Intra-Arterial Delivery of Cell Therapies for Stroke

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Great achievements in acute stroke care have been made, to a large extent, because of increased stroke awareness. Earlier arrival of patients at dedicated stroke centers leads to a better chance of successful treatment. Nevertheless, to date, the therapeutic options for acute stroke are still limited to intravenous tissue-type plasminogen activator, mechanical thrombolysis, or delivery of fibrinolytics. Although those therapies have had a significant impact on stroke outcome, there is still a remarkable lack of adjunct therapeutic options, such as neuroprotection and neurorestoration. Cell therapies represent a new investigational approach for the treatment of stroke. Preclinical reports are abundant, and controlled clinical trials have begun to be performed around the globe. Many critical questions remain to be answered, and a consortium of scientists and clinicians is joining forces to discuss open issues and provides potential recommendations based on the best available knowledge.[1]

One of the many critical questions is about the ideal route of delivery in terms of efficacy, safety, timing of delivery, and methods by which to monitor the process. Published clinical studies have mainly used intracerebral transplantation and intravenous injection. Smaller case series have reported intra-arterial cell delivery. Selection of the cell delivery route should be based on the primary therapeutic mechanisms. Systemic effects would favor intravenous route. If recovery depends on cell–cell interactions then intraparenchymal or intra-arterial injection may be most beneficial. There seems to be a good rationale for intravascular delivery. It is less invasive than intracerebral transplantation, it is repeatable, it would allow for a systemic biological effect, and could lead to a widespread distribution in the affected brain regions.[2] This potentially would compare favorably to the focal delivery achieved with stereotactic transplantation. Even in cases of permanent arterial occlusion, which is rare, a significant number of cells can home into the ischemic brain through collateral circulation. With an increasing number of intra-arterial catheter interventions for stroke performed, it would also seem that intra-arterial cell injection would be ideally suited in the stroke setting, as well as being quite feasible. Preclinical data suggest that intra-arterial cell injection leads to a greater number of cells targeting the ischemia. The main reason for this is that cells bypass filtering organs, such as the lung, the spleen, and the liver.[3] Preclinical studies have also demonstrated that targeted delivery to the ischemic brain has well-defined molecular mechanisms, attracting cells from the intravascular to the intraparenchymal space.[4] Cell sorting or cell engineering to improve the targeted delivery needs to be further investigated. In addition, the success of targeted delivery also seems to be strongly dependent on the cell type used. Mononuclear cells of different origins, for instance, have shown very limited to no tropism to the ischemic brain tissue. It has also been postulated that cell size determines, in part, the safety profile of an intra-arterial delivery, whereas larger cell types might lead to microembolic obstruction of capillaries and strokes.[5–7] The mechanistic theories about transendothelial migration and the safety concerns have led to an additional important consideration, which is the monitoring of cell delivery. In vivo cerebral blood flow measurements[8] and advanced magnetic resonance imaging (MRI)[9] techniques to follow cell delivery in real time are being developed and should ideally be implemented in future clinical trials.

In this review, we will focus on the current knowledge related to the safety of intra-arterial cell delivery in stroke and will present novel methods that would allow monitoring of the cell delivery process. We will also put these preclinical concepts into a clinical perspective.

Safety of Intra-Arterial Injection After Stroke

Uninterrupted cerebral blood flow is critical for preserving the structure and function of the nervous tissue. Preserving blood circulation is of even greater importance in the aftermath of stroke, as homeostasis is fragile and any disturbance of nutrient/oxygen supply triggered by intra-arterial intervention may exacerbate the secondary damage. Cerebral capillaries are ≈5 to 10 μm in diameter and circulating cellular elements, including erythrocytes (7 μm) or leukocytes (6–18 μm), pass seamlessly through them. The adhesion of leukocytes and diapedesis occurs primarily at the site of postcapillary venules,[10]

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so the trophic function of capillaries is maintained. Although some degree of temporary capillary blockage may be tolerated, if a critical threshold is exceeded, this inevitably leads to local hypoxia/ischemia and microembolic lesions. The density of cerebral capillaries varies in different brain structures, with the cortex having ≈5× the density of the corpus callosum,[11] and in this context, white matter might be more vulnerable to capillary occlusion. During intra-arterial stem cell delivery, relatively large numbers of cells are infused, with the anticipation that they will be captured by the cerebral vasculature; however, the cell load or local pressure disturbances may compromise the safety of this procedure.

