Review

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Cell therapy for diverse central nervous system disorders: inherited metabolic diseases and autism

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The concept of utilizing human cells for the treatment of medical conditions is not new. In its simplest form, blood product transfusion as treatment of severe hemorrhage has been practiced since the 1800s. The advent of hematopoietic stem cell transplantation (HSCT) began with the development of bone marrow transplantation for hematological malignancies in the mid-1900s and is now the standard of care for many hematological disorders. In the past few decades, HSCT has expanded to additional sources of donor cells, a wider range of indications, and the development of novel cell products. This trajectory has sparked a rapidly growing interest in the pursuit of innovative cell therapies to treat presently incurable diseases, including neurological conditions. HSCT is currently an established therapy for certain neurologically devastating inherited metabolic diseases, in which engrafting donor cells provide lifelong enzyme replacement that prevents neurological deterioration and significantly extends the lives of affected children. Knowledge gained from the treatment of these rare conditions has led to refinement of the indications and timing of HSCT, the study of additional cellular products and techniques to address its limitations, and the investigation of cellular therapies without transplantation to treat more common neurological conditions, such as autism spectrum disorder.

Genetic and neurological conditions of childhood are incredibly challenging for all parties involved. Currently available therapies consistently fall short for affected children, leaving them with life-long disabilities and, often times, shortened lifespans. The persistent unmet need for novel therapeutic approaches for children with genetic and acquired neurological diseases and the rise of the field of regenerative medicine have sparked interest in the development of biological, cell-based therapies for these conditions. In this article, we will review the current status of cell therapies for two types of neurological conditions that manifest in childhood: hematopoietic stem cell transplantation (HSCT) in patients with inherited metabolic diseases (IMDs), and investigational cellular therapies in patients with autism spectrum disorder (ASD).

INHERITED METABOLIC DISEASES

IMDs are a heterogeneous group of genetic diseases. In most of these conditions, a genetic mutation results in lack of a particular enzyme, resulting in the accumulation of toxic substrates and/or disruption of normal cellular processes throughout the body. Many affected babies appear normal at birth but begin to develop neurological symptoms in infancy or early childhood. Though the time course varies, these diseases cause progressive neurological deterioration ultimately leading to death later in infancy or childhood.

Strategies to prevent disease progression in the IMDs have focused on replacing the missing enzyme either via recombinant enzyme replacement therapy (ERT) or HSCT. Intravenous ERT is available for selected lysosomal storage diseases and is effective in improving certain systemic disease manifestations. It has several limitations, however, including the need for lifelong intravenous infusions, the risk of an immune response to the recombinant enzyme that can render the infusion both dangerous and ineffective, and the inability to reach several tissues or organs in sufficient quantities. In particular, ERT cannot effectively cross the blood–brain barrier and therefore cannot prevent the progression of neurological symptoms (1,2). Intrathecal ERT (3), chaperone technology (4–6), and gene therapy are under investigation as alternative methods to addre.ss this limitation.

Gene therapy for selected IMDs has been the subject of preclinical (7–11) and a few small human studies. Early-phase clinical trials of *in vivo* gene transfer, in which genetic material is delivered directly to a patient, are underway using adenovirus vectors in Hurler (NCT02702115), Hunter (NCT03041234), Sanfilippo (NCT02716246), and Maroteaux–Lamy (NCT03173521) syndromes, Batten disease (NCT01414985, NCT01161576, NCT00151216), and Metachromatic leukodystrophy (MLD, NCT01801709). In one study of 10 patients with Batten disease, intracranial injections of adenovirus-associated DNA failed to prevent disease progression, although the rate of neurological decline slowed somewhat. Four patients developed an immune response to the vector, and one patient developed status epilepticus 2 weeks after treatment and died a month later (12). Another gene therapy approach involves *ex vivo* manipulation of autologous or donor cells *in vitro* that are subsequently

