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Efficacy of Stem Cell Therapy in Non-Malignant Untreatable Pediatric Diseases: An Update

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Abstract

Purpose: Within the last 25 years, stem cell therapy has shown that it can help patients with some incurable afflictions of the human body and, in some, alleviate the sufferings. The purpose of this review is to provide recent facts on numerous pediatric diseases that have no apparent cure and have been dealt with the usage of stem cells and their outcome. **Methods:** We searched electronic databases between January 2014 and July 2024, PubMed, Scopus, Web of Science, Cochrane Central Ovid Medline, Ovid Embase, EBSCO Cumulative Index to Allied Health Literature, Web of Science, and Cochrane Central with keywords of pediatric diseases, stem cell therapy, mesenchymal stem cells and autoimmune diseases. **Results:** Studies gathered were carefully looked for. Isolation of Mesenchymal Stem Cells (MSCs) and their inherent ability to self-renew and differentiate into terminal cells like osteoblasts, chondrocytes, neurocytes, and cardiomyocytes made an essential panacea in treating many diseases. The features of MSCs are attributed to the secretion of paracrine factors, extracellular vesicles, and cytokines, the switch of mitochondria to nearby cells via hetero cellular coupling, and an effective suppressant of the inflammation process, immune reactions via direct cellular contact. The published medical trials for pediatric pulmonary, cardiac, orthopedic, endocrine, neurologic, and hematologic diseases provide proof that MSCs are indeed efficacious, but there exists a variant in examination results among studies due to quantity and quality, quantity of cells, route of administration and isolation of MSCs exist inside the treatment protocols. **Conclusions:** There is compelling proof of the efficacy and safety of autologous stem cells for the treatment of diseases in orthopedic, neurological, and autoimmune diseases. This can inspire clinicians and researchers to research appropriately at different centers with similar protocols, so that stem cell therapy turns into a part of the standard of care sooner instead of later.

Keywords

Pediatric, Stem Cell Therapy, Autoimmune Diseases, Incurable

1. Introduction

A significant amount of research is going in the world, which grew 22% between 2017 and 2022. Many diseases were brought under the umbrella of treatable diseases and it is expected that many diseases will soon come under control. Numerous risk factors causing serious diseases were identified. Scientific research over the last four decades has led to remarkable achievements in pediatric medicine. Over the last four decades, there have been dramatic decreases in global mortality and improvements in quality of life. The speed and depth of research progress have been prodigious with adequate funding in basic research and discoveries that have led to effective treatments. Unfortunately, it appears that the overall growth of research has fallen to less than 1% in the last few years [1] and this has affected research of pediatric diseases. This funding has remained low and flat [2]. It has been accepted that research has shown that children's health is the foundation for adult health, hence there should be increased funding in the newer methods of research and treatment and one such aspect is Stem Cell therapy.

There are two main types of stem cells: embryonic stem cells and adult stem cells. Stem cells are usually categorized as multipotent (able to give rise to multiple cells within a lineage), pluripotent (able to give rise to all cell types in an adult) and totipotent (able to give rise to all embryonic and adult lineages). ESCs are derived from the inner cell mass of the blastocyst, which is a stage between the 4th to 7th day after fertilization and has about 150 cells [3] [4]. They will multiply and differentiate extensively to make the many types of cells needed to form the entire animal. Some of the cells in the inner cell mass are pluripotent: they can make every type of cell in the body [5] [6]. Embryonic stem cells are pluripotent, meaning they are able to differentiate to generate primitive ectoderm, endoderm, and mesoderm.

Adult stem cells, also called somatic stem cells, are undifferentiated cells that are found in many different tissues bone marrow, adipose tissue, umbilical cord blood, placenta and amniotic fluid, menstrual blood, nervous system and other tissues and are usually restricted to become any type of cell in the tissue or organ that they reside (called multipotent) [7]. When these cells are properly stimulated and required by the body, they contribute to creation of all mature cells in the human body [8]. Stem cells are undifferentiated cells that are self-renewable and multipotent and are capable to give rise to other types of cells by lineage of differentiated cells, which are then transferred to the needy tissues or organs. The function of these cells is to enable the healing, growth, and replacement of cells that are lost every day. Among the different types of adult stem cells (Hematopoietic Stem Cells, Mesenchymal Stem Cells (MSCs), Neural Stem Cells, Epithelial Stem Cells and

Skin Stem Cells), mesenchymal stem cells are the most studied and used cells in the clinical trials to treat diseases [9]. A MSC is the cell that adheres to plastic in normal culture procedures and has the ability to undergo terminal cells, like adipocytes, chondrocytes, osteoblasts and neurocytes differentiation. The cultured MSCs also express on their surface CD73, CD90 and CD105, and lack the expression of other surface markers like CD11b, CD14, CD19, CD34, CD45 and CD79a surface markers [10].

Embryonic or somatic stem cells are now routinely grown in the laboratory by controlled procedures by addition of growth factors and maintained in an environment that supports the property of self-renewable. Apart from the Embryonic or somatic stem cells, induced pluripotent stem cells or iPSCs were created by introduction of four genes (which are named Myc, Oct3/4, Sox2 and Klf4), encoding transcription factors, that could convert somatic cells into pluripotent stem cells. These iPSCs can differentiate into any type of cell in the body and proliferate indefinitely in culture.

Stem cells are being used in many clinical trials in the field of medicine for the treatment of various diseases. By the year 2022, 416 clinical trials were published, which evaluated the efficacy of MSCs and MSC-derived Extracellular Vesicles (EVs)/exosomes in many diseases [11].

Recent advancements in stem cell technology open a new door for patients suffering from diseases and disorders that have yet to be treated. Stem cell-based therapy, including human Pluripotent Stem Cells (hPSCs) and multipotent mesenchymal stem cells (MSCs), has recently emerged as a key player in regenerative medicine [12]-[14].

In this review, we present the role of MSCs, bone marrow Mononuclear Cells (MNCs), Neural Stem Cells (NSCs), in the treatment of the different pediatric diseases of which generally has no cure nor the regular treatments which could give better outcomes and improve the quality of life of patients without causing any harm for long term use.

2. Osteo-Articular Diseases

Many pediatric osteoarticular disorders if are not treated early can have long-term ramifications that affect the quality of life of patients when they reach adulthood. It has been shown that MSCs has the ability to cure diseases which are labelled as incurable and if not cured completely the treatment alleviates the symptoms and bring about the comfort in the life. Contrary to this method, many clinicians are giving supportive therapy and wait and watch viewpoint. Studies in pediatric population with osteoarticular afflictions have been reported [15]-[18].

