Intra-Arterial Delivery of Cell Therapies for Stroke

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Cell therapy is a novel investigational approach to enhance stroke recovery. Intra-arterial (IA) delivery has the potential advantage of selectively targeting cell therapies to the ischemic brain tissue. Over the past 10 years, IA cell delivery has been under investigation in patients with cardiac and peripheral vascular disease, and these studies have reported promising results. This article reviews the trial methodology and procedural details of these studies and discusses the rationale and challenges in designing IA cell therapy trials for ischemic stroke.

Introduction

Cell therapies represent a new investigational approach for the treatment of stroke, but the optimal route of delivery for most cell therapies is currently unknown [1,2]. How cells should be administered in patients likely depends upon a number of factors, including the intended mechanism of action, supporting preclinical data, and the invasiveness of the procedure. Initial clinical trials of cell therapies in acute stroke patients have involved intravenous (IV) delivery since it is least invasive among delivery routes and the majority of animal studies reporting benefit have administered cells IV in rodent models of stroke [3]. Only a handful of small case series of stroke patients have reported an intra-arterial (IA) delivery of cells into the carotid or middle cerebral artery [4]. We discuss the rationale for an IA approach for the delivery of stem cells in stroke, review completed IA cell therapy studies in other medical conditions, and outline the critical issues involved in the design of future IA studies for stroke patients.

Rationale for IA Delivery of Cells in Stroke

Although IV tissue plasminogen activator remains the only proven therapy for acute ischemic stroke (AIS), there is an increasing utilization of catheter-based delivery of fibrinolytics and catheter-based mechanical reperfusion devices for AIS, the so-called intra-arterial therapy. The Food and Drug Administration has approved IA mechanical devices to remove clots and the American Heart Association finds Class B evidence for IA fibrinolysis in patients with acute large vessel occlusions [5]. In a similar manner, an IA delivery for cell therapies, in contrast to IV delivery, may more selectively target cells to the injured brain. Intravenous delivery of cells leads to trapping within peripheral organs such as the lungs, liver, and spleen [6]. IA delivery bypasses the filter of the peripheral organs and may direct a larger number of cells to the brain. Indeed it has been shown that IA delivery results in higher and sustained cell presence at the ischemic site compared to IV infusion [7–9]. One study demonstrated smaller infarct volumes and greater improvement in motor function with IA bone marrow mononuclear cell delivery compared to IV infusion in rats with transient focal cerebral ischemia [7]. The better outcomes were attributed to higher cell numbers in the ischemic brain after IA injection during early reperfusion [7].

An intracerebral injection of cells is the most direct approach to deliver a purported therapeutic agent but results in nonuniform distribution of cells—requiring injection at multiple sites potentially resulting in further tissue injury [10,11]. In contrast, an IA infusion has been shown to spread cells uniformly throughout the ischemic area [9,12]. Furthermore, patients with ischemic stroke receive anti-platelets or anticoagulants, which can increase the risk of bleeding after intracerebral cell implantation [13]. An intracerebral delivery also poses the risk for seizures due to cortical transgression with some loss of cerebrospinal fluid and accumulation of intracranial air around the injured brain tissue [13]. In fact, intracerebral implantation of neural cells in pilot human studies did lead to postoperative complications, including seizure, asymptomatic subdural hemorrhage, and cortical vein occlusion [13,14]. These events would not be expected to occur during an IA delivery approach.

IA Studies in Cardiac and Peripheral Vascular Disease

There is precedence in the medical literature from which we can draw lessons about the IA delivery of cells in patients with other vascular diseases. We performed a Medline search of all prospective human studies investigating IA delivery of cell in patients with myocardial infarction (MI) and peripheral vascular disease (PVD). For nearly 10 years, clinical trials have been assessing the safety and efficacy of IA cell therapies (mainly derived from bone marrow) in patients with MI and PVD and follow similar methodologies.
in which the patient undergoes catheterization and then infusion of cells into a target vessel.