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delivered to the patient. The only published data of this technique in IMDs involved autologous HSCT using CD34+ cells genetically modified via lentiviral transduction and then reinfused in patients with adrenoleukodystrophy (ALD) (13) or MLD (14,15) after conditioning with busulfan+/ – cyclophosphamide. The two patients with ALD showed an arrest of cerebral demyelination 12–16 months after treatment (13). The first nine patients with MLD treated with gene therapy demonstrated transduced cell engraftment of 14–95% with improvement of enzyme levels in the peripheral blood and clinical benefit without evidence of antibody formation or malignancy with a median follow-up of 3 years (14). Follow-up of the entire study cohort is ongoing. Although gene therapy approaches have been encouraging in animal models, issues regarding the possibility of ongogenesis, development of immune responses to the vector or novel protein, and unclear ability of vectors and enzymes to traverse the blood–brain barrier remain potential limitations in their translation to clinical use. Currently, the only effective therapy to halt neurological progression in certain IMDs is allogeneic HSCT.

Mechanism of HSCT in IMDs

Following successful HSCT, donor-derived cells engraft in the bone marrow and distribute throughout the body, including peripheral tissues and the central nervous system, and serve as a constant endogenous source of the missing enzyme, thereby slowing or halting the progression of disease (16,17). The basis for this concept was first introduced in the 1960s by Elizabeth Neufeld, who demonstrated that co-culture of fibroblasts from patients with two different IMDs (Hunter and Hurler syndromes) resulted in correction of each condition via intercellular enzyme transport between cells (18). This phenomenon of 'cross-correction' is the primary mechanism of ERT and of cellular therapy used for that purpose. In the brain, donor-derived microglia cells of myeloid origin are thought to be the source of ERT after HSCT (19). These donor-derived cells secrete a portion of their lysosomal enzymes that can then be taken up by neighboring cells, thereby cross-correcting the metabolic defect in affected host cells (19–21). In addition to acting as a permanent source of ERT, engrafted donor-derived cells may potentially aid in reducing the burden of accumulated toxic substrates in the brain and/or exert anti-inflammatory and pro-neurogenic effects through paracrine signaling.

Clinical Experience in Subtypes of IMDs

There are hundreds of different IMDs. HSCT is currently indicated or under investigation for a subset of these disorders, including lysosomal storage diseases, peroxisomal storage diseases, and a few select others (see **Table 1**).

Table 1. IMDs for which HSCT is indicated or under investigation

HSCT indicated*	HSCT investigational	ERT first-line therapy
Lysosomal storage disorders	*Lysosomal storage disorders*	*Lysosomal storage disorders*
Mucoploysaccharidoses	Mucoploysaccharidoses	Mucoploysaccharidoses
Hurler (MPS IH), severe phenotype	Hunter (MPS II), with CNS disease	Hurler (MPS IH/S, IS), attenuated phenotypes
	Sanfilippo (MPS IIIA–D)	Hunter (MPS II), without CNS disease
	Morquio (MPS IV)	Maroteaux–Lamy (MPS VI)
	Sly (MPS VII)	
Sphingolipidoses	Sphingolipidoses	Sphingolipidoses
Globoid leukodystrophy (Krabbe)	GM1 gangliosidosis	Fabry
Metochromatic leukodystrophy (MLD)	GM2 Gangliosidosis, type 1 (Tay–Sachs)	Gaucher, types 1/3
	GM2 gangliosidosis, type 2 (Sandhoff)	
	Farber	*Other*
	Gaucher, neuronopathic type	Pompe
	Neimann Pick – A/B	
Oligosaccharidoses		
Alpha-mannosidosis	*Peroxisomal storage disorders*	
Fucosidosis	Adrenomyeloneuropathy	
Other LSDs		
Mucolipidosis II (I-cell disease)	*Other*	
Wolman disease	Batten disease	
	Pelizaeus–Merzbacher disease	
Peroxisomal storage disorders		
Adrenoleukodystrophy (ALD)		

CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplantation; IMD, inherited metabolic disease; MPS, mucopolysaccharidosis.
*Suitability for HSCT is dependent on the symptom severity and functional status of the patient as well as donor availability and is considered on an individual basis.

