J Neuroimmune Pharmacol (2013) 8:1062–1076
DOI 10.1007/s11481-013-9456-6

PERSPECTIVE

Towards Clinical Application of Mesenchymal Stem Cells for Treatment of Neurological Diseases of the Central Nervous System

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Received: 6 January 2013 / Accepted: 31 March 2013 / Published online: 12 April 2013

Abstract The diagnosis of a neurological disease of the central nervous system (CNS) is often associated with the anticipation of an irreversible and untreatable disability. This is the case also of multiple sclerosis (MS) where approved treatments effectively modulate the autoimmune attack to myelin antigens, but poorly affect neurodegeneration and do not promote tissue repair. Thus, stem cell-based therapies are increasingly being considered a possible strategy for diseases of the CNS. Mesenchymal stem cells (MSC), the safety of which has been demonstrated in the last 20 years through clinical trials and case studies, are of particular interest in view not only of their neuroprotective, but also of their immunomodulatory properties. Here, we review the therapeutic features of MSC that make them relevant in the treatment of CNS illnesses and discuss the pioneer clinical experience with MSC-based therapy in neurological diseases.

Keywords Mesenchymal stem cells · Neurological diseases · Multiple sclerosis · Amyotrophic lateral sclerosis · Alzheimer's disease · Parkinson's disease · Multiple system atrophy · Stroke · Brain ischemia · Spinal cord injury

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Introduction

Despite a vast amount of research, unknown etiologies and complex pathophysiological pathways make difficult to devise effective treatments for primary degenerative, traumatic, and inflammatory diseases of the central nervous system (CNS), where the loss of neural cells appears to be an irreversible process.

The lack of effective drugs protecting neural tissues undergoing degeneration and possibly reverse disability leading to recovery of neurological functions in these diseases has prompted research into alternative treatments with the potential to promote repair of the damaged CNS. In this context, administration of mesenchymal stem cells (MSC), which are likely to be safe as suggested by several small studies in more than 10 years of clinical experience, is at the vanguard of such treatments as MSC represent the one of the most promising approach, not only because of their tissue-repair potential, but also because they can control the inflammatory activity associated with tissue degeneration occurring in many neurological diseases.

Mesenchymal stem cells: general properties and early preclinical studies

Stem cells are characterized by the capability to self-renew and give birth to more differentiated cells of the same embryonic lineage and, sometimes, also of other lineages. MSC, a population of adult stromal progenitors of the mesodermal lineage, were first described by Friedenstein after isolation from bone marrow (BM) (Friedenstein et al. 1974). Although subsequent studies showed that MSC can be isolated from almost every connective tissue, they have been characterized mainly upon isolation from BM and adipose tissue (Meirelles et al. 2006). BM-derived MSC (BM-MSC) are characterized by the

presence of stromal markers and the lack of hematopoietic markers, and by their ability to differentiate into chondrocytes, adipocytes, and osteocytes both in vitro and after transfer in vivo (Prockop 1997). Within the BM, MSC and stromal cells are essential components of the hematopoietic stem cell (HSC) niche, which is articulated in different specialized compartments, supporting hematopoiesis (Mendez-Ferrer et al. 2010).

The endogenous location of MSC in the BM, where immune cells develop, prompted the study of their interaction with adult cells derived from the BM and involved in the immune response, such as lymphocytes. The first pivotal studies revealed that MSC strongly suppress lymphocyte proliferation, possibly through the release of soluble factors, and that they have an immunosuppressive clinical activity, prolonging the survival of allogeneic skin transplants in animal models (Bartholomew et al. 2002; Di Nicola et al. 2002). Since then several studies demonstrated that MSC have the properties to modulate effector functions of T and B lymphocytes, dendritic cells, NK, γδ T cells, monocytes and macrophages through mechanisms requiring cell to cell contact and, in most cases, the release of soluble molecules (Uccelli et al. 2008). These immunomodulatory properties were exploited in animal models of autoimmune diseases. (Zappia et al. 2005; Zhang et al. 2005, 2006; Gerdoni et al. 2007; Kassis et al. 2008; Gordon et al. 2008; Rafei et al. 2009).

As detailed in the following paragraphs, different strategies have been chosen in order to prove the feasibility, safety and efficacy of MSC in preclinical settings. First of all, MSC have been administered through different routes, including local delivery to the affected tissue, intra-arterial, intraperitoneal, and intravenous administration. The rationale for local administration in early studies was to permit MSC to engraft into the injured tissue and possibly transdifferentiate into local cells. However, studies in experimental neurological diseases clearly showed that MSC poorly engraft in the tissue despite clinical effectiveness (Gerdoni et al. 2007). Moreover, intra-arterial and i.v. administration have often shown comparable efficacy to local delivery. Clinical benefit is achieved in spite of the fact that, regardless of the route of administration, only small numbers of MSC reach the target tissue (Morando et al. 2012) and, under some experimental condition, conditioned medium from MSC suffices to ameliorate EAE and experimental epilepsy promoting tissue repair (Bai et al. 2012; Voulgari-Kokota et al. 2012). These findings highlight the possibility that MSC may affect tissues without or with limited local engraftment mainly through the release of soluble factors (Uccelli and Prockop 2010) and emphasize the concept that interaction with cells of the recipient remarkably affects the host immune response (Chiesa et al. 2011). While the site where the cross-talk between MSC and the host-microenvironment is not fully understood, it is clear that events occurring in the lungs, where MSC are entrapped shortly after i.v. administration, are pivotal in mediating their immunomodulatory effect (Lee et al. 2009a). This new paradigm supports the concept that MSC are cells delivering either locally or at distance factors in a paracrine fashion without the requirement of integration in tissues (Caplan and Dennis 2006; Uccelli and Prockop 2010) (Fig. 1). It may also explain the positive results obtained with allogeneic or xenogeneic MSC in animal settings, as well as in clinical trials (which employed either allogeneic or autologous MSC), despite the evidence that allogeneic MSC are susceptible to immune rejection (Eliopoulos et al. 2005).