We found 12 randomized placebo-controlled clinical studies investigating IA cell delivery in patients with MI (Table 1) [15–32]. Patients in most cardiac studies underwent endovascular reperfusion of a target coronary artery before intra-coronary cell infusion. In the PVD literature, we identified 3 single arm and 2 randomized placebo-controlled studies (Table 2) [33–37]. Patients in these studies underwent IA cell infusion in the superficial and deep femoral or profunda femoris arteries. Unlike in the cardiac studies, most patients with PVD did not receive any prior surgical or endovascular reperfusion therapy.

**Cells**

All studies to date involving IA delivery of cells in patients with cardiac and PVD have mainly administered autologous bone marrow cells. This choice likely reflects the ease of using a patient’s own bone marrow, which obviates concern for immune rejection and avoids the ethical or political problems associated with embryonic and fetal cells.

**Summary of safety results**

Trials involving patients with MI have reported only minimal adverse events. In one study, 3 patients developed coronary artery dissection after balloon inflation during the cell infusion and the dissection was treated with stent placement [15]. In another study, 2 patients had transient arrhythmias (before cell infusion in one, and 6 days postinfusion in the second) that responded to treatments, including defibrillator implantation [16]. As seen in Table 1, most studies did not report if there was an increase in cardiac enzymes or if arrhythmias occurred after the infusion procedure, which presumably was interpreted to mean that these events did not occur. An asymptomatic elevation in creatinine kinase-MB fraction was observed in one study where the cells were infused within 1 h of percutaneous coronary intervention [17]. Most trials did report such adverse events as heart failure, arrhythmias, re-infarcts, in-stent restenosis, and stent thrombosis in long-term follow-up, but most of these events occurred late (about 12 months) and were less frequent in the cell treated patients than controls, and none were attributed to the cell infusion (Table 1). In the PVD literature, there have been no reported significant adverse events (Table 2).

**Summary of functional outcomes**

Many of the MI studies showed improvement in functional indicators such as left ventricular ejection fraction, or end diastolic or end systolic volumes. Several studies suggested a potential benefit of cell therapy when given at least 4 days after an MI (Table 1). In contrast to these studies, other cardiac studies have found no benefit in patients with MI treated with cell therapy compared with controls [16,17]. A meta-analysis found that there was a significant improvement in cardiac function and improved outcomes in MI patients treated with IA cell therapy as compared to controls [19]. Most of the PVD studies have also reported some measure of benefit—improved ankle brachial index, or pain-free walking distance (Table 2). Only one study did not show any significant ABI improvement postcell therapy, but even that study did find improved ulcer healing [35].

**IA Studies in Neurological Disorders**

**Stroke**

There are only limited case reports of infusion of bone marrow mononuclear cells in patients several days after an AIS [38,39]. The largest case series involves 6 patients receiving 100 million to 500 million cells by infusion into the middle cerebral artery at least 2 months after symptom onset [4]. With continuous heparinized saline, the investigators infused the cells in a total volume of 10 mL at 1 mL/min into the M1 under local anesthesia and conscious sedation. Clinical and laboratory evaluations showed no adverse events during the procedure or follow-up and no patient worsened on neurological scales. One patient developed spike and wave activity on electroencephalogram, which was asymptomatic. Two patients developed generalized seizures 200 days postinfusion (treated with anti-epileptic drugs), which was unlikely related to the procedure. In the United States, there is currently one ongoing IA study evaluating the safety and efficacy of infusing aldehyde dehydrogenase bright bone marrow cells into the internal carotid artery of patients at 13–19 days after an ischemic stroke [40]. Another clinical trial is currently being planned, based on promising preclinical studies, to investigate the IA delivery of bone marrow mesenchymal stem cells (MSCs) in stroke patients [41,42]. Other phase I/II studies are being conducted in the United Kingdom, Brazil, and Spain [43–45].