Mucopolysaccharidoses. The mucopolysaccharidoses (MPS) are lysosomal storage diseases in which a particular enzyme deficiency leads to progressive accumulation of incompletely degraded glycosaminoglycans in lysosomes, causing broad disease manifestations, including psychomotor retardation, musculoskeletal manifestations, vision and hearing impairment, and life-threatening cardiopulmonary failure. The first HSCT for an IMD was performed in 1980 in a 1-year-old child with Hurler syndrome (MPS1) using bone marrow from his parents (22). Since then, >500 transplants have been performed worldwide in patients with Hurler syndrome, making it the most transplanted and well-studied IMD.

Numerous reports have demonstrated the efficacy of both bone marrow and umbilical cord blood transplantation (CBT) in Hurler syndrome, including improvements in neurocognitive function, joint integrity, motor development, growth, hydrocephalus, corneal clouding, cardiac function, hepatosplenomegaly, hearing, visual and auditory processing, and overall survival (23–29). However, survivors still experience a variable degree of residual disease burden (30). Factors associated with superior clinical outcomes include transplantation early in the course of the disease and the ability to attain full donor chimerism and normal enzyme levels posttransplant (30,31). HSCT in other MPS types has also been performed in small numbers and suggest benefit in Hunter and Sanfilippo syndromes (32,33). Outcomes in other subtypes have been variable, raising the possibility that some MPS diseases may be more responsive to HSCT than others (34–41).

Leukodystrophies. Krabbe disease, a leukodystrophy caused by mutations in the enzyme GALC, leads to the accumulation of psychocine that causes apoptosis of myelin-forming oligodendrocytes and Schwann cells and increased inflammation in both the central and peripheral nervous systems. In the most common early infantile form, babies develop symptoms, including irritability, spasticity, developmental regression, and seizures within the first 6 months of life and die within 2 years. In 2005, the outcomes of 11 asymptomatic babies with Krabbe disease who underwent CBT in the first month of life were reported along with 14 infants transplanted after the onset of symptoms (42). With a median follow-up of 3 years, survival was dramatically increased in babies who were transplanted prior to the development of symptoms (100% vs. 42.8%). Newborns who underwent transplant with minimal-to-no symptoms of disease exhibited substantial neurodevelopmental gains in all areas of development compared with symptomatic infants and untreated patients. Nonetheless, some degree of gross motor function deficit became apparent in all the children. A more recent analysis of late outcomes demonstrated that babies transplanted <30 days of age have superior outcomes than those transplanted at >30 days (43).

MLD is a lysosomal storage disease caused by a deficiency in the enzyme arylsulfatase A, leading to accumulation of sphingolipids and a progressive loss of myelinating cells. The time of onset and severity of symptoms correlate with residual arylsulfatase A activity and vary widely from early- or late-infantile to juvenile and adult-onset forms. Neurological manifestations may include spasticity, neuropathy, dementia, seizures, and optic atrophy. Series of patients with MLD treated with HSCT report a 5-year overall survival of 59–74% and suggest that later-onset phenotypes may benefit more, particularly if HSCT is performed early in the course of the disease (44,45). Despite transplantation, may patients with MLD continue to experience progression of peripheral nervous system disease, although at a slower rate than expected by natural history.

X-linked ALD is a peroxisomal disorder of very long-chain fatty acid metabolism, resulting in their accumulation in tissues and plasma. Symptoms include cerebral demyelination, adrenal insufficiency, and progressive neurological deterioration. Patients are followed for the development of symptoms clinically and radiographically. The Loes score, a severity scale used to determine the extent and damage to myelin in the brain via magnetic resonance imaging, is predictive of the course of disease progression and is used to aid treatment decisions (46). This score has also been associated with neurological outcome post-HSCT, with boys transplanted with a lower Loes score and less clinical symptoms faring better than those in later stages of the disease (47,48).

HSCT: Lessons Learned

Although IMDs are rare, certain general principles have emerged from worldwide experience in HSCT for these conditions over the past few decades.

