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Clinical Trials of Adult Stem Cell Therapy in Patients with Ischemic Stroke

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Stem cell therapy is considered a potential regenerative strategy for patients with neurologic deficits. Studies involving animal models of ischemic stroke have shown that stem cells transplanted into the brain can lead to functional improvement. With current advances in the understanding regarding the effects of introducing stem cells and their mechanisms of action, several clinical trials of stem cell therapy have been conducted in patients with stroke since 2005, including studies using mesenchymal stem cells, bone marrow mononuclear cells, and neural stem/progenitor cells. In addition, several clinical trials of the use of adult stem cells to treat ischemic stroke are ongoing. This review presents the status of our understanding of adult stem cells and results from clinical trials, and introduces ongoing clinical studies of adult stem cell therapy in the field of stroke.

Key Words stroke, clinical trials, stem cells.

INTRODUCTION

Stroke is one of the leading causes of death and physical disability among adults, with one-quarter to half of stroke survivors being left with complete or partial dependence on others. Stem cell therapy is an emerging paradigm in the field of stroke treatment, and is considered a potential regenerative strategy for patients with neurologic deficits. Studies involving animal models of ischemic stroke have shown that stem cells transplanted into the brain can lead to functional improvement.[1] Various cell types have been used to improve function and the recovery after stroke, including embryonic stem cells (ESCs), immortalized pluripotent stem cells (iPSCs), neural stem/progenitor cells (NSCs), and nonneuronal adult stem cells such as mesenchymal stem cells (MSCs) and bone marrow mononuclear cells (MNCs). Most clinical trials involving patients with stroke have used adult stem cells, such as MSCs, MNCs, and NSCs. The International Cellular Medicine Society classifies culture-expanded autologous MSCs as a clinical cell line, unlike ESCs, iPSCs, and genetically modified stem cells. MSCs can migrate to injured brain regions (tropism) and self-renew, reportedly without inducing carcinogenesis. Sufficient numbers of MSCs can be easily obtained within several weeks of culture expansion.

This review presents the status of the current understanding regarding adult stem cells and the results from clinical trials. The most recent advances in preclinical studies are discussed, and ongoing clinical studies of adult stem cell therapy in the field of stroke are described.

MECHANISMS UNDERLYING STEM CELL ACTION IN STROKE RECOVERY

Stem cells aid stroke recovery via various mechanisms of action depending on the specific

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cell type used. Transplanted ESCs, iPSCs, and NSCs can replace the missing brain cells in the infarcted area, while nonneuronal adult stem cells, such as MSCs and MNCs, provide trophic support to enhance self-repair systems such as endogenous neurogenesis. Most preclinical studies of stem cell therapy for stroke have emphasized the need to enhance self-repair systems rather than to replace lost cells, regardless of the type of cells used (MSC[1] and iPSC[2]). A recent study found that although iPSC-derived NSCs induced neurogenesis, they enhanced endogenous neurogenesis via trophic support, in a manner similar to adult nonneuronal stem cells (e.g., MSCs), rather than by cell replacement with exogenous iPSC-derived NSCs.[2] In addition, there are hurdles associated with using cell replacement to restore neuronal function after stroke. True neuronal substitution requires specific anatomic and functional profiles, such as the need for biodegradable scaffolds (longitudinal channel-like structures for axonal connections) and topologic transplantation of different types of stem-cell-derived neurons (cortical neurons, interneurons, and oligodendrocytes).[3]

The above-described features mean that adult stem cells such as MSCs may be a good choice for stroke therapy because they secrete a variety of bioactive substances—including trophic factors—into the injured brain, which may be associated with enhanced neurogenesis, angiogenesis, and synaptogenesis.[4-7] Besides trophic factors, MSCs release extracellular vesicles to deliver functional proteins and microRNAs to NSCs or neuronal cells.[8] In addition, MSCs exert their actions by attenuating inflammation,[9,10] reducting scar thickness (which may interfere with the recovery process),[11] enhancing autophagy,[12] and normalizing microenvironmental/metabolic profiles[13] in various brain diseases. Preclinical studies have found that most injected stem cells disappear within a few weeks, which makes it unlikely that the transplanted stem cells were functionally integrated into the brain.[14,15] However, it was also reported that subpopulations of MSCs (e.g., multilineage differentiating stress-enduring cells) were able to differentiate into neuronal cells, and were integrated into the peri-infarcted cortex and acted as tissue repair cells.[16] Thus, MSCs are thought to play multiple roles (Fig. 1).