To date, over 50 intra-arterial cell delivery studies in stroke have been published, and many studies have reported procedure-related complications. Important lessons on safety were learned, and several factors have been identified as critical for the safety of intra-arterial cell delivery. The most important variables that were identified are cell type and size, cell dose, infusion speed, and preservation of arterial blood flow in the feeding vessel during infusion. Other important factors to consider are timing after stroke onset and the anatomic considerations of the target (Figure 1). Comprehensive overview of the experimental conditions is included in Table I in the online-only Data Supplement. Details pertaining safety are included in Table II in the online-only Data Supplement.

Cell Type and Size

Stem cell diameters range from 7 μm for bone marrow mononuclear cells, 13 to 15 μm for neural stem cells (NSCs), and over 25 μm for mesenchymal stem cells (MSCs). Mononuclear cells are a diverse population including lymphocytes, monocytes, hematopoietic progenitor cells, and a small fraction of MSCs. MSCs are frequently selected based on adhesion on to plastic and characterized by large size and expression of specific markers including CD44, CD90, CD106, or Stro-1. With large size cells, such as MSCs, there is an obvious risk that the cells, rather than rolling and adhering to the postcapillary venule walls, clog up the entire capillary lumen, eliminating its function as a nutrient supplier and gas exchanger.

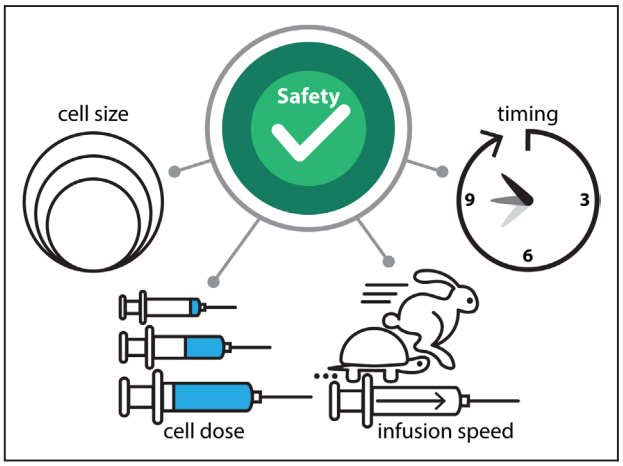

Figure 1. Safety and success of intra-arterial (IA) cell delivery has been shown to depend in part on cell type and size, cell dose, infusion speed, and timing of cell transplantation after stroke onset.

Of the reviewed studies, 19 report on the transplantation of bone marrow or cord blood mononuclear cells and none have reported any complications. Seven studies used NSCs and two of these reported on a minor increase in mortality or compromised cerebral perfusion.[8,12] MSCs are associated with the highest risk of adverse effects, as, of 29 studies, 11 reported various adverse effects, including reduced cerebral blood flow, increased mortality, and neurological impairment. Notably, microembolic lesions frequently occur in the white matter,[6,8,13] indicating its vulnerability to capillary occlusion. Detailed references to individual studies are included in Table I in the online-only Data Supplement.

Cell Dose

Although intra-arterial injection has the potential for efficient cell targeting to the brain, there must be a balance between maximizing engraftment and maintaining sufficient perfusion, thus ensuring safety. A wide range of cell doses has been studied in several species, including the mouse, the rat, dogs, and humans (Table II in the online-only Data Supplement). In an attempt to normalize the dose across tested species, we divided the reported dose of injected cells over the average weight of the brain in grams (mouse=0.4 g; rat=2 g; dog=72 g; and human=1350 g). In mouse studies, cell doses ranged between 0.1 and 12.5×10^5/g of brain tissue and complications were reported only for the highest doses, with 7.5×10^5/g of MSCs leading to micro-occlusions as detected by multiphoton microscopy.[7] At a dose of 12.5×10^5/g of C17.2 NSCs, increased mortality has been observed.[12]