The possibility that pre-treatment of MSC with particular drugs could enhance or modulate their effect has been addressed through in vitro and pre-clinical studies. It was proposed that MSC treated with the inhibitor of the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase atorvastatin could be employed in clinical trials aimed at assessing their effectiveness in diabetic retinopathy; indeed, pre-treatment with atorvastatin inhibits the secretion by MSC of trophic factors such as vascular endothelial growth factor (VEGF) that would be detrimental in the retinal microenvironment (Mottaghi et al. 2013); however, while this is an interesting hypothesis, it has not yet been tested. Other molecules, such as the steroid hormone progesterone, were reported to shape the function of MSC and increase their immunomodulatory properties in vitro (Zhao et al. 2012). Another strategy employed to boost MSC properties or promote their differentiation to neuron-like cells is to genetically engineer MSC to produce neurotrophic/neuroprotective or angiogenic factors, or molecules relevant to specific neuronal function, such as production of dopamine (Lu et al. 2005). Similarly, "neuralization" of MSC has also been used to boost their neuroregenerative potential (Dezawa et al. 2004). This type of strategy has been tested in preclinical studies on animal models of neurodegeneration, as detailed in the following paragraphs (Dezawa et al. 2004; Suzuki et al. 2008; Lu et al. 2005). The concept to increase the therapeutic effect of MSC is attractive; however, the potential risks of modifying the cells prior to administration, which could lead to side effects unexpected from MSC treatment, need to be taken into consideration through further stringent pre-clinical studies. In addition, modification of MSC would need to be tailored to the particular disease or tissue involved. For example, while inhibition of VEGF production upon exposure of MSC to atorvastatin might be of benefit in diabetic retinopathy (Mottaghi et al. 2013), pre-treating MSC with atorvastatin could be detrimental in cases where MSC-driven angiogenesis is beneficial, such as for spinal cord injury (see below).

Pioneer clinical studies

Because of the role of MSC in the HSC niche, early studies explored their use in subjects with hematologic diseases or

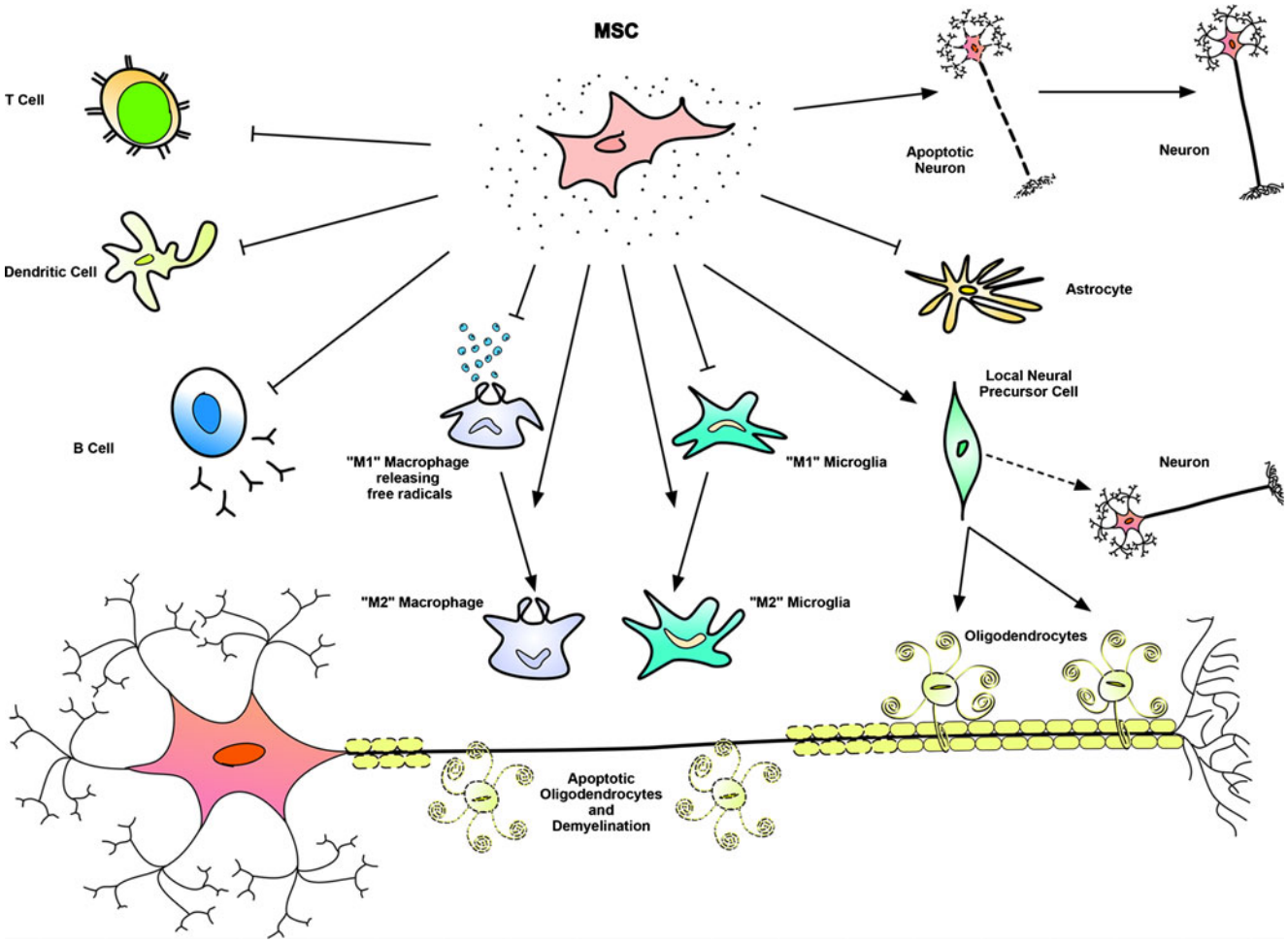

Fig. 1 Postulated mechanisms of tissue repair exerted by MSC within the CNS. Preclinical studies in EAE and other experimental models of neurological diseases have shown that MSC could downregulate inflammation through their action on immune cells (T cells, B cells, dendritic cells and macrophages), mainly in the periphery, and on resident cells (microglia, astrocytes) in the CNS. Within the CNS, MSC may promote alternative activation of microglia and macrophages, inhibit proliferation of astrocytes, rescue neurons from apoptosis and induce endogenous neurogenesis

