Cellular therapy for childhood neurodegenerative disease. Part II: clinical trial design and implementation

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Cellular replacement therapy attempts to improve functioning of the diseased human central nervous system (CNS). In this second installment of a 2-part review, the authors discuss the major challenges to the translation of in vitro and animal studies of neural stem cell (NSC) therapy in the clinical setting. This analysis details the problems unique to the design of clinical trials using human NSCs, outlines patient selection practices, describes surgical techniques for cellular transplantation, and reviews the regulatory issues and ethical concerns in trials involving neurologically impaired children. (DOI: 10.3171/FOC/2008/24/3-4/E22)

KEY WORDS • cell replacement therapy • cell transplantation • central nervous system clinical trial • neural stem cell • neurodegenerative disease • restorative neurosurgery

NERVOUS system repair has become a serious therapeutic goal and the target of intensive basic and clinical research. Cellular repair of the human CNS poses significant scientific, translational, regulatory, and ethical challenges. The design and implementation of a current Phase I safety trial of human CNS stem cell transplantation for neuronal ceroid lipofuscinosis Types 1 and 2 has exemplified many of these issues and allowed insight into this developing field (A Phase I Study of the Safety and Preliminary Effectiveness of Human CNS Stem Cells [HuCNS-SC] in Patients With Neuronal Ceroid Lipofuscinosis Caused by Palmitoyl Protein Thioesterase 1 [PPT1] or Tripeptidyl Peptidase 1 [TPP-I] Deficiency, USA FDA BB IND No. 12174; http://clinicaltrials.gov/show/NCT00337636). This second of 2 parts will focus on the host environment and transplantation techniques, clinical trial design and implementation, regulatory issues, and ethics.

Host Environment: Effect of Patient Factors on Successful Transplantation

The Timing of Transplantation

Two factors lead to a tendency to enroll very severely affected patients in trials of cellular therapy for the CNS. First, patients who are in advanced disease stages (or their families) may be appropriately motivated to consider investigational interventions, even if the prospect for benefit is uncertain. Second, many investigators and institutional review boards consider it most ethical to enroll patients in innovative Phase I trials who may, due to advanced disease and lack of viable options, have a more acceptable risk/benefit profile than patients early in the disease course.8,10,16

However, multiple factors argue against enrollment of patients in the late stages of disease, particularly in the case of neurodegenerative and other neurological disorders that result in significant end-stage debility. First, patients in the late stages of disease are susceptible to anesthetic, medical, and surgical complications due to disease comorbidities, including pneumonia and other infections, aspiration, metabolic or drug side effects, exacerbation of disease-associated seizure disorders, and others. Second, in the event an experimental treatment successfully interrupts disease progression, the patients participating in the trial may have missed an opportunity to benefit at an earlier disease stage with greater preservation of function and quality of life. Third, many neurodegenerative disorders in the late stages are associated with significant, often irreversible, end-stage organ damage that might create an inhospitable environment for potential cellular repair. For example, NCL results in the progressive loss of cortical and cerebellar neurons in the late stages of disease, and earlier intervention might result in better neuronal rescue. Many neurodegenerative diseases are associated with significant inflammatory and gliotic changes that may pose an impediment to donor cell

Abbreviations used in this paper: CNS = central nervous system; CSF = cerebrospinal fluid; ESC = embryonic stem cell; FDA = Food and Drug Administration; GMP = good manufacturing practice; GTP = good tissue practice; IND = investigational new drug; MS = multiple sclerosis; NCL = neuronal ceroid lipofuscinosis; NSC = neural stem cell; PD = Parkinson disease.
engraftment and survival. In Phase I trials, a balance between these competing priorities must emerge from an interaction between investigators, regulatory bodies, and potential trial participants.

It is helpful for safety (Phase I) clinical trials and important for efficacy trials to enroll relatively homogeneous populations of affected patients. The chances of confirming or convincingly denying the presence of a beneficial treatment effect are advanced by studying patient populations with similar disease severity. In the case of focal episodic disorders such as CNS injuries from trauma or stroke, time between injury and enrollment, the exact injury location (for example cortical versus basal ganglia stroke), and injury mechanism (for example, ischemic versus hemorrhagic stroke) should be comparable.1,13,17 Ideally, patients should also suffer from similar comorbidities and have the same general health status. Although homogeneous populations are scientifically ideal for studying efficacy, they may fail to identify susceptibility to adverse effects or alternatively to detect benefit in particular patient subpopulations not represented in the initial studies.17 Thus, the presence of some variation in participants in Phase I trials may be appropriate.

