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Review Article

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Spinal Muscular Atrophy and the Possible Use of Stem Cells as Therapy

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ABSTRACT

Spinal Muscular Atrophy (SMA) is a rare, inherited, recessive genetic disorder that causes deterioration in the motor neurons in the anterior horn of the spinal cord in the CNS. This deterioration results in progressive weakness of all muscles in individuals diagnosed with SMA. SMA exhibits a range of phenotypes spanning from type 0 (congenital) to type IV (adult), with varying physical abilities and biological functions between and within SMA types. The treatment of SMA has been currently approved for molecular and genetic interventions, as the etiology of SMA stems from a loss in the SMN1 gene and low SMN2 copy numbers, both of which produce a lack of the SMN protein that is vital for motor neuron function. Stem cells, or cells that are capable of proliferation and differentiation, are currently being assessed in the treatment of many diseases, including motor neuron diseases such as SMA. The animal studies showed promising results for the possible improvement of SMA symptoms, however there is little conclusive research in this area on humans thus far. One novel program is being conducted in Thailand that shows results, however, there needs to be much more research to fully understand how effective stem cells can be either on their own or in combination with established therapies in the treatment of spinal muscular atrophy.

List of Abbreviations

ALDH	:	aldehyde dehydrogenase
ALS	:	amyotrophic lateral sclerosis
hESCs	:	human embryonic stem cells
hMNPs	:	hESC-derived motor neuron progenitors
iPSCs	:	induced pluripotent stem cells
C-to-T	:	cytosine to thymine
DMD	:	Duchenne muscular dystrophy
GI	:	gastrointestinal
GFP	:	green fluorescent protein
GVHD	:	graft versus host disease
MLPA	:	multiplex ligation-dependent probe amplification
NGF	:	nerve growth factor
NJ	:	nasojejunal
NT-3	:	neurotrophin-3
NT-4	:	neurotrophin-4
OT	:	occupational therapy
PCR	:	polymerase chain reaction
PLS	:	primary lateral sclerosis
PT	:	physical therapy
PMA	:	progressive muscular atrophy
ROM	:	range of motion
SCI	:	spinal cord injury
SMA	:	spinal muscular atrophy
SMARD1	:	spinal muscular atrophy with respiratory distress type 1
SMN	:	survival motor neuron
SMN1	:	survival motor neuron 1 gene
SMN2	:	survival motor neuron 2 gene
U.S.	:	United States
VEPTR	:	vertical expandable prosthetic titanium rib
VEGF	:	vascular endothelial growth factor

Introduction

Incidence and Epidemiology

Spinal muscular atrophy is the second most common cause of mortality that is inherited in a recessive autosomal manner: the first being cystic fibrosis. SMA occurs in 1 in every 6,000-

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11,000 births and the SMN1 mutation is found to lay dormant in 2-3% of the population, making these people carriers of the disease [1]. The disease is seen twice as often in white and Asian populations than it is in black and Hispanic populations and research has not shown a significant difference in the incidence of SMA between males and females [2,3].

Etiology

Around 92-95% of patients with SMA have a homozygous SMN1 deletion with the remainder of patients exhibiting point mutations or mutations on another gene that caused the disease [4]. The telomeric SMN1 gene and the centromeric SMN2 gene are both found on human chromosome 5 and each contain nine exons that code for the survival motor neuron (SMN) protein. SMA is usually caused by the deletion or point mutation of the SMN1 gene and can be exacerbated by the C-to-T base pair transition in exon 7 of the SMN2 gene. This base pair transition on SMN2 causes a cascade of events that ultimately excludes exon 7 during transcription and a truncated, quickly degraded SMN2 protein is produced [3].

The disease phenotype of SMA is exhibited due to the lack of SMN protein, and therefore the degradation of alpha-motor neurons in the anterior horn of the spinal cord and the breakdown of the motor unit [3]. This motor unit dysfunctionality presents as the muscle weakness seen in SMA patients. In addition to the problems associated with the lack of SMN protein produced by SMN1 mutations, the SMN2 gene produces a fully functional SMN protein only 10-15% of the time, with the other transcriptional events producing the truncated version. Different individuals can have different copy numbers of the SMN2 gene, resulting in a higher quantity of SMN protein produced. With more SMN protein, individuals with SMA can exhibit a less severe phenotype [1].

Screening

Almost all newborns (~97%) were screened for SMA after birth as of 2022 with the hope that every future child will be screened. Spinal muscular atrophy can be screened for in three different ways: (1) preconception carrier screening, (2) prenatal testing, and (3) targeted diagnostic testing. Preconception carrier screening is recommended to all couples, regardless of race, ethnicity, or family history of SMA due to the relatively high carrier rate. Carrier screening should start with the individual who will be carrying the child and if this produces a positive result for the SMN deletion, the gamete of the donor or the individual's partner should be tested for the SMN deletion as well. Prenatal testing is a relevant way to test whether a child has a normal SMN1 gene rather than a mutation that will produce SMA. The tests can be performed using amniocentesis to obtain fetal DNA from the extracted amniotic fluid or by chorionic villus sampling. It can also be performed using the multiplex ligation-dependent probe amplification (MLPA) technique or by extraction of fetal cells from the mother's circulation. As of the last way to screen for SMA is by taking blood from the heelstick of a newborn and testing it for deletion of exons 7 or 8 in the SMN1 gene [3].