**Movement disorders**

Lee et al. studied the safety and feasibility of autologous MSCs in patients with multisystem atrophy (MSA) [46]. In this study, 11 patients received cells and 18 served as controls. Cells were infused over 60 min into the cervical segments of both internal carotid arteries and 1 proximal vertebral artery (20 million cells per artery). In addition, 40 million cells were infused IV every month for 3 months. In 7 patients receiving MSCs, magnetic resonance imaging (MRI) diffusion weighted imaging (DWI) sequences showed small spotty lesions <5 mm, which were asymptomatic. In addition, 6 cell-treated patients developed fever immediately after the IV infusion. These results are concerning and need better descriptive information, but apparently the events recorded had no clinical consequences. Brazzini et al. studied the safety and feasibility of autologous bone marrow cells in 53 patients with Parkinson’s disease [47]. Mononuclear CD34 + cells (80–120 mL in solution) diluted in normal saline (at concentration 2 mL in 10 mL saline) were infused by hand injection over 90 to 120 min into the posterior segment of the Circle of Willis close to the perforating arteries supplying the substantia nigra. While the investigators reported no adverse events, 1 patient died suddenly of an MI 4 days after cell injection. Follow-up imaging found no evidence for ischemic injury. These studies illustrate that more information is needed to understand the rationale and safety profile of an IA injection of bone marrow cells for movement disorders.

