SCT in Parkinson’s Disease and Atypical Parkinsonian Disorders

Subjects: Neurosciences

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Stem cell-based therapies (SCT) may hold greater promise in the treatment of neurodegenerative disorders, such as Parkinson’s Disease (PD), atypical parkinsonian disorders (APD). Initial randomized trials, particularly in amyotrophic lateral sclerosis (ALS) have been promising, but further research is required to determine the feasibility, safety, and efficacy of this novel approach.

movement disorders stem cell therapies neurodegeneration

1. Introduction

Neurodegenerative disorders result from a complex interplay between genes and environment. Due to their complexity and our limited understanding of the underlying pathological mechanisms, modelling these diseases in the laboratory has proven to be extremely challenging. Many cell and animal models have provided important mechanistic insight into neurodegenerative diseases but, thus far, there is a disconnect between therapeutic successes in animal models and those in clinical trials in humans.

Human stem cells (pluripotent and multipotent) are increasingly being studied as models or therapies for human disease. In most cases, stem-cell based therapies (SCTs) for neurodegenerative disorders rely on replacing lost cell types (e.g., replacing degenerated cells with new ones), thus exerting a symptomatic therapeutic effect. However, while cell replacement may provide rescue and neurorestorative effects, it is likely that disease-modification should rely on precision medicine approaches, matching molecular therapies to biological subtypes of disease. Within the precision medicine approach, which involves combination of multi-drug treatments, rather than a monotherapy, SCT may play a significant contribution in the treatment of neurodegenerative disorders [1].

Over the years, there has been significant hope that SCT would lead to curative therapies in these diseases, but unfortunately, that has not been observed thus far. It can be proposed that, unless it addresses the inciting etiology, which is expected to vary among affected individuals, it will never be completely curative. However, with the recent development of newer and more effective cell lineages, differentiation processes, and grafting techniques, the once-imagined regenerative utopia may still be possible. Many review articles have been written on the possible utilization of stem cell therapies in various animal models and/or in patients with dementia, but very few have specifically discussed this topic in patients with movement disorders [2][3][4][5][6].

Stem cells can be classified on their intrinsic ability to differentiate into the end organism [7]. There are five main categories of stem cells: totipotent, pluripotent, multipotent, oligopotent, and unipotent (**Glossary**). Stem cells can also be categorized as embryonic stem cells (ESCs)—cells derived during early development—and adult stem cells— rare, undifferentiated cells present in many adult tissues [8]. Special attention has been given to pluripotent ESCs, which can differentiate into any embryonic cell; initial trials required harvesting it at the blastocyte stage, but, in 2007, induced adult pluripotent stem cells (iPSCs) were artificially reprogrammed back from human fibroblasts or blood cells [9]. The ability to develop iPSCs, a non-embryonic source of multipurposed cells, was a breakthrough that avoided many ethical pitfalls as they can be derived from the patient's own cells (e.g., autologous stem cells), and they avoid the risk of immunological rejections that are associated with non-autologous or heterologous stem cells [10]. Mesenchymal cells derived from the mesoderm and neuroectoderm were initially obtained from bone marrow; common sources now include adipose tissue, placenta, and umbilical cord, and they have the ability to differentiate into cell types from all three embryonic layers [11]. Interestingly, they can grow towards inflammation through the expression of chemokine receptors, making it an attractive candidate for cell loss, secondary to inflammatory conditions [12]. Totipotent cells are infrequently used in research as they are difficult to isolate and, once again, ethical questions arise. The above provides a simplified description of these categories to understand the following concepts.

2. Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative syndrome which results in a loss of dopaminergic neurons, leading to nigrostriatal degeneration [13]. The pathogenesis of neuronal degeneration in PD likely involves the polymerization of alpha-synuclein, with a subsequent loss of normal, soluble synuclein and degeneration. As such, PD belongs to the category of "synucleinopathies" [14]. While serotonin and acetylcholine are involved to some extent, the mainstay of therapy has always been and continues to be dopamine replacement [15]. The loss of dopaminergic neurons is mainly located in the substantia nigra (SN)-*pars compacta* and its projections to the striatum. SCT cannot address the disease-causative mechanisms but can replace dopaminergic-producing cells.

Stem cell transplants in PD started in the mid-1990s, with variable results. Olanow et al. showed that fetal stem cell transplants could improve motor symptoms (as measured by the Unified Parkinson's Disease Rating Scale (UPDRS)-part III) up to 9 months after the transplant, and that this effect was not maintained at 12 or 24 months (e.g., primary endpoint not met) [16]. This transient improvement in UPDRS scores coincided with the duration of immune-suppressant post-transplant, suggesting a loss of the transplanted tissue. This was more evident in patients with somewhat less severe PD (UPDRS-III score < 49) when compared to those with more advanced PD (UPDRS-III score > 49). Overall, PD patients in early SCT trials had a range of responses; from no response, disabling dyskinesias (mainly due to heterogeneous fetal grafts containing both dopaminergic and serotonergic cells) to discontinuation of oral levodopa medication, it was hard to predict how patients would respond [17]. Failure of these trials was attributed to factors like including non-motor predominant patients, insufficient amount of transplanted tissue, older age, and more diffuse loss of dopaminergic neurons. Those who had dopamine neuronal loss, restricted to putamen, benefited more from this treatment [18]. A few encouraging single case reports have