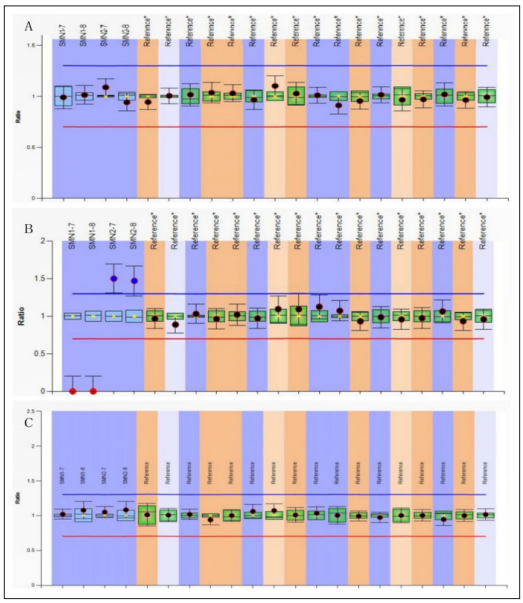

Figure 1: Example of MLPA test results to determine prenatal diagnosis of SMA. Charts A and C show normal parameters for SMN gene presence. Chart B shows no copies of SMN E7 and E8, producing a diagnosis of spinal muscular atrophy [5].

Diagnosis

The diagnosis of SMA has progressed from past electromyography and muscle biopsies to current genetic testing and other newer techniques. The most common way for a genetic test to confirm a 5q-SMA diagnosis is for the results to show a biallelic mutation on SMN1 where either both exons 7 and 8 are spliced out or just exon 7 is spliced out. The copy number of SMN2 is also a point of interest for diagnosticians as it can provide information on the possible severity of the disease and whether the patient should begin treatment. The specific genetic tests that can be done to determine these two parameters are quantitative real-time PCR, digital PCR, MLPA, and next-generation sequencing methods. The preferred test to determine the number of SMN2 copies an individual has is currently MLPA, although research has shown that it is not without its flaws and may have problems determining copy numbers greater than two. Serum creatine kinase (CK) and serum creatinine levels are also tested in patients with SMA to determine muscle abnormalities and chest radiography is another technique to visualize anatomical deformities in patients with Type I SMA [3].

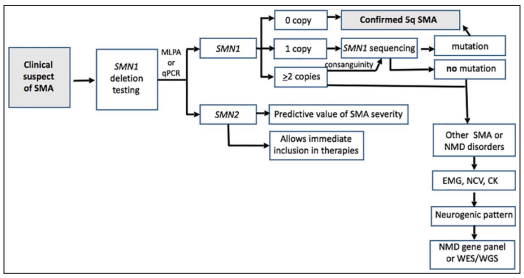

Figure 2: Flowchart depicting the process to diagnose SMA in individuals in which the disease is suspected (NMD: neuromuscular disorders; NCV: nerve conduction velocity; WES: whole exon sequencing; WGS: whole genome sequencing) [6].

Typing

SMA is typed based on the age of onset of the individual with the disease and the maximum motor function the individual

has without any treatments or interventions. It is important to note that not all patients with the same type of SMA have the exact same abilities, as every individual is genetically and anatomically unique and may have undergone differing therapies across their lifespan. The information that follows is the most seen presentations of each type of SMA and can vary depending on the individual with SMA [2,7].

Type 0 SMA, also called congenital SMA, is the most severe type with decreased fetal movements detected prior to birth. Newborns with type 0 SMA present with difficulty feeding and breathing at birth along with severe weakness. Respiratory failure and death is often seen at birth or within the first month of life in patients with type 0 SMA. The most common type of SMA is type I, or severe, SMA. Around 60% of patients with SMA are diagnosed with this type and it is also named Werdnig-Hoffman disease. Patients with type I SMA are usually diagnosed before six months of age and present with trouble breathing, coughing, and swallowing as well as limited head control. Severe muscle weakness and decreased muscle tone (hypotonia) is also seen in type I individuals. Without breathing support or any other interventions, these individuals usually die before the age of two. Type II SMA is an intermediate type and is also called Dubowitz disease. It is typically noticed and diagnosed between 6-18 months of age and patients experience hypotonia and worsening muscle weakness affecting the lower extremities more than the upper extremities. These individuals can usually sit without support but cannot stand or walk. Around 75% of individuals with type II SMA live until the age of 25, with some living into their 30s. The most common cause of death in type II patients is respiratory failure. Type III SMA, often called mild SMA or Kugelbert-Welander disease, is noticed after 18 months of age. Individuals with this type can usually walk independently but may have difficulty, especially after they have hit puberty. They may have trouble doing more strenuous physical motor skills such as rising from a chair, running, or climbing stairs. Individuals with type III SMA do not typically experience respiratory issues, allowing a normal life expectancy. Lastly, type IV SMA, or adult SMA, develops after 18-21 years of age and often presents as mild to moderate leg muscle weakness. These individuals remain mobile, and the disease does not typically affect life expectancy [2,7].