CLINICAL TRIALS OF STEM CELL THERAPY IN PATIENTS WITH STROKE

The number of studies of stem cells in stroke has increased markedly recently (Fig. 2). With current advances in the understanding of the effects of introducing stem cells and their mechanisms of action, several clinical trials of stem cell therapy have been conducted in patients with stroke since

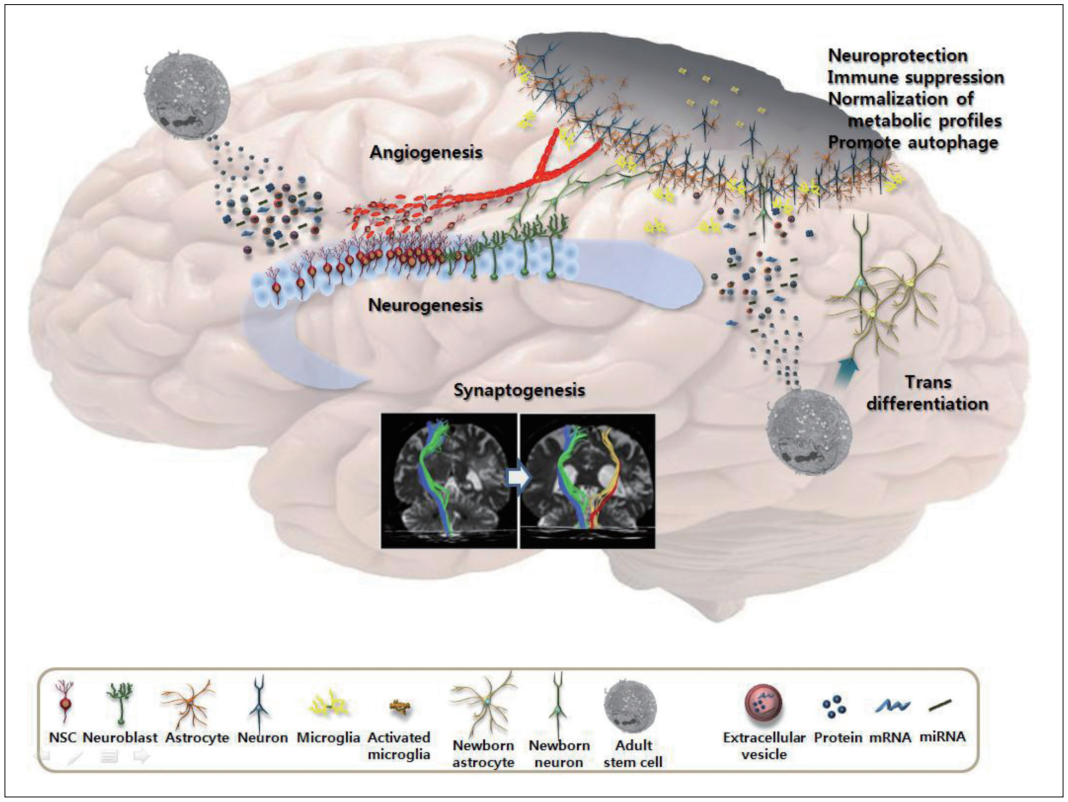

Fig. 1. Mechanisms of action of mesenchymal stem cells in stroke recovery.