The majority of preclinical studies have been performed in rat models, and injected cell doses ranged between 0.05 and 150×10^5/g. Notably, injection of bone marrow mononuclear cells, even at extremely high doses of 100×10^5/g[14] or even 150×10^5/g,[15] was not associated with any adverse effects. This is reassuring and indicates the excellent safety of mononuclear cell injection, but it also raises the question of the efficacy of endothelial capture. Six studies have reported the use of NSCs, and only 1 listed microembolic complications with mouse NSCs at a dose of 5×10^5/g, but that complication was eliminated when cells were infused with preserved blood flow in the carotid artery.[8] The highest frequency of complications was associated with the use of MSCs, which has been reported in 12 studies. Microembolic lesions have been reported with cell doses as low as 1.2×10^5/g[13] and were observed with high reproducibility across different studies when the dose exceeded 5×10^5/g. Notably, there is 1 research group that showed, in several studies, that a cell dose of 10×10^5/g resulted in significant functional benefit without any reported complications.[16,17]

Three studies report on the use of a dog model, with cell doses ranging from 0.14 to 0.69×10^5/g, and microembolic complications at doses of 0.4×10^5/g of MSCs[18] and 0.69×10^5/g of injected adipose-derived pericyte progenitors.[19] There were 12 papers on clinical studies. All used bone marrow mononuclear cells at relatively low doses ranging between 0.002 and 3.3×10^5/g, and none reported adverse effects related to cell injection. Overall, mononuclear cells are safe at any dose, with the upper limit for NSCs $<7.5\times10^5$/g, and for MSCs, the safety threshold seems to be at 1×10^5/g in rodents and $<0.4\times10^5$/g in dogs.

Infusion Speed

Intra-arterial cell injection in the clinical setting is part of a neurointerventional procedure, with the advancement of an endovascular microcatheter under X-ray guidance into the cerebral arteries. The correct placement of the microcatheter is confirmed by an arteriogram, which requires a bolus injection of a contrast agent, and frequently exceeds 5 mL/s, an extremely high speed beyond a physiological perfusion rate of ≈3.4 mL/s for the basilar artery or ≈2.3 mL for the middle cerebral artery.[20] An injection at a rate exceeding physiological perfusion may lead to increased pressure downstream from the catheter tip. Indeed, microcatheter contrast injections have been reported as a potential contributor to intracranial hemorrhage risk in the context of intra-arterial thrombolysis.[21] In a rat model, the infusion of phosphate-buffered saline into the internal carotid artery at a very high velocity of 3 mL/min resulted in focal T2 hyperintensities on MRI consistent with vascular injury. After the infusion rate was reduced to 0.2 mL/min, no injury was observed.[6] Microinfarcts were observed in another study with an injection velocity at 0.3 mL/min.[22] Similar lesions were also observed with the injection of phosphate-buffered saline at a rate of 0.16 mL/min.[13] T2 abnormalities were similar to those observed in patients who undergo routine cerebral angiography.[23,24]

Timing

The acute period of the initial hours and days after stroke is when the risk of complications is particularly high and complications from the intra-arterial injection of stem cells are frequently reported.[25–27] The risk elevation deserves a closer look, as the acute and subacute phases are also an opportune period for the initiation of cell-based treatment. Neurons and glia that are subject to secondary damage could be a target of cell therapy and any delay of the intervention could reduce the impact of such therapy. The vulnerability during the acute stroke phase coincides temporarily with endothelial injury, blood–brain barrier breakdown,[28] and with the massive wave of leukocyte infiltration that peaks around 48 to 72 hours after stroke.[29] An arterial/endothelial system modified at that time to maximize the shuttling of leukocytes into the stroke lesion may offer a unique opportunity for effective intra-arterial delivery of stem cells. Ironically, complications observed after the intra-arterial injection of stem cells in acute stroke may be because of highly successful homing and excessive cell engraftment, which leads to micro-occlusions and local hypoperfusion.[26] This challenge may be addressed by introducing techniques to monitor cell infusion and will be discussed in a subsequent section.

Anatomic Site

As mentioned above, the vulnerability to complications seems to be region specific, with the white matter more susceptible.[6,13] The microstrokes can be clinically silent or result in neurological deficits depending on their anatomic location. It is likely that the complications of intra-arterial injection in the brain stem could potentially lead to more severe consequences and these studies would particularly benefit from precise control and monitoring of cell infusion.