**Summary of Logistical Issues in IA Studies**

**Safety**

Most of the studies in the cardiac and PVD literature have shown minimal or no adverse effects associated with the IA
<table>
<thead>
<tr>
<th>Study type</th>
<th>Cell type/control</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>No. of cells infused</th>
<th>Follow-up</th>
<th>Event to infusion (days)</th>
<th>Outcome in cell group compared with control</th>
<th>Reported adverse events in cell group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al.18</td>
<td>GCSF + PMNC</td>
<td>10</td>
<td>59.4</td>
<td>1.5×10⁹</td>
<td>6 months</td>
<td>2–5</td>
<td>↑ LVEF</td>
<td>Restenosis with GCSF hence study stopped; ↑ CKMB (12 h postinfusion)</td>
</tr>
<tr>
<td></td>
<td>GCSF</td>
<td>10</td>
<td>54.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>7</td>
<td>52.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Traverse et al.20</td>
<td>MNC</td>
<td>30</td>
<td>52.5 Median</td>
<td>1×10⁸</td>
<td>&gt;6 months</td>
<td>5.2±2.3</td>
<td>No ↑ LVEF</td>
<td>2 patients (7%) required nontarget vessel revascularization</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>10</td>
<td>57.5 Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wollert et al.,21</td>
<td>MNC</td>
<td>30</td>
<td>53</td>
<td>(25±9.4)×10⁶</td>
<td>18 months</td>
<td>4.8±1.3</td>
<td>6 mo: ↑ LVEF; 18 mo: No ↑ LVEF</td>
<td>Fatal sub-acute stent re-thrombosis 5 days postinfusion in 1 patient (3%); stent rethrombosis at day 3 in 1 patient with coagulation disorder; 1 patient had balloon inflation-related thrombus emboli, causing ↑ cardiac enzymes</td>
</tr>
<tr>
<td>Schaefer et al.,22</td>
<td>MNC</td>
<td>30</td>
<td>53</td>
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<tr>
<td>Meyer et al.23</td>
<td>Control</td>
<td>30</td>
<td>53</td>
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<tr>
<td>Assmus et al.24</td>
<td>MNC</td>
<td>9</td>
<td>55</td>
<td>(245±172)×10⁶</td>
<td>4 months</td>
<td>4.3±1.5</td>
<td>↑ LVEF (PMNC=BMC)</td>
<td>Coronary artery dissection (4%) caused ↑ CKMB; VT needing defibrillation (1%); MI (6% in PMNC grp, during initial hospital stay); HF (1%); syncope (3%); repeat revascularization (9%)</td>
</tr>
<tr>
<td>(4 month follow-up)</td>
<td>Control</td>
<td>10</td>
<td>52</td>
<td>(10±7)×10⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MNC</td>
<td>9</td>
<td>55</td>
<td>(213±75)×10⁶</td>
<td>12 months</td>
<td>4.5±1.5</td>
<td>↑ LVEF (PMNC=BMC)</td>
<td>Coronary artery dissection (4%) caused ↑ CKMB; VT needing defibrillation (1%); MI (6% in PMNC grp, during initial hospital stay); HF (1%); syncope (3%); repeat revascularization (9%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11</td>
<td>55</td>
<td>(16±12)×10⁶</td>
<td></td>
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</tr>
<tr>
<td>Schächinger et al.25</td>
<td>MNC</td>
<td>35</td>
<td>60</td>
<td>(205±110)×10⁶</td>
<td>6 months</td>
<td>&gt;3 months</td>
<td>↑ LVEF (MNC only) at 3 months &amp; in the crossover study at 6 months</td>
<td>Coronary artery dissection (4%) caused ↑ CKMB; VT needing defibrillation (1%); MI (6% in PMNC grp, during initial hospital stay); HF (1%); syncope (3%); repeat revascularization (9%)</td>
</tr>
<tr>
<td>(1 year follow-up)</td>
<td>PMNC</td>
<td>34</td>
<td>56</td>
<td>(22±11)×10⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>29</td>
<td>61</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Schächinger et al.26</td>
<td>MNC</td>
<td>101</td>
<td>55</td>
<td>(236±174)×10⁶</td>
<td>2 years</td>
<td>3–6</td>
<td>↑ LVEF †survival</td>
<td>Ventricular arrhythmias (6%), prostate cancer (1%); cardiac death (3%), target vessel repeat revascularization (19%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>103</td>
<td>57</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Janssens et al.29</td>
<td>MNC</td>
<td>33</td>
<td>56</td>
<td>(304±128)×10⁶</td>
<td>4 months</td>
<td>1</td>
<td>↓ infarct size; No significant ↑ in LVEF</td>
<td>Death due to hemorrhagic shock-in 1 patient; VT (8%); in stent stenosis (3%); squamous laryngeal carcinoma (1 patient)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>34</td>
<td>58</td>
<td></td>
<td></td>
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<tr>
<td>Chen et al.30</td>
<td>MNC</td>
<td>34</td>
<td>58</td>
<td>(48 to 60)×10⁹</td>
<td>6 months</td>
<td>&gt;18</td>
<td>↑ LVEF</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>35</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunde et al.16</td>
<td>MNC</td>
<td>50</td>
<td>58</td>
<td>68×10⁶</td>
<td>6 months</td>
<td>4–8</td>
<td>No ↑ LVEF</td>
<td>Mild chest pain (68%) &amp; ST deviation (72%) during balloon catheter inflation; V fib (1 patient) treated with implantation of cardiac defibrillator.</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>50</td>
<td>57</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bartunek et al.31</td>
<td>MNC</td>
<td>19</td>
<td>51</td>
<td>12.6±2.2×10⁶</td>
<td>10 months</td>
<td>11.6±1.4</td>
<td>At 4 mo: ↑ LVEF; ↑ Perfusion; ↑ LVEF; ↓ Infarct size &amp; mortality</td>
<td>Stent re-stenosis (14%); 1 case of sustained VT (2 days postinfusion)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>16</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NM</td>
</tr>
<tr>
<td>Yousef et al.32</td>
<td>MNC</td>
<td>62</td>
<td>51.4</td>
<td>6.1±3.9×10⁷</td>
<td>5 years</td>
<td>7±2</td>
<td>↑ LVEF</td>
<td>Death (1.25%); MI (1.8% in both selective and nonselective MNC patients); repeat revascularization (15.6%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>62</td>
<td>50.7</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tendera et al.17</td>
<td>Selected MNC</td>
<td>80</td>
<td>58</td>
<td>1.9×10⁶</td>
<td>6 months</td>
<td>3–12</td>
<td>↑ LVEF in patients with LVEF &lt; median value &amp; event to PCI time &gt; than median for the groups.</td>
<td>Stent re-stenosis (14%); 1 case of sustained VT (2 days postinfusion)</td>
</tr>
<tr>
<td></td>
<td>Non Selective MNC</td>
<td>80</td>
<td>55</td>
<td>1.78×10⁸</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>40</td>
<td>59</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

