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Stem Cells in Neurological Diseases: Indian Perspective

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Abstract

Stem cell therapy is under investigation in neurological diseases with currently sub optimal or no treatment available. They are hypothesized to produce new cells, or act as "chaperones or scaffolds" to repair and reconstruct neuronal circuitry and release the relevant neurotransmitters for ultimate functional improvement in the individual. They have the potential either to divide or multiply or differentiate into one or more cell type, usually in response to some kind of signal. In recent years, bone marrow derived stem cells have been successfully exploited as neurorestorative tool to augment brain recovery. In this review we have discussed the types and sources of stem cells, notable clinical studies published and ongoing trials in India involving Stroke, Parkinson's disease, Spinal cord injury, ALS, Multiple Sclerosis etc and discuss the future prospects for more trials. All these studies proved the safety and feasibility of cell transplantation. Steady and focused progress in stem cell research in both preclinical and clinical settings in Indian subcontinent should support the hope for development of cell-based therapies as treatment in near future.

Introduction

Stem cells can be defined as clonogenic cells that have the capacity to self-renew and differentiate into multiple cell lineages [1]. These cells were first to be present in the bone marrow of mouse about 45 years ago followed by discovery of cells known as Hematopoietic Stem Cells (HSCs), which give rise to cells of hematopoietic lineage like monocytes, endoethelial stem cells and endothelial progenitor cells. Another population of cells [2] population of cells with stem cell-like characteristics present in the marrow were found having colony forming unit-fibroblasts [now known as Mesenchymal Stem Cells (MSCs), or stromal stem cells]. Stem cells are also divided according to the body's development process and their ability to form other cells. Totipotent stem cells are capable of giving rise to an entire organism and can be derived from fertilized oocytes and cells of the developing zygote up to the eighth cell stage. They have the potential to differentiate into derivatives of all germ layers (ectoderm, endoderm and mesoderm). Pluripotent stem cells can give rise to all tissue types, from any of the three embryonic germ layers, but unlike totipotent cells cannot give rise to an entire organism. These cells can give rise to different types of cells representing derivatives of two different germ layers e.g. skin (ectoderm) and muscle (mesoderm). Multipotent stem cells are able to differentiate into multiple types of cells, but within one organ system (e.g. blood). Oligopotent and unipotent stem cells have more restricted and limited differentiation potential, with the former capable of producing more than one type of cell (e.g. myeloid or lymphoid cells) [3]. Progenitor cells are those cells generated by stem cells, which differentiate into mature cells (e.g. endothelial progenitor cells) and can only divide a limited number of times, lieing at an intermediate position between stem cells and fully differentiated cells [4].

The omnipresent nature of these cells, their clear role in neural tissue development, their presumed participation in repair and regeneration and the irrefutable success of bone marrow stem cell therapy have raised high expectations to cure diseases that have thus far proven resistant to conventional therapy such as degenerative neurological disorders [5,6]. The success of "bench to bedside" of cell transplantation in the last decade has seen a spurt of stem cell therapy in various pathological disorders. Albeit all such clinical studies are/were phase 1/2 which aimed at safety and feasibility of cell transplantation. In this review, we summarize the nature, type and sources of stem cells with special reference to bone marrow derived cells. We also state the advancement of cell transplantation in Indian scenario in diseases like stroke, cerebral palsy, amyotrophic lateral sclerosis, Parkinson's disease and spinal cord injuries and comparison with other countries.

Sources of Stem Cells

Human embryonic stem cells (ES)

These cells are derived from the blastocyst inner cell mass of embryos generated by in vitro fertilization, can provide an unlimited source of cells and can be directed into neural precursors which can generate neurons, oligodendroglia and glia both in culture and in-vivo. Park et al. [7] and Perrier et al. [8] demonstrated in-vitro and in-vivo differentiation of human embryonic stem cells into dopamine neurons [7]. It may be mentioned that over the years, culture conditions that rely on the use of various cytokines and growth factors, have made it possible to induce the differentiation of a high proportion of ES cells into selected cell types such as neurons, pancreatic islet cells, cardiomyocytes etc. [8].

