Perspective

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Regenerative Medicine

Mesenchymal stem cell therapy for the treatment of amyotrophic lateral sclerosis: signals for hope?

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Based on the distinctive cellular, molecular and immunomodulatory traits of mesenchymal stem cells (MSC), it has been postulated that these cells may play a critical role in regenerative medicine. In addition to the participation of MSC in the repair of mesodermal-derived tissues (bone, cartilage), robust data have suggested that MSC may also play a reparative role in conditions involving damage of cells of ectodermal origin. The above content has been supported by the capability of MSC to differentiate into neuron-like cells as well as by a competence to generate a 'neuroprotective' environment. In turn, several preclinical studies have put forward the concept that MSC therapy may represent an option for the treatment of several neurological disorders and injuries, including amyotrophic lateral sclerosis. We expect that the above foundations, which have inspired this review, may result in the founding of an effective and/or palliative therapy for amyotrophic lateral sclerosis.

Keywords: ALS • amyotrophic lateral sclerosis • cell-based therapy • mesenchymal stem cells • MSC

The intention of this review is to examine the most representative biomedical literature dealing with cellular, molecular and preclinical studies that have strengthened the notion that cellular therapy represents a feasible and robust option for the treatment of amyotrophic lateral sclerosis (ALS). Current proposals dealing with the use of cellular therapy in ALS patients, perhaps epitomize a strong support to the effort of a group of biomedical pioneers that without the venia of the pertinent regulatory (and restrictive) agencies, performed the first (in the USA) clinical trial infusing autologous bone marrow stem cells to ALS volunteers [1]. For ALS patients having no illusion of a panacea, the opening of that clinical trial symbolized the awaited right of hope.

Amyotrophic lateral sclerosis

ALS is a chronic neurodegenerative disease involving parts of the nervous system associated with the voluntary control of muscle movement. Given that the disease is progressive, motor neurons are gradually lost. As a consequence, the muscles they control progressively become weak and lastly nonfunctional. Usually, primary symptoms of ALS (encompassing muscle trembling, weakening, hardiness and/or toughness) are disregarded. As the disease progresses, muscle tissue are lost and arms and legs begin to look thinner and speech becomes difficult.

As the disease progress, muscles of the respiratory system deteriorate and in most cases, 2–5 years from diagnosis ALS patients die from respiratory failure. Most people who develop ALS are between the ages of 40 and 75 years, with the majority over 60 years of age. It has been estimated that the incidence of the disease is roughly two people per 100,000 per year.

The manifestations of ALS are highly variable from one individual to another. Ultimately, ALS is a clinical diagnosis made by a neurologist. There is no definitive diagnostic test for this disease. It has been calculated that in the USA, every day, an average of 15 people

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are newly diagnosed with ALS and as many as 30,000 Americans may currently be affected. Annually, ALS is responsible for two deaths per 100,000 people [2,3].

Exploring the cause(s) of ALS

Researchers are actively involved in exploring the causes and factors that trigger selective motor neurons to degenerate in ALS. It has been reported that in a type of familial ALS, mutations occurring in the gene coding for the copper/zinc superoxide dismutase (Cu, Zn-SOD1) are associated with the genesis of an inherited form of the disease. In addition, it has been demonstrated that mutations in the Cu, Zn-SOD1 (superoxide dismutase 1) induces motor neuron death through molecular mechanisms that are not yet completely established, including endoplasmic reticulum degradation, activation of apoptosis signals and/or cell death pathway machinery [4].

Recent studies have documented that insoluble forms of mutant SOD1, via protein miscoding, accumulate in neural tissues of ALS patients as well as in the spinal cord of animal models expressing these polypeptides. These findings suggest that mechanisms and effectors involved in mutant SOD1 accumulation may play a central role in the onset, development of early diagnosis and probably in the identification of potential targets for treatment of ALS [5,6].

In a significant population of ALS patients, as well as in patients suffering frontotemporal lobar degeneration, intracellular inclusions of protein TDP-43 (a DNA-binding protein) occur in the CNS [7]. Since, TDP-43 is normally concentrated in the nucleus but also travels in/out to the cytoplasm, it has been difficult to define whether the presence of TDP-43 causes neurotoxicity by a loss- or gain-of-function process [8]. This information as well as recent proof of accumulation of free radicals [9], loss of production of neurotropic factors and regulation/deregulation of apoptosis have contributed to the better understanding of the genesis of ALS and, thus, in the development of therapies to slow its progression.