Limitations. Although HSCT has been effective in extending life for decades and preserving function in certain IMDs, it is currently ineffective in several IMDs and is not able to eradicate all sequelae of any given IMD. The degree of benefit varies among the different conditions and even among organ systems within a given condition. The reasons for this are still incompletely understood but include the possibility that thresholds of donor cell engraftment and enzyme production required to prevent disease progression differ between diseases and even between tissues in the same disease. Particular limitations are noted in diseases involving the peripheral nervous system, where peripheral nerve progression may occur despite stabilization of the central nervous system disease. Additional approaches are necessary to fully address the multifaceted tissue pathology in these diseases and normalize functional outcomes for patients. Augmented cellular therapies, such as CB-derived microglial-like cells (DUOC-01) (49–51) and others (52), gene therapies (15), supplemental enzyme therapy (53), and chaperone therapy, alone or in combination with HSCT, are all being investigated for this purpose.

Considerations of graft source and conditioning regimens. Particularly in Hurler syndrome, the IMD with the most data available, improved outcomes have been

associated with the ability to attain full donor chimerism and normal enzyme levels posttransplant (30,31). As most IMDs are inherited in an autosomal-recessive manner, many relatives are heterozygous carriers and therefore have lower than normal levels of the affected enzyme, making them less favorable donors. A retrospective study conducted by the European Group for Blood and Marrow Transplantation demonstrated statistically significant increases in both full-donor chimerism (93% vs. 67%) and normal enzyme levels (100% vs. 72%) when umbilical CB was utilized as a graft source compared with bone marrow or peripheral blood stem cells (54), and these high incidence levels have been reported in other series of CBT in Hurler syndrome and other lysosmal storage diseases (23,32,34,42,55). Among patients receiving CBT for Hurler syndrome, a shorter interval between diagnosis and CBT ($<$4.6 months 82% vs. $>$4.6 months 57%) and a conditioning regimen containing busulfan and cyclophosphamide (busulfan/cyclophosphamide 75% vs. other 44%) have been associated with a significantly higher event-free survival (56).

Based on these observations, current guidelines developed by the European Group for Blood and Marrow Transplantation for HSCT in MPS patients prioritize CB as a donor source in the absence of a non-carrier matched sibling or fully matched unrelated donor and recommend myeloablative conditioning with busulfan/cyclophosphamide (later replaced with busulfan/fludarabine) with exposure-targeted intravenous bulsufan. Since these guidelines were instituted in 2005, transplant outcomes in patients with Hurler syndrome have improved significantly. Engrafted survival rates are now 95%, with low transplant-related toxicity (29). As a result, fully matched CB grafts are now considered one of the most appealing cell sources, if not the most appealing cell source, for HSCT in patients with MPS.

Timing. Time is critical in the treatment of IMDs. The most favorable outcomes are achieved when patients undergo HSCT early in the course of the disease, either before symptoms develop or when they have minimal evidence of neurological disease (27,42,45). This has multiple implications. It is imperative to establish an accurate diagnosis as soon as possible. To that end, newborn screening for Krabbe disease has been implemented in six states. In addition to identifying eight patients with early infantile Krabbe disease, approximately 100 novel mutations of unknown significance have been identified in the *GALC* gene. Thus, while newborn screening may lead to diagnosis in the presymptomatic state, thereby enabling transplantation earlier in life, it has also highlighted the challenges of implementing a diagnostically challenging screening program and counseling families and providers regarding indeterminate results.

After a diagnosis has been made and a through evaluation completed, minimizing the time to transplant is often critical. In addition to advantages of CB as a donor source in terms of post-HSCT chimerism and enzyme levels, CB is readily available and has less stringent HLA matching criteria, often making it the most time efficient and thus preferable donor source.