Human umbilical cord blood cells (UCB)

These cells are derived from umbilical cord blood which has the potential of differentiation into neural lineages. When exposed to nerve growth factor and retinoic acid, the derived umbilical cord blood cells produce progeny that shows positivity of neural and glial cells markers. However, biology of these cells is poor understood, and it is

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likely that positive effects of these cells are related to their neurotropic action, rather than actual neuronal circuitry formation. A better understanding of these cells is needed before clinical transplantation studies ensue, although experimental data in animal models of stroke have shown functional benefits [9].

Immortalised cell lines

In view of the ethical difficulties in transplanting embryonic cells and technical problems in xenotransplantation, alternative sources of graft cells have been devised. One of these cell lines, called "immortalized cell lines" have been an important technical advance in the field of neurotransplantation. These cell lines are derived by infecting neuroepithelial precursor cells from predefined CNS regions before terminal mitosis, with a retrovirus encoding an immortalizing oncogene [10].

Foetal neural stem cells

These cells are harvested from the post-mortem human fetal brain; they maintain a normal karyotype for a significant number of passages in culture and can produce a large number of neurons and astrocytes. These possess a relatively high proliferative capacity without any evidence of tumorogenesis following transplantation. These are mostly progenitor cells and not true ESCs [11,12].

Adult neural stem cells (NSC)

Adult stem cells are multipotent stem cells found in developed organisms, which are used to replace cells that have died or lost function. They can be obtained from adults as well as children, including umbilical cord blood. They have been identified within many different organ systems, including bone marrow, brain, heart, skin and bone. Adult stem cells make up 1-2% of the total cell population within a particular tissue type. They are usually quiescent and held in an undifferentiated state until they receive a stimulus to differentiate [13]. It has been claimed that adult neural stem cells can be harvested from brain tissue, post-mortem or through biopsy and expanded in culture both in rodents and humans, however, their proliferative capacity is limited. NSCs are defined as undifferentiated cells that are able to self - review as well as generate three major cell types that constitute the CNS: neurons, astrocytes and oligodendrocytes, signifying their pluripotent nature [1].

These features have led to many studies aiming at characterizing, isolating, expanding and transplanting these cells [14]. Although the identification process and isolation of NSCs is tedious [15], these cells can be expanded to a particular clone using free floating "neurosphere" cultures and the lineage potential can be assayed using clonal monolayer cultures.

Bone marrow derived cells

These cells are naïve mononuclear cells which abundantly reside in bone marrow [16]. Mobilized Peripheral Blood (MPB) is also a clinical source of HSCs, which is now replacing bone marrow as harvesting peripheral blood, is easier for the donors than harvesting bone marrow. MPB contains a mixture of hematopoietic stem and progenitor cells that are normally passed through a device that enriches cells that express CD34, a marker on both stem and progenitor cells [17,18]. These cells have the potential to regenerate the brain tissue by release of neurotrophic growth hormones which explains the usage of these cells worldwide. The other component of bone marrow contains mesenchymal stem cells or Multipotent Stromal Cells (MSCs) which are isolated from the bone marrow of adult organisms. These are described as Colony-Forming Units (CFUs) that adhere to cell culture surfaces and can be expanded to 500-fold through as many as 50 generations to produce billions of cells and can differentiate into osteoblasts, adipocytes and chondrocytes [19]. Colonies derived from a single MSC vary to some extent in differentiation capacity and expansion potential [20]. Entry of MSC into senescence is almost undetectable, and they lose their stem cell characteristics and differentiation potential from the sixth passage onwards. MSCs secrete interleukin-6 (IL-6), IL-7, IL-11, IL-12, IL-14, IL-15, Leukaemia Inhibitory Factor (LIF), Macrophage Colony Stimulating Factor (M-CSF), Stem Cell Factor (SCF) and flt-3 ligand [21,22].

Induced pluripotent cells (iPS)

These cells, called iPS were found to be similar to human embryonic stem cells in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes and telomerase activity [23]. Adult human cells from skin were transformed to a pluripotent state using genetic engineering techniques which could help generate patient and disease specific cells [24]. Further, these cells could differentiate into cell types of the three germ layers.