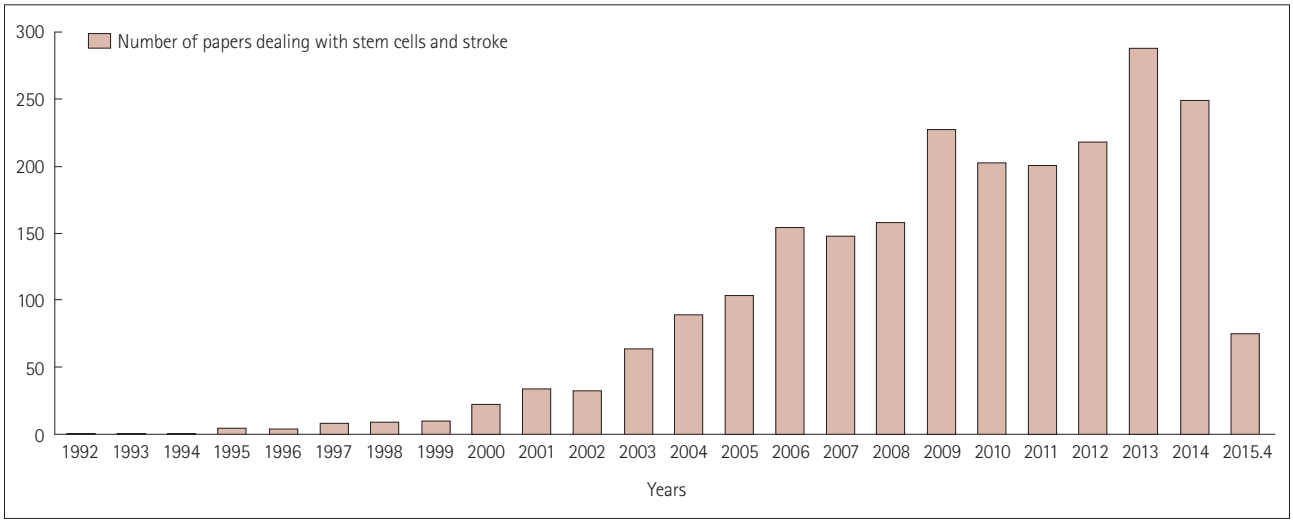

Fig. 2. Number of papers on stem cells and stroke.

2005, including studies using MSCs,[17-20] MNCs,[21-26] and NSCs (Table 1).[27,28]

For stem cell therapy to be useful in augmenting the recovery after stroke, it needs to be safe and effective, applicable to a broad spectrum of patients with stroke, and cost-effective.[29] Most clinical trials using various types of stem cell have demonstrated that stem cell therapy following stroke is both feasible and safe, and may improve recovery. However, these trials varied in terms of the patient characteristics, cell therapy timing, dose and type of cells delivered, and mode of treatment. In addition, many factors that could be critical to the transplantation success, including the location and the extent of lesions, were not adequately considered. Moreover, the assessments of functional improvement, adverse effects, and pretreatment screening tests for safety have varied greatly among the studies. None of the studies aimed to determine the efficacy of MSC therapy in patients with stroke. All of the studies aimed to assess the feasibility and safety of stem cell treatments, and most were small series and did not include a control group. While stem cells appeared to be of some benefit in several studies, there was significant bias in subsequent studies (Fig. 3). A recent multicenter randomized controlled clinical trial (RCT) of intravenous infusion of autologous bone marrow MNCs failed to show any effectiveness.[26]

Presently, rigorous reasoning is required to replicate experimental results in patients with stroke. The Stem cell Therapies as an Emerging Paradigm in Stroke (STEPs) committee recently suggested guidelines for bridging the gap between basic and clinical studies,[30] early stage clinical trials,[31] and phase II/III trials[32] of stem cell therapies in stroke. According to these recommendations, studies should be RCTs. After randomization, experimental procedures may not be blinded, because applying stereotaxic sham surgery or bone marrow sham aspiration to control patients may increase the risk of adverse effects. Patient selection and a cell dose that is equivalent to that used in animal studies should be used. Patients with stroke in the middle cerebral artery territory (or anterior circulation) and those with moderately severe neurologic disabilities could be ideal candidates. The mode of application of stem cells may significantly influence the number of cells delivered to target regions, as well as the incidence of adverse effects. For example, one study demonstrated that intra-arterial transplantations resulted in superior delivery of stem cells in the ischemic brain compared to intravenous infusions,[33] but this may cause arterial occlusion, resulting in stroke.[33,34] There have been relatively few studies directly comparing the efficacy of intravenous and intra-arterial delivery of MSCs.[35] The mode of treatment should be based on the severity and location of lesions, and the timing of application. In addition to the clinical outcomes measured, laboratory and neuroimaging findings should be used as surrogate markers of efficacy. Advanced technologies such as multimodal magnetic resonance imaging (MRI; e.g., resting-state functional MRI or diffusion-tensor imaging) can be used to monitor the response to restorative therapy.[36,37] Finally, patients should be followed for more than 90 days. Long-term monitoring (>6 months) is likely to be unnecessary because autologous MSCs are a clinical cell line and die within days or weeks of administration.[31]

ONGOING CLINICAL TRIALS

Among the various adult stem cells, MSCs have been most commonly used in the clinical trials for patients with stroke. There have been several recent efforts to improve the effects

