

Review

Recruiting Patients With Stroke Into Cell Therapy Trials

A Review

Vivek Misra, MD; William J. Hicks, MD; Farhaan Vahidy, MD; Susan Alderman, RN; Sean I. Savitz, MD

IMPORTANCE Clinical trials are under way to test the safety and efficacy of different types of cell therapies in patients with ischemic stroke. The informed consent process for recruitment of patients with stroke in cell therapy trials is complex and requires extensive discussions on multiple aspects.

OBSERVATIONS Various issues in approaching patients with stroke and their families and discussing participation in cell therapy studies are described, including participation in clinical trials, clarifying the perception of stem cell therapy and the risks of bone marrow harvest, and discussing risks vs benefits, cell-based therapies for chronic stroke, and consent for minority and immigrant populations.

CONCLUSIONS AND RELEVANCE Informed consent for cell therapy studies in patients with stroke requires lengthy discussions about several issues unique to clinical trials in stroke patients. Careful thought is needed to create an informative consent process.

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Author Affiliations: Department of Neurology, The University of Texas Health Science Center at San Antonio (Misra); Department of Neurology, The University of Texas Health Science Center at Houston (Hicks, Vahidy, Alderman, Savitz).

Corresponding Author: Sean I. Savitz, MD, Department of Neurology, The University of Texas Health Science Center at Houston, 6431 Fannin St, Houston, TX 77030 (sean.i.savitz@uth.tmc.edu).

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With an ever increasing number of stroke survivors worldwide, the significant global burden of disability posed by stroke raises pressing needs for new stroke therapies. Despite the success of reperfusion approaches to improve outcomes in patients with acute ischemic stroke, most patients with stroke still have permanent disability. Regenerative medicine offers new opportunities to develop restorative treatments using cell-based approaches for stroke and other neurologic disorders.¹ After nearly 2 decades of preclinical studies investigating cell-based therapies, clinical trials have been initiated worldwide to examine the safety and efficacy of various stem cell therapies and other types of cell therapies in patients with ischemic stroke. Most of the early human studies have been investigating autologous bone marrow-derived cells, while industry-sponsored trials are focusing on allogeneic cells derived from healthy donors or fetal tissue.

Several groups have completed early-stage clinical trials investigating the safety and feasibility of autologous bone marrow-derived cells in patients with acute or recent stroke.²⁻⁴ Conducting such trials poses several practical challenges to participant recruitment and clinical care, as described elsewhere.⁵ We discuss the unique aspects, based on our experience, of approaching patients with stroke and their families and discussing participation in stem cell trials.

Consenting Patients With Stroke in Cell Therapy Trials

Patients with relapsing-remitting multiple sclerosis or those in the early stages of neurodegenerative disease typically understand the

risks of investigational therapies when considering whether to participate in a clinical trial. In contrast, most patients with an acute or recent stroke have cognitive deficits and frequently are unable to grasp details of their illness, the treatment plan, and the potential benefits vs risks of participating in a clinical trial that will test an investigational therapy. In our stroke center, for any clinical trial, the treating physician performs a neurologic assessment of cognitive function to determine if any potentially eligible patient understands the risks and benefits of the intervention. For patients unable to comprehend the discussion, investigators obtain informed consent from a legally authorized representative (LAR). For the past 20 years, most trials testing new therapies for stroke have focused on the acute period immediately after the stroke occurs, in which decisions to enroll patients must be made quickly in a matter of minutes, so as to not delay thrombolytic therapy.⁶ A thorough discussion of the risks vs the benefits of a clinical trial often does not allow the patient or the LAR time to confer with colleagues, private physicians, friends, or family members before making a decision.

In contrast, most published cell therapy clinical trials are targeting the subacute period within the first few days or weeks after stroke symptoms, in which the intended goal is to modulate the postischemic inflammatory response and stimulate endogenous repair mechanisms.¹ In an autologous bone marrow study, enrollment occurred within 1 to 3 days after the onset of stroke,² while other studies have enrolled patients within 1 week.^{3,4} This expanded window allows investigators to engage in more lengthy discussions with patients and their families over days rather than minutes or hours. In our experience, the patient or LAR often seeks advice from other family members or friends who can heavily influence decisions to participate in cell therapy clinical trials. The discussion may need to

be repeated multiple times to include other family members or close friends traveling long distances or seeking further information and clarification.