Regenerative Approaches in Neurological Diseases

Neurological disorders can be divided according to their pathophysiology and etiology. The first class is the ones, caused by an acute injury. These diseases include stroke, traumatic brain injury, spinal cord injury, and neonatal hypoxia-ischemic encephalopathy [25]. Stroke is the second leading cause of mortality in India (third leading cause of death in the world), in which the infarcted core in the ischemic zone, may not respond to any pharmacological or interventional therapies. It is for these reasons that repairing the injured nervous system using stem cells seems so promising. Cell transplantation works through neurorestoration principle aiming to promote repair processes such as neurogenesis, synaptogenesis and growth factor upregulation, and may also complement host organism's endogenous repair mechanisms [26].

A second category is the chronic neurodegenerative diseases like Parkinson's disease, Huntington's chorea, Amyotrophic lateral sclerosis, Alzheimer's disease and Vascular dementias. The timing of onset in such diseases is not known but the diseases processes and pathogenesis is active even when the clinical symptoms have not yet become apparent. The pathological process of cell death and injury continues slowly but there is loss of specific cell populations. For such cases, stem cell therapies may have both a neuroprotective effect (reduce neuronal apoptosis) and a neurorestorative effect.

The third category of neurological disease is composed of the chronic inflammatory and immunologically mediated conditions such as Multiple sclerosis. While chronic inflammation plays an important role early in the disease, in the later stages, there is a larger degenerative component with axonal degeneration. Stem cell therapy especially mesenchymal stem cells act via repairing and remyelinating the axons and recovery through immune mediated mechanisms [27].

The fourth category includes genetic diseases in children like neuronal ceroid lipofuscinosis, mucopolysaccharidoses, and the leucodystrophies such as adrenoleucodystrophy, globoid cell leucodystrophy (Krabbe's disease), metachromatic leucodystrophy and various forms of muscular dystrophies. These diseases are product of inborn errors of metabolism where an enzyme is missing leading to abnormal storage of glycolipids or proteins in lysosomes, or lack of normal muscle proteins.

Hope or Hype?

The hope to create a better environment with respect to clinical, emotional and psychological domains for patients with neurological diseases is a challenge for researchers in clinical practice. Currently there are a large number of centres involved with research on various clinical diseases using stem cell therapy. The Indian government with the Ministry of Health welfare and organisations like Indian Council of Medical research (ICMR) and Department of Biotechnology (DBT) has laid guidelines for stem cell research in 2012. The Guidelines propose a system of review and monitoring of the field based on a National Apex Committee (NAC) for Stem Cell Research and Therapy and, at the institutional level, Institutional Committees for Stem Cell Research and Therapy [28]. These guidelines apply to all stakeholders viz. institutions, organizations, individual researchers, sponsors, oversight committees and others associated with research on stem cells or their derivatives, both basic and clinical including autologous or allogenic, embryonic or fetal or adult, with or without manipulation. It was made mandatory for all clinical studies, to obtain a prior approval of, and be registered with NAC. According to the source of stem cells and nature of experiments, the research on human stem cells is categorized into following three areas: prohibited, restricted and permissible areas of research [29]. Prohibited areas of research include reproductive cloning, implantation of a human embryo into the uterus after in vitro manipulation, and transfer of human blastocysts generated by Somatic Cell Nuclear Transfer (SCNT) into a human or nonhuman uterus.

We searched all trials listed in clinical trialsgov, ctri.nic.in and published (full reports / abstracts) and found 10 known clinical studies, 8 ongoing trials and 7 unknown clinical trials across the country.

Reported/Published Clinical Studies in India

Stroke

Acute stroke: A non-randomized controlled phase 1 study was conducted in which autologous mononuclear stem cells were transplanted in eleven subacute ischemic stroke patients within 7 to 30 days of onset. Outcomes measured for safety included immediate reactions after cell infusion and evidence of tumor formation at one year in whole body PET scan. Patients were followed at 1, 4-6, 24 and 52 weeks to determine clinical progress using National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), modified Rankin Scale (mRS), MRI, EEG and PET. Mean 80 million with CD-34+ mean 0.92 million cells were infused intravenously. No serious adverse events were noted and favourable outcomes were observed in 7 of 11 (64%) in BI, 5 of 10 in NIHSS (50%) and 6 of 11 in mRS (54.5%). Its efficacy will be examined in a multicentric trial (NCT01501773) [30].