Table 1. Clinical trials of stem cells in patients with stroke

Ref.	Study design control:cell group	Characteristics of stroke	Manipulation (cell dose)	Route	Efficacy	Adverse effects
Autologous bone marrow mononuclear cells						
21	None:5 patients 1-year f/u	Chronic Ischemic or ICH	Isolation using normal saline	IC	N/A	None
22	None:6 patients 6-month f/u	Subacute MCA infarct	Isolation using human albumin-containing normal saline ($0.6–5\times10^8$)	IA	N/A	Seizure after 200 days
23	None:10 patients 6-month f/u	Acute Large MCA infarct	Isolation using human albumin-containing normal saline ($0.6–5\times10^8$)	IV	Limited study design	None
24	None:20 patients 6-month f/u	Acute Nonlacunar infarct	Isolation using human albumin-containing normal saline ($0.6–5\times10^8$)	IA	Limited study design	None
25	40:60 patients 6-month f/u	Acute ICH	Isolation using normal saline (1.33×10^{13})	IC	NIHSS and BI improved	None
26	60:60 patients	Subacute MCA/ACA infarct	Isolation using normal saline (2.8×10^8)	IV	BI and mRS at day 180	Similar in the two groups
Autologous bone marrow-derived mesenchymal stem cells						
17	25:5 patients 1-year f/u	Subacute Large MCA infarct	*Ex vivo* culture expansion using fetal bovine serum (1×10^8)	IV	BI improved at 3 months	None
18	36:16 patients 5-year f/u	Subacute Large MCA infarct	*Ex vivo* culture expansion using fetal bovine serum (1×10^8)	IV	mRS 0–3, increased in MSC group	None
19	None:12 patients 1-year f/u	Subacute to chronic Variable	*Ex vivo* culture expansion using autologous serum (1×10^8)	IV	Limited study design	None
20	6:6 patients 24-week f/u	Chronic Ischemic or ICH	*Ex vivo* culture expansion using serum-free media ($5–6\times10^7$)	IV	Modest increase in FM and mBI	None
Allogeneic neural stem/progenitor cells						
27	None:5 patients Terminated early	Chronic MCA infarct affecting striatum	*Ex vivo* culture expansion of NSCs obtained from primordial porcine striatum	IC	Limited study design	Seizure, aggravation of hemiplegia
28	None:8 patients 2-year f/u	Subacute to chronic MCA/ACA infarct	*Ex vivo* culture expansion of NSCs obtained from fetal brain	IC	Limited study design	Transient low-grade fever only

ACA: anterior cerebral artery, BI: Barthel index, FM: Fugl-Meyer score, f/u: follow-up, IA: intra-arterial, IC: intracerebral, ICH: intracerebral hemorrhage, IV: intravenous, mBI: modified Barthel index, MCA: middle cerebral artery, mRS: modified Rankin Score, MSC: mesenchymal stem cell, N/A: not available, NIHSS: national Institutes of Health Stroke Scale, NSCs: neural stem/progenitor cells.

of MSC therapy. For example, MSCs can be isolated from various tissues, such as umbilical cord, endometrial polyps, menses blood, adipose tissue, and bone marrow.[38] While a long culture period is required to obtain sufficient stem cells from the patient's own bone marrow, allogeneic MSC therapy can form the basis of 'off-the-shelf' products. In addition, MSCs are heterogeneous with respect to their developmental potential and trophic supports. The use of functionally distinct subpopulations of MSCs was found to improve their effects.[39] Finally, presenting appropriate stimuli to cells may promote a transient adaptive response (preconditioning) so that injury resulting from subsequent exposure to a harmful stimulus is reduced. Anoxic preconditioning of stem cells has been tested for the promotion of cell survival after transplantation in ischemic disease conditions.[40,41]

It is interesting that earlier clinical trials (i.e., performed during 2005–2010) used autologous naïve MSCs, whereas several recent trials performed since 2011 have examined allogeneic or manipulated MSCs, including by isolating functional subpopulations or the preconditioning of stem cells (Fig. 4). At the time of writing, we were aware of at least 15 active clinical trials using adult stem cells to treat ischemic stroke (http://clinicaltrials.gov) (Supplementary Table 1 in the online-only Data Supplement). It should be noted that seven of these trials were RCTs that aimed to determine the efficacy of MSC therapy, five tested the efficacy and safety of allogeneic MSCs in patients with stroke, and four studies used manipulated (conditioned or selected) MSCs. In the