Monitoring and Guiding Intra-Arterial Delivery With Imaging

The benefits of intra-arterial delivery are undisputed, but with a few decades of experience in this area, there is a growing consensus about the need to monitor therapy noninvasively.

The need is driven, to a large extent, by uncertainty about the destination of injected cells, as their biodistribution is affected by multiple factors, including the size of the ischemic lesion, the time after ischemia, hemodynamics, infusion velocity, cell type and size, etc). Without detailed knowledge about cell biodistribution, as well as the precision and efficiency of targeting to a stroke lesion, it is difficult or impossible to fully evaluate and optimize the therapeutic procedure (Figure 2). Histopathology is still the gold standard for the assessment of preclinical studies, but besides being labor intensive and plagued with the unreliability of the quantification, terminal studies lack dynamic information about the entirety of the journey of the injected cells from the catheter to the arteries through the capillaries to their final destination. Another important motivation for incorporating imaging into therapy protocols is safety. As discussed above, the complications of intra-arterial injection have been reported in a relatively large number of studies. Excessive cell engraftment seems to be the primary source of complications, and with high patient-to-patient variability in cell engraftment,[26] monitoring cell homing in real time during the infusion procedure is very appealing. Finally, real-time imaging of intra-arterial cell injection may help improve the precision of cell injection and ensure their placement at the desired destination.

Imaging After Completed Cell Injection

Several imaging modalities have been used for the longitudinal assessment of cells after intra-arterial transplantation in a stroke setting, including MRI, single-photon emission computed tomography (SPECT), and bioluminescent imaging (BLI). Each modality has its own strengths and limitations. The advantages of using MRI are the clinical applicability, the excellent anatomic detail, and the cell detection sensitivity at the single-cell level,[30] but a key limitation of nanoparticle-based cell labels is a dilution of the contrast, with cell division and transfer to phagocytes after cell death, limiting the reliability of long-term tracking.[31] MRI has been successfully applied to visualize intra-arterial–injected superparamagnetic iron oxide nanoparticle (SPIO)–labeled MSCs in a rat stroke model immediately after injection, and it was instrumental in demonstrating the high animal-to-animal variability of cell engraftment in the brain. MRI also showed that the highest engraftment correlated with reduced cerebral blood flow and led to increased mortality.[26] The propensity of MSCs to induce micro-occlusions was also observed in several other studies where MRI cell tracking was instrumental in developing safe transplantation protocols.[6,13,22,32,33] Similarly to MSCs, biodistribution of NSCs (C17.2) injected intra-arterial in a mouse model of hypoxia/ischemia was visualized on MRI scans shortly after injection.[3] Several studies attempted to longitudinally assess intra-arterial–injected MSCs and showed gradual clearance of SPIO-labeled, cell-derived hypointensities from