Route of Administration, Delivery Method, and Anatomical Target

In general, the blood–brain barrier precludes the delivery of cellular therapy to the CNS via intravascular injection. Three direct routes of administration to the CNS are possible: intraparenchymal, intraventricular, and intrathecal. The chosen route of CNS administration must be influenced by the disease being treated, the nature of the cellular transplant material, and the biological goals intended for successfully engrafted cells.

In the most complex situation, cellular grafts are intended to differentiate into mature neurons, establish appropriate afferent control, and deliver specific neurotransmitters to a defined (and possibly distant) target. An example of such a strategy would be the implantation of prospective nigrostriatal dopaminergic neuronal precursors into the pars compacta of the substantia nigra in patients with PD. This strategy requires precise stereotactic injection of cellular material into a specific target and at least theoretically might be aided by stereotactic injection of growth factors or other helper molecules into a separate target nucleus. A slightly less ambitious approach, which has been used in the majority of clinical trials of cellular therapy for PD, is to inject dopaminergic precursor cells into the target area (the striatum) with the intention that these neurons provide neurotransmitters, neurotransmitter substrates, trophic factors, or a combination of these substances, to aid in the effective functioning (and/or protection of) residual intrinsic neuronal circuitry. This approach also requires directed stereotactic injection, with the added challenge of delivering cellular material to a much larger volume nuclear structure, with a complex 3D shape.

Treatment of victims of stroke, trauma, and spinal injury with cellular therapy also poses the need to deliver implanted cells to specific anatomical targets. This can be accomplished surgically or through the use of cellular transplants that express tropism for injured tissue. Such tropism could be based on the expression of soluble growth or repair factors by injured tissues, combined with intraventricular and/or intrathecal administration of cells with the potential to migrate to and engraft themselves within tissue expressing these factors. Such tropism could be an intrinsic property of a stem cell line, or be encouraged by the genetic engineering of cell lines.

Treatment of globally expressed, heritable neurodegenerative disorders, by contrast, requires delivery of therapeutic material to the entire CNS. The goal in these diseases is generally to provide cellular “factories” that will express the missing soluble enzymes or process waste material that cannot be handled by the constituent neurons and glia, thus preserving the survival and function of the intrinsic neuronal circuitry. In human patients, whose total CNS length and volume are large, the most obvious pathway to disseminate any substance throughout the CNS is via ventricular and subarachnoid CSF. However, little information is available concerning the ability of transplanted neuronal and glial precursors to engraft in the human CNS either near to or distant from the site of CSF injection; nor is there knowledge about the depth to which cells injected into the CSF can penetrate into the adjacent neural parenchyma.

The first attempt at neural repair therapy for NCL involved the use of viral vectors for delivery of normal copies of the defective gene.9 This strategy has a number of important limitations. First, every disease requires the creation, regulatory approval, and preclinical and clinical testing of a novel therapeutic engineered virus. For NCL, which is actually a constellation of diseases involving different genetic defects, a specific virus is required for each disease subtype. Second, viruses do not migrate through tissue (although they can spread via successive transfection of neighboring cells). Thus, the NCL viral therapy trial used a technically challenging strategy of injecting a virus at 12 injection sites with lengthy injection times at each site to promote intracerebral diffusion of the injected material.

Stem cells, by contrast, have the ability in certain preclinical models to spontaneously produce trophic or missing metabolic factors in injured or diseased tissue, an ability that in some cases might be enhanced by ex vivo genetic engineering or directed differentiation of the cells. Stem cells also appear to migrate within CNS tissue away from the site of intraparenchymal injection in animal models. Treatment of the entire CNS in humans using intraparenchymal injection, however, would require either extensive migratory ability or numerous surgical injections into the prodigious volume of the cerebral hemispheres as well as the cerebellum, brainstem, and length of the spinal cord. The current Phase I trial of human CNS stem cell transplantation for NCL uses a strategy of multiple hemispheric intracerebral injections combined with bilateral ventricular injections, all performed in a single transplant surgical procedure. One of the tenets of CNS regeneration is that a disproportional clinical response may result from a small level of repair. Thus, widespread engraftment, although ideal, may not be necessary to produce a clinical benefit.