Chronic Stroke: A non randomized study was conducted by the authors in which forty (n = 40) chronic stroke patients were recruited with the inclusion criteria as: 3 months to 2 years of index event, power of hand muscles of at least 2; Brunnstrom stage: 2–5. Fugl Meyer (FM), modified Barthel Index (mBI), Medical Research Council (MRC) grade for strength, Ashworth tone scale and functional MRI was done at baseline, 8 and 24 weeks. Average 55 million cells were infused intravenously in 20 stroke patients over 2–3 hours. No mortality or cell related adverse reactions were reported. Modified Barthel Index (mBI) showed statistical significant improvement ($p < 0.05$) in the stem cell group. An increased number of cluster activation in Brodmann areas BA 4, BA 6 was observed post stem cell infusion indicating neural plasticity [31-33].

Motor neuron disease

Till date, one study has been published to assess the feasibility, efficacy and safety of autologous bone marrow-derived stem cells in patients of Amyotrophic Lateral Sclerosis (ALS) in India. This was an open-label pilot study of ten patients with ALS transplanted with 1.81×10^8 million cells intrathecally. Primary end point was improvement in the ALS Functional Rating Scale (ALSFRS-R) score at 90, 180, 270 and 365 days post therapy. Cell therapy proved safe in such patients with no significant adverse events being reported and there was no significant deterioration in ALSFRS-R composite score from baseline at one-year follow-up (p=0.090) [34].

Cerebral palsy

An open label study was conducted by authors to evaluate the safety, feasibility and efficacy of intra-arterial infusion of autologous bone marrow derived mononuclear cells in thirty (n=30) patients with cerebral palsy. 15.7 million cells were infused in each carotid artery with assessment on muscle power, spasticity, dystonia, abnormal movements scale and the activities of daily living scale by modified Barthel Index. No adverse events were noted on a 12 months follow up and functional improvement was observed in all clinical scales, and predominantly in the disability scores [35].

Muscular dystrophy

A study was conducted on 150 patients diagnosed with muscular dystrophy variants like Duchenne muscular dystrophy, limb-girdle muscular dystrophy, and Becker muscular dystrophy. They were administered autologous bone marrow-derived mononuclear cells intrathecally and intramuscularly at the motor points of the antigravity weak muscles followed by vigorous rehabilitation therapy. No significant adverse events were noted. Improvement was observed in 86.67% of patients at follow-up of 12 months in trunk muscle strength (53%), gait parameters (10%), and a favorable shift on functional independence measure and Brooke/Vignos Scales. 6 patients showed changes to muscle regeneration and a decrease in fatty infiltration on musculoskeletal magnetic resonance imaging and 9 showed improved muscle electrical activity on electromyography [36].

Another group [36] conducted study on 71 children suffering from muscular dystrophies, spinal cord injuries and other neurological disorders. They were intrathecally and intramuscularly administered autologous bone marrow-derived mononuclear cells. Assessment after transplantation showed neurological improvement in muscle power and a shift on assessment scales such as FIM and electrophysiological recordings. On an average follow-up of 15 ± 1 months, overall 97% muscular dystrophy cases showed subjective and functional improvement, with 2 of them also showing changes on MRI and 3 on EMG. Spinal cord injury cases showed improvement with respect to muscle strength, urine control, spasticity, etc. 85% percent of cases of cerebral palsy improved, out of which 75% reported improvement in muscle tone and 50% in speech among other symptoms. No significant adverse events were noted and cell transplantation proved to be is safe, efficacious, and also improves the quality of life of children with incurable neurological disorders and injury [37].

Multiple sclerosis

To our knowledge there is no published report of cell therapy in multiple sclerosis. There is an ongoing clinical study (NCT01883681) which examines the combination of bone marrow derived and umbilical cord blood derived mesenchymal stem cells with a dose of 100 million (6 doses) in one month [38].