Standards of Care

The international standards of care for spinal muscular atrophy were first established in 2007 and updated in 2017. The 2017 update was led by Professors Richard Finkel from the United States and Eugenio Mercuri of Europe. Fifteen core individuals collaborated with over 100 experts through conference calls, e-mails, and surveys to develop a multidisciplinary approach of nine key areas of care for SMA [8]. This document divides each discipline into its standards for non-sitters (patients with SMA who cannot sit up on their own), sitters (patients with SMA who can sit up on their own but cannot walk), and walkers (patients with SMA who can walk).

The first approach mentioned in the official updated standards of care is neuromuscular and musculoskeletal rehabilitation. For all three categories of SMA patients mentioned (non-sitters, sitters, and walkers), three considerations are made: positioning and bracing, stretching, and promoting function and mobility. In terms of positioning and bracing, non-sitters use seating systems, support for posture and positioning of the body, bracing for the thorax, and cervical bracing for supporting the head daily. These patients are recommended to utilize orthoses on upper and lower limbs, static knee immobilizers, and hand splints. Stretching and range of motion (ROM) exercises are recommended 3-5 times per week and bracing is recommended at least 5 days per week to be effective. Positioning and bracing are similar for sitters to non-sitters, but sitters do not always require cervical bracing. Stretching at body regions such as the hip, knee, ankle, and wrist which are at a high risk for contracture are important for sitters, as well as the use of orthoses. Some recommended exercises for sitters to promote function and mobility include swimming, hippotherapy (horseback riding as therapy to practice balance, strength, and coordination), and wheelchair sports. Walkers with SMA should engage in aerobic and general conditioning to promote function and mobility, as well as stretching 2-5 times per week to maintain flexibility [6].

Orthopedic management is important in SMA patients and most often comes in the form of spine deformity management. It begins with a clinical examination of the spine, a further spinal x-ray, and determination of the angle of scoliosis in the patient. Patients with an angle of less than 15-20° will be monitored for further angle curvature, whereas patients with angles of scoliosis greater than 15-20° will undergo intervention. Thoracic bracing and monitoring are the standard of orthopedic spine care for any scoliosis angle between 15-20° and 50°, and surgical interventions will be suggested to patients with an angle greater than 50°. Within this most severe spinal deformation subtype of patients, skeletally immature patients will be considered for growing rods, vertical expandable prosthetic titanium rib (VEPTR), and magnetic bars, whereas skeletally mature patients will be considered for spinal fusion [6].

Regarding nutritional management, swallowing, and gastrointestinal (GI) dysfunction, a Video Fluoroscopic Swallow Study is usually done on patients with more severe subtypes of SMA. A plan of care can then be assessed based on the results of this study. A failure on the study can result in a nasojejunal (NJ) tube being placed until a gastric-tube can be placed. If the study is passed, meaning it is safe for the patient to swallow, he/she will be referred to a specialist for feeding therapy/modification. Levels of nutrients, vitamins, minerals, and electrolytes should be monitored via a dietician for mostly all patients with SMA to ensure proper growth and development. It is important to consider other GI concerns in patients with SMA, such as gastroesophageal reflux, constipation, etc. Researchers have seen a recent rise in metabolic abnormalities in patients with SMA, leading to further complications [6].

Managing the pulmonary function in individuals with SMA is important due to the key role it plays in survival. Pulmonary assessment in SMA patients contains a physical examination, end tidal CO2 measurement to evaluate hypoventilation, sleep studies/pneumograms in patients who may exhibit nocturnal hypoventilation, and assessment of esophageal reflux. Pulmonary interventions that are common for non-sitters with SMA are support of airway clearance, airway suctioning, physio/respiratory therapy, manual chest therapy, a cough insufflator/exsufflator, and a bilevel NIV to support ventilation. If the patient

has asthma or a positive bronchodilator response, they should be given a nebulized bronchodilator. Patients should also receive customary vaccinations, such as palivizumab through 24 months and the influenza vaccination annually after 6 months. The standard of care for sitters is very similar to that of non-sitters, and ambulant patients, or walkers, are suggested to just receive supportive care when needed and customary immunizations [9].

