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Potential benefits of serial cell transplantation in a case of Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy is the commonest and the most devastating of the muscular dystrophies. With no known cure, new advances, such as gene therapy, exon skipping and cell therapy are being explored as treatment options. Gene therapy using viral and non-viral vectors is however, restricted due to safety issues. Although a drug, eteplirsen, has been recently approved, it is specifically indicated for patients with a mutation in the dystrophin gene that is amenable to exon 51 skipping. The ability of bone marrow mononuclear cells to replenish the stem cell pool and facilitate muscle repair, makes cell therapy with bone marrow mononuclear cells a promising treatment option in this relentlessly progressive disorder. We report a seven-year and eight month old patient with Duchenne Muscular Dystrophy treated with serial autologous bone marrow mononuclear cell therapy offered as a last resort therapy followed by long term multi disciplinary rehabilitation. No adverse events were reported after the procedure and up to 14 months follow up duration. Functional improvements were seen as an improved North Star Ambulatory Assessment score from 18 to 20 over a 14 month follow-up period. 2-minute walk test distance improved from 63 meters before the intervention to 85.8 meters, 10 months post first cell therapy. 6-minute walk test distance improved from 178.2 meters at 10 months post first cell therapy to 191.4 meters at 14 months post first cell therapy. Objective improvements were seen in the musculo skeletal magnetic resonance imaging with the fractional anisotropy values in the posterior thigh muscles decreasing from 0.603 on the right side and 0.600 on the left side to 0.482 on the right and 0.415 on the left side. These objective and functional improvements suggest possible potential benefits of cell therapy coupled with neurorehabilitation in Duchenne muscular dystrophy and need to be explored further.

Keywords

cell therapy; Duchenne muscular dystrophy; bone marrow mononuclear cells; musculoskeletal magnetic resonance imaging

Abbreviations

DMD: Duchenne Muscular Dystrophy; MMT: Manual Muscle Test; NSAA: North Star Ambulatory Assessment; FIM: Functional Independence Measure; MSK MRI: Musculoskeletal Magnetic Resonance

imaging; FA: fractional anisotropy.

Introduction

Duchenne muscular dystrophy (DMD) is the commonest and the most devastating of the muscular dystrophies affecting all ethnicities, nationalities and socioeconomic groups. It is inherited as an X –linked disease and is characterized by progressive muscular weakness and wasting caused by lack of production of a protein called dystrophin. Over time body cannot repair the accumulated muscle damage resulting in muscle atrophy and progressive disability, with patients being wheelchair-bound by the age of 12 years and death occurring in their early twenties. There is no known cure for DMD and the current treatment options consist of medical, surgical and rehabilitative management but are however unsatisfactory.

Glucocorticoids are the current standard pharmacologic treatment for DMD. The drug prolongs time to loss of ambulation, but offers limited improvement. There are significant side effects which need close monitoring [1].

Newer therapies, such as gene therapy, exon skipping and cell therapy are being explored as treatment options. A possible treatment option is exon skipping so that it becomes its nearest in-frame Becker's muscular dystrophy. Eteplirsen has received approval for treatment of DMD patients with a mutation of dystrophin gene amenable to exon 51 skipping [2]. Skipping exon 51, however, adds up to a total of only 13% of all DMD patients. Also, the degree of uptake and efficacy is highly variable within and between muscles even with repeated treatments. Lifelong administration is required because of rapid clearance from the circulation, increasing the risk of toxicity and cost of treatment. Another limitation of this drug is that it does not affect cardiac muscle which is a major cause of death in DMD patients. These limitations along with cost and applicability in clinical settings need to be overcome [3].

Gene therapy using viral and non-viral vectors is restricted due to safety issues. Before viral vectors can be used clinically two challenges need to be overcome; they are too large and unable to cross the extracellular matrix surrounding the mature muscle fibers and, there are not many attachment receptors on the muscle fiber membrane [4]. Delivery of non-viral deoxyribonucleic acid is inefficient in muscle tissue [5]. Another option is the use of chimeroplasts, to repair genes but is still inefficient [5].