Therapeutic options for ALS

It is commonly mentioned that ALS has no prejudice, since it occurs worldwide, with no age, ethnic or economic boundaries [10–12]. Although a cure for ALS has not yet been found, ongoing research has never been more active or more promising. Quite a few studies are in progress to assess novel drugs targets, medications [13–15], and several other drugs/products to treat ALS, as indicated in the database of ClinicalTrials.gov [73]. Simultaneously, alternative medicines, that can help to combat, prolong, reduce and/or improve the quality of life of patients with ALS, have been explored [16–18].

The prospective use of cell-based therapies to treat ALS has been a resilient concept in progress since the end of the last century. The notion has been constantly strengthened with the information emerging from cellular, molecular and animal studies revealing the exclusive traits of stem cells that support their use in the treatment of various conditions [19].

Abundant cellular and molecular data have demonstrated the capability of certain types of embryonic, fetal and/or adult stem cells to adopt a neuronal or glial fate and/or to deliver distinctive signaling molecules (neurotrophins, neurotropic factor family ligands and neuropoietic cytokines), distinctive of the neural microenvironment [19,20].

These attributes of stem cells epitomize the hope of a therapy that might restore function, delay degeneration and/or alleviate the symptoms of the disease in ALS patients, probably by mechanisms not necessarily involving cell replacement [19–22].

Mesenchymal stem cells (MSCs), a type of mesoderm-derived stem cell present at low quantities in some adult tissues (e.g., bone marrow, fat), as well as in umbilical cord blood and Wharton jelly, have been considered as an attractive paradigm for developing clinical protocols to treat various conditions [23].

The above approximation has been based on the cellular and molecular features of MSCs including a self-renewal potential and a capacity to commit and differentiate into a variety of mesenchymal and non-mesenchymal cell types [24–26]. Furthermore, MSCs produce a vast array of cellular mediators, such as growth factors, interleukins, chemokines and extracellular matrix molecules. In addition to an easy/skillful procurement and *ex vivo* expansion, MSCs minimally express MHC-I but do not express MHC-II or costimulatory molecules (CD80, CD86, CD40) on their cell surface. All these attributes have been considered for the use of MSCs in autologous and/or allogeneic cellular therapies [27,28].

A number of above-described traits of MSC (self-renewal, differentiation potential and immunophenotype) delineated what has been denominated a "minimal criteria for defining multipotent mesenchymal stromal cells" [29]. However, these traits are dramatically modified after MSCs interact either with multifactorial panels of cytokines, matrix molecules, exosomes, microRNAs and/or after cell-to-cell communication with other cell types.

Depending on the nature of the regulatory molecules and that of the cell-to-cell interactions, MSCs trigger a 'distinctive' differentiation pattern into cells of the neural lineage and/or become capable of generating a wide range of neuroprotective signals. The cellular and molecular evidences that support the

above contention are succinctly reviewed in the next two sections.

MSC differentiation into neural-like cells

Data evolved from tissue culture studies have demonstrated the capability of MSCs (*ex vivo* expanded from various sources) to differentiate under diverse conditions, into cells displaying both a morphology and an immunophenotype characteristically exhibited by neural cells [30–35].

The capacity of MSCs to express a fate into a neuron-like cell involves the expression of specific developmental programs, as convincingly demonstrated by sophisticated cellular and molecular techniques. In turn, the contribution of proteomic and genomic studies has contributed significantly to elucidate important pathways utilized during MSCs' neural differentiation as well as in the identification of new proteins and putative targets for therapeutic intervention [36,37]. Representative information on these studies has been gathered in Box 1.

Neuroprotective regulatory signals produced by MSCs

The likely utilization of MSCs in cell-based therapies for the treatment of neurological disorders has been reinforced by a number of studies disclosing the competence of MSCs to produce neuroprotective signals. While it is not possible to display a comprehensive listing of such studies, the outcomes of the investigations summarized in Box 2 will facilitate a better understanding of the clinical projection of this particular feature of MSCs.

Preclinical studies performed to assess the 'neurological signature of MSCs

Since the end of the last century, and motivated by the alluring option to utilize cell therapy to treat certain diseases, numerous preclinical studies have addressed the issue of whether the infusion of different types of stem cells/progenitors is feasible, safe and clinically efficient. In the specific case of MSCs, studies have been performed to investigate several features linked with the route of MSC infusion, dose, destination, homing and/or the production of a beneficial effect in a particular impaired organ or tissue [27,28].