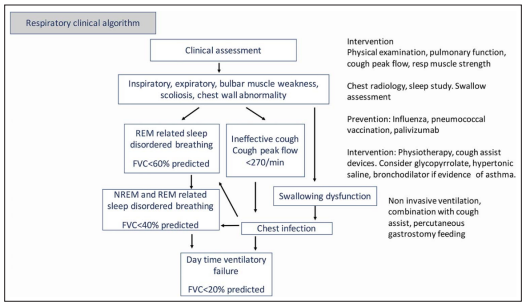

Figure 3: Clinical algorithm for pulmonary testing in patients with SMA and associated interventions [9].

It is vital to recognize and plan for the acute care of individuals with SMA. These individuals are particularly vulnerable to infections, aspirations, respiratory decomposition, and impaired secretion clearance. It may be necessary for the individual to go to the hospital if they become dehydrated, obtain a fever, or have any other signs of illness. Care plans are recommended for individuals with SMA that include outlines for airway clearance, ventilation, nutrition, hydration, antibiotics, and emergency contact measures. Caretakers of individuals with SMA should be equipped with homecare technology for possible acute incidents especially related to pulmonary problems. When being transported to a hospital, non-sitters and sitters should be taken to a tertiary care center with SMA expertise and screened for nutrition, cardiac abnormalities, airway status, etc. before undergoing any procedure. Medications and supplements that do not specifically target the SMA disease mechanism but are commonly prescribed/recommended to individuals with SMA are albuterol, bisphosphonate, calcium, drugs for gastroesophageal reflux, and annual influenza and pneumococcal vaccinations [9].

Cardiac abnormalities are sometimes seen in patients with type 0 SMA but occur much less frequently in types II and III SMA. Endocrine dysfunction can occur leading to diabetes and hyperleptinemia, as well as mitochondrial dysfunction being seen in patients with SMA. Since other organ involvement is not consistently seen in all types of SMA, clinicians base other organ involvement on current symptoms of the individual with SMA [9].

The outlined standards of care for SMA state that it is important for individuals with SMA and their families to be educated on both interventions and palliative care to decide what is best for them. Palliative care is often associated with end-of-life care, however the two are not synonymous. Palliative care can take place over many years for debilitating chronic conditions such as SMA. Overall, palliative care and interventional treatment are not mutually exclusive when it comes to SMA and benefits and risks should be weighed with both options, as well as considering quality of life of the individual with SMA [9].

Current Treatments

Since 2017, three approved therapies for SMA have emerged: nusinersen (Spinraza®) by Biogen, onasemnogene abeparvovec (Zolgensma®) by Novartis, and risdiplam (Evrysdi®) by Roche [10]. Nusinersen is an antisense oligonucleotide that inhibits splicing factors in the SMN2 pre-RNA. This alters the splicing process of the RNA by allowing exon 7 to be included in the transcribed protein product, resulting in a full-length fully functional SMN protein. Having more SMN protein can reduce the degradation of motor neurons in patients with SMA and improve symptoms. Nusinersen is injected intrathecally via lumbar puncture every four months to patients who receive the therapy. Individuals of all ages and types of SMA can be considered for therapy with nusinersen [11].

Risdiplam is a small molecule splicing modifier that is administered orally as a tablet once a day. It is approved for patients with SMA older than 2 years of age and works to promote the inclusion of exon 7 in the SMN protein transcript, creating a fully functional SMN protein to counteract the severity of symptoms and disease progression of patients with SMA types I-III [12].

Onasemnogene abeparvovec (Zolgensma) has been recently approved for individuals with SMA under the age of 2. It is more time- and cost-effective than nusinersen and risdiplam (once obtained and administered) for patients who are diagnosed with SMA at an early age [13]. It is a single-dose of an adeno-associated vector 9 (AAV9) which functions in gene delivery [14]. The vector is administered intravenously and crosses the blood-brain barrier. It uses enhancers and silencers to create a functional copy of the SMN1 gene, leading to the production of SMN protein to counteract the patient's spinal muscular atrophy [13].

Patients with SMA who are identified in newborn screening as having the disease are recommended for "bridging" therapy to keep their symptoms from progressing. This intermediate therapy would be administered in the time from when they are identified to have SMA to when they are able to be approved for and obtain the onasemnogene abeparvovec treatment. As of 2022, the primary drug used for this intermediate situation is nusinersen, but researchers are suggesting the use of risdiplam instead due to its less invasive administration route and a shorter time to achieve steady state (2 months for nusinersen, 1 week for risdiplam) [12].

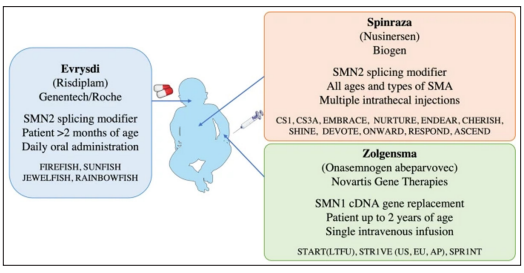

Figure 4: Summary of the FDA-approved therapies targeting SMN depletion for patients with spinal muscular atrophy [15].