In certain clinical circumstances, such as a recent traumatic injury, or an inflammatory or autoimmune process causing damage to the blood–brain barrier, there is at least the theoretical possibility of delivering effective cellular therapy to the CNS via peripheral intravenous injection.9,20 In general, the timing of such therapy relative to the time of
injury occurrence may offer only a narrow window of efficacy. Finally, recent work in animal models suggests that the surgical delivery of cells within semipermeable capsules may allow transplants with limited or no immunosuppression, transplantation of xenografts, or other novel strategies. Encapsulation may also protect against misdirected differentiation of transplanted stem cells due to transient inflammatory changes caused by the surgical implantation procedure.

**Cell Dose**

The appropriate dose of stem cells for implantation depends on a host of complex factors involving the transplanted cells, host environment, and the transplantation target and technique. The theoretical goal is the implantation of the largest number of viable therapeutic substrates (cells), so that the greatest local beneficial effect can be achieved and the largest number of cells be provided with the potential to migrate to surrounding tissue. However, more may not always be better. For example, the microenvironment created around a pocket of cells implanted into a small intraparenchymal cavity may affect cell viability and differentiation.

The gliotic changes within the CNS parenchyma and brain in some neurodegenerative disorders may also limit the volume of cell suspension that can be physically accepted within a single injection site, even with a slow rate of injection.

**Regrafting of Cells**

The potential for long-term viability of transplanted stem cells has not been assessed in human patients. This raises the question of whether effective cellular therapy for the CNS will require successive transplantation procedures over time, and the issue of potential immune challenges created by transplantation of a second allograft.

**Clinical Trial Design for Neurodegenerative Disease Trials Using CNS Cell Transplantation**

The design of clinical trials for rare diseases presents major scientific, organizational, and clinical challenges. Identifying appropriately sensitive and discriminating outcome measures for patients with neurodegenerative diseases is difficult. Clinical trials for rare neurodegenerative disorders face the challenges of limited patient numbers and disease prevalence. Traditionally designed efficacy studies of disorders with only a dozen living affected individuals will not have sufficient sample size or power to demonstrate a statistically significant effect on outcome of an intervention such as NSC transplantation. Even relatively common neurodegenerative disorders present trial recruitment challenges. Affected individuals are often disabled and may have difficulty traveling to the study site, understanding the informed consent process, and maintaining adequate general health required for safe participation in a trial.

In addition to the challenges of patient recruitment for clinical trials, the design and implementation of outcome measures in rare neurodegenerative disorders remains a major barrier to optimal trial design. Standard psychometric tests are not often suitable for many neurodegenerative disorders. For example, most psychometric tests of cognitive function are limited in their applicability to subjects with vision and/or motor impairment, which are common features of neurodegenerative disorders. Furthermore, most standardized psychometric tests perform poorly in evaluation of functional status. Disease rating and/or severity of disability scales have been developed and customized individually for a subset of disorders. Such scales have been developed to assess disease progression for various forms of NCL, but the variables measured and outcome scales are crude. These disease-specific scales may not be sensitive enough to detect small changes in clinical status. Indeed, a comprehensive clinical rating scale has been developed for juvenile NCL, including assessment of motor, behavioral, and functional capability with some evidence of reliability and relevance for clinical trials.

Nevertheless, many existing severity rating and disability scales are not ideally suited to clinical trials of CNS cellular transplantation. The clinical assessments typically required by such scales are intrinsically subjective and thus prone to bias by unblinded investigators. Crystal and colleagues, who have carried out clinical trials of gene transfer for infantile NCL, had to design their own unique outcome measure, expanding on an existing little-used measure. Their Weil Cornell Late Infantile NCL Scale was developed in response to inadequacies of the modified Hamburg Late Infantile NCL Scale. The expanded disability status scale is another example of a severity rating and disability scale commonly used to quantify neurological disability (originally disease progression in patients with MS). The expanded disability status scale, however, has limited utility in clinical trials of treatment interventions for MS.