Recent studies have revealed that the intrinsic defects in DMD reduce the generation of the myogenic progenitors necessary for muscle regeneration [6]. Impaired regeneration resulting from the intrinsic satellite cell dysfunction also plays a vital role. Thus, effective treatment requires aiming at replenishment of stem cell pool and facilitating muscle repair. Through its potential for cell renewal and contribution to replenishing of stem cell pool, cell therapy currently may be one of the most promising methods for treating this progressive disorder. Preclinical studies of cell therapy have shown that bone marrow mononuclear cells possess myogenic and neurogenic potential [7-9] and may even participate in regeneration of cardiac muscle [10]. Also, they are easy to isolate, and are excluded from ethical concerns. They also have other advantages including ease of access and transplantation [11]. These cells are safe and are marked by a lower risk of immunogenicity and tumorigenicity [12,13]. Cell therapy with autologous bone marrow mononuclear cell transplantation in humans has been found to be safe and has shown positive clinical effects in patients with muscular dystrophy [14,15].

We present a case of DMD, treated with serial autologous bone marrow mononuclear cell transplantation followed by long-term neurorehabilitation. Several scales that assess different aspects of function were used to assess disease progression and treatment outcome, and were compared with the natural course of disease progression on these scales. Migration and implantation rates of cells in the target sites have been shown to be greater with multiple transplantations than a single transplantation. Repeat injection of cells has been shown to be safely more efficacious than single injection in clinical application [16,17]. Therefore, repeat cell therapy was administered at 6 months post 1st cell therapy.

Case Presentation

A 7 year and 8 months old boy presented with difficulty in getting up from sitting position, in climbing stairs, and in jumping, pain in calves after walking for a long period of time, difficulty in performing overhead activities, inability to remove t-shirt and dressing the lower body in standing. His symptoms began at the age of 2 years and 6 months when his parents noticed that he was getting up from the sitting position with difficulty. They consulted a pediatric neurologist for the same. Based on clinical findings, creatine phosphokinase, genetic testing and electromyogram, he was diagnosed as a case of DMD. He was started on rehabilitation but continued to deteriorate functionally.

On examination, there was bilateral pseudo hypertrophy and tightness in calf muscles. He sat with rounded shoulders and in standing, displayed an increased lordotic posture with a tendency to keep both feet in plantar flexion. He presented with hyporeflexia, hypotonia and walked with a wide base of support and waddling gait. Muscular strength was measured by manual muscle test (MMT), using a scale devised by our experienced physiotherapists based on the Medical Research Council's MMT scale. In our scale (modified Medical Research Council's MMT) all the grades were subdivided (Appendix 1) to be able to measure the subtle changes in the strength as observed in patients with DMD. He scored 18 out of a total of 34 on the North Star Ambulatory Assessment (NSAA) scale; was partially dependent in all the activities of daily living with a score of 105 out of a total of 126 on Functional Independence Measure (FIM) scale. On the 2-minute walk test, he walked a total distance of 63 meters and had no sensory or cognitive impairment.

Musculoskeletal magnetic resonance imaging (MSK MRI) of the extremities suggested severe diffuse muscular atrophy and fatty replacement involving all the compartments of bilateral gluteal and thigh regions. There was relative sparing of the bilateral sartorius, gracilis, adductor longus, semi membranosus and semitendinosus muscles. There was moderate diffuse muscular atrophy and fatty replacement in both the legs and arms. There was mild diffuse muscular atrophy and fatty replacement in both the forearms. Musculoskeletal spectroscopy revealed pronounced peaks of extramyocellular and intramyocellular lipids. Smaller peaks of other muscle metabolites were also noted. Musculoskeletal diffusion tensor imaging performed through both thighs showed moderately reduced muscle bulk. The fractional anisotropy (FA) values in the posterior compartment thigh muscles were approximately 0.603 on the right side and 0.600 on the left side.