undergoing HSC transplantation, with the aim of assessing whether the MSC would support the BM environment after chemotherapy and/or facilitate engraftment of transplanted HSC in the host (Lazarus et al. 1995; Koc et al. 2000; Lee et al. 2002). In parallel, other studies assessed the feasibility of treatment with MSC in subjects with diseases involving the mesenchymal compartment, including children with osteogenesis imperfecta or adults with aplastic anemia (Horwitz et al. 1999; Fouillard et al. 2003); results showed that MSC could replace, at least partially, a defective stroma. At the same time, advancement on our understanding of the immunomodulatory features of MSC led to the first attempts to treat immune-mediated diseases such as graft-versus-host disease which culminated in a successful phase II clinical trial showing safety and efficacy of MSC transplantation for this potentially lethal disease (Le Blanc et al. 2008).

Clinical experience with neurological diseases dates back to 2002, when allogeneic MSC were administered to subjects with metachromatic leukodystrophy (MLD) who had previously received HSC (Koc et al. 2002). Transplantation of HSC alone was not sufficient to revert neurological abnormalities in those patients. In contrast, subsequent MSC infusion resulted in some improvement in peripheral nervous system measures in 4 out of 6 subjects with MLD (Koc et al. 2002).

The dose of MSC administered varies considerably among studies. In the study on children with MLD or Hurlers disease, administered doses varied from 2×10^6 to 10×10^6/Kg; regardless of the dose, infusion was well tolerated without any major side effects (Koc et al. 2002).

An important point resulting from most published studies in animals and humans is that MSC appear to be safe. As MSC are multipotent cells with immunosuppressive features, possible concerns about MSC therapy are: a) excess of immune suppression leading to a condition of immunodeficiency; b) ectopic tissue formation; c) carcinogenicity. Excess of immune suppression, leading to a significant increase in the

incidence of viral infections, was not observed even in transplanted, immunocompromised patients (Lucchini et al. 2012). However, a retrospective study from another group showed a possible association between treatment with MSC and death from pneumonia in patients previously treated with HSC transplantation (Forslöw et al. 2012); this possibility needs to be addressed through further prospective randomized clinical trials.

Ectopic tissue formation has been observed by Tolar et al. who infused 1×10^6 allogeneic MSC in different mouse recipients after 6 passages in culture, observing ectopic ossicle formation in the lungs and sarcomas in the extremities (Tolar et al. 2006). In another study, bone marrow-derived MSC injected via intracerebroventricular transplantation resulted in the formation of fibrogenic cellular masses and local damage within the CNS parenchyma (Grigoriadis et al. 2011). Despite these reports, MSC transplanted in nude mice are commonly considered to have an undetectable disposition to oncogenic transformation after in vitro culture and in vivo implantation (Vilalta et al. 2008). In order to avoid potential risks of transformation, few culture passages before transplantation and intravenous administration are advisable and are currently performed in humans. An indirect carcinogenic effect of MSC could be through their immunosuppressive properties, as shown by a study where co-administration of melanoma cells and MCS, but not of melanoma cells alone, lead to melanoma survival in allogeneic animals (Djouad et al. 2003). However, neither ectopic tissue formation nor carcinogenicity have been linked to MSC treatment in clinical studies published so far (Sensebé et al. 2012).

In the following paragraphs we will report on preclinical and clinical studies published so far in some of the most common neurological diseases.

Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a relentless degenerative disease involving upper and lower motor neurons with a fatal outcome within a few years after clinical onset. Oxidative stress damage, dysfunctions in RNA-processing proteins, protein degradation impairment, and defects in autophagy mechanisms may concur to cause the disease (Hughes 2011). There is no available treatment that prevents degeneration of motor neurons.. In the first pioneering experiment in a preclinical model of ALS, Zhao and colleagues reported that pre-symptomatic mice expressing a mutated human superoxide dismutase gene (SOD1-G93A) experienced a significant delay in disease onset and progression and an increased average lifespan upon pre-symptomatic i.v. treatment with human MSC (hMSC) from healthy donors (Zhao et al. 2007). Vercelli et al. reported similar results in 2008 after intraspinal cord administration of hMSC; they observed increased survival, reduced astrogliosis and microglial activation, higher motor neuron counts, and some engraftment of hMSC in the recipient spinal cord (Vercelli et al. 2008). Different results were obtained by Morita et al., who treated $SOD1^{Leu126delTT}$ mice before disease onset with rat-derived MSC, combined with immunosuppressive drugs in order to prevent immune rejection. No clinical effect in the overall population was observed, however treated female mice had an increased survival compared to female controls (Morita et al. 2008). Obviously, the possibility cannot be excluded that a different mouse model and origin of the MSC might have affected the outcome. Delivery of allogeneic MSC via lumbar puncture to affected rats was also effective in decreasing motor neuron loss in the lumbar spinal cord, preserving motor functions and extending the survival of the hSOD1(G93A) rats (Boucherie et al. 2009). In another study, MSC expanded from the BM of ALS patients were intra-cisternally administered to SOD1-G93A mice. Results showed that h-MSC from subjects with ALS delayed the decline in motor performance and improved survival, in a dose-dependent fashion and diminished motor neuron loss, providing evidence that MSC from ALS patients are functional (Kim et al. 2010). In all the above studies, MSC were administered before the onset of disease; obviously, this cannot be translated into human trials aimed at testing MSC for the treatment of sporadic ALS. In a recent study the therapeutic potential of MSC in SOD1-G93A mice with ongoing disease was evaluated (Uccelli et al. 2012b). Allogeneic (from another mouse strain) MSC were effective even when administered after disease onset, leading to significantly prolonged survival and amelioration of pathological findings. Similar results were observed in rats treated at disease onset with intrathecal plus i.v. administration of allogeneic MSC (Forostyak et al. 2011), and, in a different mouse model of ALS, with intra-spinal cord injection (Pastor et al. 2011). Injection of MSC into the muscle of affected mice was attempted using hMSC transfected with glial cell-line derived neurotrophic factor (GDNF) gene in order to boost their properties; the GDNF-MSC were superior to wild type MSC in promoting survival and in increasing the number of neuromuscular connections and motor neuron cell bodies in the spinal cord at mid-stages of the disease (Suzuki et al. 2008).