Discussion

Stem Cell Overview

Stem cells are cells that can self-renew and differentiate into varying cell types. The two main categories of stem cells are pluripotent stem cells which can differentiate into virtually any

cell type in the body and somatic, or adult, stem cells which are multipotent and can only differentiate into specific cell types. The two main types of pluripotent stem cells are human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). Human embryonic stem cells are derived from the inner cell mass of the blastocyst during embryonic development, whereas iPSCs are genetically reprogrammed adult somatic cells that are altered to be pluripotent. The two main types of somatic stem cells are hematopoietic and mesenchymal stem cells. Hematopoietic stem cells are derived from bone marrow (BM), umbilical cord blood (UCB), and peripheral blood, while mesenchymal stem cells are derived from adipose tissue, BM, UCB, dental pulp, perivascular cells, and the placenta [16].

The use of stem cells in the field of regenerative medicine is a popular area of current research. Stem cells can either be allogeneic or autologous, meaning the stem cell donor is someone other than the recipient (allogeneic) or the stem cell recipient is their own donor (autologous). In terms of using stem cells to treat neurodegenerative disorders like SMA, researchers have focused on neural stem cells that are derived from hESCs. By using retinoic acid, sonic hedgehog (a signaling molecule in embryonic development), and neurotrophic factors, neural stem cells are believed to differentiate into motor neurons, improving the SMA disease phenotype [17].

Animal Studies

Four different animal studies completed on mice showed encouraging results for the future of stem cell use to help treat spinal muscular atrophy. The first study was published in December, 2005. The researchers conducting this study investigated the possibility of stem cells to change disease progression in nmd mice: the animal model of spinal muscular atrophy with respiratory distress type 1 (SMARD1). This disease differs slightly from SMA in that it is characterized by the lack of the immunoglobulin μ-binding protein 2 instead of the SMN1 protein, but many of the symptoms of the two diseases are the same. The stem cells used in this study were neural stem cells isolated based on aldehyde dehydrogenase (ALDH) activity. The researchers injected ALDHhiSSClo neural stem cells intrathecally into B6.BKS lghmbp2nmd^-2j mice (nmd mice) with an average lifespan of 3.5-4 weeks. The stem cells displayed multipotency and self-renewal by producing motor neurons in the ventral horns of the mice's spinal cord. This generation of new neurons delayed the progression of the mice's disease and thus increased their lifespan by 74.9 +/- 13.3 days in males and 88.3 +/- 17.1 days in females with the longest survival being 107 days (256.7% increase) in the male population and 127 days (323.4% increase) in the female population. The results also showed an increase in mean body weight in treated nmd mice compared to untreated nmd mice, improved motor function on the accelerating rotarod compared to untreated nmd mice, a longer lifespan as previously mentioned, and improved limb extension during the drop-test of the nmd mice (Figure 5). This study overall showed promising results in the mice population, so further studies were conducted to continue investigation of this therapy [18].

A study published in 2008 was done on mice lacking the SMN gene but with two copies of the human SMN2 gene and additional SMN cDNA lacking exon 7 (SMNΔ7 mice). These mice exhibit a type I SMA phenotype and have an approximate lifespan of 15 days. The SMNΔ7 mice were injected intrathecally with spinal cord neural stem cells. These stem cells were previously recovered from healthy mice expressing green fluorescent protein (GFP) in their motor neurons only. When injected into SMNΔ7 mice, the neural stem cells migrated to the parenchyma and produced a small proportion of motor neurons, leading to improved neuromuscular function, improved motor unit pathology, and an increase in lifespan in the SMA mice by ~21% [19].

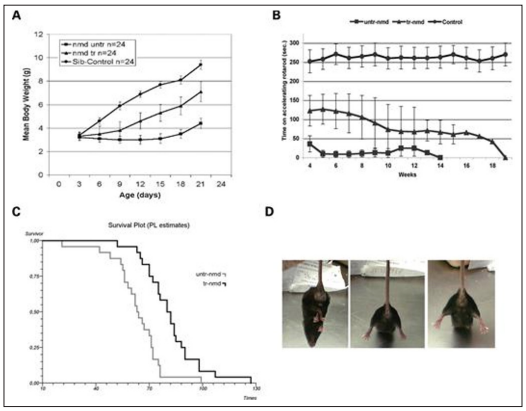

Figure 5: Various results of the study done by Corti et al. published in 2006. Graph a shows the mean body weight of wild-type mice, ALDHhiSSClo neural stem cell treated nmd mice, and untreated nmd mice. Graph b shows these three models' results on the accelerating rotarod, graph c shows the lifespan increase between treated and untreated nmd mice, and the images in figure d show the limb extension of untreated, treated, and wild-type mice during the drop test [18].