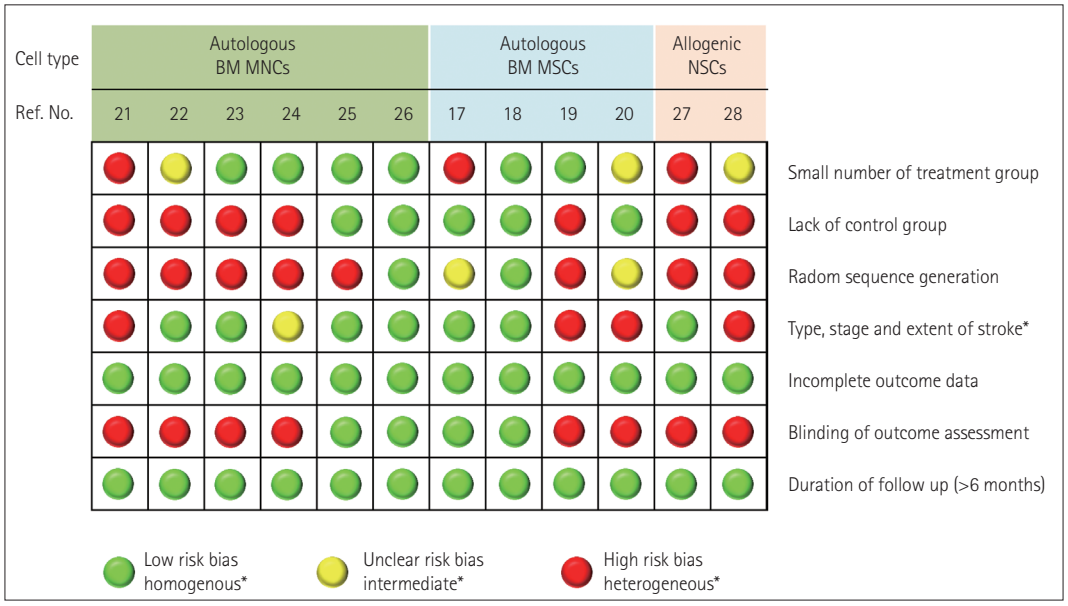

Fig. 3. Summary table for the risk of bias from different items for each clinical trial of stem cells in patients with stroke. BM: bone marrow, MNCs: mononuclear cells, MSCs: mesenchymal stem cells, NSCs: neural stem/progenitor cells.

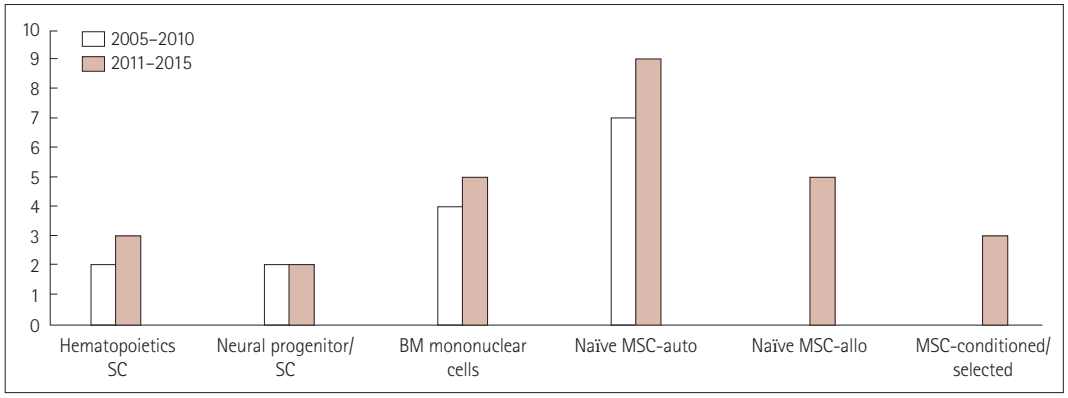

Fig. 4. Number and types of stem cells in clinical trials for patients with stroke. allo: allogeneic, auto: autologous, BM: bone marrow, MSCs: mesenchymal stem cells, SC: stem cell.

STem cell Application Research and Trials In NeuroloGy-2 (STARTING-2) trial, we are incorporating ischemic preconditioning using ischemic serum, blood-brain-barrier manipulation, and strict selection of candidates in order to improve the therapeutic effects and safety of MSCs.[42]

CONCLUSIONS

It is too early to conclude whether MSC therapy can improve functional outcomes in patients with stroke. A recent meta-analysis in the field of cardiology concluded that transplanting adult bone marrow cells improved left ventricular function, infarct size, and remodeling in patients with ischemic heart disease compared with standard therapies. This conclusion was reached after analyzing data from 50 studies (involving 2,625 patients), in which patients received echocardiographic evaluations and long-term follow-up.[43] In the field of hematology, a developmental history of 60 years was required to develop the first successful stem cell therapy—the transplantation of hematopoietic stem cells. This suggests that development of a dramatically new therapy will require patience and constant dialogue between basic scientists and the physicians performing the clinical trials.[44] More evidence from RCTs is needed. Further advances at both the bench and bedside would advance the understanding of the basic mechanisms underlying stem cell therapy as well as improve the therapeutic efficacy and safety of applying stem cells to patients with stroke.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.3988/jcn.2016.12.1.14.

Conflicts of Interest

The author has no financial conflicts of interest.

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