Electromyography was suggestive of a myopathic pattern involving predominantly proximal muscles. Genetic test results showed duplication of dystrophin gene involving multiple exons from exon 8 to exon 12. 2-dimensional echocardiogram showed normal study with left ventricular ejection fraction

of 60%. The electrocardiogram showed sinus tachycardia. Serum creatine phosphokinase was elevated (17220 IU/L). Serological, biochemical, and hematological blood tests, chest X-ray were done a week before the intervention, establishing preoperative fitness.

Methodology

Selection of this patient was based on the World Medical Association Revised Declaration of Helsinki [18]. Ethical approval was obtained from the Institutional Committee for Stem Cell Research and Therapy and a signed informed consent for the procedure was obtained from the parents.

Granulocyte colony-stimulating factor 300 mcg was administered subcutaneously 72 hours and 24 hours prior to the mononuclear cell transplantation to enhance the mobilization of bone marrow mononuclear cells [19].

Following a detailed neurological examination, muscles of functional importance were selected for intramuscular injection of bone marrow mononuclear cells. Motor points, which is the skin area overlying the point where the innervating nerve enters the muscle belly, were identified and marked.

On the day of cell transplantation, 100 ml of bone marrow was aspirated from the right anterior superior iliac spine and was collected in heparinized tubes. Density gradient method was used to separate the mononuclear cell fraction. The purified mononuclear cells were tested for total cell count, viability and CD34+ cell content by fluorescence-activated cell sorting analysis. CD34+ count was found to be 1.39%. The total number of cells injected was 1.2×10^8 with 98% viability. With half the cell fraction being injected intrathecally at the level between the fourth and fifth lumbar vertebrae, the remaining cells were diluted by the patient's own cerebrospinal fluid for its properties of harboring cell growth [20] and then injected intramuscularly at the respective motor points of Triceps, Glutei, Quadriceps, back extensors and Abdominals bilaterally.

Methyl Prednisolone 600 mg in 500 ml Isolyte P was given intravenously to reduce the immediate inflammation.

Bone marrow mononuclear cell transplantation was followed with neurorehabilitation during the subsequent 4 days before discharge. This included therapies given by a physiotherapist, an occupational therapist and a psychologist. At discharge, the patient was given a detailed home program.

Positive response as explained in the results provided the rationale for a second cell therapy 6 months post first cell therapy. The total number of cells injected was 1×10^8 with 94% viability. With half the cell fraction being injected intrathecally, the remaining cells were intramuscularly injected in the respective motor points of bilateral Deltoid, Glutei, Biceps, Triceps, Quadriceps, Abdominals and back extensors. A detailed follow-up assessment including modified Medical Research Council's MMT, MSK MRI scan was repeated prior to subsequent cell therapy with the same parameters as before. No adverse events were reported by the patient through the 14 months follow-up duration. The follow up procedure and outcome measures tested at each follow up are presented in Figure 1.

Results

After the first cell therapy, at 3 months follow-up there were subjective improvements which were as follows. He could apply soap onto his back which he was earlier unable to do, could remove his t-shirt,

and became almost independent in toileting. He could cycle longer from an earlier duration of 15-20 minutes to 30-35 minutes. Earlier he could cycle under supervision and now he needed less supervision. There were fewer falls than before.

The Brooke and Vignos scale score was 3 before the cell therapy and was maintained at three months follow-up. FIM score improved from 105 to 110. NSAA score was maintained at 18.

At 6 months follow-up, there was a further increase in the FIM score to 114 that was noted. He could cycle on his own without supervision for a distance of 1 km. Number of falls further reduced. There was an improvement in the posture, with a reduction in the lumbar lordosis. NSAA score improved to 20. A repeat cell therapy was done 6 months after the first cell therapy.

At 10 months post 1st cell therapy, the Brooke and Vignos score was maintained, FIM was maintained at 114, 2-minute walk test showed an improvement from 63 meters before cell therapy to 85.8 meters. At this time, the 6-minutewalk test distance was 178.2 meters. The improved NSAA score was maintained. His stamina had further improved and could now cycle 1 and a half kilometers without fatigue.

At another follow up 14 months post 1st cell therapy, his gait showed improvement with reduced toe walking although waddling persisted. The improved NSAA was maintained at 20. Distance walked on 6-minute walk test showed an improvement from an earlier 178.2 meters to 191.4 meters.

