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ABSTRACT

Ischaemic stroke remains a leading cause of death and disability. Current stroke treatment options aim to minimise the damage from a pending stroke during the acute stroke period using intravenous thrombolytics and endovascular thrombectomy; however, there are no currently approved treatment options for reversing neurological damage once a stroke is completed. Preclinical studies suggest that cell therapy may be safe and effective in improving functional outcomes. Several recent clinical trials have reported safety and some improvement in outcomes following cell therapy administration in ischaemic stroke, which are reviewed. Cell therapy may provide a promising new treatment for stroke reducing stroke-related disability. Further investigation is needed to determine specific effects of cell therapy and to optimise cell delivery methods, cell dosing, type of cells used, timing of delivery, infarct size and location of infarct that are likely to benefit from cell therapy.

INTRODUCTION

Until recently, intravenous recombinant tissue plasminogen activator was the only proven effective treatment for acute stroke. Endovascular thrombectomy has now been added to our arsenal for acute stroke treatment following the publication of five randomised trials demonstrating highly significant treatment effects favouring endovascular therapy.^{1–6} Outcome data support advancements in acute stroke care and neurorehabilitation with a significant increase in stroke survivors over time.⁷ However, despite these advancements, stroke remains a leading cause of long-term disability.⁸ For patients with residual deficits after stroke, we have no currently approved therapy for restoring function.

Cell therapy is one approach to enhancing recovery after stroke. In animal models, delivery of several different types of stem cells reduce infarct size and improve functional outcomes.⁹ Clinical trials of cell therapy completed in the 2000s mostly treating small cohorts of patients with chronic stroke demonstrated adequate safety and a suggestion of efficacy with the use of cell therapy. Kondziolka and colleagues used N-Tera 2 cells derived from a lung metastasis of a human testicular germ cell tumour that when treated with retinoic acid generate postmitotic neurons that maintain a fetal

neuronal phenotype indefinitely in vitro (LBS neurons). LBS neurons were stereotactically implanted around the stroke bed of chronic subcortical ischaemic stroke. This study demonstrated safety and feasibility of stereotactic cell implantation, although there was no significant improvement in functional outcomes.^{10 11} Using a similar stereotactic approach implanting cells into the basal ganglia, Savitz and colleagues transplanted LGE cells (fetal porcine striatum-derived cells, Genvec) in five patients. Two patients showed improvements, but two patients experienced adverse effects including delayed worsening of neurological symptoms and seizure resulting in early termination of the study.¹² Bang and colleagues reported the safety and feasibility of intravenous infusion of autologous mesenchymal stem cells (MSCs) with no reported adverse effects in five patients treated with intravenous MSCs. Although they reported some initial motor improvements, at 12 months, there was no significant difference in motor scores.¹³ These early clinical trials mostly focused on chronic subcortical strokes, but more recent trials are now investigating cell therapy for treatment of both cortical and subcortical infarcts. This review discusses the considerations for design of cell therapy trials and summarises the results of more recent studies.

Cell types

Several cell sources have been used for cell therapy. Each cell type requires individual testing for safety and efficacy. The optimal timing and route of administration may differ depending on the characteristics of the cell and the presumed mechanism of action. Neural progenitor cells (NPCs) have been identified in the adult human brain, can migrate towards damaged tissue and may play a role in endogenous repair after ischaemic injury. NPCs can be harvested from embryonic, fetal or adult tissue, are easily expandable and are capable of differentiating into multiple cell types. Disadvantages of NPCs include ethical concerns involving the use of embryonic and fetal cells as well as their propensity to form tumours. Immortalised



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cell lines are cell populations derived from primitive tumours or cells transformed by exposure to an oncogene that have been subsequently maintained in cell culture and can be cryopreserved. These cell lines must undergo some differentiation prior to transplantation to reduce the chance of malignant transformation at the expense of limiting potential cell types subsequently produced. Induced pluripotent stem cells (iPSCs) are somatic cells reprogrammed into an embryonic state. Although iPSCs offer the potential for autologous cell transplant, generating adequate cell numbers for transplantation is challenging and there are concerns for oncogenic transformation. MSCs have become an increasingly popular choice for stroke cell therapy. MSCs can be derived from bone marrow, adipose tissue, umbilical cord and dental pulp from the patient (autologous) or from one of many existing allogeneic sources. In preclinical studies, MSCs have not been shown to differentiate into unwanted cell types or form tumours and do not seem to promote an inflammatory reaction even when allogeneic cells are used. MSCs are transiently engrafted into the brain and have been shown to deliver multiple trophic factors inducing neurogenesis, synaptogenesis and angiogenesis.