Development of unique outcome measures for each rare neurodegenerative disorder is impractical, but more refined and sensitive common module scales of disease rating severity and disability that could be used across many different disorders (and age ranges) would be helpful. Different modules for example, could be developed for disorders with major motor impairment, while others would be best applied in disorders with visual impairment. Core modules, however, could probably be developed that would be applicable to a wide group of rare neurodegenerative disorders, with more specific modules (such as those for visual or motor impairment) utilized in the appropriate patient group.

It is unlikely that outcome measures for rare neurodegenerative disorders will be optimized soon. Surrogate markers of treatment efficacy therefore take on great importance in clinical trials for rare neurodegenerative disorders. Surrogate markers are indirect indicators of the efficacy of an intervention such as NSC transplantation, rather than direct clinical measures. Typically, these are physiological or biochemical parameters that are assumed to correlate with clinical outcome but are easier to measure and/or more objective. Occasionally, regulatory agencies approve therapies based on the response of surrogate markers. Plasma cholesterol level is an example of a widely accepted surrogate marker of atherosclerotic coronary artery disease. The slow and unpredictable progression of neurodegenerative disorders contributes to the difficulty in designing outcome measures and increases the appeal of surrogate markers. The most obvious surrogate measures for NSC transplantation are serum or CSF levels of relevant proteins or metabolites, or brain magnetic resonance imag-
Brain volume for example, might be expected to correlate inversely with atrophy, and atrophy, in turn, to correlate with actual disease progression. Proposed surrogate markers of neurodegeneration studied in MS\textsuperscript{15} and Alzheimer disease\textsuperscript{16} may also prove useful in other neurodegenerative diseases under consideration for clinical trials of NSC transplantation. It should be stated that the value of the surrogate marker only comes with validation to known clinical outcomes. Validated surrogate markers should be used whenever possible and developed for use in trials as necessary. Until surrogate markers are proven to correlate with clinical outcomes, they should be included along with clinical outcome measures.

Overall study design poses significant challenges to the study of rare neurodegenerative disorders. In fact traditional, randomized, controlled clinical trials of NSC transplantation may be difficult or impossible to perform, in part due to a small available patient sample size. The logical comparison groups for such trials are transplanted and non-transplanted cohorts. However, the supportive procedures necessary for accomplishing CNS transplantation (such as general anesthesia, skull trephination, infusion of carrier medium into the brain and/or ventricles, and concomitant medications such as steroid and immunosuppressive agents) could all independently affect outcome. The ideal scientific comparison would therefore be between a transplant group and one receiving all the same interventions (including general anesthesia, immunosuppression, and neurosurgery) but with infusion of a carrier medium devoid of stem cells. Such a study, particularly in minors, is unlikely to be approved by institutional review boards in North America or Europe. Institutional review requires the possibility of benefit for any minor patient (including those in the comparison group) experiencing more than a small increase over “minimal risk.” Because there is no possibility of benefit in the untransplanted group using an optimally controlled design, it is not viable in children. Although this design has been utilized in 2 cellular transplantation studies of patients with PD (which included anesthesia, skin incision, and trephination, but not dural opening or sham injection), it is rarely used even in adult participants.\textsuperscript{10,16}

Although a randomized and blinded trial design is always preferable and should be undertaken wherever possible, alternative clinical trial designs are needed for some diseases. One approach is to carefully document the natural history of the disease and compare it with the outcome in transplanted patients in an open-label clinical trial. This design has been successfully utilized recently in a study of a new intravenously administered enzyme replacement therapy for Pompe disease.\textsuperscript{12} Alternatively, a trial design comparing various doses of transplanted cells without a placebo group is a viable approach. Finally, the site or route of injection could be varied and the outcome compared between groups. Although it might be difficult to prove efficacy using these latter 2 trial designs, if a high-dose group or a multisite-injection group demonstrated improved outcome, this would provide strong support for treatment efficacy.