Parkinsons disease

Seven Parkinson's disease PD patients aged 22 to 62 years with a mean duration of disease 14.7± 7.56 years were enrolled to participate in a prospective, uncontrolled, design of single-dose infusion of Autologous Bone-Marrow Derived Mesenchymal Stem Cells (BM-MSCs) via stereotactic surgery. All patients were followed up from 10 to 36 months. No serious adverse events were noted in these patients. The mean baseline "off" score was 65 ± 22.06, and "on" score was 50.6 ± 15.85. Three of seven patients showed steady improvement in their "off"/"on" Unified Parkinson's Disease Rating Scale (UPDRS). The mean "off" score at last follow-up was 43.3 with an improvement of 22.9% from the baseline whereas the mean "on" score at last follow-up was 31.7, with an improvement of 38%. Hoehn and Yahr (H&Y) and Schwab and England (S&E) scores showed similar improvement from 2.7 to 1.5 in H&Y and 14% improvement in S&E scores, respectively [39].

Spinal cord injury

A study was conducted in which 100 (69 males and 31 females) spinal cord injury patients were implanted with autologous stem cells injection with an average of 4.5 years of disease. The CD 34/CD45 counts ranged from 120-400 million cells in the total volume. All patients were followed by MRI, urodynamics and SSEP (Somatosensory Evoked Potentials) tests at baseline, 3 and 6 months post cell transplantation. Cell therapy proved to be beneficial in total of 18 patients whereas 8 patients had more than 2 grades of motor power improvement, 3 were able to walk with support and 1 patient with T12/L1 injury was able to walk without support. Twelve patients had sensory tactile and pain perception improvement, 8 had objective improvement in bladder control and muscle contractility [40].

Another group studied efficacy of mesenchymal stem cells in thirteen patients with chronic complete spinal cord injury. Harvested cells were administered at the site of injury after laminectomy. The protocol used included three injections: the first dose was given directly at the site of injury followed by two doses given via lumbar puncture within a span of 21 days of the first injection. Average 3-8 million cells/kg body weight were infused. One patient had improvement in motor power; two patients had a patchy improvement in pin prick sensation below the level of injury [41].

One group of authors [42] transplanted BM-MSC in thirty patients with clinically complete SCI at cervical and thoracic levels. Patients with <6 months of post-SCI were recruited into group 1 and patients with >6 months of post-SCI were included into group 2. BM MSC were infused at a dose of 1×10^6 cells/kg body weight via lumbar puncture in these patients. The results indicated safety of cell transplantation in chronic SCI patients without any side effects.

There are several unresolved issues with the cell therapy. These include aspects such as (a) the optimal type of cells, (b) dosage of cell, e.g., primer dose, booster dose (c) optimum timing of treatment; (d) optimum route of delivery and (e) outcome measures; primary safety end points and efficacy measurements. Other areas of interest include is in-vivo tracking of transplanted cells, in vivo spectroscopy of brain especially in stroke, paracrine and autocrine mechanisms of stem cells etc which are essential to further our understanding of distribution and mechanism of action of cells [43]. Potential approaches to this