Although LARs can consent to standard of care for therapies and procedures, there is great variation as well as ambiguity among different nations on the scope of authority for enrollment in a clinical trial.^{7,8} A study of institutional review boards across multiple US institutions also discovered significant variability in acceptance of surrogate consent for research involving individuals with impaired decision-making ability.⁹ Legally authorized representatives have legal authority to consent to procedures that are in the patient's best interests. However, studies suggest that most patients are also comfortable with their surrogates making decisions about participation in research trials.¹⁰ In general, older Americans demonstrated a favorable attitude toward surrogate consent for research, particularly in the setting of patient impairment owing to dementia.^{11,12} Patients with stroke who were interviewed within 72 hours of symptom onset were more willing to participate in research, compared with their LARs.¹³ Some clinical investigators have suggested the use of research about advance directives and mechanisms to identify appropriate surrogate decision makers.^{14,15} These measures, however, may require legislation. When approaching potential candidates for research, we have adopted an all-inclusive approach of discussing the clinical trial with all available family members and the LAR while encouraging interactive communication to address their concerns. Even when a patient is able to make decisions on participation in a clinical trial, our preference is to proceed with enrollment only if the family is in agreement with the patient.

Clarifying the Perception of Stem Cell Therapy

When approaching patients and LARs, investigators need to spend additional time assessing their perception and understanding of stem cells and other types of cell-based therapies. Some patients have the misconception that stem cells are created only from human fetuses or embryos and have concerns that participating in such trials could facilitate or promote the practice of abortion. To alleviate these concerns, we clarify that the cells for an autologous trial are derived from the patient and that the overall concept is very different from embryonic stem cells. Trials testing allogeneic cells involve samples from bone marrow or adipose tissue of healthy adults or umbilical cord blood or placental tissues derived from healthy births. Because of their close association with newborns, it is important to stress to patients and families that umbilical cord and placental cells do not involve the destruction of fetuses or embryos.

At a global level, the term *stem cells* can invoke the myth that they are a panacea to treat various ills. Several clinics abroad and in the United States offer cell therapies to patients with many neurologic disorders.^{16,17} Published reports of patients being harmed by injection of cells highlight the danger of inappropriate infusion of cells in the absence of rigorous scientific evidence to guide their use.^{18,19} Consequently, there is much skepticism and confusion about the testing of stem cells for medical disorders. Those trying to perform clinical research within approved regulatory guidelines must address patients' perceptions and clarify misunderstandings. Detailed conversations on the precautions and safety aspects of clinical trials, including frequent follow-ups, are essential to these discussions.¹⁶

Even though social media has contributed to the myths about the uses of stem cells, studies suggest that social media may also be a source for improving patient awareness about stem cell research and may increase communication between patients and clinical researchers.²⁰

Autologous Cell Therapy and Risks of Bone Marrow Harvest

Given the discussion above, we designed our first clinical trial in 2007 using autologous cells from the patient's own bone marrow. In our experience, patients have generally found cells from autologous sources more attractive because they originate from their own tissues; however, a bone marrow aspiration from the hip is an invasive procedure and is not the standard of care for any patient with stroke. Patients and LARs express concerns about the placement of a large-bore needle in the hip even under analgesia and conscious sedation. We discuss in detail the potential risks of harvesting bone marrow, including the possibility of local and systemic infection and pain. Because we chose to place the patient in an intensive care unit for conscious sedation and close monitoring during and after the harvest process and subsequent infusion, some patients and families perceived the transfer to the intensive care unit as an escalation in care, which ran counter to expectations for clinical improvement and transitioning out of the hospital.

During the subacute period, families and patients are beginning to grapple with the sudden devastating changes and impairments that the patients are experiencing after stroke. Under these circumstances, some families are not comfortable discussing the possibility of an invasive bone marrow harvest procedure that is unnecessary for patient care. When patients show profound deficits, such as hemiplegia, some families may ask to wait a few days before agreeing to a bone marrow harvest procedure in the hopes of clinical improvement rather than agree to an investigational therapy that involves an invasive procedure requiring conscious sedation. In our experience, in the weeks to months after a stroke, when disabilities persist and hope for improvement begins to fade, the preference of not accepting such risk changes, but by this point such patients are no longer eligible for many clinical trials that are testing cell-based therapies for stroke.

The application of allogeneic cells does not require invasive procedures for the patient and therefore does not pose the same ethical issues. As "off the shelf" products, several allogeneic cell types can be stored and thawed before infusion.^{21,22}

Discussing Risks vs Benefits

More than 10 years of laboratory studies have elucidated some of the biological processes underlying how cell-based therapies improve outcomes after a stroke and other neurologic disorders; however, the precise mechanisms are not yet fully understood.¹ Consequently, during the consent process, it is important to indicate that the potential risks are not yet fully known, owing to the innovative nature of the intervention. Some types of stem cells might lead to tumor formation depending on their pluripotency, although there has been no evidence that adult bone marrow cells lead to neoplasia.

sia. Intracranial delivery of fetal tissue with neural stem cells in a child, however, has been reported to lead to a brain tumor.¹⁹