Box 3 summarizes illustrative preclinical studies designed to elucidate the onset of neural-associated mechanisms elicited after the administration of MSCs either to normal and/or appropriate mouse models of ALS. The encouraging outcome of these studies has convincingly supported the cautious clinical translation of MSC-based cell therapies as an appealing treatment for human ALS.

Mesenchymal stem cell therapy for the treatment of ALS: signals for hope?

The cellular, molecular and preclinical features of MSCs, as indicated in the previous sections, have encouraged both basic and clinical actors to endorse the formulation of MSC-based clinical studies as well as to initiate clinical trials to evaluate the therapeutic benefit that this type of adult stem cell may have in patients suffering from ALS.

In a comprehensive report published 3 years ago [66], it was stated that even though the "…development of

Box 1. Mesenchymal stem cell differentiation into neural-like cells: genomic & proteomic data.

- Differentiation of MSCs into functional neurons was explored after coculture with cerebellar granule neurons. Under these condition, MSC-derived neuron-like cells express neuronal markers (nestin), several genes (*sox, pax, notch, delta, frizzled, erbB2, erbB4*) and a capability to respond to various neurotransmitters [38]
- The differentiation of human bone marrow-derived MSC to a neural lineage was assessed by the expression of Nestin, Enolase2, MAP1b, KI67 and neural-related transcription factors (Engrailed-1 and Nurr1) [39,40]. It was found that neuronal marker's expression occurred mainly in MSC prepared from young but not old donors. This donor-related heterogeneity must be considered prior to any projected MSC-transplantation strategy
- Cell surface proteome analysis of human MSC demonstrated expression, among many other proteins, of 33 cell adhesion molecules, 26 signaling receptors and 41 CD markers. The expression of these markers was found to be distributed homogenously, but modulated during differentiation to various lineages, including neuroectodermal [41]
- WJ-MSC exposed to glial growth factors (bFGF, PDGF) differentiate in spindle-like cells that express glial markers and secrete BDNF, NGF and NT-3. Results suggest that WJ-MSC could be a suitable substitute for Schwann cells for clinical nerve repair [42]
- To further validate the hypothesis that MSCs stimulate neurite outgrowth from spinal neurons, the later cells were cocultured with MSCs, fibroblasts, MSC-conditioned medium or control medium. Neurite outgrowth was significantly greater in the presence of MSC and modulated by the release of BDNF and GDNF [43]
- Notch signaling participation in the neurogenic commitment of periodontal-derived MSC involves increased expression of β3-tubulin, neurofilament and Notch signaling target genes Hes-1 and Hey-1. Resulting cells exhibit neurite-like extensions and an increased expression of neurogenic mRNA markers [44]

MSC: Mesenchymal stem cell; WJ-MSC: Wharton's jelly-derived mesenchymal stem cell.

Box 2. Production of neurotropic factors, extracellular matrix components, cytokines/growth factors and anti-inflammatory signals.

- In animals with brain damage, implanted MSC improved motor function, which is associated with an increased expression of neural markers (MAP2, GFAP) and the production of BDNF [45]
- In SOD1-mutant transgenic mice ('ALS-mice': the animal model of familial ALS), intracerebral injected MSC migrated/differentiated into glia and neuronal cells (doublecortin+, CXCR4), via production of β1 integrin and neurotropic factors. Concomitantly, neurological function and cortical neuronal activity was improved [46]
- In an ischemic stroke animal model, the infusion of MSC (via cell homing in the damaged zone) improved neural-behavioral function. Concurrently, expression of neural-specific markers and release of G-CSF, VEGF and BDNF occurred [47]
- Injected MSCs in SOD1 mice during the symptomatic stage of disease, improved survival and motor functions. In addition, MSCs reduced accumulation of ubiquitin agglomerates and of activated astrocytes and microglia in the spinal cord of MSC-treated animals. Infused cells turned around the upregulation of metallothionein mRNA expression, the activity of glutathione *S*-transferase and reverted both spontaneous and stimulus-evoked neuronal release of D-aspartate. These findings provide a sustainable rationale for the use of MSCs in ALS [48,49]

ALS: Amyotrophic lateral sclerosis; MSC: Mesenchymal stem cell; SOD1: Superoxide dismutse 1.

relevant therapies for ALS has been challenging and elusive. just one ALS clinical trial using MSC was in progress". In the referred study [67], the implantation of autologous bone marrow-derived MSCs was assessed in four ALS patients. Despite the occurrence of minor and transient adverse events, the main conclusion of this pioneer clinical trial was that the infusion of *ex vivo*-expanded MSCs into the spinal cord of ALS patients was safe as well as tolerated and promising.