2.1. Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a rare genetic disorder involving mutation in the *COL1A1* and *COL1A2* genes on chromosomes 17 and 7. The reported prevalence of OI is around 16.3 per one million population [19] and the mutation causes the

abnormal production of type I collagen [20]. Signs and symptoms range from mild to severe and there are at least 8 different types of the disease.

Multiple fractures can be visualized in utero to fractures occurring during childbirth. Death occurs due to compression injury of skull and ribs with intracranial bleeds and collapse of the lungs.

A multidisciplinary approach is essential in taking care of these children. At present there is no cure for OI and present treatments do not take into consideration the to address the pathology. The available treatment of OI attempts to reduce the risk of fractures and to prevent deformities in which prevention of domestic trauma plays an elemental role. Pamidronate, a bisphosphonate, is known to correct the imbalance between bone formation and resorption and reduces the risks of fractures [21]. As early as in the year 2002, Horwitz *et al.* [17] treated OI patients with bone marrow transplant and MSCs infusions and reported satisfactory results. Infante *et al.* (2021) [22] treated two patients with MSCs which were isolated from bone marrow aspirates obtained from healthy siblings five times during 2 years 6 months period. These children had 15 fractures in one patient and 11 in second child from birth and through childhood. Post treatment patients had three and two fractures only. A second trial which will soon publish their results is the open label, multiple doses, multicenter phase I/II BOOSTB4 trial which is using allogeneic fetal MSCs as a treatment of severe OI type III/IV compared to matched controls. Patients received 4 doses of MSCs at 4-month intervals. The treatment groups are compared to matched controls: Fifteen postnatal babies and 3 fetuses prenatally from 7 different European countries. Four infants have received all 4 doses of MSCs. In total, 32 postnatal doses and 3 prenatal doses have been administered. No significant short-term adverse reactions have been identified in the infant, pregnant woman or fetus. To date, 17 participants have received 1 - 4 doses of same-donor MSCs in the BOOSTB4 trial with no short-term complications recorded.

Each subject receives four intravenous doses of 3×10^6/kg BOOST cells at 4-month intervals, with 48 (doses 1 - 2) or 24 (doses 3 - 4) hours in-patient follow-up, primary follow-up at 6 and 12 months after the last dose and long-term follow-up yearly until 10 years after the first dose. Prenatal subjects receive the first dose via ultrasound-guided injection into the umbilical vein within the fetal liver (16 + 0 to 35 + 6 weeks), and three doses postnatally. The primary follow-up is currently being performed and is expected to be completed in January 2024, and the long-term follow-up will be completed in 2032 [23].

2.2. Osteonecrosis of the Femoral Head

Osteonecrosis of Femoral Head (ONFH) is a condition in which there is lack of supply to the developing head of femur leading to death of the subchondral bone which makes the head to collapse. The common causes are Sickle Cell Disease (SCD), Legg-Calve-Perthes Disease (LCPD), secondary to trauma, and corticosteroid therapy [24]. ONFH can also occur after post fracture neck of femur or

dislocation of hip. The main cause of ONFH is the vascular interruption which could be partial and complete. In all these conditions, early diagnosis and treatment is mandatory to early diagnosis and treatment is essential for preventing the femoral head collapse and preserving the hip joint.

Legg-Calve-Perthes Disease (LCPD) is an idiopathic osteonecrosis of the femoral hip in children. In this disease vascular supply is affected, bone gets infarcted and ends in necrosis and collapse of the head of femur follow. LCPD is a necrosis of the femoral head which affects the range of motion of the hips. The incidence of LCPD varies between 0.4/100,000 to 29.0/100,000 children between 3 - 12 years of age [25]. The current understanding of pathophysiology of LCPD is based on the biopsies of the animal studies in baby pigs in whom surgical ischemic necrosis was induced. Piglets developed LCPD changes which are similar to humans (**Figure 1**).

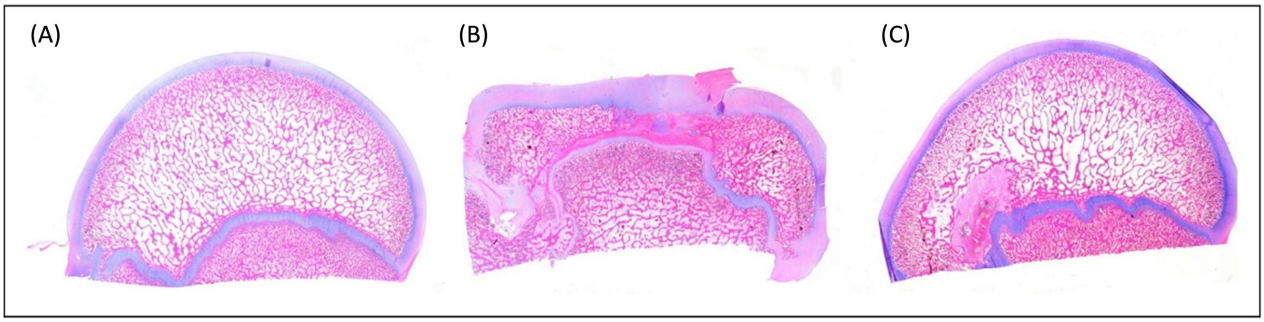


Figure 1. Photomicrograph of normal Femoral Head (FH) of immature piglet (A). (B) Photomicrograph of the saline-treated group FH of immature piglet at 4 months after induction of ischaemia. (C) Photomicrograph of the MSC-treated group FH of immature piglet at 4 months after induction of ischaemia. All images are macro-microphotographs (1×) with HE staining. FH: femoral head; HE: haematoxylin-eosin; MSC: mesenchymal stem cell. Figure modified and republished Courtesy of Courtesy of Sage publishing company; Martínez-Álvarez S, Galán-Olleros M, Azorín-Cuadrillero D, Palazón-Quevedo Á, González-Murillo Á, Melen-Frajlich GJ, Ramírez-Orellana M, Epeldegui-Torre T, Forriol F. Intraosseous injection of mesenchymal stem cells for the treatment of osteonecrosis of the immature femoral head and prevention of head deformity: A study in a pig model. Sci Prog. 2023 Apr-Jun; 106(2): 368504231179790.

There is no immediate cure for LCPD but to wait and observe the revascularization process of the head of femur. During this period weight-bearing and physical activity is restricted and keeping the head of the femur in the joint (containment). The affection of the head of femur and progression to osteonecrosis and collapse of the head is not clearly understood but the initial size of the lesion and stage at when the patients present of have been shown to predict clinical outcomes [26].