The patient should be informed that the delivery route is another factor that can pose additional risks. Because intravenous administration delivers cells to the lungs, the potential for pulmonary complications should be discussed as part of informed consent.²³ On the other hand, intravenous delivery of mesenchymal cell therapies are also being investigated as potential therapeutics for various pulmonary diseases.²⁴ As intravenous administration is the most common delivery approach, it is important in early-stage trials to monitor for organ injury and acute infusion-related toxic effects. Several other studies are pursuing intracarotid infusion of cell therapies. In our experience, for these trials, the consent process requires additional and detailed explanations of angiography and intra-arterial procedures. Animal studies have reported risks of embolism after intracarotid infusion of certain types of stem cells²⁵ but thus far initial clinical studies have reported that the infusions are safe.^{3,4}

Finally, the issue arises whether the patient stands to gain any possible benefit from participating in cell therapy trials. For the patient to derive any possible benefit, in initial safety trials, we recommend administering cells in time windows that match the intended pathophysiological targets based on preclinical data. In our experience, patients and families are more willing to enroll in a single-arm safety study vs a randomized trial. We have encountered several instances in which there is a high level of enthusiasm from patients and their families to receive stem cells, even to the extent that they question the logic of a randomized, placebo-controlled, 2-arm design. Such designs have actually led some patients to refuse participation because they want to receive their own stem cells and blinded randomization does not allow them to know whether they received their own cells or placebo. Furthermore, randomized trials involving a bone marrow harvest require a sham procedure in which patients assigned to the sham group derive no benefit. The intent of the sham is to keep the patient blinded to treatment allocation but the design of the sham is designed to minimize discomfort and risk.

Cell-Based Therapies for Chronic Stroke

As patients move into the chronic stages of stroke, we have encountered widespread enthusiasm from the public to participate in stem cell trials. In the subacute setting, some patients and families are risk adverse, whereas the opposite reaction occurs in the setting of chronic stroke. We frequently receive requests from patients with chronic stroke or their family members to join a stem cell study. The high level of enthusiasm raises an ethical issue because of the potential for selection bias of trial participants. The science of applying stem cells in the chronic setting months to years after a stroke is emerging.²⁶⁻²⁸ Initial early-stage regulated clinical trials have now led to the launch of larger studies in the United States and United Kingdom, testing intracerebral injections of stem cells in patients with chronic stroke.^{29,30} Patients have high expectations that stem cells will be effective to treat their disability³¹ even if the risks are unknown; these expectations may be a challenge for investigators assessing long-term outcomes. For the design of clinical trials, it is important to set realistic outcomes based on biological mechanisms.

In our experience, many patients are seeking physicians who are willing to treat their disabilities with stem cells, whether as part of a

clinical trial or part of the physicians' clinical practice. Such desperation makes these patients vulnerable to the lure of unproven stem cell injections.³² Human protection guidelines demand a sound scientific rationale to justify using stem cells in patients with chronic disabilities from a stroke. It is incumbent on physicians to inform such patients about the potential dangers of seeking unproven stem cell treatments in unregulated settings.¹⁶ The practice of off-label use of stem cells in patients with chronic stroke creates challenges to conducting rigorous placebo-controlled studies as the criterion standard approach to provide evidence for potential benefit.³³ However, the limited number of registered trials with strict inclusion and exclusion criteria may also be another reason why patients may seek physician practices that offer stem cell treatment.

Consent for Minority and Immigrant Populations

Other special circumstances relevant to minority populations have affected enrollment into cell therapy trials. In our experience working in Texas 4 decades after the Tuskegee study became public, African American individuals continue to show concern about participating in clinical research approved by the US Food and Drug Administration and institutional review boards. Traditionally, African American individuals have viewed clinical research with suspicion.^{34,35} The book *The Immortal Life of Henrietta Lacks* showcased the illegitimate creation of the HeLa cell line from the cervix of a woman, without her permission, at one of the leading university hospitals in the United States.^{36,37} As some cell therapy trials involve aspirating bone marrow or adipose tissue to manufacture cell therapies directly from the patient, it is possible that the unethical creation of the HeLa cell line might affect decisions to consider enrollment into these trials. In our informed consent forms, we have indicated that we will not use the patient's cells to grow cell lines. However, no matter how thorough and informative, the consent process may not provide sufficient assurances to some patients and their families that they are being fully informed of the risks or that they would be protected from inappropriate use of their own stem cells.

Language barriers represent another area affecting the consent process. For patients and LARs who understand little or no English, important words may not be translated correctly or the translator may not fully understand the details of the investigational procedures. In some languages, there are no equivalent translations for *stem cells*. These issues illustrate the importance of communicating through an appropriate or certified interpreter. We recommend having a separate discussion with the interpreter before beginning the consent process explaining the details of stem cells, the rationale for the clinical trial, and the clinical trial process, as well as how to present the information to patients.

Conclusions

Informed consent for cell therapy stroke studies requires lengthy discussion of several issues unique to stroke clinical trials. Some bioethical issues change along the temporal course of stroke. Future investigators must dedicate careful thought to creating an informative and respectful consent process.

ARTICLE INFORMATION

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