GCSF, granulocyte-monocyte colony stimulating factor; CKMB, creatinine kinase-MB fraction; HF, heart failure; NSTEMI, non-ST segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; SVT, supra-ventricular tachycardia; ST, segment on electrocardiogram; MNC, bone marrow-derived mononuclear cells; NM, not mentioned; PMNC, peripheral blood circulating mononuclear cells; PCI, percutaneous coronary intervention.
procedures. The catheterization and infusion procedures have therefore been found to be safe in the majority of studies. In particular, there have been no clear instances where autologous cell injection led to arterial occlusion, reduction in blood flow, or MI. Given their comparable size with red blood cells, bone marrow mononuclear cells are likely to pass through microvessels and capillaries. The preponderance of the data from these studies highly supports that autologous mononuclear and circulating progenitor cells do not have an adverse effect in patients who have diseased arterial vessels. However, there are too few patients to conclude if IA delivery of cells is safe in neurological disorders and there needs to be better justification for the type of cell and specific neurological disorders that investigators believe would potentially benefit from cell therapy.

**Rationale for dosing**

In the studies we reviewed here, the number of cells infused ranged from $10^6$ to $10^9$. All neurological studies and most cardiac studies used MNCs at a dose of $>10^6$. There appears to be little scientific basis for the doses chosen beyond the number of cells extracted from the bone marrow. Choosing an initial dose for IA infusion, however, is challenging. Extrapolating the dose, for example, based on animal studies is problematic since a weight-based translation, while applicable for pharmacologic drug studies, does not take into account the size of the intended target organ or arteries from animals to humans. It remains unclear what is the minimum number of cells needed to exert a therapeutic effect within the injured area of the target organ for any of the diseases discussed.

**Procedural details**

Most of the cardiac studies infused cells via an over-the-wire balloon catheter at ~1 cc/min. Most patients in cardiac studies underwent percutaneous coronary intervention with stent placement (Table 3). A balloon catheter was used to occlude the target artery in order to increase engraftment of cells into the myocardium. Typically, the target vessel is balloon occluded for a few minutes during which cells are infused, followed by reperfusion. This approach follows the methodology of a 2002 report, with some variations [48]. Unfortunately, none of the PVD studies indicated the infusion rate. The neurological studies have reported more varying rates with 1.0 mL/min for stroke, 1.67 mL/min for MSA, and about 6 mL/min for Parkinson’s disease (Table 4). Anticoagulation is always used during the procedure for these studies, and some trials also gave GIIb/IIIa inhibitors as well as aspirin and clopidogrel.

**Timing**

Most of the IA studies have occurred in the absence of defining a therapeutic window in animal studies. In most of the cardiac studies, the cells were infused within 1–8 days of an MI, while 3–6 months post-MI appears to be the maximum time point in one study [26–28]. In contrast to the cardiac studies, the only published case series of IA cell delivery in stroke has administered cells in the chronic setting several weeks after symptom onset [4].

**Fate of cells**

Ideally, we wish to monitor the fate of transplanted cells after delivery in patients. MRI techniques are being developed that would permit cell tracking with use of cells labeled with superparamagnetic iron oxide nanoparticles [49]. None of these labeling techniques to date have thus far advanced after delivery in patients. MRI techniques are being developed that would permit cell tracking with use of cells labeled with superparamagnetic iron oxide nanoparticles [49]. None of these labeling techniques to date have thus far advanced into clinical trials. It therefore remains unknown how many cells reach the target area of injury, where do the excess cells migrate, and how long the cells survive.

**Moving Forward with IA studies in Stroke**

As cell therapy studies for stroke begin to escalate around the world, many issues need to be addressed in considering an IA route of delivery.

**Choice of cell**

There is an increasing number of cell therapies under investigation for stroke. These cells are derived from embryonic/fetal sources, tissues associated with birth (umbilical cord/placenta), and adult organs (bone marrow). The
majority of studies using non-neural tissues mainly involve isolating and manufacturing allogeneic cells to stimulate the brain’s intrinsic repair mechanisms and modulate the immune system. The use of neural cells, however, to replace lost brain tissue and recreate lost circuitry after stroke remains a long range goal for some investigators. Neural cells derived from patient specific induced pluripotent stem cells or from other somatic cells are exciting options for the future and need further investigation. Autologous cells from bone marrow remain an attractive option but do involve having to perform a bone marrow harvest on stroke patients.