Route of administration

More recently trials of cell therapy for stroke extended the results of the early intraparenchymal studies to additional routes of administration. Intravenous, intra-arterial, intraparenchymal and intrathecal routes have been used—each with their own pitfalls. While intravenous administration of cells is the quickest and least invasive, they are filtered through the lungs, carry the risk of multiorgan exposure and require infusion of higher cell volumes. Intra-arterial therapy is more invasive and can result in cell clumping within the smaller intracranial vessels but affords the use of lower cell volumes and more direct exposure to the tissue of interest. Similarly, intrathecal injections allow for intracranial cell delivery that could potentially migrate to damaged areas although it requires an invasive procedure for delivery and there is a potential risk of cell adherence to the ventricular wall resulting in obstructive hydrocephalus. Stereotaxic infusion, or direct intracerebral injection, is the most invasive and carries the associated surgical risks but allows for the most direct infusion into the tissue of interest while using the smallest volume of cells.

Timing of administration

The timing of cell therapy administration should depend on the expected mechanism of action of the transplanted cells. For instance, iPSCs and NSCs have been shown to induce neurogenesis, although their main effect may be via trophic support, whereas most transplanted MSCs are no longer present in the brain within a few weeks and their major effect may be achieved by reducing inflammation and later scar formation.¹⁴ Cell therapy trials in the acute and subacute stroke setting might focus on cell therapies aimed at cell preservation while trials in the

chronic phase should focus on restoring lost functions. Stroke location and severity also need to be considered as severe strokes may have more early complications making it difficult to separate cell therapy adverse effects from the natural history of the stroke. Mild strokes may also be difficult to investigate given the goal of early discharge for rehabilitation and thus cell therapy may increase length of stay and cost for these patients.

Mechanism of action

Ischaemic strokes simultaneously damage various neuronal subtypes, glial populations and endothelial cells. The proposed mechanism of action should be considered in choosing the cell type, method of delivery and timing of administration for cell therapy. Some cell types exert their clinical benefits through release of trophic factors while others may directly replace cells. For instance, more differentiated cell types have limited fates and may not be as useful for infarctions involving multiple neuronal cell types or white matter tracks. Recent evidence suggests that one of the mechanisms of intravenous MSCs is suppression of the immune response after stroke, preventing release of inflammatory cells from the spleen and limiting infarct size.^{15 16} Both MSCs and neural stem cells that reach the infarct either by direct intracerebral placement or through the blood brain barrier release a variety of trophic factors, growth factors and cytokines that may enhance the local recovery process. Direct replacement of cells with functional connections is less likely given the complexity of neural networks and the short time frame in which improvement is seen. Multiple mechanisms may be operative in some cases contributing to overall functional improvement. In the acute to subacute phase after stroke, the intravenous route might be best as a neuroprotective or anti-inflammatory strategy. At later time intervals, intra-arterial or intrathecal routes might be preferable to better reach ischaemic areas and deliver trophic factors. In chronic stroke, direct intracerebral injection is likely necessary to deliver cells to brain areas surrounding infarction that might be capable of enhancing recovery. Additional information regarding mechanism for each cell type will be helpful in finding the optimal route of administration and timing.

RECENT CELL THERAPY TRIALS

Stem cell studies previously included cells obtained from embryonic and fetal tissues or immortalised tumour cells, but continuation of these studies was limited due to ethical concerns and oncogenic potential. Human stem cells may also be obtained from a number of sources including adult neural tissue, peripheral blood, adipose tissue and bone marrow. Notably, many of these cell lines are composed of heterogenous cell populations including stem cells and have a variety of proposed functions once within the nervous system.⁹ Several of the most recent cell therapy trials (table 1) used bone marrow-derived MSCs due to the ready availability, polymorphic effects and