Studies	Disease	Age/sex	Experiment N=number	Route	Type of cells	Outcome measures/phase
Prasad et al.	Acute Stroke	30-70 yrs	11(non randomized)	Intravenous	BM MNC	No AE, seven patients had favourable outcomes.
Srivastava et al.	Chronic stroke	20-65yrs	20(non randomized case control)	Intravenous	BM MNC and BM MSC	No AE, Modified barthel index statistically significant (p=0.04)
Prabhakar et al.	MND (ALS)	Mean 49.1 yrs	10 (open label)	Intrathecal	BM MNC	No AE, No significant deterioration in ALSFRS-R score
Srivastava et al	Cerebral Palsy/ staticencephalopathy	16-30yrs	30 (open label)	Intra-arterial	BM MNC	No AE, functional improvement observed.
Sharma et al.	DMD	unknown	150 (open label)	Intrathecal and intramuscular	BM MNC	No AE, 53% cases increase in muscle strength
Sharma et al.	Cerebral palsy DMD	unknown	71 (open label)	Intrathecal/intramuscular	BM MNC	75% showed improvement in muscle tone, 50% in speech
Bhanot et al.	Chronic spinal cord injury	18-52yrs	13 (open label)	Intrathecal	BM MSC	No AE, improvement in ASIA scale
Raj kumar et al.	Spinal cord injury	8-55yrs	100	intrathecal	BM MNC	No AE, functional improvement observed
Venkatramana et al	Parkinson's disease	22-62yrs	7 (open label)	Stereotactic Surgery	BM MSC	UPDRS score improved to 28%, 2.7 point change in Y & H scale
Pal et al	Chronic spinal cord injury	unknown	30 (open label)	Intrathecal	BM MSC	No SAE
NCT01883661	Multiple Sclerosis	18-65yrs	15 (open label)	Intravenous	BM MSC+UCMSC	Phase 1/2
NCT00976430	Parkinson's disease	35-70yrs	5 (open label)	Stereotactic	BM MSC	Phase 1/2
NCT01984814	ALS	26-76yrs	57 (open label)	Intrathecal/intramuscular	BM MNC	Phase 2
NCT01834040	DMD	4-20yrs	30 (open label)	Intravenous/intralesional	HUCMSC	Phase 1/2
NCT01834066	DMD	6-25yrs	25 (open label)	Intravenous	BM MNC	Phase 1/2
NCT02027246	Spinal cord injury	8mo-63yrs	166 (open label)	Intrathecal	BM MNC	Phase 1
NCT02009124	Spinal cord injury	12mo-65yrs	250/250 (non randomized)	Intrathecal	BM MNC	Phase 2
NCT01833975	Spinal cord injury	18-55yrs	50 (open label)	Unknown	BM MNC	Phase 1/2
NCT01186679	Spinal cord injury	20-55yrs	6/6 (non randomized)	Intralesional/Intrathecal	BM MNC	Phase 1/2
NCT01834053	Huntington's chorea	35-45yrs	50 (open label)	Intravenous	BM MNC	Phase 1/2

Table 1: Clinical studies with cell transplantation in India. Trials enlisted at clinical trial.gov with registration number.

include labelling of cells with a magnetic label (e.g. super paramagnetic iron oxide particles) allowing MRI tracking of the cells. This has yet to enter the clinical arena in stroke, though it has shown promise in rodent models of stroke [44,45]. Long-term bio safety studies are essential in cell transplantation, particularly with a threat to potential for tumorogenicity, particularly with systemic delivery of cells. Furthermore, appropriate quality assurance and control standards must be in place to allow the standardization of cell preparations (Table 1) [46].

Cell therapy in american, european and other asian countries

A recent review by Karausis et al. [47] reflects the importance and depth of cell transplantation in countries other than India also. Attempts have been made in diseases like Stroke, Huntington's (HD), Parkinsons (PD), ALS and other neurodegenerative diseases (Table 2). Early open labelled studies have provided data on the safety and feasibility of cell transplantation in cerebrovascular diseases. In one of them [48], neuronal cells derived from neural progenitors were transplanted into 12 patients from 0.5 to 6 years after basal ganglia stroke. No adverse events were observed up to 5 years of transplantation and patients showed some clinical improvement. Another safety study was conducted in a randomized design by Korean group who transplanted 100 million autologous mesenchymal cells in subacute stroke [51]. Studies in PD showed an improvement in symptoms, along with trend of increased dopaminergic neuronal function, as demonstrated by PET imaging after cell transplantation. However, three controlled clinical trials in which patients received fetal embryonic grafts from aborted fetuses into the striatum or retinal pigment epithelial stem cells, showed little benefit compared with the placebo group [65,66]. In one pilot study in Huntington's disease, three out of five patients showed a plateau of motor and cognitive improvements already 2 years after transplantation of fetal neural grafts into the left and right striatum, which faded over the following four years for motor disabilities, whereas cognitive function remained stable.