The above mentioned outcome measure scores have been shown in Table 1.

As seen in Table 2, the trunk muscles (upper and lower Abdominals) and Extensor Pollicis Brevis showed improvement in strength on modified Medical Research Council's MMT. There was a slight decline in the muscle strength of the Quadriceps and Extensor Digitorum Longusmuscle of the leg. The strength in the other muscle groups was maintained through the 14 month period. A comparative MSK MRI done six months post first cell therapy, showed no further increase in fatty infiltration or muscular atrophy (**Figure 2**). The FA values in the posterior compartment thigh muscles were approximately 0.482 on the right and 0.415 on the left side, decreasing from the earlier 0.603 on the right side and 0.600 on the left side (**Figure 3**).

Discussion

DMD, results from a genetic fault that prevents the production of a protein, dystrophin. Dystrophin has a structural role in muscle, linking the internal cytoskeleton to the extracellular matrix. The absence of dystrophin leads to a reduction in all of the dystrophin-associated proteins, disrupting the linkage between the cytoskeleton and the extracellular matrix. The disruption of the linkage renders the muscle fibers susceptible to injury [21]. Further, due to continuous cycles of muscle injury and regeneration, satellite cell reserves are exhausted and lose their capacity to mediate repair, resulting in the muscle tissue being progressively replaced by adipose and fibrotic tissue [22]. The current management of DMD is limited and aims at reducing the inflammatory process and slowing of fibrosis. Steroids are routinely used to slow down muscle wasting but they have many side effects, including osteoporosis, hypertension and delayed growth. Physiotherapy may help in maintaining muscle strength and flexibility. These medical measures only delay the imminent course of the disease process.

There is still a loss of ambulation and functional independence. New advances in the management of DMD using exon skipping, gene therapy, and cell therapy have shown promise in altering the disease process to a certain extent. While practical difficulties have prevented gene therapy from being a clinically feasible and viable option at present [23], autologous bone marrow mononuclear cell transplantation is safe and has shown positive clinical effects in people with muscular dystrophy [14,15]. Recent studies suggest that cell therapy can contribute to muscle repair and replenish the satellite cell pool [24]. Bone marrow-derived stem cells are known to exert therapeutic benefits through secretory paracrine mechanisms namely, angiogenesis, inhibition of apoptosis, anti-inflammation, immunosuppression, homing stimulation of endogenous cells, and possible regulation of specific metabolic pathways [25].

Although DMD is primarily a disease of the muscles, dystrophin is also a structural component of neurons in particular regions of the central nervous system [26]. Nervous system impairment can be seen in children with DMD as neurodevelopmental delay, in the first years of life. Cognitive and behavioral difficulties have been identified in DMD patients. The role of dystrophin in the development and function of these cells is not as well defined as that in muscles but is presumed to influence synaptic activity [27]. Therefore, part of the cell fraction was given intrathecally. The neuromuscular junction is also impaired in muscular dystrophy due to synaptic abnormalities [28]. Injecting the cells at the motor points ensures repair of both the muscles and the nerves.

Following cell therapy, neurorehabilitation was given. Exercise further enhances the effect of stem cells by activation and proliferation of the local stem cells, muscle angiogenesis and release of cytokines and nerve growth factors [29].

This patient showed an increase in 2-minute walk test distance in the first 10 months' follow-up. 6–minute walk test distance improved from 178.2 meters at 10 months follow-up to 191.4 meters at 14 months follow-up. Above age 7, the natural course of the disease shows a decrease in 6-minute walk distance by 42 meters during the first year and about 80 meters during the second year [30].

The NSAA score increased from 18 to 20 over the 14 month period post cell therapy. Above the age of 7, the natural course of the disease shows a decrease of about 3 points during the first year and more than 4 points during the second year on the NSAA [30].

The NSAA has shown to have a moderate to good correlation with 6-minute walk distance and provides information on different aspects of motor function [31].

Thus, an increase in the NSAA score along with an increase in the 6-minute walk distance indicates an improvement in the motor function following the intervention.