Various mechanisms are likely to concur in mediating the therapeutic effect observed in the above-described studies. All the studies found an increased survival of motor neurons into transplanted animals. Other findings include reduced chronic inflammation and glial scarring, with decreased microglial activation and astrogliosis (Vercelli et al. 2008; Morita et al. 2008; Uccelli et al. 2012b). In some cases MSC injected into the cerebrospinal fluid were reported to transdifferentiate into healthy astrocytes (Boucherie et al. 2009). However significant transdifferentiation was not observed in other studies upon local delivery (Vercelli et al. 2008; Morita et al. 2008); MSC engraftment was observed upon i.v. injection (Zhao et al.

2007), but was scarce and transient in other studies, despite clear efficacy of the treatment mediated by a significant inhibition of glutamate-mediated excitoxicity (Uccelli et al. 2012b).

These preclinical studies have paved the road to a number of small phase I clinical trials using hMSC in ALS, which have proven the feasibility and safety of the procedure (Karussis et al. 2010; Mazzini et al. 2008, 2010). In particular, Mazzini et al. performed two small phase I studies (Mazzini et al. 2008, 2010), using in vitro expanded, autologous MSC delivered intraspinally in ALS patients. Patients did not experience major adverse events. Long-term observation (up to 9 years) of these subjects confirmed the safety of the procedure and suggested some effect on disease progression (Mazzini et al. 2012). A third study, conducted by Karussis et al. in 19 ALS patients, analyzed safety and efficacy of intrathecally, or intrathecally plus intravenously, transplanted autologous MSC (Karussis et al. 2010). The most common adverse events were febrile reactions and headaches (likely correlated to the injection procedure). From the efficacy point of view, while the mean ALS Functional Rating Scale clinical score deteriorated slightly during the 2 months preceding MSC injection, it remained stable during the six-month follow-up, suggesting that MSC transplant may slow disease progression (Karussis et al. 2010).

In conclusion, phase I clinical trials confirmed safety of intrathecal or intrathecal plus intravenous injection of MSC in ALS; while preliminary data of efficacy were reported in these small anecdotal studies, phase II studies, involving larger numbers of patients with proper controls, are required to evaluate the effectiveness of MSC treatment in ALS.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of degenerative dementia, characterized by (i) extracellular amyloid plaques (aggregates of amyloid-beta protein) (ii) neurofibrillary tangles (intraneuronal thick strands composed of hyperphosphorylated tau protein), and (iii) neuronal granulovacuolar degeneration, mostly seen in the pyramidal layer of the hippocampus, resulting in neuronal cell death (Ballard et al. 2011). The lack of other than symptomatic treatment has prompted the exploration of MSC administration as an alternative therapeutic approach.

Several in vitro and in vivo reports, starting from 2009, showed promising results for the use of MSC in animal models of AD. In particular, Lee et al. showed that BM-MSC injected intracerebrally are able to reduce accumulation of amyloid-β (Aβ) in brain in an experimental model of acute AD induced in C57BL/6 mice by direct Aβ injection in the hippocampal dentate gyrus (Lee et al. 2009b). The decrease in Aβ concentration in MSC-treated mice (compared to sham-transplanted animals) was linked to morphological changes of microglia. Subsequently, the same group showed that intracerebral BM-MSC transplantation in amyloid precursor protein and presenilin one (APP/PS1) double transgenic mice improves cognitive function and induces a switch in activated microglia from a detrimental to a beneficial phenotype permitting the clearance by microglia of the Aβ protein and reduction of Aβ plaques in the brain. Moreover, treated mice showed a reduction in hyperphosphorylated protein tau levels (Lee et al. 2010b). In another study the effects of intracerebral injection of xenogeneic human umbilical cord blood-derived MSC (hUCB-MSC) were evaluated in the acute model of AD showing an improvement of cognitive function, decreased levels of neuronal apoptosis and reduced activation of astrocytes and microglia (Lee et al. 2010a). Very recently, the same group confirmed the efficacy of hUCB-MSC in improving clinical performance and pathological scores (reduction in Aβ deposition, β-secretase 1 levels, and tau hyperphosphorylation) in APP/PS1 double transgenic mice, confirming a key role for alternative microglial activation in mediating the effects of MSC treatment. (Lee et al. 2012a). Treatment of mice that display neuropathological, but not yet cognitive features of AD, was also effective at reducing Aβ deposition and improving synaptic transmission (Bae et al. 2012). Babaei et al. showed that BM-MSC injected intracerebrally can also improve the ability to learn and memorize in both age- and chemically induced rat models of AD (Babaei et al. 2012). An in-vitro study described the induction of a neuronal-like phenotype in MSC cultured in presence of toxic forms of Aβ (Jin et al. 2009); however, it is not clear whether this observation has a clinical correlation, as in-vivo studies did not support such an hypothesis of MSC transdifferentiation as mechanism of action for their effect in AD models (Lee et al. 2010b).

Other studies focused on mechanisms involved in Aβ degradation induced by MSC. Kim et al. demonstrated that soluble intracellular adhesion molecule-1 (sICAM-1) is released by hUCB-MSC and acts paracrinally on microglial cells, inducing the expression of the Aβ-degrading enzyme neprilysin (Kim et al. 2012). Another study highlighted an important role for MSC-derived chemotactic molecule CCL5 in recruiting alternatively activated, neprilysin and IL-4 secreting, microglia into the brain of the affected animals (Lee et al. 2012b).

Although these results highlight the valuable potential of MSC as a treatment for AD, the complex and partially understood pathogenetic mechanisms and the poorly reliable animal models may slow down the translation of these results into a therapy. This could also explain the limited number of ongoing trials to assess MSC efficacy in AD registered in public clinical trial databases.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative affliction after AD. Two main pathological findings are 1) loss of dopaminergic pigmented neurons in the mesencephalic substantia nigra pars compacta and 2) presence of intra-neuronal masses of alpha-synuclein (αSYN), called Lewy bodies, which are distributed throughout the entire nervous system leading to dysfunctional circuits and symptoms of neurological impairment of increasing severity (Braak and Del Tredici 2008).