Table 1 Summary of recent human cell therapy trials for stroke

Clinical trial/sponsor	Age	Time after stroke	Additional selection criteria	Cell type	Route	Stroke location	Patients (n)	Safety results	Efficacy results
MASTERS/Athersys	18–83	24–48 hours	NIHSS 8–20, infarct 5–100cc, premorbid mRS 0–1	Multistem adult-derived stem cell product	Intravenous	Cortical	129	Similar SAE at 1 year 22(34%) versus 24 (39%) placebo. Lower mortality—5 deaths (8%) versus 9deaths (15%) in placebo ¹⁹	No effect on 90-day Global Stroke Recovery Assessment (mRS 0–2, NIHSS increase by 75%, Barthel Index >95) but trend towards improved outcome with earlier delivery of cells ¹⁹
InveST/Department of Biotechnology, India	18–75	7–29days	NIHSS >7, GCS >8, BI <50, paretic arm or leg stable >48hours	Autologous marrow-derived stem cells	Intravenous		120 (58 cell therapy)	61 AE (33%) and eight deaths versus 60 AEs (36%) and five deaths placebo ²²	No effect on 180-day Barthel Index Score, mRS shift or score >3, NIHSS, change of infarct volume ²²
RECOVER-Stroke/Aldagen	30–75	13–19days	NIHSS 7–22, mRS >3	ALDH ^{br} autologous marrow-derived stem cells	Intracarotid infusion distal to ophthalmic	Anterior circulation ± subcortical	29 IA, 19 sham	12 SAE IA, 11 SAE sham; 0 cell-related SAE ²³	No difference in mRS, Barthel, NIHSS at 90 days or 1 year
PISCES-II/ReNeuron	40–89	2–13 months	Paretic arm with NIHSS motor arm score 2–3	CTX0E03 DP allogeneic human fetal neural stem cells	Stereotaxic infusion into ipsilateral putamen		21	Pending	Pending
Sanbio	18–75	6–60 months	NIHSS>7, mRS 3–4, stable symptoms>3weeks	SB623 allogeneic marrow-derived stem cells transiently transfected with plasmid encoding Notch1 ²²	Stereotaxic infusion peri-infarct	Subcortical ± cortical component ²⁴	18	28 SAE, 0 cell-related SAE ²⁵	Improved ESS at 6 months (p<0.01) and 12 months (p<0.001) Improved NIHSS at 6 months (p<0.01) and 12 months(p<0.001) Improved Fugl-Meyer at 6 months (p<0.001) and 12 months(p<0.001) ²⁵
PISCES/ReNeuron	≥60, male only	6–60 months	Persistent hemiparesis, Stable NIHSS over 4 weeks (Pt 2	CTX0E03 DP allogeneic human neural stem cells	Stereotaxic infusion into putamen	Subcortical	11	16 SAE (in nine patients), 0 cell-related SAE ²⁶	Improved NIHSS at 2 years (p=0.002), No change, Barthel Index, MMSE, Ashworth, mRS ^{28,29}

AE, Adverse Event; ARAT, Action Research Arm Test; BI, Barthel Index; DP, drug product; ESS, European Stroke Scale; IA, intra-arterially; MASTERS, Multistem Administration for Stroke Treatment and Enhanced Recovery Study; MMSE, Mini-Mental Status Examination; mRS, modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale; PISCES, Pilot Investigation of Stem Cells in Stroke; SAE, Serious Adverse Events.

lack of immune response. The cell types used in recent studies were either allogeneic (SB623) transformed cells, an autologous subpopulation of MSCs (ALD401, ALDH^{br}), an adult-derived multipotent adult progenitor cell population (Multistem) or allogeneic neural stem cells (CTX0E03 DP). Allogeneic cell preparations allow for more homogenous cell populations that can be highly expanded for a consistent product. Some of these can be stored for years affording an always available 'off-the-shelf' product, although they must be thawed and resuspended prior to administration. Although the most recent clinical trials using allogeneic cells (SB623, Multistem, CTX0E03 DP) did not require immunosuppression, the potential for allergic reaction remains. Autologous cells require bone marrow harvest, resulting in variable stem cell yield and require time for expansion prior to administration, but carry less concern for allergic reaction or rejection.

Cell therapy targeting subacute strokes

In the first few days after stroke, the target of cell therapy is most likely an inflammatory process that enhances the extent of brain injury and impedes the recovery process.¹⁷ Localisation of cells to the site of injury may not be as important as immune modulation and intravenous delivery may be as effective as direct intracerebral injection. Clinical trials of cell therapy for early or subacute stroke used intravenous or intra-arterial administration of allogeneic or autologous cells.