Surgical treatment of LCPD has been attempted by core decompression of the vascular lesion. Animal studies confirmed that this could be carried out with good results. Studies in animals showed that when immature femoral heads were treated with mesenchymal stem cells versus normal saline showed that there was severe femoral head deformity in 11 of the 14 animals (78%) in the saline group and in only 2 of the 13 animals (15%) treated with mesenchymal stem cells [27].

Tomaru *et al.* (2023) [28] showed in piglets that Core decompression combined with bone marrow-derived mesenchymal stem cell transplantation prevented col-

lapse of the avascular epiphysis.

Surgical treatment of LCPD can be achieved by decompression of the femoral head drilling the necrosed area using small cannulated drills. This will serve a two point purpose one by reducing intramedullary pressure and thereby prevents further vascular impingement and allows for new bone formation [29] and secondly to inject MSCs. Drilling and injection of the MSCs is widely accepted and the results are favorable in the early stages of osteonecrosis [30]-[33]. A major concern in children after core decompression is the premature halt in growth of the proximal femur due to growth plate damage. But animal studies did not show any complications of the epiphysis with three small-drill core decompressions [34], and the healing was not upto the satisfactory level and hence it was advocated that osteoprogenitor cells are required for acceptable healing even in young patients [35]. This review did not find any data on decompression and MSCs injections in children but there is robust evidence from animal trials the benefits are abundant with no or minimal complications should encourage pediatricians to conduct clinical trials on LCPD with small drill decompressions and injection of MSCs.

2.3. Osteonecrosis Due to Sickle Cell Disease and Other Causes

Sickle Cell Disease (SCD) is the most common inherited blood disorder in the Middle east countries, the Indian subcontinent and the African continent. Osteonecrosis is one of the most serious complications and early presentation is seen in children. The incidence ranges between 20% - 30% [36]-[38]. The incidence of ONFH in SCD patients of 5 years of age and less was 3.9 cases per 100 patient-years and 2.1 cases per 100 patient-years in the 5 to 14 age group [39]. There is no known treatment for this group of patients (**Figure 2**).

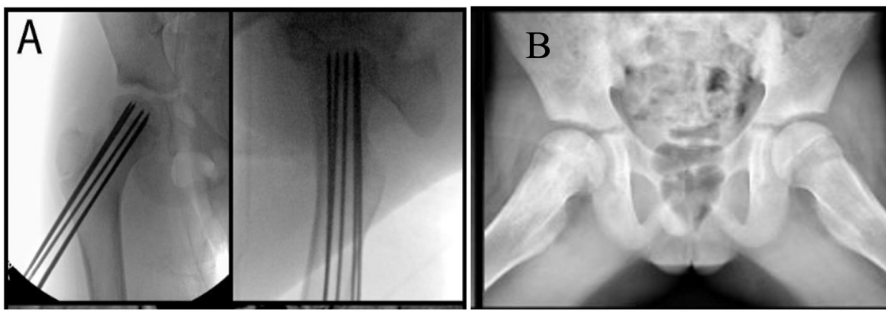


Figure modified and republished Courtesy of Elsevier Publishing company; Kim HKW, Morris WZ. Pediatric Femoral Head Osteonecrosis Secondary to Trauma, Sickle Cell Disease, and Corticosteroid Therapy. Journal of the Pediatric Orthopaedic Society of North America 2021; 2(2): 285.

Figure 2. (A) AP and lateral fluoroscopic views of right proximal femur of an 11-year-old male with SCD treated with multiple epiphyseal drilling using 2.4 mm drillable intaosseous needle and Stem Cell therapy. (B) X-ray at 18 months follow up.

2.4. Osteonecrosis Secondary to Trauma

Posttraumatic ONFH is a serious complication that can that can occur post fracture

neck of femur or post dislocation of hip in pediatric population. Both these injuries are rare, but ONFH can occur between 15% - 70% [39]-[45].

2.5. Treatment

At present, stem cell-based therapy continues to evolve with ongoing investigations for clinical trials, safety and efficacy. This type of treatment might be envisaged as a new therapeutic option specifically pediatric pathologies when there are no conventional treatments. In such a scenario with no current successful treatment, any promising therapy could be considered as a valid mode of management.

3. Neurological Diseases

3.1. Cerebral Palsy

Cerebral Palsy (CP) is a group of conditions that affect the development of motor skills in children movement, posture and balance. It's caused by damage that occurs to the developing brain, most often before birth. CP is a lifelong condition associated with intellectual disabilities, affection of speech, vision, and hearing other difficulties. The reported prevalence of CP 3 per 1000 life birth [46].

For over a century, it was wrongly believed that CP was wholly due to factors related during birth, lack of oxygen during the birth process. Now, scientists believe that with genetics studies and better understanding implicate that 10% of the CP are genetically influenced [47] [48]. The abnormal development of the brain or damage that leads to CP can occur before birth, during birth and during early life of the babies when the brain is still developing. CP related to abnormal development of the brain or damage that occurred before or during birth is called congenital CP. CP can be acquired in the neonatal period due to infection meningitis and intracranial bleeding and in many cases, the real cause remains unknown.

The symptoms of CP vary from person to person and based on the severity patients with CP require lifelong care even for walking and might need to use special braces to be able to walk or might not be able to walk at all and might need lifelong care for intellectual disability, seizures, deficiencies with vision, hearing, or speech, musculoskeletal deformity like scoliosis and joint contractures.

Treatment: There are four main types of CP: Spastic cerebral palsy, Dyskinetic cerebral palsy, Ataxic cerebral palsy and Mixed cerebral palsy. Management is always based on type of CP we are dealing with. Standard treatment is only supportive and sometime surgical but the outcomes of treatment were never satisfactory, hence clinicians and scientists were on the lookout for new innovative way to treat these children. Initial breakthrough came from the case report of Purandare *et al.* (2012) [49] in their patient they used autologous bone-marrow-derived mononuclear cells five intra-thecal infusions and observed notable motor, sensory, cognitive, and speech improvement and there were no adverse effects of the stem cell therapy. Luan *et al.* (2012) [50] used Neural Progenitor Cells (NPCs) in a randomized control study of 90 patients with CP and injected cells into the lateral ventricle.

After 12 months post injection GMFM, the Peabody Developmental Motor Scale-Fine Motor (PDMS-FM) test, developmental level in each functional sphere (gross motor, fine motor, and cognition) of the treatment group was remarkably higher compared to the control group. No complications were observed. Similar were the results of Chen *et al.* (2103) [51]. Cox *et al.* (2022) [52] reported after a randomized bone marrow derived stem cells and placebo control study with 12 month follow up found that stem cell therapy was safe and some patients had improvements in myelination which correlates with modest improvements in Gross Motors Function Measure scales and 66% of patients showed enhancement in the corticio-striatal and thalamo-cortical pathways (**Figure 3**).