Site of injection

Where should the site of delivery occur in the cerebral circulation? For middle cerebral artery (MCA) strokes, should the carotid or MCA be chosen? A more distal injection into the MCA entails a higher periprocedural risk while a more proximal injection could take into account collateral circulation that could direct therapeutic cells not only to the injured area, but the peri-infarct region as well. More proximal injections (e.g., cervical carotids), there is a higher likelihood that cells might migrate to other unintended areas of the brain or into the ophthalmic artery. However, in patients with larger infarcts involving anterior as well as middle cerebral artery territories, cell infusion in the carotid is a more logical approach. Similarly for posterior circulation infarcts, cell infusion in the vertebral artery would be considered.

Infusion rates

The infusion rate into the carotid artery should depend in part on standard resting flow rates, assuming normal blood-nucleated cell counts. The additional amount of cells placed into the central nervous system (CNS) should then be considered based upon the percent increase in flow and percent increase in nucleated cells that flow to the CNS in that time frame. For example, the mean blood flow rate into the cervical internal carotid artery is about 350 mL/min [50]. Therefore, a 1 cc/min flow rate delivering about $10^6$ cells would add a negligible number of additional cells per min into the cervical carotid arterial circulation. However, the intracranial arteries are typically 2–4 mm in diameter and would have much lesser flow rates [51]. Other agents have been administered IA in the intracranial circulation at 1 cc/min such as verapamil for vasospasm and t-PA for central retinal artery occlusion [52–54]. Delivery of oxygenated arterial blood distal to the occlusive thrombus during acute stroke interventions using a microcatheter has been found to be safe and feasible at a reported rate of 10cc/min [55,56]. It is conceivable that IA infusion of cells comparable in size to red blood cells in the intracranial vasculature at this rate could be safe and justified for further clinical trials. The

<table>
<thead>
<tr>
<th>Study</th>
<th>Cath placement/Cell delivery mode</th>
<th>Infusion (mL/min)</th>
<th>Duration (min)</th>
<th>Adjuvant medication</th>
<th>Balloon catheter</th>
</tr>
</thead>
</table>
| Myocardial infarction
Kang et al.18 | BC after PCI | NM | NM | Nicorandil, NTG, Heparin | Yes |
| Traverse et al.20 | Microcatheter infusion | 1 | 20 | Heparin | No |
| Wollert et al.,21 Schaefer et al.,22 Meyer et al.23 | BC inflated in stent | NM | 10–20 | NM | Yes, SFT |
| Assmus et al.24 Schächinger et al.25 | BC after PCI | 1.1 | 15 | Abciximab, heparin, clopidogrel, aspirin | Yes, SFT |
| Assmus et al.15 Schächinger et al.,26 | BC | 1.1 | 15 | Heparin, Abciximab | Yes, SFT |
| Assmus et al.28 | BC after PCI | 1.1 | 15 | Heparin, Abciximab | Yes, SFT |
| Janssens et al.29 | BC after PCI | 1.1 | 15 | NM | Yes, SFT |
| Chen et al.30 | BC after PCI | NM | NM | Heparin | Yes, SFT |
| Lunde et al.31 | BC after PCI | NM | NM | NM | Yes, SFT |
| Bartunek et al.32 | BC after PCI | 1.1 | 15 | NM | Yes, SFT |
| Yousif et al.32 | BC after PCI | NM | 16 | Dipyridamole, Dobutamine, Microalbumin aggregates | Yes, SFT |
| Tendera et al.17 | BC after PCI | 1.1–1.5 | 15 | Heparin | Yes, SFT |
| Peripheral vascular disease
Ruéz-Salmeron et al.33 | BC proximal to distal FA or popliteal artery | NM | 3 min | NM | Yes, SFT |
| Bartsch et al.34 | FA | NM | NM | None | No |
| Walter et al.35 | Hand injection in FA (BC in 20 pts with fast distal runoff) | NM | NM | Heparin | Yes |
| Van Tongeren et al.36 | IM injection in gastrocnemius; IA injection in FA/PF after catheterization | NM | NM | None | No |
| Lenk et al.37 | Hand injection FA | NM | NM | None | No |

BC, over-the-wire balloon catheter; FA, femoral artery; PF, profunda femoris artery; SFT, stop flow technique—balloon catheter inflated for few minutes (prevents retrograde blood flow), while cells are infused (allows maximum chances of implantation at lesion). Repeated in 3–4 cycles. Balloon deflated between cycles to ensure antegrade flow.
infusion rate should also take into account biocompatibility of the given cells with the microcatheter used [57].