MASTERS TRIAL

The MASTERS trial was a randomised double blind dose escalation trial evaluating allogeneic, adult-derived stem cells (Multistem, Athersys) in the treatment of early cortical strokes. Multistem cells are a distinct subpopulation of adherent bone marrow cells that are easily expandable to generate sufficient quantities for intravenous delivery and have shown efficacy in animal models of ischaemic stroke. When administered intravenously, Multistem downregulates immune activation and inflammatory responses while upregulating neurogenesis and differentiation. Reduction in spleen size that occurs following stroke is prevented by Multistem administration consistent with immune suppression as an important mechanism of action of these cells.¹⁸ The MASTERS trial enrolled patients aged 18–83 with a cortical stroke measuring 5cc–100cc, an NIH Stroke Scale (NIHSS) of 8–20 and a baseline modified Rankin score (mRS) of 0–1. Multistem cells were given intravenously 24–48 hours after symptom onset¹⁹ increased from an initial window of 24–36 hours due to slow enrolment.^{20 21} Of 129 patients randomised, there was no difference between the groups in treatment emergent adverse events but fewer life-threatening adverse events or death (12% multistem vs 25% placebo (PI), $p=0.08$) and reduced infections (39% multistem vs 48% PI, $p=0.30$) in the treated group. No significant difference was observed in the primary efficacy outcome of global recovery (mRS ≤ 2 , Barthel Index

(BI) ≥ 95 , NIHSS $\geq 75\%$ improvement) at 90 days (OR 1.08, 95% CI 0.55 to 2.09) or in secondary outcomes including mRS, BI, NIHSS or excellent outcome (mRS ≤ 1 , NIHSS ≤ 1 , BI ≥ 95). However, in post hoc analysis of earlier treatment in the 24–36 hour window and excluding patients with combined intravenous tissue plasminogen activator (tPA) and endovascular therapy according to the original protocol, there were greater differences between the groups favouring patients receiving Multistem although only the Rankin distribution and excellent outcomes reached statistical significance.¹⁹ At 1 year follow-up, differences between the groups continued to increase and some additional secondary endpoints reached statistical significance.¹⁹ Following Multistem administration, there was a significant reduction in circulation CD3+ T cells at 48 hours as well as significant reductions in interleukin (IL) 1 β , tumor necrosis factor (TNF) α , IL-6 and interferon (INF) λ at 7 days that were normalised at 30 days.¹⁹ These findings are consistent with the presumed immune modulatory mechanism by which Multistem may improve functional outcomes. Patients treated with Multistem also had substantial cost savings at least in part related to 30% less secondary infections and shorter average hospital stays (3 days less than placebo, 30% reduction) and intensive care unit stays (1.2 days less than placebo, 10% reduction). Based on these promising results, a phase III trial is planned.

InveST

A phase II clinical trial in India evaluated autologous, bone marrow mononuclear stem cells (BMSC) in the treatment of late subacute strokes. Patients were enrolled aged 18–75 who had subacute stroke within the past 7–29 days (median 18.5 days), NIHSS >7 , GCS >8 , BI <50 and a paretic arm or leg that was stable ≥ 48 hours. Of 120 patients enrolled, 58 received intravenous infusion of mean 280.75 million (SD 162.9) autologous cells. No significant difference was reported in adverse events or deaths. No difference was reported in the coprimary endpoints of BI (63.1 BMSC vs 63.6 PI, $p=0.92$), Rankin shift ($p=0.53$) or mRS score >3 (47.5 BMSC vs 49.2 PI, $p=0.85$) at 6 months, or in secondary outcomes of NIHSS or change of infarct volume at 90 or 180 days after cell infusion.²² There were no new areas of 18-fluorodeoxyglucose uptake on positron emission tomography (PET) scanning in the treatment group following treatment. Although treatment was safe, there was no signal of efficacy using this type of autologous bone marrow-derived cell therapy at a late subacute time interval after stroke onset.

RECOVER

In this clinical trial autologous, bone marrow-derived stem cells were infused intra-arterially (IA) for treatment of late subacute strokes. This phase IIa safety study of locally infused intra-arterial ALDH^{br} (ALD401) cells enrolled patients with predominantly cortical stroke,

30–75 years old who had persistent symptoms with NIHSS 7–22 and mRS of 3 or greater. Within 13–19 days after onset of stroke symptoms, cells were delivered IA in the carotid artery just distal to the ophthalmic artery of the affected hemisphere. Results from 48 randomised patients presented at the 2015 European Stroke Organisation Conference reported 12 serious adverse events (SAEs) from 29 IA treated patients and 11 SAEs from 19 sham control patients. There were no significant differences in mRS, BI or NIHSS at 90 days or at 12 months after cell infusion.²³

Cell therapy targeting chronic strokes

In patients with residual deficits months or years after stroke, there is typically minimal if any further recovery and no effective therapies. In this late time frame, inflammation is likely less important and the major targets of cell therapy are neurogenesis, angiogenesis, synaptogenesis and enhanced plasticity in cells bordering an area of infarction. Trials in this time frame target direct injection using stereotactic techniques delivering cells to the surround of the infarcted region to enhance repair and recovery most likely through secretion of growth factors or small molecules that may stimulate the local environment.