Pretherapy PET scan (Top Figure)f indings: Third ventricle more dilated. Impaired motor, language social, and memory functions indicated by presence of more blue-purple area in the frontal lobe.
Bottom Figure: Posttherapy PET scan findings: A decrease in the third ventricle dilation and increase in the yellow-orange area in the frontal lobe indicating improvement of motor, language social, and memory functions indicated by presence of more blue-purple area in the frontal lobe.

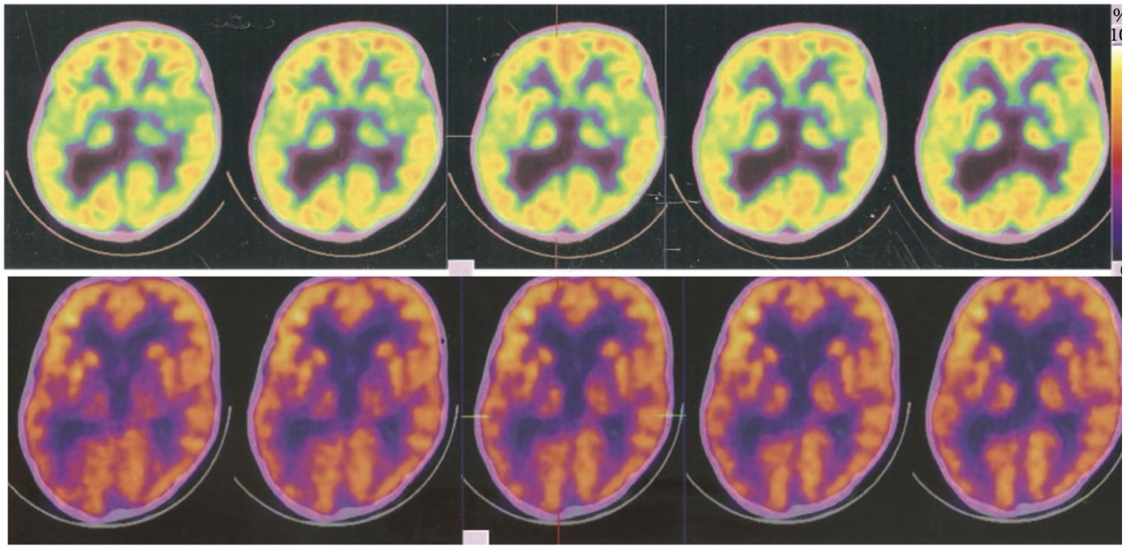


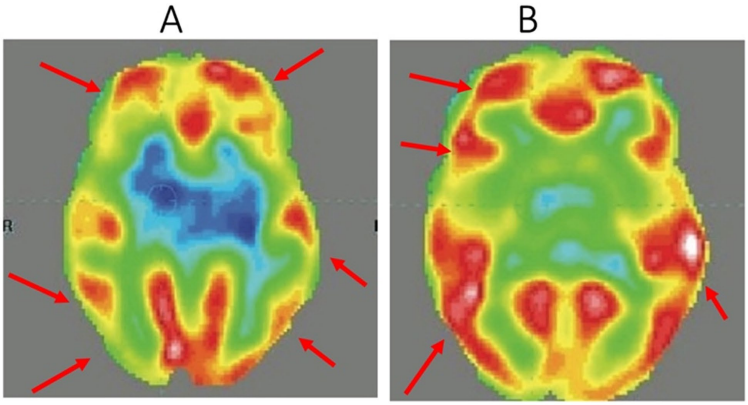
Figure 3. The changes on PET scan before and after the cell-based therapy. Figure modified and republished Courtesy of Wiley publishing company; Purandare C, Shitole DG, Belle V, Kedari A, Bora N, Joshi M. Therapeutic potential of autologous stem cell transplantation for cerebral palsy. Case Rep Transplant. 2012; 2012:825289. https://doi.org/10.1155/2012/825289. Epub 2012 Oct 4. PMID: 23259143; PMCID: PMC3505957.

3.2. Autism: There Is No Epidemic of Autism. It's An Epidemic of Need

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders characterized by communication inabilities, stereotypic behaviors and being part of social integration [53]. The U.S. Centers for Disease Control and Prevention (CDC) believes the incidence of ASD in the range of 1% - 2% of all children, according to the U.S. Centers for Disease Control and Prevention [54]. Recently, CDC stated that in 2006, 1 in 110 children were reported autistic, which increased to *1 in 36 children* has autism in 2021. Despite the incidence is on the rise researchers are still unable to pinpoint the etiology as ASD patients present with different symptom characteristics [55] and this makes the definite treatment difficult thus there is no definitive treatment for ASD patients [56]. There is convinc-

ing proof of efficacy and safety of stem cell therapy in patients with ASD [57] [58]. Sharma *et al.* (2013) [59] completed a proof of concept study using Autologous Bone Marrow Mononuclear Cells in 32 patients and showed improvement in 91% of patients and the difference between pre- and postscores was statistically significant ($P < 0.001$). Recently, Nguyen Thanh *et al.* (2020) [60] reported a two-year study which was an open-label clinical trial in which thirty children who fulfilled the autism criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and had Childhood Autism Rating Scale (CARS) scores > 37 were Mononuclear cells of two doses of 1 million per Kg body weight. The same procedure was repeated 6 months later. After 2 months of the first intra-thecal injection. The symptoms of ASD were significantly reduced, from 50 (range 40 - 55.5) to 46.5 (range 33.5 - 53.5) ($P < 0.05$). Adaptive capacity increased, from 53.5 to 60.5. Social communication, language, and daily skills improved markedly within 18 months after transplantation. The repetitive behaviors and hyperactivity were remarkably decreased. They concluded that Autologous bone marrow mononuclear cell transplantation in combination with behavioral intervention was safe and well tolerated in children with ASD.

The objective assessment of efficacy of stem cell therapy in autism patients was based on Positron Emission Tomography (PET). PET-CT scans are most broadly used for neuroimaging PET-CT scan to record the functional activity of the brain. It measures 18 Fluorodeoxyglucose (FDG) uptake which is related to the glucose metabolism at the cellular level which correlates with the activity of the area of the brain under study. It was reported that there was notable hypoperfusion of frontal lobes, superior temporal gyrus and superior temporal sulcus in children with autism compared to the control children (**Figure 4**).



PET-CT scan before (A) intervention showing reduced FDG uptake in the areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe. (B) PET-CT scan six months after intervention comparison shows increased FDG uptake in the areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe.