The Brooke and Vignos scale scores increase linearly with age [32]. Our patient showed maintained Brooke and Vignos Scale score through the 14 months follow-up period.

As shown in table 2, muscle strength improved in the Abdominals and Extensor Pollicis Brevis over the 14-month post cell therapy period. Since the disease is progressive, the natural course of the disease shows a reduction in muscle strength by 0.3 MMT units/year in muscle strength [33]. Lue et al found a 3.9% reduction in muscle strength every year [34].

The FA values in the posterior compartment thigh muscles were approximately 0.603 on the right side and 0.600 on the left side pre-intervention. Comparative MSK MRI done 6 months after 1st cell therapy, showed no further increase in fatty infiltration or muscular atrophy. The FA values in the posterior compartment thigh muscles were approximately 0.482 on the right and 0.415 on the left side 6 months post intervention. Studies have revealed that FA values positively correlate with age and negatively with muscle strength [35]. With disease progression, FA values increase. Both MMT and MSK MRI are objective measures of muscle pathology and can be used for monitoring of disease progression, treatment planning, and to assess the efficacy of a therapeutic intervention [36,37]. These positive objective changes on MSK MRI and MMT reveal a possible positive alteration in the disease process.

There is a slight decline in the muscle strength of the knee extensors (Quadriceps) and Extensor Digitorum Longus. The reason for the decline could be that Quadriceps being a large muscle group, only motor point injection of cells may be insufficient. Extensor Digitorum Longus could be considered for intramuscular injection of stem cells in the subsequent intervention, and a larger number of intramuscular injections could be considered for the Quadriceps muscle [7].

Sharma et al reported similar improvements in FIM with no further increase in fatty infiltration on MSK MRI in another case report [15]. Similar significant functional improvements and improvements in muscle strength with MSK MRI showing muscle fiber regeneration and a decrease in fatty infiltration have been reported in another case report [38].

All of these are indicative of positive clinical benefits of cell therapy combined with neurorehabilitation.

Lack of control is one of the limitations of this case study. But, this patient could serve as self-control because of the fact that, before cell therapy, there was functional deterioration despite physiotherapy. And after administration of cell therapy in conjunction with neurorehabilitation, functional improvements were noted.

Figures

Figure 1: Follow up procedure and outcome measures used

Outcome measures	Pre-cell therapy	3-month post 1st cell therapy	6-month post 1st cell therapy	10 months post 1st cell therapy	14-month post 1st cell therapy
MMT	✓	✓	✓	✓	✓
2-minute walk test	✓	X	X	✓	X
6-minute walk test	X	X	X	✓	✓
NSAA	✓	✓	✓	✓	✓
FIM	✓	✓	✓	✓	X
Brooke and Vignos scale	✓	✓	X	✓	✓
MSK MRI	✓	X	✓	X	X

✓- outcome measure performed at follow up, X- outcome measure not performed at follow up

Tables

Table 1: Changes in various outcome measures over a period of 14 months.

Outcome measures	at assessment (before 1st cell therapy)	at 3 months post 1st cell therapy	at 6 months post 1st cell therapy	at 10 months post 1st cell therapy	at 14 months post 1st cell therapy
FIM	105	110	114	114	
NSAA	18	18	20	20	20
2-Minute walk test (meters)	63			85.8	
6-Minute walk test (meters)				178.2	191.4

Table 2: Changes in the muscle strength over 14 months as measured by our modified Medical Research Council's MMT scale