Conclusion

Our review suggests therapeutic advancements of stem cell therapy in India. These cells are safe and feasible when transplanted in neurodegenerative and ischemic neurological diseases. As cell therapy is in its nascent stage (phase 1 primarily), a conclusive evidence of

Authors	Disease	Cell type	Route of administration	Results, any serious adverse events (SAE)
Koc et al [48].	Hurlers syndrome, metachromatic leukodystrophy	Allogenic BMT following BMT	Intravenous	No clinical improvement, NO SAE
Kondziolka et al. [49]	Basal ganglia CVA	Human neural cells generated from human neural progenitors	Stereotactic surgery	Improvement in 6 patients, no SAE
Kondziolka et al. [49]	Basal ganglia CVA	Human neural cells generated from human neural progenitors	Stereotactic surgery	Safe and feasible, improvement in some patients, AE: syncope, subdural hematoma, seizures
Savitz et al [50].	Basal ganglia CVA	Porcine cells treated with anti MHC1 antibody	CT guided stereotactic transplantation	Two patients showed in speech and language, FDA termination. AE: seizures, worsening of motor deficits
Bang et al. [51]	MCA CVA	Autologous MSC	Intravenous	Some clinical improvement. No SAE
Olanow et al [52].	PD	Fetal niagral cells	Stereotactic implantation	Some improvement. AE: dyskinesias
Mendez et al [53].	PD	Fetal mesencephalic cells	Stereotactic implantation	Some improvement. No AE
Reuter et al [54].	HD	Fetal striatal allografts	Stereotactic implantation	Improvement in motor function. PET showed cell differentiationand integration of transplanted tissue. No AE.
Lee et al [55].	MSA	Autologous BM, MSC	Intra arterial and repeated intravenous	Significant clinical and radiological improvement. No AE
Deda et al [56].	ALS	Autologous BM HSCT	Cervical spinal cord implantation	Safety indications of clinical satblisation. Improvement confirmed by EMG in some patients. AE: 3 patients died from lung infection and ml
Karussis et al [57].	MS	Autologous BM MSC	Intrathecal and intravenous	Safe and feasible. Some indications of disease stabilization. No AE
Karussis et al [57].	MS	Autologous BM MSC	Intrathecal and intravenous	Safe and feasible. Indiaction of clinical benefits by in vivo imuunomodulatory effects. No AE
Connick et al [58].	MS	Autologous BM MSC	intravenous	Safe and feasible. Neuroprotection evidence by end points parameters. No AE
Burt et al [59].	MS	Intense immunosupression followed by autologous HSCT	intravenous	No effective in patients with progressive MS and high disability scores. AE: 2 patients died.
Saccardi et al [60].	MS	Autologous HSCT	intravenous	Prolonged clinical stabilization in severe progressive MS resulting in sustained treatment free periods and quality of life improvement. No SAE. Infections only to three month period post transplantation
Sampaolesi et al [61].	MS	Autologous HSCT	intravenous	Some clinical benefits in PMS. AE: 2 patients died of severe pneumonia and VZV.
Burt et al [62].	MS	Non myeloablative autologous BM HSCT	intravenous	Safe and clinical improvement seen. No AE
Krasulova et al [63]	MS	Autologous HSCT	intravenous	Clinical improvement. No AE
Mancardi et al [64].	MS	Autologous BM HSCT	intravenous	Suppression of disease progression in RRMS. No AE.

MS: Multiple Sclerosis, PD: Parkinsons disease; ALS: amyotrophic lateral sclerosis, MSA: multiple system atrophy; HD: Huntingtons Disease, CVA: cerebrovascular accident; MCA: middle cerebral artery

Table 2: A partial list of clinical studies of cell transplantation other than India [47].

efficacy would want more number of studies to be undertaken. Cell transplantation worldwide needs a stringent regulation under social, financial, medical and legal contexts [52,53]. A premature translation of crude data and concepts can bring new hypes but may not prove meticulous for diseases. The government of India continues to lend financial and infrastructural support to various government institutes, private sector undertakings and industries to conduct stem cell research which would help to decrease the load of disability and improve cost of living and functional status of patients suffering from neurological disorders. To date no trial has shown a level of effectiveness that gives hope they may be useful as mainline therapies in 2014. With time, progress will be made; but only by following well established methods of translation from the lab to the clinic. Abandoning such approaches and rushing to the clinic poses a real threat of derailing the whole process by disastrous results of an ill thought of treatment. Using unproven commercially driven cells of today will confuse and demean the field of stem cell therapies which promises to be of great use in future.

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