Even after HSCT, the timing of migration and engraftment of donor-derived cells in the brain is unknown. Based on clinical observations, however, it is likely several months after hematological engraftment. As a result, patients often experience a progressive loss of neurological function for the first few months after HSCT before sufficient numbers of donor cells engraft in the brain and produce adequate levels of the deficient enzyme resulting in disease stabilization. Most patients are left with some degree of residual and irreversible neurological impairment. To try to address that issue, a CB-derived microglial-like cell product (DUOC-01) is under investigation at Duke University. This product is being tested in a phase I study as an intrathecal injection 4–6 weeks after CB transplant (NCT02254863).

Collaboration. Given the rarity and complexity of the IMDs, progress has only been made possible through the worldwide collaboration of multiple centers and disciplines. International registries, guidelines, and cooperative studies will be key to further refining indications for HSCT, optimizing transplant procedures, and developing approaches to address the current limitations of HSCT.

AUTISM SPECTRUM DISORDER

ASD, a neurodevelopmental disorder with onset in early childhood, is characterized by repetitive behaviors, a restricted range of activities, and impairments in social communication (57). It is a common disorder with a male predominance, with $>$2 million Americans and approximately 1 in 68 American children identified as falling on the autism spectrum (58). ASD is often accompanied by intellectual disability and is typically a chronic, disabling disorder. Though the severity of symptoms varies, the majority of individuals with ASD are unable to live independently and require lifelong support or accommodations, resulting in a societal cost of $1.4–$2.4 million per person (59). Current treatments of ASD are often multimodal, including countless hours of behavior, occupational, and speech therapies as well as specialized educational and vocational assistance and certain medications. These approaches target specific symptoms, such as irritability, that are associated with ASD, but they do not modify the underlying disease. Thus there is a substantial need for novel, effective, disease-modifying medical treatments for ASD.

The etiology of ASD remains unknown, though evidence suggests that it is likely to result from a complex interplay between genetic and environmental risk factors, potentially mediated through inflammatory and/or immune processes. Both animal models and observational human studies have linked immune activation in pregnant mothers to the development of ASD in their offspring. In addition, many cytokines and molecules classically associated with immune regulation are now also recognized as having roles in normal neurodevelopment. Thus, one hypothesis regarding the development of ASD is that immune-mediated changes in fetal brain cytokine profiles may result in abnormal development in the central nervous system, either directly or

indirectly via microglial activation. Abnormalities in the number, function, and gene regulation of microglia as well as in localized brain inflammation, pathological astrocyte activation, and synaptic dysfunction have all been described in various models of ASD (60–62).

Potential Mechanisms of Action

Cellular therapies are currently under investigation in clinical and preclinical studies with the goal of improving the core symptoms of ASD. There are multiple paracrine mechanisms through which cell therapies could potentially exert therapeutic effects. Cell-mediated immunomodulation, possibly via inhibition of T-cell proliferation and reduced production of pro-inflammatory cytokines such as tumor necrosis factor-α and interferon gamma (63), may reduce ongoing inflammation. Additional neuroprotection may be offered via molecular mechanisms by inhibiting toxic processes, such as neural apoptosis, microglial activation, astrocyte proliferation, and production of oxidative stress molecules (64). Cells may also have a role in stimulating the restoration and/or generation of functional synaptic pathways (65). These and other potential mechanisms may not be mutually exclusive and are the subject of ongoing research. Additional knowledge regarding the pathophysiology of ASD will be essential in further defining mechanisms by which cellular therapies might provide beneficial effects. This will also allow for further refinement of cell type, timing, and duration of therapy that may be useful.

Animal Models

As a disorder primarily of human social behavior and communication, establishing robust animal models of ASD is challenging. Many preclinical models have been developed utilizing mouse or rat models with single gene disorders associated with ASD, such as Fragile X, Rett, and Angelman syndromes. Studies of cell therapy approaches have been conducted in these models, though the results may not be generalizable to individuals with idiopathic ASD.