	Muscle Groups	Modified Medical Research Council's MMTgrade at assessment (before 1st cell therapy)		Modified Medical Research Council's MMT grade at 3 months post 1st cell therapy		Modified Medical Research Council's MMT grade at 6 months post 1st cell therapy		Modified Medical Research Council's MMT grade at 10 months post1st cell therapy		Modified Medical Research Council's MMT grade at 14 months post 1st cell therapy	
K	Extensors	Right 3+	Left 3++	Right 3-	Left 3-	Right 3-	Left 3-	Right 3-	Left 3	Right 3-	Left 3-
Ankl and foot	Extensor Digitorum Longus	Right 3++	Left 3++	Right 3	Left 3	Right 3	Left 3-	Right 3	Left 3	Right 3	Left 3-
Ankle and foot	Extensor Digitorum Longus	Right 3++	Left 3++	Right 3	Left 3	Right 3	Left 3-	Right 3	Left 3-	Right 3	Left 3-
Trunk	Abdominals upper Abdominals lower	1 1++		2+ 3+		2+ 3+		2 2++		2 2+	
Forearm, wrist and hand	Extensor Pollicis Brevis	Right 3+	Left 3++	Right 3+	Left 3++	Right 3++	Left 3++	Right 4	Left 4	Right 4	Left4

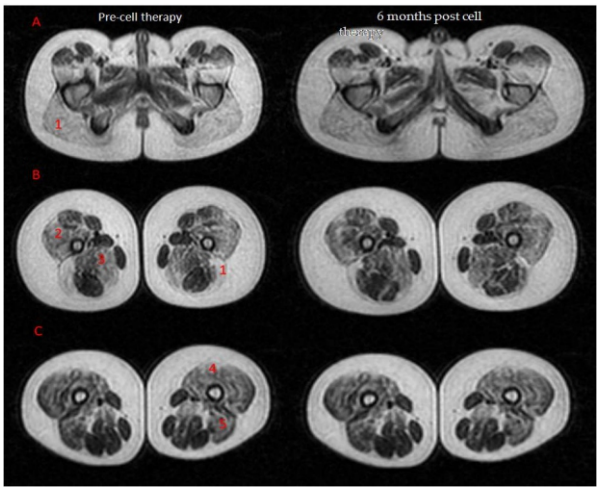

Figure 2: T1W axial MR images of (A) pelvic girdle, (B) upper thigh, and (C) lower thigh.

Severe fatty infiltration seen in 1: Gluteus maximus, 2: Vastus medialis, lateralis and intermedius, 3: Adductor brevis.

Moderate fatty infiltration seen in 4: Rectus femoris, and 5: Biceps femoris.

Relative sparing of Semitendinosus, Semimembranosus, Gracilis, Sartorius and Adductor longus muscles. There was no further increase in fatty infiltration 6 months post 1st cell therapy.

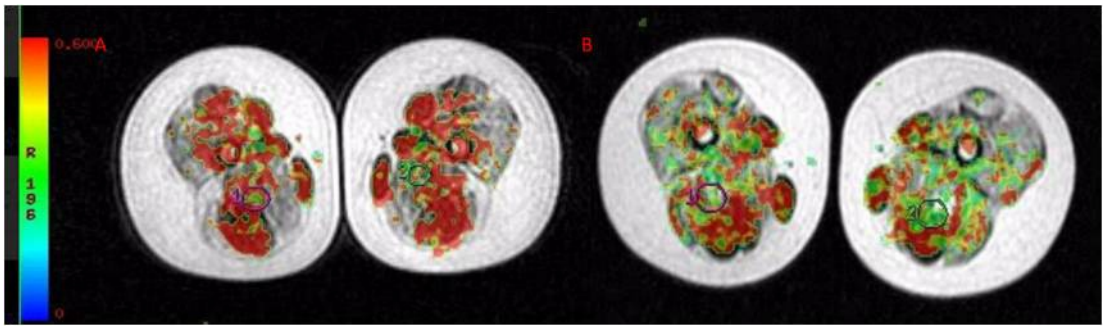

Figure 3: Muscle fiber tracking of the posterior thigh muscles in axial vivo. A) FA values before cell therapy are approximately 0.603 on the right side and 0.600 on the left side.

B) FA values 6 months after 1st cell therapy is approximately 0.482 on the right and 0.415 on the left side.

Conclusion

Although cell therapy is in its early stage, this case report suggests possible benefits of cell therapy coupled with rehabilitation. However, since the results cannot be generalized, controlled trials will be needed to effectively establish the therapeutic benefits of cell therapy in DMD. MSK MRI may be used as an objective tool to assess the efficacy of cell therapy.

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