Since 2005, an increasing number of reports have highlighted promising results obtained in the development of MSC-based therapy for PD, both in vitro and in vivo (Lu et al. 2005). In the first report, MSC were used as a gene delivery vector in a rat model of PD; cells were transfected with the gene coding for the tyrosine hydroxylase (TH) protein, which is the rate-limiting enzyme for dopamine synthesis, and were administered by intra-striatal injection. The authors report successful transfer and expression of the TH gene in the rats striatum and clinical improvement (Lu et al. 2005). Subsequent in vitro studies showed that MSC-conditioned medium, or MSC them-selves, protect dopaminergic neurons from toxic and inflammatory insults (Shintani et al. 2007; Park et al. 2008; Kim et al. 2009). MSC conditioned medium was also shown to promote the survival of grafted xenogeneic dopaminergic neurons into affected mice (Shintani et al. 2007). i.v. administration of hMSC significantly decreased the loss of dopaminergic neurons in rats treated with the proteasome inhibitor MG-132, which causes a neurodegenerative disease similar to PD (Park et al. 2008). i.v. injected hMSC effectively reduced the loss of dopaminergic neurons also in other models of disease, induced by injection of lipopolysaccharide into the substantia nigra or by intraperitoneal injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); this was associated with decreased microglial activation in MSC-treated mice (Kim et al. 2009). Some level of MSC transdifferentiation to dopaminergic neurons under particular stimuli has been shown (Dezawa et al. 2004; Trzaska et al. 2007; Barzilay et al. 2008), but, as per many other clinical conditions, functionality of these cells is controversial (Thomas et al. 2011). However, in one study treatment of the neuralized MSC with glial cell line-derived neurotrophic factor (GDNF) increased the proportion of TH-positive and dopamine-producing cells and, upon intrastriatal implantation, resulted in clinical improvement in a 6-hydroxy dopamine rat model of PD (Dezawa et al. 2004). The same group showed that intrastriatal administration of dopaminergic neuron-like MSC led to some improvement in motor function in parkinsonian macaques which was associated to restoration of dopaminergic function (Hayashi et al. 2013). Similarly, intra-striatal injection of MSC, cultured under conditions favorable for neuronal differentiation, ameliorated the clinical symptoms in murine models of PD (Bouchez et al. 2008; Offen et al. 2007; Levy et al. 2008); however, one study showed comparable efficacy using undifferentiated MSC (Bouchez et al. 2008). Intra-striatal injection of genetically-engineered MSC or their neuron-like derivatives SB623 cells delivering neurotrophic factors such as GDNF, was also beneficial in murine models (Glavaski-Joksimovic et al. 2010; Moloney et al. 2010; Shi et al. 2011).

In humans, one pilot clinical trial involving seven PD-affected patients, aged between 22 and 62 years has been reported (Venkataramana et al. 2010). In this study, patients received a single dose of autologous BM-MSC transplanted in the sub-ventricular zone using stereotaxic surgery and were followed for a period ranging from 10 to 36 months. Three out of seven patients showed an improvement in their symptoms with a decrease in "off"/"on" periods in Unified Parkinson's Disease Rating Scale; authors also reported subjective improvement of symptoms and some reduction in drug dosage in two subjects (Venkataramana et al. 2010). Unfortunately, in spite of these encouraging reports, the limited number of enrolled patients and the open label nature of the trial did not permit to demonstrate a statistical significance of treatment efficacy.

Multiple system atrophy

Multiple system atrophy (MSA) is a rare, adult-onset, sporadic neurodegenerative disease with a poor prognosis, characterized by parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic failure. One hallmark of MSA is the presence of cytoplasmic inclusions containing αSYN in glial cells, predominantly in oligodendrocytes. Other pathological features of the disease are selective neuronal loss and gliosis in cerebellum, olivary nuclei, pyramidal fibers, basal ganglia, intermediolateral column, and Onuf's nucleus (Ubhi et al. 2011). A few studies addressed the possibility of using MSC in preclinical model of MSA. Park et al. showed positive effect of i.v. injection of hMSC on motor behavior and protection against toxin-induced neuronal loss in a double-toxin-induced animal model of MSA (Park et al. 2011). Stemberg et al. investigated the effects of murine MSC transplantation in aged transgenic (PLP)-αSYN mice (Stemberger et al. 2011). There was no improvement in the survival rate and in the behavioral tests in the MSC-treated group, probably due to the advanced age (18 months) of the animals resulting in neurodegeneration at a "point-of-no-return" stage. However, the i.v. administration of MSC led to a rescue of dopaminergic neurons, evidenced by an increased number of tyrosine hydroxylase-positive cells in the MSC treated group, which was not related to a decrease in αSYN concentration in midbrain-brainstem lysates (Stemberger et al. 2011).

An open-label study was carried out in 11 MSA patients who received an intra-arterial injection followed by monthly

i.v. injections over a three-month period; outcome, as measured by long-term prognosis, clinical score and neuroimaging, was compared to that of 18 untreated MSA patients (Lee et al. 2008). The MSC-treated patients showed improved clinical score (unified MSA rating scale, UMSARS) and an increased glucose metabolism, suggestive of decreased neurodegeneration, in the frontal and cerebellar grey matter, as assessed by positron emission tomography scan in a subgroup of patients (5 in the treated group and 10 in the untreated group), during the 12-month follow-up. However, small brain ischemic lesions were detected at MRI in seven treated patients, albeit without related clinical symptoms or signs (Lee et al. 2008). This pioneer study was followed by a placebo-controlled randomized double-blind study with the same treatment schedule, where 31 patients received either autologous MSC or placebo. The study met the primary endpoint (clinical improvement at the UMSARS scale) and some secondary endpoints. However, about one-third of the patients in both groups had evidence of acute ischemic lesions in multiple brain areas at MRI, probably related to intra-arterial administration (Lee et al. 2012c). Umbilical-cord derived MSC have also been tested on ten patients with MSA in an open label study with a protocol of multiple weekly intrathecal injections; there were no serious adverse effects and some clinical benefit was suggested (Dongmei et al. 2011).