**Regulatory Review of Stem Cell–Based Therapy**

Stem cell–based therapies require the regulatory oversight of the FDA for investigational use in humans and ultimately in the licensing of the product. The regulatory process for cellular products is complex and continues to evolve. Cells that are minimally manipulated do not require an IND number for investigation or clinical use. Most, if not all, stem cell–based interventions fall outside this classification and are typically manipulated to substantial degrees. The regulatory process is detailed in the Code of Federal Regulations and the US FDA Center for Drug Evaluation and Research (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm; http://www.fda.gov/CDER). The basic framework for FDA review and regulation of stem cell therapies is explained below.

The regulatory scope of the FDA covers many aspects of stem cell therapeutics including preclinical studies, human investigations, cell production, licensing, and ultimately, marketing. Stem cells qualify for regulation under several regulatory definitions, the most applicable of which is the category of human cells, tissues, and cell- and tissue-based products. The governing statute for this product category is derived from the Public Health Safety Act, Sections 351 and 361. As with other biological products, the FDA has jurisdiction over stem cell–based therapy involving the transplantation of human cells into patients, and requires the review and approval of an IND application before any human trial may be initiated.

The primary IND review by the FDA relates to the safety and potential efficacy of the product. The approach is articulated in a recent health policy report published in the New England Journal of Medicine by a former FDA commissioner.\textsuperscript{11} The safety and efficacy components analyzed by the FDA include the following inquiries: “Does the product pose a risk of infectious or genetic disease transmission? Does the cell product risk contamination or damage to the host tissue? What are the final cell types, purity, and potency? Will the proposed cell product be safe and offer possible effectiveness when transplanted into the human patient?”

The FDA has established compliance requirements for GTP and current GMP to address some of these critical questions. Both the GTP and GMP standards are designed to prevent the transmission of communicable diseases and to assure a standard quality assurance of tissue procurement, processing, expansion, and banking. The compliance requirements for GTP in the setting of Phase I trials has recently been described in an interim final rule issued by the FDA in late 2006 (http://www.fda.gov/cder/guidance/6164dft.pdf). Stem cell–derived products are inherently complex, and these GTP and GMP standards have been developed to address the derivation, expansion, manipulation, banking, and characterization of the specific cell of interest.

The regulatory review process focuses on several biological characteristics of the final cell product. These characteristics include cell type, purity, and potency. Specific cell populations may be identified by a definitive and precise cell sorting method. The purity of the cell population is also critical for delivery into human patients. Understanding and documenting the percentage and type of potential contaminating cells that could affect safety is critical. Cell populations intended for human transplantation require extensive toxicology studies in animals to deter-
mine if any harmful effects result from either the intended cell, accompanying contaminating cells, or other components involved in stem cell production. Safety testing of human cells can be complicated by the nature of xenotransplantation and therefore requires a platform of either immunodeficient or immunosuppressed animal models. Establishing potency measures for a specific stem cell product also poses challenges for investigators. Certain clinical indications may have more direct potency assays available than others. For example, enzyme or trophic factor secretion can be assessed using in vitro assays, but assessing donor cell differentiation to a desired functional phenotype in vivo poses a greater challenge. Furthermore, in vitro potency measurements may not reflect in vivo function and the clinical outcome of cellular transplantation.

The regulatory review process also involves establishing the overall safety of the cell product and its potential for efficacy. Safety issues include biodistribution, tumorigenicity, and the potential for contamination or the production of undesirable cell types. This is particularly relevant to cellular interventions using embryo-derived cells. Establishing the purity of a cell population with regard to contaminating undifferentiated ESCs before human testing is critical. Regardless of the cell of origin, determining the potential for uncontrolled growth within the transplanted cell population is important.

Tumorigenicity and karyotype stability studies are required to specifically address the potential for neoplastic transformation of donor cell populations. This is particularly true given that stem cell therapies require significant cell passage and expansion to create a sufficient amount of cells for human transplantation. Finally, preclinical efficacy testing of the proposed cell-based therapy requires animal models that recapitulate the human disease under study. Species barriers can complicate cell engraftment and survival. Not all animal models of human disease can be easily backcrossed to an immunodeficient background that will permit xenotransplantation with human cells. Alternatively, immunosuppression of immunocompetent animals adds an additional variable and may impair the animals’ health. Despite these challenges, proof-of-concept experiments in animal models are likely to become more critical from the regulatory perspective before Phase I stem cell–based clinical trials are allowed to proceed.