Another study investigating the use of stem cells on SMA mice was conducted and published in 2011. The researchers focused on three conditions that are characterized by motor neuron degeneration: amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and spinal cord injury (SCI). Human embryonic stem cells (hESCs) were differentiated into high purity hESC-derived motor neuron progenitors (hMNPs) and the growth factors secreted by these progenitors were observed when the progenitors were injected into varying animal models. Growth factors have previously been attributed to some of the functional recovery seen after hESC-derived oligodendrocyte progenitor cell transplantation into SCI models, so the researchers aimed to widen this application to all three conditions studied. Experiments looking at the effect of transplanted hMNPs were done both in vitro and in vivo in this study, but this analysis will be focusing on the in vivo effect in the SMA animal model as it relates to the overall SMA-stem cell relationship. The SMA model (SMNΔ7 mice) were injected with 20,000 hMNPs (10,000 cell/μL) which were transplanted bilaterally into the spinal cord. After injection of the hMNPs, the researchers observed human cells with the young motor neuron marker Islet-1 in the ventral horns of SMNΔ7 mice treated with the hMNPs and not in the control mice. However, they did not observe the markers ChAT and SMI-32 that are expressed by mature motor neurons. Thus, the researchers concluded that the SMNΔ7 mice did not live long enough for the stem cells to have time to differentiate even though they showed proliferation in the appropriate biological location for SMA. These markers, and thus proven differentiation of the hMNPs, were found within the SOD1 G93A (ALS mice) and SCI animals who lived for

2 and 3 months, respectively, post-transplantation. The growth factors assessed in this study were nerve growth factor (NGF), neurotrophin-3 (NT-3), vascular endothelial growth factor (VEGF), and neurotrophin-4 (NT-4). When measuring these growth factors secreted by the hMNP transplant, a significant increase in NGF, NT-3, and NT-4 was observed between the vehicle control and the hMNP transplanted animals, while no significant increase in VEGF was observed between the two groups (Figure 6) [20].

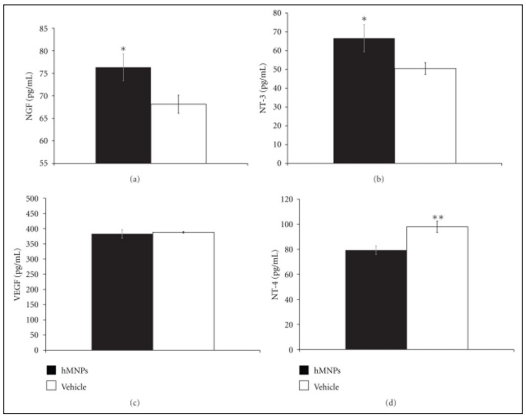

Figure 6: In vivo measurements of NGF (a), NT-3 (b), VEGF (c), and NT-4 (d) taken by the enzyme-linked immunosorbent assay (ELISA) [20].

These results were followed by an observed increase in the number of spared endogenous neurons in all three animal models, suggesting that neurotrophic factors introduced by hMNPs are an important aspect in the motor neuron maintenance in diseases such as ALS, SMA, and SCI, and that stem cell progenitors could be a possible therapy with further research [20].

In December 2012, another study was conducted investigating the use of iPSCs in vitro and in vivo. Human iPSCs were generated from human patients with SMA and differentiated into motor neurons, resulting in motor neuron degeneration as expected. The researchers then used an oligonucleotide (like nusinersen) to permanently genetically modify a nucleotide in SMN2 exon 7 that resulted in its inclusion to create full-length SMN2 transcripts and thus more fully functional SMN protein. The phenotypes of SMA-iPSC treated- and untreated-derived motor neurons were then compared in vitro by splicing analysis and by using gene expression data. This comparison in the motor neurons was also assessed by injecting transgenic SMA mice intrathecally with the SMA-iPSCs. The stem cell motor neurons engrafted in the appropriate biological location (the anterior spinal cord) of the SMA mice were seen to improve the SMA type I phenotype. SMA mice transplanted with the genetically modified SMA-iPSCs exhibited a ~50% increase in lifespan compared to control mice. This result was enhanced by using heterozygous iPSCs (HET-iPSCs) along with the genetically modified SMA-iPSCs. The results seen by this transplantation of motor neuron stem cells does differ from transplantation of other material, such as fibroblasts, providing some hope for the use of stem cell therapy for the treatment of SMA. However, the results are not comparable to other therapies like gene therapy using drugs such as Zolgensma, so the combination of therapies may be the best option in the future for individuals with SMA [21].

Human Clinical Trials

Three clinical trials involving patients with spinal muscular atrophy and the possible treatment of stem cells were started over the past 20 years with varying updates on where they are in their progress. The first human clinical trial began in 2009 in Jerusalem, Israel by the Hadassah Medical Organization. It has an enrollment of 120 individuals, all over the age of 18. There are 20 individuals in the control group without neurological diseases, and there are 100 individuals representing 10 different neurological diseases (10 in each group). This is an observational study that takes samples of patients' skin or hair to obtain their fibroblasts. These fibroblasts are then genetically reprogrammed into iPSCs by forced expression of transcription factors to study the pathogenesis of each disorder and possible treatments. The trial was last updated on March 25, 2025, with an active recruiting status and its estimated completion is December of 2030, thus the trial has no current published results [22].