Figure modified and republished Courtesy of Wiley publishing company; Authors: Sharma A, Gokulchandran N, Sane H, Nagrajan A, Paranjape A, Kulkarni P, Shetty A, Mishra P, Kali M, Biju H, Badhe P. Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study. Stem Cells Int. 2013; 2013: 623875.

Figure 4. PET scan pre- and post-stem cell therapy.

These findings are consistent with the theory of social brain. We used PET-CT scan to observe the metabolic activity of the brain before and after cellular therapy. The scan was done in a standardized manner, maintaining similar conditions before scanning to ameliorate confounding factors and therefore the changes in the 18-FDG uptake may be attributed to the intervention.

3.3. Traumatic Brain Injury

Traumatic Brain Injury (TBI) in pediatric age group is a serious injury which can lead to disabilities throughout their life time. The mortality after TBI is also quite high [61] [62].

In 2014, US statistics show 2.87 million cases of TBI out of which 837,000 of those cases in children [63] and 13.5 million people struggle with disability from TBI [64].

The standard of care of TBI in children is to drain and blood collected around the brain, debridement of dead tissue and control the hemostatsis. Secondary to these immediate interventions, it is mandatory to keep intracranial pressure low and prevent and neuroinflammation [65]. Pharmacological-based therapies have failed to achieve satisfactory and functional results in patients with TBI [66] and hence it was reasonable for clinicians to look for alternate mode of treatment.

The recovery from TBI is minimal depending on the extent of the injury due to irreversible loss of neurons, and then body's ability for self-regeneration remains limited which results in permanent neurological deficits. The study of Neumane *et al.* (2021) [67] reported that after TBI with adequate treatment, severe functional impairment was present during the initial 3 months. With some recovery in the succeeding years but 80 percent of the children remained moderate to severe disabled at 24 months. This report suggests that with the available management of TBI at present, it is not sufficient to reverse the neural insult and more therapies are needed.

The presence of stem cells in the brain tissue of children has been demonstrated which are called as Neural Stem Cells (NSCs) and Neural Progenitor Cells (NPCs) in the Subventricular area (SVA). These cells are multipotent which has the ability to generate neurons; initially into gliogenic cells and later into astrocytes and oligodendrocytes [68] [69]. These cells get depleted as early as 2 years of age and not detectable, hence any recovery of the brain injury due to these cells is limited [70]. This suggests that after TBI, the body's ability to repair itself by neural stem cells is limited and stem cells from other sources are required. Mesenchymal Stem Cells (MSCs) have the ability to migrate to the site of injury, and initiate the regenerative process [71].

MSCs has shown great potential limiting and repairing TBI and results of clinical studies bear the proof of this belief. Even in the acute phase of TBI MSCs when injected intrathecally or intravenously cross the blood-brain barrier and travel to the site of injury, neurotrophic factors and nerve growth factor, recruit local progenitor cells and modulate appropriate anti-inflammatory response to reduce cell death and favor repair [72] [73]. MSCs has the ability to differentiate into different cell lineages, neurons and glial cells, endothelial-derived cells and Schwann cells

and autologous derived cells have no immunogenicity power and risk of rejection [74] [75].

In a study in children with TBI of <14 years with a Glasgow Coma Score of 5 - 8; treated with intravenous autologous bone marrow mononuclear cell therapy (dose of 6×10^6 stem cells per kilogram of body weight) within 2 days of injury. Children treated with concurrent stem cell therapy had a less intensive treatment regime for intracranial pressure management, with significant reduction beginning at 24 h post-treatment to within the first week of treatment. Reduced organ injury severity and decreased duration of neurointensive care were also reported. These findings demonstrated that MSCs were able to reduce the inflammation effect in acute TBI and initial acute treatment intensity and duration and secondarily it was found a favorable neuropsychological and functional outcomes at 6 months' follow-up. Tools used to evaluate functional outcome (Glasgow outcome scale, Glasgow outcome scale—expanded for children, pediatric injury functional outcome scale and adaptive behavior assessment system II) all showed significant improvement. A significantly improved neuropsychological outcome was measured with the Wechsler abbreviated scale of intelligence, coding, grooved peg-board, listening recall and verbal learning. Magnetic resonance imaging also revealed no progressive post-TBI brain tissue loss [76] [77].

The report of Tian *et al.* (2013) [78] in adult patients were very encouraging as out of 24/97 patients in continuing vegetative state post TBI of 1 month duration were treated with Intrathecal administration of autologous bone marrow stem cells. Significant improvement in brain function was found in 38 of 97 patients ($P = 0.007$), improved consciousness was found in 11 of 24 patients with persistent vegetative state ($P = 0.024$) and improved motor function was found in 27 of 73 patients with disturbances in motor activity ($P = 0.025$). Surprisingly, outstanding improvement was observed in patients who were younger. The results suggest that early treatment with MSCs will confer better results. Children's developing brain typically have a worse prognosis than adults who suffer similar injuries. The brains of babies and children are still developing, consequently children with TBI should be treated early with stem cell therapy for total or near total recovery. As of 2024, 13 clinical trials are registered and ongoing on stem cell therapy in TBI [79].

3.4. Pulmonary Diseases

Chronic Respiratory diseases are the leading cause of death in children under the age of 5 years old and is a leading cause of morbidity and mortality. Moreover, many adult chronic lung disease, which is the one of the leading causes of deaths globally, has its origins in childhood [80]. It is recognized now that it is paramount that the lung diseases should be treated early in life to prevent long term side effects [81] [82]. At present treatments for paediatric respiratory diseases like bronchopulmonary dysplasia, cystic fibrosis and interstitial lung disease can control partially the symptoms but there is no cure for these diseases on the horizon.

In recent years, stem cell therapy was tried in clinical trials and has given astounding results.

3.5. Bronchopulmonary Dysplasia

BPD is a chronic respiratory disease affecting mainly the preterm infants leading to immaturity of the lung in the last weeks of gestation [83]. It is estimated that in US 10,000 to 15,000 newborns develop BPD every year but the figures in Europe, indicate the BPD in preterm is around 30% in newborns below 30 weeks gestation [84]. Alshehri *et al.* (2020) [85] reported the incidence from Saudi Arabia to be 30.5% in preterm neonates, while in State of Qatar, it was reported to be 29.3% [86]. The current treatment for BPD is only supportive by way of corticosteroids and surfactants. This way of management in double edge sword as it enhances lung compliance but also leads to an arrested lung development. As the child grows the lungs become totally unable to support the increased respiratory demand and this leads to a become dependent on mechanical ventilation, which, in turn, leads to increased pulmonary damage.