Sanbio SB623

SB623 cells are MSCs transiently transfected with a plasmid that codes for the Notch I intracellular domain. In rodent stroke models, SB623 cells were superior to traditional bone marrow-derived stem cells in tests of motor and cognitive performance.²⁴ A phase I/II clinical trial of 18 patients evaluated SB623 cells delivered under stereotactic guidance to the area surrounding the site of infarction in a standard, dose escalation paradigm using 2.5, 5 or 10 million cells. Only patients with subcortical strokes with or without a cortical component occurring within the past 6–60 months were included. Notably, stability of symptoms for at least 3 weeks with an NIHSS ≥ 7 and mRS 3–4 was required. There were no serious cell-related complications in the 18 patients enrolled. European Stroke Scale, NIHSS and Fugl-Meyer Score were all improved compared with baseline at 6 and 12 months after cell infusion.²⁵ Cognitive testing, MRI and PET studies were performed before and after transplant. On MRI, increased T2 FLAIR signal was observed along the cannula track at 7 days but not at 1 day, 30 days or 60 days following cell transplantation in 15/18 patients with a mean area of 2.16 cm². The presence and size of FLAIR abnormality correlated with clinical improvement. Preliminary analysis of PET imaging revealed increased fluorodeoxyglucose (FDG) uptake in 3/5 patients predominantly in cortical areas contralateral to stem cell injection.²⁶ Cognitive testing at 6 months and 12 months versus baseline revealed significant improvement in verbal learning recall at 12 months independent of stroke location.²⁷ A blinded randomised controlled trial of SB623 cells is currently underway comparing intracerebral

implantation of SB623 cells to sham controls in patients with chronic stroke.

PILOT INVESTIGATION OF STEM CELLS IN STROKE TRIAL

The Pilot Investigation of Stem Cells in Stroke (PISCES) trial also evaluated intraparenchymal cell therapy for chronic stroke, using cells derived from human fetal cortical neuroepithelial cells genetically modified by retroviral insertion of *c-myc*ER TAM (CTX0E03 DP) similar to the PISCES II trial. PISCES was a phase I/II dose escalation trial evaluating four doses of CTX0E03 cells delivered into the ipsilateral putamen using stereotactic guidance. Men greater than 60 years old with persistent hemiparesis and stable NIHSS over 4 weeks from a subcortical stroke occurring 6–60 months (mean 29 months, SD 14) prior were included. In a median of 44 months of follow-up, there were no serious cell-related complications reported from the 11 patients treated with cell implantation. All SAEs were considered related to the stereotactic procedure or other medical conditions but were related to the cells. One patient with chronic sun exposure developed superficial malignant melanoma. Efficacy evaluation was limited but demonstrated improvement in several scores including NIHSS, Ashworth score and BI. Disability as measured by mRS improved in four patients at 12 months and three patients at 24 months.²⁸ Preliminary report of functional MRI change at 1 month versus baseline revealed increased contralateral putaminal activity that correlated with reduced spasticity, whereas increased contralateral prefrontal cortical activity correlated with increased spasticity.²⁹ FLAIR hyperintensity was seen on MRI along the needle track in five patients but were not found to be associated with clinical change.²⁸ The PISCES II trial evaluated the safety and efficacy of the same CTX0E03 cells in 21 patients with subacute stroke 2–13 months following onset. The trial has been completed and detailed efficacy and safety results are currently pending.

CONCLUSION

Recent clinical trials of cell therapy have demonstrated cell safety and some efficacy in reducing poststroke disability. Cell therapy during the subacute stroke period was associated with stable clinical and imaging outcomes in the InveST and RECOVER trials, while the MASTERS trial demonstrated promising clinical efficacy trends similar to that observed in rodent models.³⁰ Cell therapy during the chronic stroke period was associated with improved clinical outcomes in both the Sanbio and PISCES trials. The clinical trials reviewed here used a variety of different cell types, delivery methods and delivery locations each delivered with a variable delay from the time of initial infarction. Despite these differences in trial design, there were no reported cell-related SAEs.

There are many proposed mechanisms by which cell therapy may help improve recovery, which include immune modulation, enhancement of angiogenesis and neurogenesis and secretion of growth factors and

cytokines. Further investigation is needed to determine the specific effects of each type of cell therapy in order to develop the best combination of cell delivery method, cell dosing, type of cells used, timing of delivery, infarct size and location of infarct that may benefit from further cell therapy for ischaemic stroke.

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