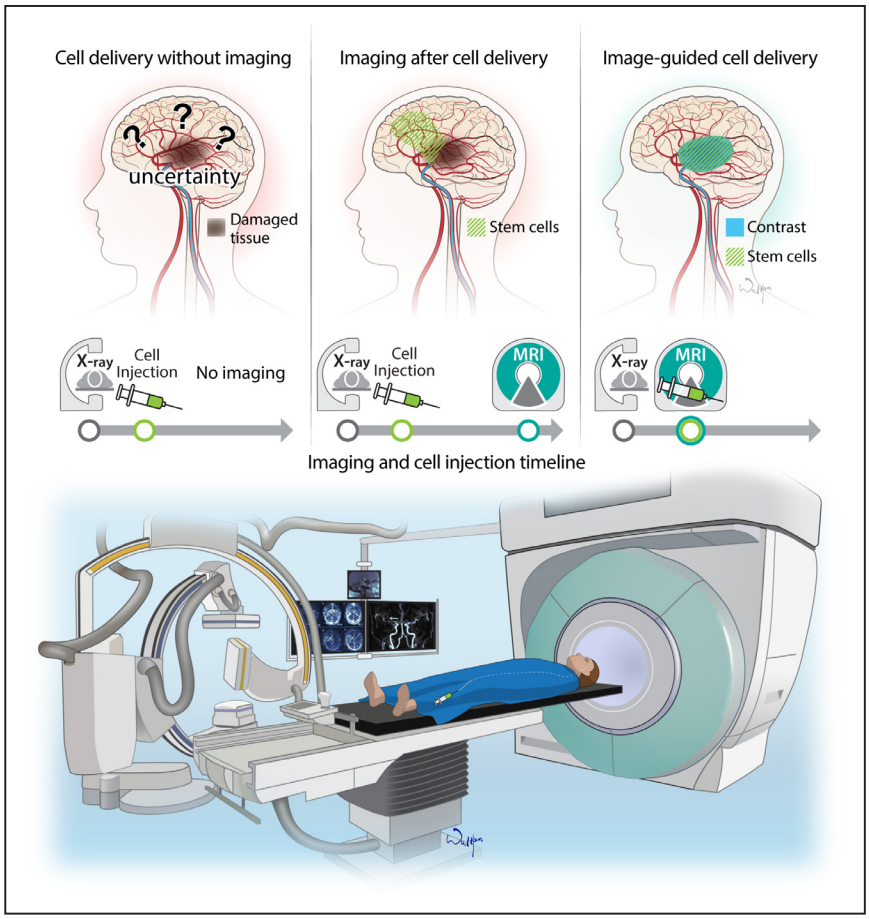

Figure 2. Clinical Perspective on therapeutic intra-arterial (IA) cell delivery after stroke. Imaging of cell delivery should become an integral part of cell transplantation studies. Modern imaging has the potential to demonstrate the anatomic biodistribution of cells after injection. Recent advances in magnetic resonance imaging (MRI) enables real-time monitoring of cellular delivery and anatomic distribution. Hybrid operating room suite may offer the necessary infrastructure for state-of-the-art IA cell transplantation.

the brain, with some signal detectable at 2 weeks[34] or even 4 weeks after injection.[18]

SPECT is a nuclear medicine technique that, compared with MRI, has much lower spatial resolution, but its sensitivity and specificity are high. SPECT also enables whole-body imaging and provides reliable data on global biodistribution of transplanted cells. An important disadvantage is the short imaging window related to the half-life of radioisotopes, allowing cell tracking from 24 to 48 hours. SPECT has been used to show the biodistribution of ^{111}indium oxine–labeled NSCs in a middle cerebral artery occlusion rat model and intra-arterial, but not intravenous injection, resulted in cerebral engraftment. Detection sensitivity has been estimated at ≈1000 cells, and labeling was not detrimental to cell function.[35] In another study, SPECT was used to track human MSCs, and although a large proportion of the cells were trapped in the brain immediately after injection, the majority disappeared after 24 hours, redistributing to filtering organs.[36] The same group has shown the differential clearance of rat versus human MSCs within the first 6 hours after intra-arterial injection, with a faster washout of human cells.[37] Because SPECT is a clinically applicable technique, it has been used by several groups to track intra-arterial–injected cells in patients, thus providing unique data about the early biodistribution of cells. A case report of a study performed in Brazil in a patient who was intra-arterial transplanted with autologous bone marrow mononuclear cells, 9 days after stroke, showed accumulation of the cells in the ipsilateral hemisphere, as well as in the liver and spleen.[38] A subsequent report from this same group included 6 patients, and although cell accumulation was detected in the ipsilateral hemisphere in all patients 2 hours after injection, at 24 hours, it was detectable in only 2 patients.

Currently, the most sensitive techniques for cellular imaging rely on labeling with contrast agents or radioactive tracers, and although these clinically applicable techniques are reliable for cell tracking over a period of days (SPECT) or even the initial few weeks (MRI) after transplantation, long-term tracking with these techniques is not feasible because of either the decay of the tracer (in the case of SPECT) or low specificity (in the case of MRI).[39] For reliable long-term tracking, the imaging tag must be replenished after cell division and rapidly lost after the death of labeled cells. These requirements are perfectly addressed by reporter genes. Reporter genes have been developed for several imaging modalities, including positron emission tomography[40] and MRI,[31,41] but the most widely used systems are based on BLI. Although the spatial resolution of BLI is low, it lacks tomographic capabilities, and its use is limited to small rodents, it is an excellent tool for the longitudinal assessment of cell survival and biodistribution. Indeed, BLI has shown that intra-arterial–injected neural cells engraft in the hypoxia/ischemia-injured brain and engraftment efficiency for intra-arterial injection was 12× higher compared with intravenous delivery. Cells were detectable in the brain for 2 weeks.[8] NSCs injected intraparenchymally were detectable on BLI for several months[39]; thus, signal loss after intra-arterial injection may indicate overall long-term