The present treatment of BPD is only supportive and includes nutritional supplementation, fluid restriction, diuretics, and perhaps inhaled bronchodilators and, as a last resort, inhaled corticosteroids. Respiratory infections occur commonly which require early diagnosis and appropriate treatment. Even with recent advances in neonatal intensive care, still BPD remains a major cause of mortality and long-term respiratory morbidities. The mortality of BPD is 15.1/1000 children in outpatient setting [87] and has a prolonged and serious morbidity with suffer substantial life-long burdens of pulmonary and neurodevelopmental sequelae [88] [89].

The ineffectual treatment modality of BPD made clinicians to look for alternate and more effective treatment. Once such avenue was of cellular therapies using MSCs. Animal studies have shown functional improvement of the lungs [90]-[92] (**Figure 5** and **Figure 6**).

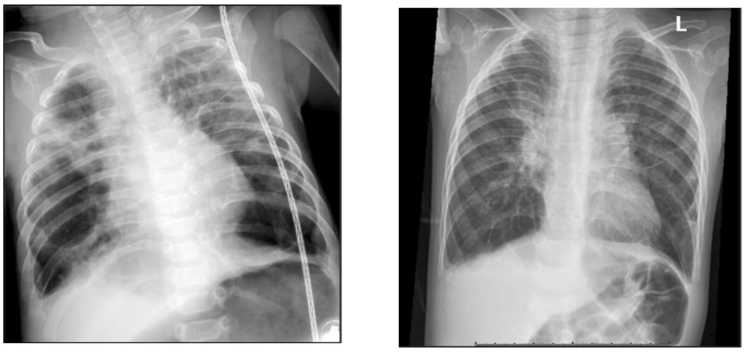


Figure modified and republished Courtesy of BioMed Central: Nguyen LT, Trieu TTH, Bui HTH, Hoang VT, Nguyen ATT, Trinh NTH, Nguyen KT, Hoang DM. Allogeneic administration of human umbilical cord-derived mesenchymal stem/stromal cells for bronchopulmonary dysplasia: preliminary outcomes in four Vietnamese infants. J Transl Med. 2020 Oct 20; 18(1): 398. https://doi.org/10.1186/s12967-020-02568-6. PMID: 33081796; PMCID: PMC7576694.

Figure 5. Radiograph of pre-term infant with broncho-pulmonary dysplasia pre- and post-treatment with mesenchymal stromal cell therapy.

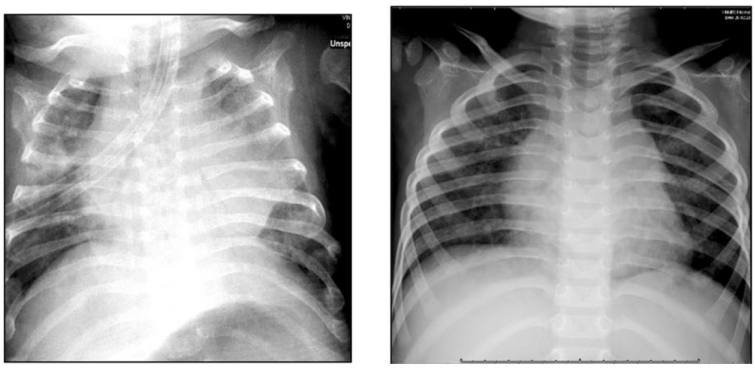


Figure modified and republished Courtesy of BioMed Central: Nguyen LT, Trieu TTH, Bui HTH, Hoang VT, Nguyen ATT, Trinh NTH, Nguyen KT, Hoang DM. Allogeneic administration of human umbilical cord-derived mesenchymal stem/stromal cells for bronchopulmonary dysplasia: preliminary outcomes in four Vietnamese infants. J Transl Med. 2020 Oct 20; 18(1): 398. https://doi.org/10.1186/s12967-020-02568-6. PMID: 33081796; PMCID: PMC7576694.

Figure 6. X-ray chest of a premature baby with Broncho-Pulmonay dysplasia treated with stem cells pre- and post-treatment.

A phase I clinical using intratracheal transplantation of hUCB-derived MSCs in preterm infants at high risk for Bronchopulmonary Dysplasia (BPD) showed BPD severity was significantly lower in the children who received stem cells [93]. Chang *et al.* (2014) [94] and Ahn *et al.* (2017) [95] reported similar results after a two year follow up and added that the treated infants did not show any deficits in neurological, respiratory, or growth parameters even after 24 months. The case report of Yilmaz *et al.* (2021) [96] showed that MSCs treatment in BPD is effective and safe. At present, the clinical trials have corroborated the safety and potency of treatment with MSCs in reduction in inflammation and lung damage, fibrosis, promoting regeneration of pulmonary tissues in BPD (**Figure 7**).

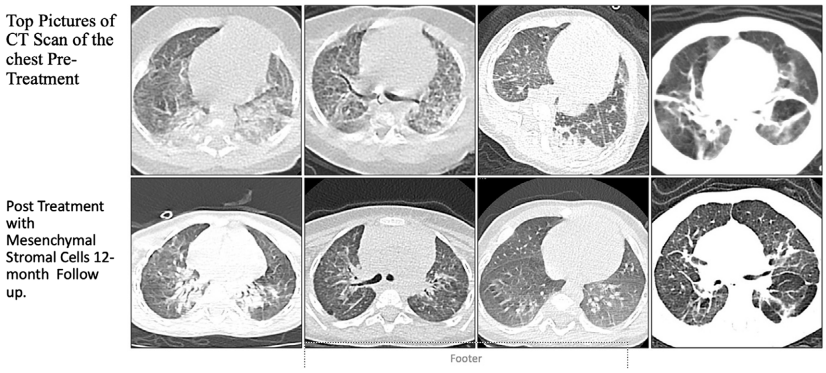


Figure modified and republished Courtesy of BioMed Central: Nguyen LT, Trieu TTH, Bui HTH, Hoang VT, Nguyen ATT, Trinh NTH, Nguyen KT, Hoang DM. Allogeneic administration of human umbilical cord-derived mesenchymal stem/stromal cells for bronchopulmonary dysplasia: preliminary outcomes in four Vietnamese infants. J Transl Med. 2020 Oct 20; 18(1): 398. https://doi.org/10.1186/s12967-020-02568-6. PMID: 33081796; PMCID: PMC7576694.

Figure 7. CT scans of pre-term infant with broncho-pulmonary dysplasia pre- and post-treatment with mesenchymal stromal cell therapy.

