuses were assessed in the trial. However, after an amended procedure change, only 15 infants and 3 fetuses were assessed. 15 patients obtained four postnatal intravenous infusions of human first trimester liver-derived MSCs, while the three fetus patients received one prenatal and three postnatal infusions. The prenatal infusion was performed through the umbilical vein within the fetal liver using ultrasound guided techniques and was delivered between week 16 and week 35 and 6 days of gestation. The first postnatal infusion was delivered before the patient turned 18 months old. All intravenous infusions were set at a dosage of 3×10^6 cells/kg and each infusion was given in four-month intervals with 48 hours, for infusions 1 and 2 or 24 hours, for infusions 3 and 4, in patient follow-up. Each patient had a primary follow-up 6 or 12 months after the last infusion and had a long term follow up annually until 10 years post first infusion. All subjects received bisphosphonate treatment with at least one dose administered prior to first MSC infusion in the postnatal group, while the prenatal group obtained their first dose of bisphosphonates after birth [32].

The primary outcome of the BOOSTB4 trial is to determine the safety and tolerability of repeated BOOSTB4 cell infusions. To measure this outcome, the researchers focus on vital signs, immune reactions and material and fetal adverse events. Before, during and until 48 hours (infusions 1 and 2) or 24 hours (infusions 3-4) after each infusion dose, the vital signs of both the pregnant woman and child are documented and monitored, using ultrasound to monitor the fetus. Also, blood status, liver and kidney enzymes and electrolytes are analyzed and monitored through peripheral blood before and at the first hour after each dose, while monitoring 24 hours after each dose and 48 hours after the first and second dose infusion. Peripheral blood monitoring did not apply to the fetus [32].

The secondary outcome of the BOOSTB4 trials is to determine efficacy of repeated MSC infusions in children with OI. They mainly explored the improvement of fractures over time in association with increased infusions, while also looking at the time when the first fracture was documented after each infusion and determining the number of fractures in the prenatal group.

They also measured height, length and weight growth and change in body bone mineral density using a DXA, as well as exploring biochemical bone turnover in peripheral blood samples. The documented and analyzed biochemical bone turnover before each dose infusion, as well as every 6 to 12 months. Other exploratory outcomes a part of this research trial was the impact that the cell-based therapy had on the patient's quality of life, quantitatively measuring it with the ITQOL Questionnaire, as well as studying the paracrine effects and endogenous immune cells through the peripheral blood samples with ELISA and flow

cytometry. Currently the trial is still on going, as the long-term follow-up will be completed in 2032, but the primary follow-up was performed in January of 2024 [32].

Summary

In both adult and fetal MSC clinical trials, there were many similarities in clinical observations. All the clinical trials focused on the skeletal defects of OI in terms of fracture documentation, body bone mineral content and linear growth. After an allogeneic MSC transplantation or a BMT or AAV vector exposure, each patient showed an improvement in fracture rate and increased bone mineralization. Almost all the clinical trials used bisphosphonates as a secondary treatment to the MSC skeletal treatments, suggesting combination therapy as a method to assist with symptoms and characteristics of OI. Overall, research from all the clinical trials determined that the transplantation or infusion of MSCs, whether adult or fetal, was safe and feasible for the treatment of pediatric patients with OI. They determine this through clinical observation, genetic testing and patient follow-up after transplantations. There are still clinical trials that are occurring, such as the BOOSTB4 clinical trial and there is a lot of research that still needs to be done. Many of the patient follow-ups that occur after these clinical trials are short-term, so it is still unknown of the long-term benefits that these different treatment options have on pediatric OI patients. However, through clinical trials, it has been suggested that repeated MSC infusions or transplantations are necessary to elongate clinical benefits, as they tend to plateau at a certain period after previous transplantation.

Ethics in Embryonic Stem Cell Biology

In the realm of stem cell biology, there are ethical concerns and limitations that are important considerations in clinical trials and treatments. The use of hESCs is an example of how ethics and morality are associated with the development of clinical therapies, as the termination of a human embryo is required. There is legislation specific for countries around the globe in regulating hESC research with countries such as Italy, who completely banned hESC research. But, for example, the United Kingdom allows research on hESCs, however prohibits NT for artificial reproductive or therapeutic purposes. In the United States, hESC line productions involving the termination of an embryo are illegal, limiting the scope of possible hESC research in the country [33].

Conclusion

Ultimately, MSCs are a frontrunner for possible treatment for pediatric patients with OI. Many clinical trials that focus on MSC therapy with OI focus on the skeletal defects, physically and genetically, as many OI types are results of mutations in type I collagen genes. OI expressed many clinical manifestations that affect the skeletal system and non-skeletal systems. Clinical trials have focused on different mechanisms to treat severe OI pediatric patients, such as BM-MSC transplants, allogeneic BM-MSC engraftments, AAV vectors for COL1A1 disruption and human first-trimester fetal blood or fetal liver MSCs. Although each clinical trial was different, all of the clinical trials found that, whether it is adult or fetal MSCs, MSC therapy is safe, feasible and effective for patients with OI during prenatal and postnatal periods. Since the skeletal manifestations were heavily acknowledged in all the trials, for future research it may be a possibility to look towards a better understanding of how to treat adult OI patients and the extra-skeletal manifestations associated with OI. Future research for MSC therapy and OI needs to include longer follow-up periods to understand the long-term effect of MSC therapy and how to elongate the clinical benefits associated with this treatment.

Conflict of Interest

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Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not applicable.

Authors' Contributions

All authors contributed equally to this paper.

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