Rett syndrome is an X-linked condition associated with ASD that is typically caused by a mutation of the *MECP2* gene, which encodes a methyl-CpG-binding protein. Mutations in *MECP2* lead to deficient phagocytic function in glial cells. In a mouse model of Rett syndrome (*Mecp2*-null C57BL/6 mice), intravenous infusion of wild-type bone marrow cells arrested disease development. Following engraftment, survival was improved, breathing patterns normalized, apneas were reduced, body weight increased, and locomotor activity was improved, indicating functional recovery (66).

Another mouse model of ASD is the BTBR T^{+} $Itpr3^{tf}I$ (BTBR) mouse strain, derived from the inbred Black and Tan BRachyury strain. In addition to impaired social behavior, aberrant communication, increased repetitive behaviors, and increased cognitive rigidity, BTBR mice also exhibit increased levels of peripheral CD4+ T cells, peripheral B cells, and serum and brain immunoglobulin levels, among other immune abnormalities (67). Following intraventricular injection of human mesenchymal stromal cells into the central nervous system of BTBR mice undergoing concomitant immunosuppression with cyclosporine, improvements in all three ASD domains—social behavior, stereotyped behaviors, and cognitive rigidity—were observed in MSC-treated mice compared with controls. Differences in anxiety-related behaviors and locomotion were not observed (68).

These mouse models suggest that, at least in certain subtypes of ASD, cellular therapies may have the potential for benefit. Although chemical models utilizing administration of valproic acid during crucial periods of neurodevelopment and environmental models of maternal infection and inflammation exist in animals, there are no reports of the effect of cellular treatment in these models.

Clinical Trials

Clinical trials of cell therapy in patients with ASD are still in the early phases, with a handful of exploratory studies underway in several different countries. Cell sources for these studies include autologous (69) or allogeneic umbilical CB, autologous bone marrow (70), fetal stem cells (71), and mesenchymal stromal cells derived from adipose tissue or umbilical cord tissue. To date, results of four clinical trials have been published.

In India, 32 patients aged 3–33 years were treated with an intrathecal injection of autologous bone marrow mononuclear cells with a mean cell dose of 8.19×10^7 (70). Procedure-related adverse events included headache (3.6%), nausea (10.7%), vomiting (17.9%), pain (7.1%), and aspiration (7.1%). In addition, new or worsening seizures were observed in 9% of patients, as well as increased hyperactivity in 18.7%. These side effects were likely due to the intrathecal route of administration. Statistically significant improvements were detected in the Clinical Global Impression-Improvement scale and Indian Scale for Assessment of Autism at the time of follow-up, which ranged from 5 to 26 months.

In Ukraine, the safety of intravenous and subcutaneous infusions of fetal stem cells was tested in a total of 45 children, aged 3–15 years (71). Patients were followed at 6 and 12 months after treatment, with improvement noted in speech, sociability, sensory, and overall health domains of the Autism Treatment Evaluation Checklist and the Aberrant Behavior Checklist (ABC). No adverse events were observed during the 1-year follow-up period, which may not be a sufficient duration of follow-up for fetal stem cells.

In the United States, the Duke ABCs trial was an open-label phase 1 safety and tolerability study of a single intravenous infusion of autologous CB conducted in 25 children, aged 2–5 years, with ASD (ClinicalTrials.gov ID: NCT02176317) (69). CB was administered as a single infusion (median infused dose: 2.6×10^7/kg, range: 1.0×10^7/kg–8.1×10^7/kg) without any immunosuppression. The infusions were safe, with no serious adverse events and occasional allergic reactions and irritability reported. Improvements in ASD symptoms were observed on caregiver-completed measures (Vineland