3.6. Auto Immune Diseases (AID) and Stem Cell Therapy

The prevalence of autoimmune disease in children is reported to be around 7.5% in general population [97]. In United States around 24 million people or over 5% of the population suffer with an autoimmune disease. Type 1 diabetes, Juvenile idiopathic arthritis, Celiac disease, Inflammatory bowel disease, Graves' disease, Juvenile dermatomyositis, Multiple sclerosis, Psoriasis, Rheumatoid arthritis, Scleroderma, Chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome Inflammation, Myasthenia gravis, Sjogren's syndrome and Vasculitis. AIDs can be classified into one of the following systems: 1) gastrointestinal, 2) neuronal, 3) eye, 4) cutaneous, 5) musculoskeletal, 6) kidneys and lungs, 7) cardiovascular, 8) hematopoietic, 9) endocrine, and 10) multiple [98]. It was suggested that about 25% of patients with one AID tend to develop other comorbid AIDs and these children have a longer life span to face the disease for an extended period of time with more notable and severe complications [99]. This makes the clinicians to act decisively to control the disease so that the children can grow normally with quality of life and be productive in the society as they grow older.

Treatment: At present, there is no cure of majority the AIDs, hence the central component of the management is to control the symptoms. Corticosteroids are the mainstay of the medications which control the inflammations by suppressing the immune system. Depending on the system involved the other drugs in use are steroids, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Disease-Modifying Anti-Rheumatic Drugs (DMARDs), Intravenous Immunoglobulin (IVIG), Biologics, the new class of DMARDs and Plasmapheresis. Majority of the children in addition to the medical therapy require physical and occupational therapy, to learn to adjust the life style. At present there are few options available to treat AID for a cure thus there is a dire need of the day to develop new therapies [100]. Stem cell therapy has long been recommended for use in the treatment of AID as MSCs provides profound immunosuppressive and immunomodulatory effects and destroy the defective immune system giving a long-term remission of AID [101].

Pre-clinical animal models, the therapeutic application of MSCs in the clinical setting has been considered for autoimmune and autoinflammatory diseases that currently have analgesic, *i.e.*, symptom-alleviating, rather than curative treatments [102].

MSCs have now been used in the treatment of many autoimmune diseases, where present therapeutic interventions failed. MSCs are cultured from many sources like, bone marrow, adipose tissue and umbilical cord blood. Wang *et al.* (2018) [103] reported the long-term results of the patients with drug-resistant Systemic Lupus Erythematosus (SLE) with kidney disease. Post intravenous injection at 5-year overall complete remission was 27% and 7% achieving partial clinical remission with survival rate of 84%. By 5th year in addition to improvements, there was noteworthy diminished in the disease activity as per the assessment of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

3.7. Stem Cell Therapy for Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis (JIA) is the most common type of arthritis in children. It typically causes joint pain and inflammation in the hands, knees, ankles, elbows and/or wrists. JIA used to be called Juvenile Rheumatoid Arthritis (JRA), but this was renamed to JIA as this was not the version of the adult disease. Juvenile Idiopathic Arthritis (JIA), previously known as juvenile rheumatoid arthritis, is the most common type of arthritis in children. It causes persistent joint pain, swelling and stiffness. Some children may experience symptoms for only a few months, while others have symptoms for many years. There are 6 types of arthritis viz: Oligoarticular juvenile idiopathic arthritis, Polyarticular juvenile idiopathic arthritis-rheumatoid factor negative, Polyarticular juvenile idiopathic arthritis-rheumatoid factor positive, Enthesitis-related juvenile idiopathic arthritis and Psoriatic juvenile idiopathic arthritis. The prevalence of JIA is 16,150 per 100,000 children [104].

The main cause of JIA is due to the body's immune system attacks its own cells and tissues and heredity and environment does seem to play a role. Since the real remains elusive the management remains supportive and symptomatic. There is no cure for JIA but remission (little or no disease activity or symptoms) is possible. Early aggressive treatment is key to getting the disease under control as quickly as possible. The goals of JIA treatment are to control pain, slow down or stop inflammation, relieve symptoms, prevent joint and organ damage, Preserve joint function and mobility, achieve remission and improve quality of life. MSC have immunomodulatory properties, and transplantation of these stem cells have been used to successfully treat immunologic induced diseases. MSCs are known to restrain inflammation when the immune system is hyperactive. MSCs are also known to express immune suppressors [105].

Recently, a retrospective case series was reported the beneficial effect of MSCs and suggested that the immunomodulatory effects can make this type of treatment as optimistic and serve as adjuvant treatment [106]. Wang *et al.* (2015) [107] treated 10 patients with JIA and used Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) of two doses at 1st and 3rd month and re-examined after 3 months and 6 months of infusion. There were no adverse reactions. Clinically, the inflammation in the affected joints decreased, medication burden of NSAIDs and steroids diminished and the blood parameters like white cell count, C-reactive protein, Interleukin-6 and Tumor necrosis factor-*α* were at normal levels. Clinical trials carried out in adults' patients with proven rheumatoid arthritis support the effectiveness of MSCs in patients in whom symptoms and disease failed to subside on standard treatment [107] [108]. Swart *et al.* (2019) [109] used allogeneic MSCs from healthy donors and treated children with JIA and gave intravenous MSCs three doses of up to 2 million/kg. They observed that there was overall improvement in VAS pain, Childhood Health Assessment Questionnaire and Quality of Life at the end of 1st year of assessment. It was reported that MSC transplantation may prove a promising adjunctive treatment option; but more research with well-

designed monitored clinical trials and protocols are needed, till then MSCs will remain as an alternative in failed exhaustive therapy. Based on the smaller studies, MSCs therapy in JIA is not a standalone mode of management but more studies are required to recommend MSCs as an effective modality of treatment. In the meantime, when patients do not respond to the standard treatments, MSCs remain an astute treatment option.

Apart for JIA, other AIDs studied using stem cell therapy are Inflammatory Bowel Disease (IBD), Systemic Lupus Erythematosus (SLE), Scleroderma (SSc), Dermatomyositis (JDMS), dermatomyositis and vasculitis. Due to the infrequency of these conditions in children the treatment is based on experience of drug therapy in adults. Inflammatory Bowel Disease (IBD) is a quite a composite disease with an exaggerated chronic inflammatory process of the mucosa lining the gastrointestinal tract. IBD is on the rise in the west as well as eastern countries [110]. A recent report from Southampton Children's Hospital shows the number of children diagnosed with IBD has doubled in the last 10 years and the annual incidence from Korea seems to have increased by more than 100-fold in the past 20 years [111]. Pediatric onset IBD appears to be a more aggressive and progresses rapidly than the adult onset [112] [113]. As we have not yet established and fully understood how the IBD is caused, hence the drug therapy is old and new is mainly symptomatic and it is still physicians find difficulty in understanding what strategy for treatment of pediatric IBD should they take. Large number of patients experience lack of or inadequate response to treatments presently available.