At present, four clinical studies designed to explore the effect(s) of MSCs administrated to ALS patients have been reported to be initiated and/or completed in different countries (Table 1A). Results proved that the intrathecal infusion of autologous or allogeneic bone marrow-derived MSCs to a cohort of approximately 50 ALS patients was safe in terms of absence of complications at the infusion site. In addition, follow-up analyses showed that cell infusion did not elicit new neurologic deficit(s) beyond those attributed to the natural progression of the disease.

In terms of efficacy, MSC infusion proved to be effective, as established by various clinical assessments, including ALS functional rating scale, forced vital capacity and/or hand held dynamometry [68–72]. Delete 250 to 252: All together, these data suggest that the infusion of MSCs (either autologous or allogeneic) produces a slowdown in disease progression, as well as meaningful survival benefits for ALS patients.

In the studies depicted in Table 1A, the nature and uniqueness of the disease (see previous section, Amyotrophic lateral sclerosis) as well as important dissimilarities in cell administration practices (i.e. infusion route, quality and quantity of MSCs, single/various infusions, etc.), make it difficult to anticipate the nature of the mechanisms involved in the beneficial effect(s) identified after MSC infusion.

Box 3. Prospects for mesenchymal stem cell-based therapies for amyotrophic lateral sclerosis: input from preclinical studies.

- After intracerebral infusion of MSCs into experimentally damaged rats, it was found that the infused cells survived, migrated and differentiated into neural lineages. MSCs produce a significant improvement/recovery of behavior and neurological function [50]
- After intracortex infusion of MSCs to 'ALS-mice', cells grafted around brain ischemic areas. At 2–4 weeks after infusion, animals show delayed ALS onset and progression, increased lifespan and an improvement in functional tests. Beneficial effects seem to be linked to differentiation of MSC into neural-like cells and an augmented secretion of neurotropic proteins [51,52]
- In various animals models involving injured spinal cord tissue, both the intrathecal and intravenous delivery of MSC proved to be feasible, safe and minimally invasive. Infused cells reach contused tissues with high grafting efficiency, differentiate to neural phenotypes and release neurological factors involved in axon outgrowth and recovery [53–59]
- The infusion of MSC to 'ALS-mice', significantly delayed motor deterioration as evidenced by higher number of lumbar motor neurons, progenitors migration and upregulated levels of nuero-trophic factors. In addition, MSCs modulate the secretome of local glial cells toward a neuroprotective phenotype [60–65]

ALS: Amyotrophic lateral sclerosis; MSC: Mesenchymal stem cell.

Table 1. The use of mesenchymal stem cells in the treatment of patients suffering from amyotrophic lateral sclerosis: information from recently completed clinical studies and ongoing clinical trials.

(A) Published clinical studies		
MSC source†/#patients/infusion route‡/aim of study	**Main observations**	**Ref.**
Auto-BM-MSC/19/IT and IV/ safety and feasibility	No major adverse effects; ALS-FRS score remained stable; MSCs detected in occipital horns; induction immunomodulatory effects	[68]
Auto-BM-MSC/19/IT/safety and efficacy	MRI revealed no structural changes/no side effects/no distinct benefits	[69,70]
Auto-BM-MSC/10/IT/safety, feasibility and efficacy	No adverse events; no significant deterioration in ALS-FRS (at 1 year); results suggest a trend towards disease stabilization	[71]
Allo-BM-MSC/1/IT/safety and efficacy	No adverse events; improvement in quantitative clinical assessments and in quality of life (18 months)	[72]
(B) Ongoing/completed clinical trials		
# patients(n)/phase	**Infusion route‡/MSC source/dose/others**	**NCT§/country**
10/I	Intraventricular/stereotaxic/auto–BM-MSC/ single dose/ safety	01759784/Iran
1/I	IT; auto–BM-MSC; single dose/safety	01142856/USA
7/I	IT; auto–BM-MSC; single dose/safety	01759797/Iran
10/I	IT; auto–BM-MSC; single dose/safety	01771640/Iran
25/I	IT; auto–adipose-MSC; dose escalation/safety	01609283/USA
30/II	IT; umbilical CB-MSC; 4 doses; safety/efficacy	01494480/China
12/I–II	IM; BM-MSC/NTF¶ to early ALS subjects; safety/ efficacy. IT; BM-MSC/NTF¶ to progressive ALS subjects; safety/efficacy	01051882/Israel
12/II	IM; BM-MSC/NTF¶ single/multiple injections, safety/efficacy. IT; BM-MSC/NTF¶ single injection; escalating dose; safety/efficacy	01777646/Israel
6/I	IT: auto-BM-MSC; single dose, safety	01082653/USA