low engraftment. In response to the need to improve endothelial capture and diapedesis of intra-arterial–injected cells, there have been efforts to either select cells with a high expression of adhesion molecules[42] or to engineer cells to induce the expression of such molecules.[13,43,44]

Monitoring the Interventional Procedure of Intra-Arterial Cell Injection in Real Time

As discussed above, imaging provides unique information about the localization and even viability of intra-arterial–injected cells. This is helpful in improving transplantation protocols, but from a clinical perspective, the practicality of this approach may be of limited value. At the time when the procedure of cell delivery is completed, imaging can show, the placement of the cells, but, should cells be misinjected or their biodistribution be suboptimal, with excessive or insufficient engraftment, it is too late to correct and potentially avoid complications. With recent progress in interventional MRI, and the development of fast imaging protocols along with the use of high sensitivity contrast agents, it is now possible to address this challenge. Indeed, it has been shown that interventional MRI can be used to track stem cells but also, more importantly, to predict the biodistribution of intra-arterial–injected cells before their administration.[44] After placement of an intra-arterial catheter under X-ray guidance, animals are transferred to the MRI scanner, and before cell injection, MRI contrast agent is infused via intra-arterial catheter. That enables visualization of perfusion territory and the tuning of that territory. Once the perfusion territory was optimized, cells could be injected into a predetermined territory of the brain. Notably, MRI at high temporal resolution (2–3 s) enables visualization of the cells as they are captured within the cerebral vasculature (Movie 1 in the online-only Data Supplement). Real-time imaging can be used in combination with adjusting infusion speed, catheter position, or dosing to assure desired and optimal cell biodistribution. In a related study, a similar approach was used for MRI-guided opening of the blood–brain barrier.[45] These studies are good examples of how noninvasive imaging can be used to improve the precision and safety of stem cell injection in a stroke setting.

Overall, the use of noninvasive imaging both to guide the procedure of cell infusion and to assess cell status over time should be incorporated into preclinical and clinical protocols to improve the reproducibility of results and to improve the safety, which would, hopefully, translate into more effective therapies.

Cell Sorting, Preconditioning, and Engineering to Improve Targeted Cell Delivery

Enhancing the capacity of stem cells to transmigrate from the vascular compartment into the ischemic brain has been one of the strategies used to improve therapeutic success. Studies have demonstrated a direct correlation between the number of cells that survive in the brain after intra-arterial transplantation and positive functional outcomes.[42] Several approaches have been described to enhance the potency of cellular targeting. They are all based on the fact that specific molecular mechanisms, such as adhesion and chemoattraction, are responsible for stem cell diapedesis. Using fluorescence-activated cell sorting to select for cell populations with a strong expression of adhesion molecules[42] or chemokine receptors[46] has been shown to significantly increase the number of cells homing to the brain. Another strategy has been to pretreat stem cells with factors that enhance chemokine receptor expression. Interaction of stromal cell derived factor-1 with CXCR4 was shown to play an important role in facilitating homing to the ischemic brain.[47] It was shown that preconditioning of stem cells with brain derived neurotrophic factor[12] or tetramethylpyrazine[48] resulted in a dramatic increase in CXCR4 expression and significantly improved migration in response to stromal cell derived factor-1. Other preconditioning strategies, such as hypoxia and exposure to inflammatory cytokines, have also been investigated.[49] Engineering cells to overexpress cell adhesion molecules and chemokine receptors,[13,43,50,51] or the use of cell surface modifications,[52] have been attempted to improve targeted cell delivery (Figure 3).