Kagia *et al.* (2019) [114] created chemically induced IBD in experimental animals and treated using MSCs derived from Umbilical cord and Bone marrow and found that the treatment with stem cells had significant clinical and histopathological improvement compared to the control group. Therapy with Hematopoietic Stem Cells (HSCs) and MSCs have shown to control the disease and prevent escalation especially in patients who are refractory to the present anti-IBD therapies [115]. Perianal fistulas in IBD are the leading cause of prolonged morbidity, up to 59% of patients are at risk of faecal incontinence and decrease quality of life. Mak *et al.* (2018) [116] reported that more than 40% of patients with Crohn's disease present with perianal disease and had poor outcome, in young age of onset and require a protracted course of multiple antibiotic use and repeated surgeries. In an extensive review, Panes *et al.* (2018) [117] found that failure of treatment either medical, surgical or combined reached up to 80%. Since the failures and relapse rate of fistulas in Crohn's disease not under control with the present therapies physicians and researchers have to look out for alternate therapies and it appears stem cell therapy looks promising. In multiple randomized control trials, MSCs injections were compared to placebo in patients with fistulas who stopped responding to immuno-modulators, anti-TNF-alpha agents, with surgery showed convincingly positive results [118]-[120]. Dietz *et al.* (2017) [121] concluded after their study of injecting MSCs in perianal fistulas cured more than 83% of cases without any adverse effects of stem cell therapy. Results of a phase III trial involving 251

patients with perianal fistulas in Crohn's disease, MSCs therapy achieved a 57% [122] and there was no relapse even after 12 months of follow up [122]. Studies have shown that both systemic and local use of MSCs has provided acceptable and efficacy in patients with IBD [123]-[125].

3.8. Juvenile-Onset SLE (JSLE)

It is a rare disease with an incidence of 0.3 - 0.9 per 100.000 children-years and a prevalence of 3.3 - 8.8 per 100.000 children [126]. The disease is seen more in ethnic population of Asians, African American, Hispanics and native Americans [127] [128]. JSLE accounts for 20% of all patients diagnosed with SLE. Children present with early symptoms which include fatigue, joint pain, hair loss and a "butterfly" rash on your child's cheeks and nose. It is a chronic inflammatory condition the cause of which is still elusive can affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body. JSLE are at a significantly higher risk of disease damage than adults but behave the same way as in adults, with similar etiology, pathogenesis, clinical manifestations, and laboratory findings. Despite the management of JSLE differs than adults as the disease impact children during their growth and takes a major toll on growth and development physically and mentally. The aim of management is to create immunosuppression which will decrease disease activity and improve quality of life, the standard treatment of JSLE from NSAIDSs to steroids, DMARDs and biologics. Approximately 70% of patients follow a path of relapsing-remitting course under the standard of care management. In JSLE, these conventional immunosuppressants, including glucocorticoids, can be associated with side effects and toxicities and 18% of the JSLE end up in refractory state in whom failure to attain clinical remission after appropriate induction immunosuppressive therapy. Under such scenarios an alternate therapy is needed which can even treat patients with refractory JSLE. As in situations like rarity of the diseases like JSLE the drug therapy is followed the adult path in the management. In a recent prospective study, Li *et al.* (2021) [129] of patients aged 12 - 62 years used MSCs and reported that with MSCs treatment the five-year survival was 83% and 59.5% had total remission. Other studies indicate that stem cell therapy in SLE showed a 5-year survival rate as high as 91% [130], and stem cell therapy added to the standard care increased the 10-years overall survival rate remission to 86.0% [131].

4. Future of Stem Cell Therapy: Funding Drug Companies

Nearly 30 years ago, the first clinical trial was conducted using MSCs in patients with hematologic malignancies, showing its safety and efficacy. In the past few years, there has been an exponential number of clinical trials revolving around stem cell-based therapies. There are over 5000 registered clinical trials involving stem cell research on ClinicalTrials.gov, with new clinical trials in this field being offered every day [132]. Recent data indicate that results of clinical trials have had great success in treating auto immune, orthopaedic and neurodegenerative dis-

eases. Many clinicians and researchers believe that adult stem cells, particularly MSCs, are the gold standard in stem cell-based therapies [133] and the use of embryonic stem cells will always remain controversial in safety, ethical and religious beliefs [134]-[137].

Few countries like China, India, Mexico, Panama, Thailand, Ukraine, and South Korea, are actively marketing stem cell therapies [138], and it was reported that as of March 31, 2021, there are 2754 clinics that supply stem cell therapies direct-to-consumer [139]. Japanese government in 2014 after realizing the benefits of stem cell therapy, adopted an accelerated approval system for stem cell treatments, conditional approval, which required only minimal safety and efficacy data [140] [141]. In short, there is compelling evidence that stem cell therapies work in various diseases, but are being overlooked by regulating agencies to approve the treatments [142].

Recently, the Food and Drug Administration (FDA) regulatory guidelines are standard for any drug to be used and want the evidence needed to ensure that cell therapy delivers on its promise for patient care. As of now, FDA has approved Hematopoietic Stem Cell Transplantation (HSCT) for blood disorders like leukemia and lymphoma, Mesenchymal Stem Cell (MSC) therapy for conditions like osteoarthritis and Crohn's disease and Cord blood stem cell therapy for certain cancers and blood disorders [143]. Standards of evidence help keep unsafe or ineffective therapies out of routine use, while permitting adoption of therapies with a favorable risk-benefit balance. Countless studies have shown that autologous MSCs and terminally derived from them are universally considered safe after continuous monitoring and prolonged follow-up [144]. Even though the failure of biologics in the AID reported to be 58% with adverse events in up to 81%, and the discontinuation rate due to adverse events in 20% of patients [145]-[147], still the biologics market continued to grow to USD 349.6 Billion in 2023 and which will double by 2032 to USD 699.5 Billion [148]. The question is why, in the eyes of FDA, stem cell therapy has taken a back seat like an orphan drug with minimal support and though there is convincing evidence of safety and efficacy in majority of reported literature. There is no doubt there is abuse and overuse and abuse of stem cell therapy by some in the world, but clinicians and researchers need to be altruistic, morally obligated to ensure that ethical considerations are not undermined in pursuit of progress in clinical translation. With failure of prescribed treatments and no standard approved treatments available for some conditions, in desperate situations, patients and caregivers take desperate decisions to get treated by stem cell therapy. To streamline this and stop the abuse, FDA should review the published data and be more forthcoming and little liberal in granting approvals for diseases where there are no known treatments available and when the standard treatment fails to cure the disease or alleviate the suffering.

Ethics Statement

As this was a review article, there was no requirement for approval of the Institutional Review Board of the Hospital.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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