†Auto: Autologous; Allo: Allogeneic.
‡IT: Intrathecal; IM: Intramuscular.
§NCT clinical trials [73].
¶Auto BM-MSCs manipulated to secrete NTFs.
ALS-FRS: Amyotrophic lateral sclerosis functional rating scale; BM-MSC: Bone marrow mesenchymal stem cell; CB-MSC: Cord blood mesenchymal cell; MSC: Mesenchymal stem cell; NTF: Neurotrophic factor.

In addition to the clinical studies reviewed above, a significant number of clinical trials (both in Phase I and/or II) have been designed and initiated to assess safety, feasibility and/or efficacy after the infusion of autologous MSCs to ALS patients (Table 1B).

In the clinical trials described in Table 1B, MSCs from various tissues sources (bone marrow, cord blood, adipose) will be *ex vivo* expanded and infused as such or after *ex vivo* manipulations, to near 100 ALS patients.

Despite the nascent condition of all these studies, it is indubitable that for ALS patients and close relatives of ALS patients, these early outcomes represent a strong enforcement of their hope for a treatment that improves functions and/or stops disease progression [74–76]. In this respect, a regulatory agency has conferred the designation of 'orphan drug' to a clinical study (FDA-IND 13729) currently under development to investigate the effect(s) of the intrathecal infusion of bone marrow-derived MSCs to ALS patients.

Based on the still nascent concept that MSC-based therapies may provide a new strategy for supporting tissue regeneration and repair in ALS-suffering patients, the necessity of designing more feasible and efficacious approaches seems to be an urgent issue. Still, it seems premature to define a consensus protocol(s) including methods and practices for the utilization of MSCs in the

treatment of ALS patients. However, there are certain issues that should be addressed by biomedical groups exploring the utilization of a MSC-based therapy for ALS patients.

Among them, we would like to call the attention to the following issues.

Use of autologous, allogeneic or both classes of bone marrow-derived MSCs (BM-MSCs)

Despite both autologous and allogeneic BM-MSCs having been safely administered to ALS individuals (Table 1A), it is not clear whether MSCs from both origins exhibit the same biological traits. In contrast to studies demonstrating that traits of BM-MSCs from ALS patients and healthy donors are rather similar [77], other studies have demonstrated important differences. Among them changes in telomerase activity, telomerase enzyme protein and telomerase RNA transcripts [78], the expression of critical primary effectors of extracellular matrix remodeling and stem cell mobilization [79], the transcriptional network regulating pluripotency (Oct4 and Nanog) and in the expression of several growth factors [80].

In the same vein, expression of two genes (*CyFIP2* and *RbBP9*) involved in post-transcriptional RNA editing exhibited a significant decrease in MSCs from ALS patients as compared with healthy individuals [81]. Since, the escalation of these differences seems to be proportional to disease progression rate [82], the significance of the therapeutic implantation of autologous MSCs in ALS patients needs to be carefully reevaluated.

The statement above is also supported by the results of several studies demonstrating that factors such as aging, sex, smoking, body mass index, alcohol and medication consumption significantly contribute to alter both the quantity (*ex vivo* expansion passages) and quality (cellular and molecular traits) of BM-MSCs [27,83,84]. Accordingly, it must be established whether the administration of allogeneic as compared with autologous MSCs, is not only faster but more effective. Accordingly, the use of healthy allogeneic MSCs seems to be a better option for cell therapy in ALS patients [72].

Delivery of MSCs

The safety and efficacy of a MSC-based therapy for ALS has been assessed after infusing the *ex vivo*-expanded cell product by using different modalities, including intravenously, intrathecally, intramuscularly and others (see Table 1). Given that the development of cell-tracking techniques is still evolving, there is no consensus on the most beneficial delivery strategy. It is without doubt that further research on this issue will impact not only the trafficking and homing of viable cells, but treatment efficacy [27,66,83,85].

Quantity or quality of the administered cell product?