One of the clinical trials known to look at SMA type I with stem cell therapy was started in June 2015 with an estimated completion of July 2017. It was sponsored by the Tehran University of Medical Sciences and was planning to investigate the effectiveness of allogeneic adipose-derived mesenchymal stem cells in the phenotypic changes of patients with SMA type I, otherwise known as Werdnig Hoffman disease. This was a non-randomized allocation study with an interventional model and single group assignment. Unfortunately, the study has no published results and hasn't been updated since August of 2016 [23].

Another nonproductive clinical trial began in September 2016 by the organization Stem Cells Arabia, where researchers transplanted purified autologous bone marrow-derived stem cells intrathecally and intravenously into human patients with varying motor neuron diseases such as ALS, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), and sometimes spinal muscular atrophies. It was an interventional study with a single group assignment. The study was estimated to be completed in August of 2019, but has not been updated since June of 2018 and has an unknown recruitment status [24].

A current phase I clinical trial being conducted in Minnesota is testing the use of stem cell-derived muscle progenitor cells in individuals with Duchenne muscular dystrophy (DMD). DMD is an inherited genetic disorder that causes progressive muscle weakness and degeneration similar to SMA. The researchers in this clinical trial are using the drug MyoPAXon, a CD54+ allogeneic muscle progenitor cell product derived from the iPSC line LiPSC-ER2.2, along with the drug Tacrolimus which is an immunosuppressant used to prevent transplantation rejection and graft versus host disease (GVHD) due to the allogeneic nature of the transplanted cells. MyoPAXon will be administered intramuscularly (IM) at four different concentrations and its intended purpose is to improve the muscle weakness and degeneration seen in DMD patients. The trial is a non-randomized allocation trial with parallel assignment and accepts any patient older than 18 years old with DMD with a few exclusion criteria. There are currently eight individuals enrolled and its estimated completion is March of 2027. This research, if found to be significant, could possibly be applied to patients with SMA in future clinical trials [25].

Beike Biotechnology Program

In Bangkok, Thailand, researchers at the Shenzhen Beike Biotechnology enterprise have founded a program to treat patients with SMA using stem cells. It is not specified in the program information which specific types of SMA patients (I-IV) this program treats. Patients stay at the program for anywhere from 15-23 days and receive 4-8 minimally invasive injections of umbilical cord-derived mesenchymal stem cells donated from healthy mothers after a normal birth. These stem cells are chosen for treatment because they can easily cross the blood-brain barrier to have a greater effect on the nervous system and they are also proven to have the least severe side effects. The stem cells are administered to patients through a standard IV drip as well as intrathecally via a lumbar puncture. Using both routes of administration has been shown to provide better results than intrathecally alone. Overall, patients receive anywhere from 120-400 million stem cells throughout their treatment. The program also provides daily occupational and physical therapy to patients in the program to help improve their symptoms along with the stem cells as well as a nutrition program to control for any confounding variables that come with gastrointestinal issues. The latest update from this program was in December of 2024 where the results of a questionnaire answered by 18 patients that went through this program were posted (Table 1) [26].

Table 1: Table showing the results from the questionnaire answered by 18 of the Beike Biotechnology program's patients [26].

	% of Patients, who noticed Improvement	% of Patients who noticed a Small Improvement	% of Patients who noticed a Moderate Improvement	% of Patients who noticed a Large Improvement
Energy	100%	43%	21%	36%
Trunk control	88%	35%	35%	18%
Movement in general	88%	35%	41%	12%
Balance	88%	41%	35%	12%
Limb muscle strength	94%	65%	24%	6%
Overall strength	88%	44%	31%	13%
Trunk muscle strength	88%	44%	38%	6%
Fine motor control	87%	40%	40%	7%
Hand control	93%	50%	43%	0%
Range of movement	81%	44%	38%	0%
Standing up	73%	53%	13%	7%
Swallowing	78%	22%	33%	22%
Spasticity	60%	50%	10%	0%
Walking	43%	29%	14%	0%
Crawling	38%	23%	15%	0%

Overall, patients saw some improvement in every symptomatic category with some improvements being more drastic than others. This provides an encouraging future for the use of stem cells to treat patients with SMA.

Case Study

The following case study focuses on a 23 year old female student obtaining a master's degree in architecture at an institution of higher learning. The student wishes to remain anonymous but has consented to be a part of the study.

When first asked what her symptoms were that sparked her SMA diagnosis, she states that she wasn't physically progressing as a normal child should. She was experiencing delays in motor skills such as rolling over, crawling, and sitting up without assistance. Her parents addressed their concerns with her pediatrician where she was then referred to a neurologist and further diagnosed with SMA type II at 13 months old. At age 4, she got her first motorized wheelchair. Since then as she has grown, she has cycled through various motorized wheelchairs which is what she uses daily to navigate her surroundings.