Spinal cord injury

Spinal cord injury (SCI) has dramatic consequences, leaving the patient with often irreversible neurological deficits depending on the lesion site. Acute inflammation occurs after SCI resulting in the multiphasic recruitment of immune cells leading to chronicity of the lesion (Beck et al. 2010).

Experiments in animal models of SCI transplanted with MSC, as reviewed by Wright et al. showed that treatment with syngeneic or xenogeneic MSC, often delivered inside the spinal cord, improves motor and sensory functions of affected rats. Additionally, MSC-based therapy might be beneficial not only in the acute, but also in the chronic phase (Wright et al. 2011).

Following the pioneer report by Akiyama et al. showing the remyelinating effect of bone marrow stromal cells after i.v. transplantation in rats where a focal demyelinated spinal cord lesion was induced (Akiyama et al. 2002), other studies compared the clinical outcome following MSC administration either via direct local transplantation or i.v.; MSC engraftment, tissue sparing and remyelination were achieved with both procedures but i.v. administration required substantially more cells to achieve results similar to direct transplantation(Inoue et al. 2003; Paul et al. 2009). The beneficial effect observed following i.v. administration on animals with SCI, is associated with an increase in the trophic factor nerve growth factor (NGF) and increased vascularization of the injured tissue, without any evidence of MSC engraftment (Quertainmont et al. 2012). Similarly upregulation of the expression of neurotrophins by the injured tissues, and particularly of NGF, leukemia inhibitory factor (LIF), and insulin-like growth factor-1 (IGF-1) in the lesion site was detected after MSC injection (Hawryluk et al. 2012). When MSC cultured towards a Schwann cell-like phenotype were injected in the spinal cord of animals in the acute phase post injury, increased expression of VEGF could be seen together with a neuroprotective effect on rostral neurons; however, there was also some aberrant axonal sprouting in the lesion zone (Park et al. 2010).

In humans, a pilot study in five patients assessed the safety and efficacy of intrathecal administration of autologous MSC. Variable numbers of culture-expanded bone marrow stromal cells were administered by lumbar puncture at the acute phase (between 8 and 17 days post-injury) in subjects with cervical cord lesion. The authors report safety of the procedure and improvement of clinical scores in some subjects (Saito et al. 2008, 2012). A trial on 30 patients at subacute (<6 months) or chronic stage (>6 months) post injury demonstrated the safety of intrathecal autologous MSC delivery at a dose of 1×10^6 MSC/Kg body weight (Pal et al. 2009). Although the trial was not powered for measure efficacy there was some improvement in sensory and bladder functions in patients treated at the subacute stage, despite unchanged electrophysiological and MRI results (Pal et al. 2009). Autologous MSC were administered to ten patients at the subacute or chronic stage by surgical procedure into the intramedullary space (8×10^6 cells) close to the lesion site, and inside the dural space (4×10^7 cells). Four and eight weeks later, the patients were given 5×10^7 cells intrathecally in two lumbar puncture procedures. Some motor improvement was observed in six subjects, of whom four were in the chronic stage at the time of treatment (Jeong et al. 2010). The safety of i.v. treatment with autologous adipose-derived MSC at a much higher dose of 4×10^8 cells has also been demonstrated in another cohort of eight patients at a chronic stage (Ra et al. 2011).

On the basis of these encouraging results on the safety of MSC transplantation, several clinical trials are ongoing or set to start according to public clinical trials registries.

Stroke

According to recent studies, one out of six people will have a stroke in their lifetime. The interruption of blood supply to a cerebral area causes a complex pathophysiological cascade which often leads to irreversible neuronal death, severe neurological impairment and sometimes to death.

Effectiveness of MSC treatment for stroke is known since the first studies showing that intracerebral administration of syngeneic non-hematopoietic bone marrow sromal cells

ameliorates the clinical signs of experimental stroke in adult mice (Li et al. 2000). Subsequent studies in rats explored the influence of the route of delivery, including i.v. and intra-arterial administration, on the clinical outcome (Chen et al. 2001) (Li et al. 2001). The authors of these studies reported on the identification of administered MSC into the injured brain upon both ways of administration, but with scarce evidence of integration into the local network, despite some expression of neural and glial markers (Chen et al. 2001) (Li et al. 2001). Similarly another study, comparing intracarotid and i.v. administration, showed comparable efficacy for the two routes of administration, despite the lack of MSC into the brain after the i.v. injection (Gutiérrez-Fernández et al. 2011). Clinical efficacy was attributed to the secretion of growth factors in the ischemic tissue, the reduction of apoptosis in the infarcted tissue and the proliferation of endogenous precursor cells, rather than to their transdifferentiation (Li et al. 2002; Yoo et al. 2008). Interestingly, the clinical efficacy of MSC treatment was demonstrated to be associated with neuronal plasticity, as shown by the increased number of axonal projections from uninjured areas (Andrews et al. 2008). Moreover, studies on intracerebral administration of MSC for neonatal ischemia showed that MSC restore the connection between the injured site and the controlateral limb, and decrease the rewiring of axons which is observed after this kind of stroke (van Velthoven et al. 2012).

In most studies, MSC were injected early after the ischemic event. The therapeutic window for the treatment with MSC is probably limited, as administration after 1 month was not effective according to another study (de Vasconcelos dos Santos et al. 2010). However, this contrasts with data obtained in another study whereby MSC injection 28 days after stroke improved clinical scores and angiogenesis in treated animals as compared to controls, albeit to a lower extension compared to what observed upon injection 7 and 14 days after stroke (Komatsu et al. 2010). Strategies of treatment with MSC genetically engineered to express neurotrophic factors were also successful, showing increased effectiveness compared to treatment with unmodified MSC (Kang et al. 2003).