Which stroke patients?
The criteria to select stroke patients for clinical trials and testing cell therapies depend upon the timing of administration and the intended therapeutic goals. For IA studies, the question of which vascular occlusions should also be addressed. An attractive possibility is to deliver cells right after IA recanalization in the acute stroke setting. Is revascularization a prerequisite for an IA cell therapy study? We would argue that occluded vessels should be considered if they are distal to the intended site of delivery. Other related issues will need to be addressed such as patients with carotid stenosis (including what percent stenosis would be acceptable?). In addition, patient-specific factors such as compliance with secondary stroke prevention therapies, glycemic control in diabetes, and cholesterol management for dyslipidemia, may also influence the outcome of cell therapy studies.

Monitoring safety
The most concerning potential adverse event resulting from IA injection of cells is cerebral ischemia. Animal studies have found that IA injection of MSCs can reduce cerebral perfusion and those animals with a reduction in perfusion had a high mortality rate [9,12]. There is therefore appropriate concern that cells could cause ischemic injury either by adhering to each other and blocking vessels or by causing microvascular plugging. What are the best methods to monitor for this potential risk? Battistella et al. in their patients undergoing IA mononuclear cell infusion have used Transcranial Doppler to assess cerebral blood flow, but this method may not detect small vessel occlusions [4]. Whole brain perfusion by computed tomography or positron emission tomography are more sensitive methods to detect changes in blood flow while MRI with diffusion-weighted sequences remains the most reliable method available to detect ischemic injury. One difficulty, however, will be separating DWI lesions due to clumps of cells from embolic infarcts due to catheter manipulation. It is also possible that DWI lesions may serve as a marker of cells homing into the area of injury or plugging of the microcirculation. As clinical safety studies move forward, it will be important to define a protocol to address if an ischemic complication occurred during the cell infusion. We would consider using a glycoprotein IIb/IIIa inhibitor for an embolic occlusion related to the cell delivery [58].

Biocompatibility with devices
We believe that all types of catheters used for injection in a planned IA study should be investigated in order to determine that they do not affect the cells as they traverse the lumen of the catheter. To satisfy regulatory requirements for safety, assays should be performed of the cells after injection through the catheter systems with studies to assess for aggregation, change in cell morphology, or changes in cellular function. A recent study reported that a flow rate of up to 2 mL/min did not alter cell viability with Excelsior SL-10 microcatheter; however, higher flow rates did result in cell death [57].
Role of adjunctive neurotrophic factor treatment

As the conditions for optimal IA cell delivery are developed from animals to patients, another intriguing issue to consider is the application of adjutant neurotrophic factors. Delivery of neurotrophic factors in combination with IA cell delivery could promote the growth and survival of the injected cells and/or provide synergistic benefits. Such an approach requires studies in animal models of ischemic stroke.

Animal stroke models to study IA delivery

Rodent models of stroke are well established to test new purported therapies in stroke. How to optimize an IA delivery method that minimizes risk for embolization has been investigated in rats [59]. Large animal models may likely be better suited to study the safety effects of IA delivery. The porcine model, for example, is well characterized to study intra-coronary delivery of cells [60,61]. However, very few large animal models have been established in stroke and primate research is limited, expensive, and fraught with ethical complications. Lastly, since numerous animal studies have shown that IV administration of cell therapies can improve stroke recovery, it is important to compare IV versus IA delivery routes in preclinical studies if the intended purpose is to develop an IA approach for clinical application in stroke.

Acknowledgments

Dr. Savitz is supported by the NIH and the Howard Hughes Medical Institute.

Author Disclosure Statement

Dr. Savitz is a senior investigator for an IA stem cell trial in stroke sponsored by Aldagen. Drs. Misra, Lal, El Khoury, and Chen have no competing financial interests to report.

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Received for publication October 29, 2011
Accepted after revision December 19, 2011

Prepublished on Liebert Instant Online December 19, 2011