The regulatory structure for cell-based therapy will continue to evolve and become more sophisticated as the biological characteristics of self-renewal, differentiation, and cell expansion are further elucidated. The effort necessary to prepare regulatory applications to support a potential stem cell trial should not be underestimated. Establishing the safety of stem cell–based interventions is as important as the potential for therapeutic benefit. Governmental agencies must balance regulating the novel aspects of stem cell–based therapies against a growing need to investigate the utility of stem cell interventions for serious and/or fatal human diseases.

Ethics

Human stem cell research and therapy have raised a host of significant bioethical issues that have captured the public and political stage. Foremost in the public debate is the issue of whether ESCs are an ethical source of tissue for organ—including CNS—repair. Detractors of research and therapy using ESCs cite the need to respect the potential human lives inherent in embryonic cells. Proponents of stem cell therapy often also cite the importance of preserving human life, but concentrate instead on the survival and quality of life of disease victims. Not surprisingly, leading public supporters of stem cell therapy include political and celebrity figures who suffer from, or whose family members suffer from, disorders for which stem cell transplantation is felt to be a promising potential therapy. Examples include actor Michael J. Fox, who suffers from PD; former first lady, Nancy Reagan, whose husband succumbed to complications of Alzheimer disease; and Dana Reeve, whose husband suffered a complete upper cervical spinal cord injury. Many ethicists have thus framed the debate in terms of the conflict between these competing and individually compelling human interests.

Ironically, the results of recent research suggest that ESCs may be a poor source of tissue for transplantation because of their potential for neoplastic transformation. Using adult or lineage-differentiated stem cells, however, does not necessarily avoid ethical challenges. For example, the NSCs used in the current study of NCL were derived originally from fetal CNS tissue.

During the preparation of this article, the attention of the world scientific community and media were captured by the work of investigators in Japan, Wisconsin, and Oregon who have derived cells with the capabilities of ESCs from adult, non–germ cell–lineage tissue. This work raises the distinct possibility of sidestepping the ethically challenging use of embryonic or fetal tissue for cellular repair. However, many other ethical issues still remain: genetic engineering of reconstituted stem cells, stem cell therapy for performance enhancement rather than health, and access to technologically demanding and expensive stem cell therapies, among others.

Although issues related to the origin of cells used for human therapy are of disproportionate interest to the public, cellular therapy also raises a host of other ethical issues, such as those related to patient participation in clinical trials. These issues are particularly difficult in trials involving the participation of vulnerable subjects who, due to CNS damage or other factors such as age, cannot directly participate in informed consent. The families and guardians of these patients, who must consent or refuse participation on behalf of the patient, are often desperate for any hope in the face of an inexorably fatal disease.

Researchers from the NCL trial of viral-mediated gene replacement therapy have reviewed the specific ethical challenges inherent in the enrollment of cognitively incapacitated children in highly experimental clinical trials. Of importance in any trial is a discussion of all the meaningful risks, including trephination, intracerebral injection, implantation of viral or cellular material, and long-term immunosuppressive therapy. Balanced against these risks are the potential benefits to society, advancing knowledge of disease treatment, and finally to that of the individual, who must accept the potential for personal benefit, even if the chance is considered small. Trials such as these that have high risk for ethical conflicts of interest and/or therapeutic misconception should therefore include measures to carefully protect the interests of trial participants. Such measures should include the use of close monitoring by an
independent safety panel, an extensive and carefully designed informed consent process for families that emphasizes safety and feasibility and deemphasizes the potential therapeutic benefit as trial goals, carefully defined and independently evaluated enrollment criteria, and separation of financial benefit (including research mission support) entirely from enrollment and clinical decisions by participating physicians and surgeons.2

Conclusions

Stem cell therapy for the human CNS is an extraordinarily complex undertaking in scientific, regulatory, and ethical terms. However, for certain serious diseases, stem cell therapy appears to offer the greatest current potential for effective treatment. Progress in this vital area requires the coordinated efforts of scientists, clinicians, surgeons, clinical trials professionals, industry leaders, regulatory bodies, ethical specialists, and public stakeholders.

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References


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