The first clinical trial in human subjects was performed a few years after the first preclinical experiments (Bang et al. 2005). The trial protocol devised the administration of autologous MSC i.v. shortly (5–7 weeks) after the ischemic event. Decreased brain atrophy (as measured by ventricular dilation) and some clinical improvement were observed at one-year follow-up in 5 patients treated with MSC compared to 25 untreated control subjects; no significant adverse events were reported (Bang et al. 2005). In another study from the same group the long-term safety and efficacy of i.v. MSC transplantation was evaluated in 85 patients with severe middle cerebral artery territory infarct. A decreased mortality was observed in the MSC-treated group with no significant side effects or increase of comorbidities(Lee et al. 2010c). In another open-label study autologous MSC were intravenously injected to treat 12 patients with stroke at various time-points within the first 6 months from the ischemic event. Results confirmed the safety of the treatment and showed some improvement in the National Institute of Health Stroke Scale and in MRI metrics (Honmou et al. 2011). Safety of this procedure was also demonstrated by another study utilizing autologous MSC cultured in serum-free media to treat patients with chronic stroke (Bhasin et al. 2011).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS, which affects about 100:100,000 subjects in developed countries. Evidence from preclinical models, including studies of brain pathology and response to treatments, suggests that MS is caused by an autoimmune aggression of adaptive and innate immune systems on myelin leading to neurodegeneration and consequent irreversible disability (Sospedra and Martin 2005; Gandhi et al. 2010). While current available therapies modulate the function of the peripheral immune system, they neither have proven neuroprotective effect nor can they revert the irreversible damage of the CNS, which is observed in most patients with time. In this context, MSC are a particularly promising therapeutic approach for MS, as they are endowed with both immunomodulating and neuroprotective features (Uccelli et al. 2011). Accordingly, preclinical studies in EAE have demonstrated the beneficial effect of MSC in inflammatory demyelinating disease. In the first published study, Zappia et al. assessed the effect of i.v. administration of syngeneic MSC i.v. to mice with chronic EAE; they showed that treatment at disease onset or at the peak of disease significantly ameliorated disease course, led to a reduction in demyelination and CNS infiltration by inflammatory cells and, more importantly, was associated with the induction of peripheral tolerance against myelin antigens (Zappia et al. 2005). These observations were later confirmed in the relapsing-remitting model of EAE showing that MSC can also inhibit the encephalitogenic potential of myelin-reactive T cells and pathogenic myelin-specific antibodies (Gerdoni et al. 2007). In this study, a limited number of labeled MSC could be detected in the CNS of treated EAE mice leading to some axons preservation but with no evidence of transdifferentiation (Gerdoni et al. 2007). Other studies using syngeneic, allogeneic (from other mouse strains) and xenogeneic (human) MSC corroborated the beneficial effect of MSC treatment on the clinical course of EAE with some evidence of tissue repair (Zhang et al. 2005, 2006; Constantin et al. 2009; Bai et al. 2009; Lanz et al. 2010). Some studies attempted to identify the optimal route of administration. Improvement of EAE was observed after both

i.v. or intraventricular injection of syngeneic MSC leading in both cases to peripheral modulation of the immune response and neuroprotection (Kassis et al. 2008). According to another study, intraperitoneal administration showed that amelioration of disease was not associated with a significant MSC engraftment into the CNS (Gordon et al. 2008). However, the recent comparison of i.v. injection with intraventricular transplantation of MSC in mice with EAE did not show any significant difference between the two routes of administration on clinical and histological parameters (Morando et al. 2012). An elegant study demonstrated that the effect of syngeneic MSC in EAE may be mediated by the modulation of the peripheral immune system through the release of molecules such the "CC Chemokine Ligand 2 antagonistic form" which suppresses Th17 responses (Rafei et al. 2009). This study highlighted the possible role of factors secreted by MSC. A key study remarkably uncovered the role of MSC secretome in recapitulating most of the beneficial effects observed following MSC administration. Bai and colleagues in fact showed that the i.v. injection of molecules secreted by BM-derived MSC, being hepatocyte growth factor a key factor, suffices to improve the clinical course of EAE modulating the autoimmune response, but also directly promoting remyelination (Bai et al. 2012). All preclinical studies so far concur on the immunomodulatory effect of MSC on EAE. The neuroprotective effect of MSC has also been clearly demonstrated in EAE with reports of enhanced differentiation of endogenous progenitor cells, increased expression of growth factors, release of antiapoptotic and anti-oxidative molecules and, albeit controversial, transdifferentiation (Zhang et al. 2005; Zappia et al. 2005; Gerdoni et al. 2007; Gordon et al. 2008; Kassis et al. 2008; Constantin et al. 2009; Bai et al. 2009, 2012; Lanza et al. 2009).

Based on positive outcome with preclinical studies, a few phase 1 clinical trials have been published. A pilot study was published in 2007, where ten subjects with progressive disease and moderate disability (able to walk without aids) received one or two doses of autologous MSC via lumbar puncture and were followed for 13 to 26 months. Authors reported mild side effects related to meningeal irritation due to the invasive procedure. Although the study was not aimed at assessing efficacy, the authors reported some effects on disability and MRI parameters (Mohyeddin Bonab et al. 2007). A subsequent study evaluated safety and feasibility of intrathecal injection of autologous MSC in seven MS patients with moderate to severe disability (Yamout et al. 2010). Authors reported a severe adverse event (transient encephalopathy) in one subject, which appeared to be dose-related and resolved completely. Despite some clinical improvement in most patients treated, MRI performed 3 months post treatment showed new inflammatory activity in some patients (Yamout et al. 2010). Intrathecal (N=10) or intrathecal plus i.v. (N=5) infusions of BM MSC were chosen by Karussis et al. for a study in patients with active MS. No severe adverse events were detected and some signs of clinical efficacy were reported together with some preliminary data on MRI improvement (Karussis et al. 2010). Recently, a study attempted to assess efficacy of treatment with i.v. administered MSC in progressive MS subjects. Ten patients with SP MS and visual pathway involvement received ex vivo-expanded autologous MSC i.v. at a mean dose of 1.6 cells × 10^6/Kg body weight (Connick et al. 2011). Efficacy on visual parameters was proven by clinical, electrophysiological and MRI examinations up to 10 months post-treatment, as compared to pre-treatment. No significant adverse events occurred (Connick