The therapeutic utilization of a MSC product has a mandatory step which is *ex vivo* expansion, a not well-defined 'recipe' to achieve the desired number of cells. Attempts to increase the number of MSCs to be infused are almost unlimited; however, cellular traits of the resulting cell populations (stemness, differentiation potential, immunophenotype, senescence control, others) are highly sensitive to the extent of *ex vivo* expansion [27,86–89]. Thus, protocols designed to manufacture a MSC product must be carefully designed to reach the proper number of fully competent cells. The above concern becomes crucial in those cases where multiple infusions of the cell product are planned; the latter alternative has been validated by several preclinical studies [27,90,91].

It is important to mention that in addition to the use of MSCs, other types of adult stem cells are currently being explored for the treatment of ALS. Among them, neural stem cells [92–94], CD133+ bone marrow stem cells [95], CD34+ bone marrow stem cells [80] and bone marrow mononuclear cells [96,97].

Future perspective

ALS is an age-related neurodegenerative disorder in which motor neuron loss in the spinal cord leads to progressive paralysis and death. In spite of the fact that the disease was described by the end of 19th century and the current accessibility to adequate and precise clinical diagnosis, today most ALS patients, as in 1870, die less than 3 years from symptom onset.

Cellular, molecular, genetic, environmental and many other sophisticated multifarious issues have been exhaustively investigated in the last decade to better comprehend the geneses of the disorder. In most cases, the results of these studies have largely generated attractive publication-quality information, but have been distant to transmit tangible hopefulness to ALS patients. Up to now, significant therapeutic trials to halt or revert the progression of the disease have been virtually inexistent. However, as discussed in this review, in the last 2–3 years a number of studies have sustained the notion that cellular therapy may well represent a treatment option for ALS patients. This is the case for MSCs, a cell type displaying cellular, molecular and immunological traits that configure a promising agent with neuroprotective potential.

Currently, numerous proposals are listed in ClinicalTrials.gov [73] to explore safety, feasibility and efficacy after infusion of MSCs to ALS patients. At the other end, a limited, but continuously rising number of clinical studies have verified that the administration of MSC to ALS patients is safe and proficient to initiate significant survival benefits, including repossession of quality of life.

We expect that results of new clinical studies, using this type of adult stem cells, will contribute to determine their therapeutic significance in treating ALS. In this regard, several procedural issues still need to be addressed by biomedical groups exploring the use of a MSC-based therapy in ALS patient. Among them, convincing evidences for the type of cell product to be used (allogeneic and/or autologous), infusion modalities (intrathecal, others) and number of infusions (single vs multiple) should be examined and put into practice.

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Executive summary

Background

- It is an undeniable fact that almost 140 years after the condition was originally described amyotrophic lateral sclerosis (ALS) patients do not have the choice of a therapy that either brings a halt to the progress of the disease, delays the fatality of the disease or, in the best case, cures medical problems permanently.
- The intention of this review was to dissect the fundamentals of an emerging therapy based on the rather new concept of regenerative medicine, via the use of adult stem cells, which suggests a potential therapeutic benefit to ALS patients.

Mesenchymal stem cells: a potential product for an ALS cell-based therapy

- The long-term established traits of mesenchymal stem cells (MSCs) include self-renewal, differentiation (to osteo, chondro and adipo lineages) and the production of several growth factors and cellular matrix components.
- However, MSCs also exhibit several neurological traits, including a potential to adopt a neural-like morphology and the generation of a wide range of neuroprotective signals. These appealing features of MSC have motivated numerous preclinical studies in an attempt to disclose possible clinical benefits of MSCs to ALS patients.

Prospects for the treatment of ALS patients with MSCs

- Several clinical trials are currently ongoing to evaluate the safety and feasibility of the administration of MSCs to ALS patients.
- In addition, at least five clinical studies have examined the clinical benefit response after the infusion of either autologous or allogeneic MSCs to a total of at least 50 ALS patients. Results have demonstrated that while the procedure is safe and practicable, it may also induce disease stabilization and/or improvement in survival, quantitative clinical assessment and quality of life.

Discussion & conclusion

- Despite MSC-mediated cell therapy for ALS patients being still a rather new therapeutic approach, the reported clinical effects anticipate promising prospects.
- It its evident that protocols developed to date to administer MSCs to ALS patients require more than a few adjustments. Among others, optimal timing for treatment, adjustment of cell dose, single or various infusions, cell delivery modality and elucidation of the dilemma: autologous (own patient's cells) or allogeneic (donor) MSCs.

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