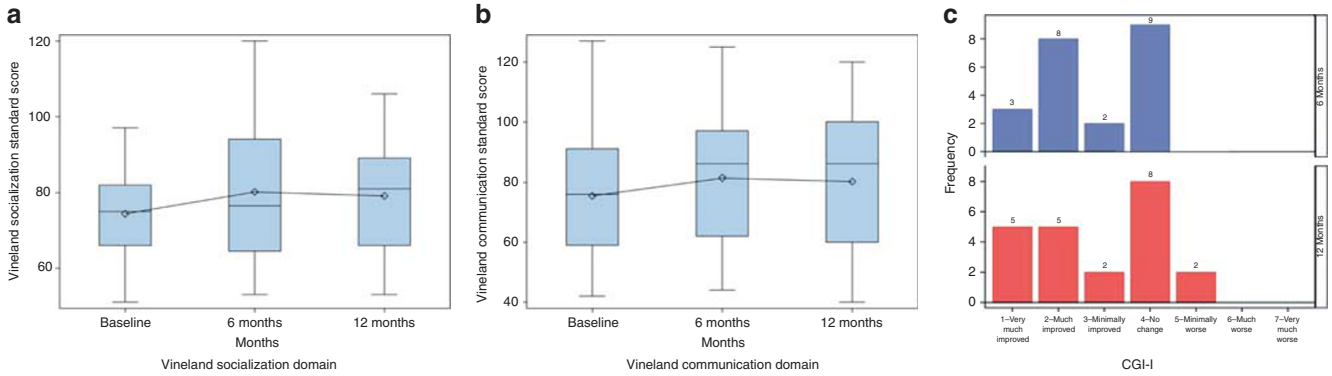

Figure 1. Changes in autism spectrum disorder symptoms after autologous cord blood infusion. (**a**) Vineland-II socialization domain standard scores at baseline and 6 months after infusion ($P = 0.02$ baseline to 6 months). (**b**) Vineland-II communication domain standard scores at baseline and 6 months after infusion ($P < 0.01$ baseline to 6 months). (**c**) Distribution of Clinical Global Impression-Improvement scale (CGI-I) scores at 6 (blue) and 12 (red) months postinfusion. Sample sizes are $N = 25$ for baseline and 6-month time points and $N = 22$ at 12 months.

Adaptive Behavior Scales-Second Edition (see **Figure 1**) and Pervasive Developmental Disorder Behavior Inventory), clinician assessment (Clinical Global Impression-Improvement scale, **Figure 1**), and computerized eye-tracking assessments. Positive changes, including increased social communication skills and receptive/expressive language and decreased repetitive behavior and sensory sensitivities were observed 6 months after infusion and maintained at 12 months. A phase 2 randomized study is underway to evaluate the efficacy of autologous or allogeneic CB therapy vs. placebo in children with ASD (NCT02847182).

Owing to their well-established immunomodulatory capacity, mesenchymal stromal cells may be an excellent candidate cell type for use in the treatment of ASD. One Chinese study has evaluated the administration of MSCs in children with ASD in conjunction with additional cells. In that trial, 37 children with ASD were treated with 4 doses of either umbilical cord blood mononuclear cells (given both intravenously and intrathecally) ($n = 14$), cord blood mononuclear cells+intrathecal umbilical cord-derived mesenchymal stem cells ($n = 9$), or standard therapy ($n = 14$) (72). The only treatment-related side effect was transient fever in five patients. At 6 months posttreatment, both treated groups demonstrated greater improvement in multiple ASD measures (Childhood Autism Rating Scale, Clinical Global Impression scale, ABC) than the placebo group, indicating a potential therapeutic response. A phase I study of intravenous administration of umbilical cord-derived MSCs in children with ASD is underway at Duke University in the United States.

SUMMARY

Although adequate treatments for many neurological disorders of childhood remain elusive, cellular therapies have potential as novel therapeutic modalities to transform the way we approach these conditions. Significant advances in the filed of HSCT for IMDs have resulted in improved survival rates and neurological outcomes in conditions that previously were universally fatal. This serves as an example of the advancements that can be made through scientific discovery, innovation, and collaboration. Although cell therapy has yet to be established as a treatment for other neurological conditions such as cerebral palsy or ASD, there is mounting preclinical and clinical evidence of potential benefit and important advances are anticipated in the coming years. Should cell therapy prove beneficial in these acquired conditions via immune modulation, neuroprotection, or other mechanisms, then there may be applications in more common conditions including, but not limited to, adult neurodegenerative diseases, multiple sclerosis, and stroke.

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