Clinical Perspective

Very recently, several clinical trials have shown the efficacy of mechanical clot removal (thrombectomy) through an intra-arterial catheter for emergent large-vessel occlusion.[53] Most importantly, intra-arterial procedures have a much longer therapeutic window when compared with intravenous treatments. The current standard therapeutic window is 6 hours. Novel clinical studies have shown (DAWN trial [Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention])[54] or are still underway (DEFUSE 3 trial [The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3]) that the treatment window can be expanded to 24 hours among patients with large-vessel anterior circulation occlusion who have a favorable imaging profile on computed tomography perfusion or MRI.

This will allow treatment of most patients with emergent large-vessel occlusion. However, despite the high rates of technical success with up to 90% successful revascularization, only 1 of 3 patients will have a disability-free survival. Importantly, thrombectomy requires the placement of an intra-arterial catheter within the cerebral arteries, providing a coincident opportunity to deliver adjuvant therapies precisely and at an optimal dose to the infarcted territory.[55] The success of intra-arterial stroke therapies has led to a tremendous effort to expand the infrastructure to deliver state-of-the-art treatments to stroke patients. In this context, adding intra-arterial cell delivery as an adjunct therapy to thrombectomy is a very appealing option. Interestingly, the newly developed interventional infrastructure could be used to treat patients with stroke who do not qualify for thrombectomy because of the absence of emergent large-vessel occlusion or missing the window of opportunity. The beneficial outcomes of thrombectomies encourage the performance of additional intra-arterial cell infusions as separate procedures at later time points. Therefore, logistically, there are favorable circumstances in which to initiate clinical trials to investigate the effectiveness of intra-arterial cell delivery.

There should, however, be a strong rationale behind the initiation of clinical trials with an intra-arterial route of cell therapy in stroke. These attempts should also be performed in a meaningful way to obtain a wide breadth of information, which could serve as a source for technical improvements. As mentioned above, there could be a particular role for real-time

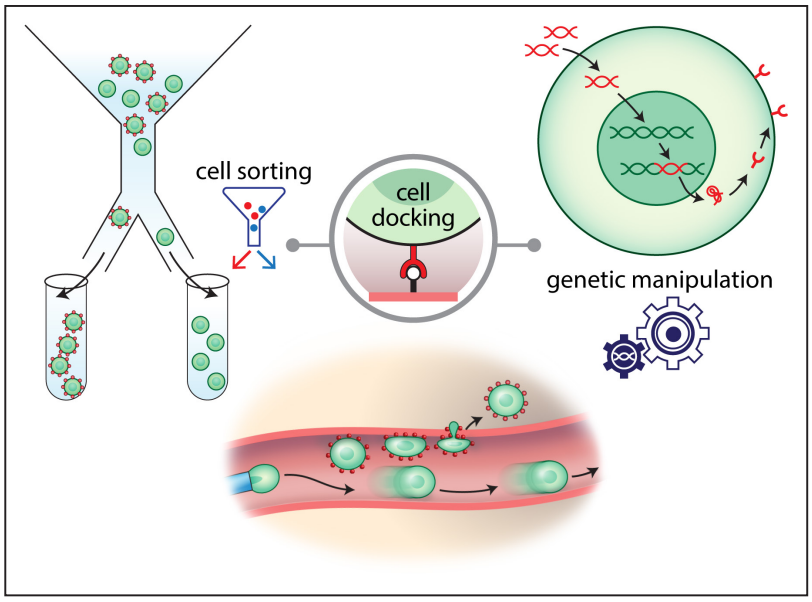

Figure 3. Improving the efficiency of cell delivery. Strategies aiming at improving transendothelial cell homing to the brain include fluorescence-activated cell sorting (FACS) to select cells with high expression of surface adhesion molecules and genetic cell modification of enhance adhesion molecule and chemokine receptor expression.