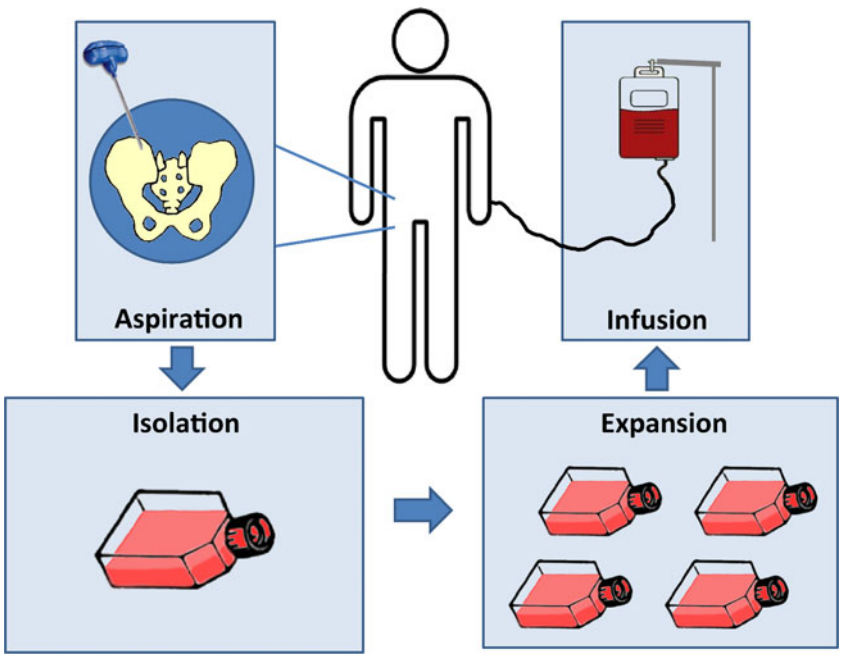

Fig. 2 Scheme of MSC preparation for human treatments according to the protocols based on intravenous administration. *Counter-clockwise from top left*: bone marrow cells are collected from the iliac crest of patients (Aspiration), cultured in appropriate medium (Isolation), and the adherent cells in vitro expanded (Expansion). After expansion, MSC are usually frozen and kept in liquid nitrogen until needed. Upon thawing, cells are infused at the proper dose, according to specific protocols (usually ranging from 1 to 5×10^6/Kg)

et al. 2011). The largest case series was published recently (Bonab et al. 2012); 25 subjects with progressive MS and moderate to severe disability received autologous MSC intrathecally. The authors reported stabilization of clinical course and MRI imaging in the majority of subjects, without the occurrence of severe adverse events.

Conclusions

This overview of the state of the art of preclinical and clinical research in MSC treatment for neurological diseases suggests that MSC may represent a valuable option for incurable diseases of the CNS. Obviously, the open label nature of most of the studies carried on so far in humans requires taking cautiously results arising mostly from uncontrolled clinical settings involving limited number of patients. Moreover further studies need to be conducted at preclinical levels to understand the mechanisms of action in the different diseases allowing to dissect effects relying mainly on the anti-inflammatory/immunomodulatory features of MSC from those based on their ability to directly promote tissue protection and foster repair. Last but not least the yet not completely resolved issue concerning the possibility for MSC to integrate into the damaged CNS as well as the promising concept that factors released by MSC may recapitulate most of the therapeutic plasticity attributed to these cells will be an attractive area of research in the near future to help defining the most appropriate utilization of MSC for clinical purposes. Understanding of these issues will allow outlining, for each disease, the most effective routes of administration, dose, source of MSC, disease stage at which treatment should be applied, and kinetics of the therapeutic effect. However, practical issues are deterring faster development of MSC treatment. Indeed, expanding hMSC to reach target doses is time and labor-consuming and requires specific facilities (GMP-approved, with adequate storage and specific incubators). In addition, utilization of cells manipulated in vitro is subjected to strict rules under control of specific regulatory agencies, which may different among countries, further hindering the development of large controlled clinical studies. Promising results arising from preclinical studies with genetically-modified MSC aimed at delivering therapeutic molecules at the lesion sites ~~have~~ require extra caution as genetic modification of MSC adds further complexity to the in vitro manipulation of these cells. Last, collaborative, often academic, efforts aimed at carrying out these projects are further impeded by difficulties in rising funds to support the exploitation of international studies not supported by the industry. In this context, the International Mesenchymal Stem Cells Study Group was established to test, through clinical trials in several centers based in Europe, Canada, and Australia, a protocol to be used to treat MS with MSC, the Mesenchymal Stem Cells for Multiple Sclerosis (MESEMS) Clinical Trial (Freedman et al. 2010; Uccelli et al. 2012a). Such a collaborative effort will involve 160 patients to assess safety and efficacy at MRI of MSC in subjects with active MS through a randomized, double-blind, placebo-controlled, crossover protocol (Fig. 2). The study design includes the harvest of BM and isolation and expansion of autologous MSC therefrom to reach a number of 1–2 million/Kg body weight. Upon randomization, patients undergo a first i.v. administration of either MSC or placebo (i.e. infusion media) which is followed, after 6 months, by a second infusion in a cross-over fashion (those who received MSC at the first infusion will receive placebo at the second one and vice versa). The patients are followed for 1 year through MRI and clinical evaluations. The i.v. route of administration was chosen for several reasons, including feasibility: i.v. treatment is more convenient, less invasive, and safer than intrathecal administration; preclinical experience showed comparable efficacy of i.v. and local delivery, as discussed before (Morando et al. 2012); and finally, i.v.-injected MSC can interact with immune cells within the bloodstream and the lung microenvironment, with potential potent immunomodulatory effect (Uccelli et al. 2012a).

This strategy of multiple clinical trials that follow the same protocol, but are each supported financially through separate funding, circumvents the financial constraints of a unique large trial, while allowing an overall analysis of the pooled data. This approach could easily be expanded to other CNS diseases to gather scientific and practical answers in the absence of industry support.

Conflict of interest statement The authors declare that they have no conflict of interest.

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