Over the course of her lifetime, she has seen an increase in the severity of her symptoms, primarily concerning an increase in overall muscle weakness. She notes that she used to participate in activities like dance until she was in the 8th grade, as well as band in middle and high school and marching band in high school and college. These activities helped retain endurance in her arm muscles. She also states that frequent physical therapy (PT) helped retain her muscles' strength. However, she has lost this endurance since being in graduate school because she cannot go to PT in the state her school is in due to insurance and government limitations. She also was not accepted into the band at her graduate school due to lack of accommodation for her needs which has ceased her involvement in this activity.

To get an accurate picture of the clinical care the student has received over the course of her lifetime, she was asked which physicians/specialists she has worked with in relation to her diagnosis. She recounts her first interaction with a physician about her SMA symptoms was her pediatrician. Her pediatrician put her in contact with an organization called Babies Can't Wait, "Georgia's statewide interagency service delivery system for infants and toddlers with developmental delays or disabilities and their families" to get her started in PT. As previously mentioned, she was referred to a neurologist who she saw a few times as a child, but the student now works with the neurologist's nurse practitioner every eight months. She has been seeing a pulmonologist once a year since she was under the age of 10 years old. She was also under the care of an orthopedic surgeon to attempt to correct musculoskeletal deformities in her feet and spine at a young age. Currently, she sees her pulmonologist and her nurse practitioner to manage her SMA.

Clinical care and therapies are an important aspect of managing any individual with SMA. The student in this case study has undergone PT since she was a small child. Throughout her younger years before college, she attended PT once or twice a week depending on her schedule. During a typical PT appointment, the physical therapist would focus on stretching the student's hamstrings, knees, and feet due to the risk of her joints and limbs in general becoming stiff and immobile. She also was in occupational therapy (OT) for a shorter period when she was younger, yet this was discontinued due to the student's busy schedule and her consistent use of her arms in daily tasks, negating the need to practice these said tasks. When she was in

kindergarten (~5-6 years old), the student underwent a heel cord lengthening surgery to attempt to improve her ankle mobility and flatten her foot. This procedure ultimately proved to be unsuccessful. The following year, she underwent an orthopedic surgery to put a metal rod in her back to correct her SMA-induced scoliosis. This correction aided in the curvature of her spine as well as allowing her lungs to function without the pressure of her spine crushing them. In addition to this, the student is monitored in an in-patient sleep study every other year to primarily assess whether the student is releasing enough CO2 during her respirations while she sleeps. During her time sleeping, her heart rate, breathing, and brain, eye, and muscle activity are also measured to ensure proper biological functioning. This sleep study is analyzed by her pulmonologist. In addition to the sleep study, the student is given a pulmonary function test to assess her lungs and breathing. Lastly, the patient has undergone the nusinersen therapy every four months (after her loading doses) since her senior year of her undergraduate studies. She was given loading doses every two weeks for three times, then another loading dose a month later, then normal treatments after that (Biogen-recommended dose every four months). She states that she feels significantly weaker in the last month before her next nusinersen treatment due to the drug effects tapering off, which is a common observation amongst people with SMA who undergo this treatment. An increase of the nusinersen dosage that is given every 4 months has been studied and is currently awaiting approval to combat this problem.

The student states that her prognosis is not mentioned during her appointments with her nurse practitioner or any other specialist. Her parents were told at the time of diagnosis to not search the disease on the worldwide web to learn limitations and life expectancy that came with the disease, but instead to allow her to achieve milestones as they came. Her prognosis is not a current topic that is discussed during her recent appointments regarding SMA. She importantly states that her physicians have never mentioned stem cell therapy as a possible remedy to SMA or its symptoms.

The spectrum of physical abilities is vast when it comes to both different- and same-type SMA. The student emphasized how two individuals diagnosed with the same type of SMA can have different abilities in different areas, such as holding a cup, moving their arms, etc. She also points out that internal biological functions can also vary between and within SMA types. Things such as breathing, digesting, swallowing, and going to the bathroom can be different experiences for different people with SMA depending on the severity of their diagnosis.

Summary & Conclusions

Overall, the evidence on the efficacy of stem cells in the treatment for SMA seems to vary and still be in the research phase. There is not enough research or evidence for the use of stem cells for the treatment of SMA to be approved by the FDA or any other agency at this time. Since the genetic and molecular therapies seem to be effective in maintaining and improving the SMA disease phenotype, the possibility for stem cell treatments to be combined with these other therapies seems like the most reasonable approach for further improvements in the treatment of SMA. There is a need for more productive clinical trials focusing specifically on the stem cell treatment of spinal muscular atrophy. Researchers could use the Beike Biotechnology program for insight into how to conduct the trials while further pinpointing the exact dose, type of stem cell, and administration route that would ameliorate the SMA symptoms in affected patients.

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