MRI to visualize the process of cell infusion. It is important to emphasize that any advantage of the intra-arterial route of cell delivery is only gained if infused cells are capable of homing at the first pass. For example, it is intriguing that infusion of bone marrow mononuclear cells at extremely high doses does not lead to complications which raises the question about the ability of those cells to home to the infarcted brain (Table I in the online-only Data Supplement). It is therefore evident that novel imaging methods are needed to monitor the cell delivery and then to document their biodistribution. SPIO nanoparticles are preferably used for MRI cell tracking; however, the SPIO nanoparticles formulation (Feridex/Endorem) used in early clinical studies[56,57] has been withdrawn from the market, and there is still no good replacement. Clinical grade ferumoxytol is available, and ferumoxytol–heparin–protamine complexes have been used to label adipose-derived stem cells injected into rats[58]; however, such complexes would still need a separate US Food and Drug Administration approval to be used in a clinical setting. In terms of imaging equipment, X-ray fluoroscopic/MRI dual suites are available and are equipped with table transfer system, which ideally fit the current needs. Although these facilities are currently not widespread, ongoing progress in interventional neuroradiology is strong drivers for further infrastructure development. In this scenario, after placement of a catheter with or without thrombectomy, a patient could be seamlessly moved from the X-ray fluoroscopic site to the MRI gantry to receive a cell infusion (Figure 3).

Summarizing, the intra-arterial route of cell delivery for the treatment of stroke is very appealing in the era of endovascular thrombectomy. The advancements in imaging methods, particularly real-time MRI, make it possible to visualize the transit of infused cells along the cerebral vasculature and the magnitude of endothelial capture, which is critically important for safety, as well as to better understand the biodistribution of transplanted cells. Engineering or sorting of cells before transplantation might be necessary to allow for

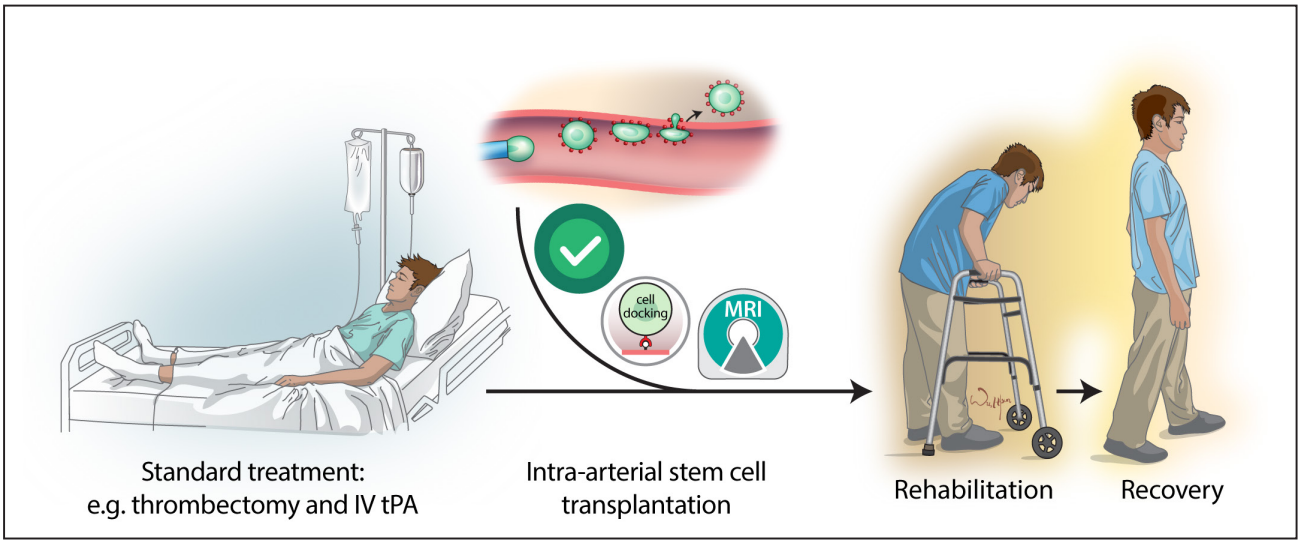

Figure 4. The role of intra-arterial (IA) stem cell–based therapy in the context of standard treatment algorithm. IV tPA indicates intravenous tissue-type plasminogen activator.

improved cellular homing. These tools may improve efficacy of intra-arterial cell transplantation that should be applied in concert with standard treatment algorithms (Figure 4). Finally, further studies to elucidate the mechanism of action that leads to stem cell–induced neuroprotection and neuroregeneration after intra-arterial cell delivery will be required.

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Disclosures

None.

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