suggested that if the graft survives after immune-suppression discontinuation, and patients are properly selected, the effects of transplanted dopaminergic-producing cells could be tangible up to 20 years after the transplant [19][20]. However, these are observations based on single cases and it is hard to generalize their effect. Additionally, after decades of failures of SCT in PD [18][21][22][23], experts tried to review and devise new strategies for clinical trials. TRANSNEURO is a current, ongoing multicenter trial that involves implantation of allogenic human iPSCs-derived into the putamen and addresses some of these past limitations [23]. Preliminary data at 36 months on 11 subjects suggests the absence of disabling dyskinesias, continued deterioration of motor signs per Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, lack of evidence for association between disease duration and clinical outcomes, and no major cognitive problems [23]. Separately, Aspen Neuroscience (ANPD001) has started recruitment for their autologous, iPSCs-derived SCT for idiopathic PD. It will avoid the need for immunosuppressants but does come at the cost of developing personalized individual cell lines for each individual. The feasibility of this approach has already been demonstrated in a single patient in whom PET imaging showed graft survival and a 6% reduction of levodopa requirement at 24 months [24].

Currently, there are fifteen ongoing clinical trials on parkinsonism and SCT. Out of these, thirteen deal specifically with PD, suggesting that momentum continues within this field. Limitations have included choosing the right stem cell source, creating a cost-effective process to derive cell lineage in sufficient quantities, proper patient selection (currently restricted to motor-predominant and levodopa-responsive individuals in "earlier" stages), appropriate placement of the graft with verification of synapse connection to host networks, and finally, ensuring the longevity of grafts. Of interest, ongoing pre-clinical and phase I trials are mainly using iPSCs or ESC, whereas phase II trials also use mesenchymal stem cells (MSC).

3. Atypical Parkinsonian Disorders

Atypical parkinsonian disorders (APD) are a broad number of conditions with PD-like phenotypes and include MSA, PSP, CBS, and dementia with Lewy bodies (DLB) [25]. APD are primarily characterized by the combination of parkinsonism with additional motor and non-motor features that are beyond the "classical" spectrum of idiopathic PD, with a more aggressive disease progression. From a pathophysiological standpoint, APD consist of the "synucleinopaties", such as MSA and DLB (with the common hallmark of soluble α-synuclein loss with corresponding insoluble α-synuclein accumulation), and "tauopathies" (characterized by soluble tau loss with corresponding insoluble tau accumulation), which include PSP and CBS [14][25]. The main studies exploring the effects of stem cells in APD are presented in **Table 1**.

Table 1. Main studies exploring stem cell treatments in patients with atypical parkinsonian syndromes.

Condition	Study Name	Phase	Number of Patients	Intervention	Design	Adverse Events	Follow-Up	Outcome
MSA-C	Lee et al., 2012 [26]	I	33	IA or IV MSC	2 arms vs. placebo	Small ischemic	12 m	Slower decrease in UMSARS

Condition	Study Name	Phase	Number of Patients	Intervention	Design	Adverse Events	Follow-Up	Outcome
						lesions in IA		
PSP-RS	Giordano et al., 2014 [27]	I	25	IA BM-MSC	Placebo-controlled crossover	Small ischemic lesions	18 m	Slower decrease in UPDRS; increased FDG-PET uptake
PSP	Canesi et al., 2016 [28]	I	5	IA BM-MSC	1 arm	NA	12 m	Stable rating scales
MSA (*n* = 4), PSP (*n* = 5), CBS (*n* = 2)	Pezzoli et al., 2008 [29]	I	11	IV GCSF	1 arm	None	3 m	UPDRS not worsened significantly

e of stem cells [30]. However, these studies have been conducted in a small number of patients (mainly MSA-cerebellar subtype and not on MSA-parkinsonian subtype) and in single centers, and without a double-blinded approach, implanting intravenous or intraarterial MSC [26][30]. These studies have not been followed by others on wider number of patients and other MSA subtypes; additionally, some of these studies have been published more than a decade ago without further confirmation studies [26], thus suggesting limited applications of stem cells for MSA patients. Furthermore, as multiple systems and cell types are affected in MSA, different cell types may be needed for a stem-cell based therapeutic approach in this condition [31].

BM-MSC, bone marrow-derived mesenchymal stem cells; CBS, corticobasal syndrome; GCSF, granulocytes colony-stimulating factors; IA, intra-arterial; IV, intravenous; m, months; MSA-C, MSA-cerebellar type; MSA, multiple system atrophy; MSC, mesenchymal stem cells; n, number; NA, not assessed; PSP-RS, PSP-Richardson's type; PSP, progressive supranuclear palsy; RS, Richardson syndrome; UMSARS, Unified MSA Rating Scale. Single case reports are not included in the present table.

PSP. It has been documented in PSP that bone marrow MSC can be safely used with a possible beneficial effect (or, at least, with stabilization of disease progression), after having excluded the placebo effect [27]. The rationale of MSC in PSP is not to replace diseased neurons, but rather to minimize the consequences of neural cell deterioration by using stem cells as treatment [28]. Single-case reports have documented encouraging results with intraarterial autologous adipose tissue-derived MSC [32] and umbilical cord blood stem cell transplantation [33] in patients with PSP.

CBS and DLB. Studies specifically conducted in patients with CBS and DLB are lacking. Only one case series has been found describing the outcomes of the intravenous administration of granulocyte colony stimulating factor (GCSF) (which stimulates the differentiation of hematopoietic stem cells) in patients with MSA, PSP, and CBS (*n* = 2). Patients with CBS showed improvement (*n* = 1) or stability (*n* = 1) in motor scales over the study period (3 months), but no follow-up was available [29].

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