Stem Cells and Management of Healthcare Costs: Stem Cell-Based Treatments and the Societal Balance Sheet

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Abstract

Proposed stem cell based therapies have the potential to be highly costly. In an era of shrinking research budgets and ballooning healthcare costs, this article discusses the feasibility of stem cell based therapies for the following conditions in light of the concept of Quality Adjusted Life Years (QALYs): 1) hematologic malignancy, 2) osteoarthritis, 3) type I diabetes, 4) amyotrophic lateral sclerosis (ALS), and 5) spinal cord injury. These case studies illustrate the following major contributors to the potential cost effectiveness of a stem cell based therapy: 1) presence of existing treatments, 2) method of transplantation, 3) potential for improvements in quality and quantity of life, 4) need for immunosuppression, and 5) single administration versus repeat treatments. We propose that strategic investment in large sum translational grants should be for projects that have the potential for both efficacy AND feasibility – that is the potential for inclusion into standard medical practice and coverage by insurance carriers.

Keywords

Stem cells; Quality adjusted life years; Regenerative medicine; Transplantation

Introduction

The emerging field of regenerative medicine holds great promise for the replacement of tissues lost to injury or disease. Transplantation of both whole organs and isolated cell preparations (bone marrow, pancreatic β-islet cells) can improve both lifespan and quality of life. Despite high initial cost, several of these interventions are now cost-effective alternatives to management of the disease without transplantation. The number of organ transplant procedures, however, is severely limited by the number of available transplants [1]. Stem cells, which can form any cell type in the body and have great capacity for self-renewal, are a widely touted source for filling this gap. Initially, stem cell treatments may be considerably more expensive than standard treatments. However, like organ transplants, stem cells have the potential to reduce morbidity, reduce long-term treatment costs, and return affected individuals to a productive life. The question is: what is the balance between cost of treatment and long-term health care savings?

Amidst the flurry of development in this burgeoning field, we sought to analyze the complex interplay of factors that will contribute to the overall cost of a proposed stem cell therapy. For a therapy to reach patients, it must be both sufficiently effective and sufficiently cost-effective to ultimately justify inclusion into standard medical practice – i.e. treatments with a reasonable expectation of coverage by private and public health insurance carriers. The first four case studies are brief discussions selected to illustrate the breadth of problems targeted for stem cell therapies as well as some of the more important considerations for implementation of a therapy into clinical practice. The final case study concerning spinal cord injury is explored in greater detail as an example of the type of market analysis that is necessary prior to moving forward with a clinical program. This final topic was chosen for more detailed analysis for three reasons. First, because of the advocacy of Christopher Reeve in the early days of stem cell research, spinal cord injury was highlighted as a likely initial target for stem cell therapy. Second, spinal cord injury was one of the first indications for which stem cell transplant-based INDs were approved in the United States. Third, the authors have a particular interest in the topic of stem cells and spinal cord injury as the basic science for two of these first stem cell based clinical trials was conducted at our center. Additionally the authors’ range of professional experience includes both the basic science of spinal cord injury and the clinical management of spinal cord injured patients.

While the cases presented here are by no means an exhaustive list of targets, they were selected to illustrate the scope of problems under investigation for stem cell based interventions as the concept of tissue replacement has the potential to touch every aspect of medicine from the lifestyle threatening – the ”Quality Adjustment” to the life threatening – the ”Life Years Adjustment.” These examples help break therapeutic paradigms into three major categories from a policy perspective: 1) therapies are part of standard practice today and should thus be covered by all insurance carriers; 2) promising paradigms that should be supported by clinical research dollars, and 3) paradigms with major theoretical bottlenecks that preclude serious development for clinical purposes at this time. For a therapy to reach the bedside it must be both clinically and economically viable, rendering such analyses critical to ensuring that limited funds maximize the overall health of the society.

Weighing quality of life, life expectancy, and cost of treatments – The QALY

In an attempt to equitably distribute limited healthcare resources, countries with nationalized healthcare have developed a formula in which the total cost of a treatment is weighted by life expectancy and the predicted quality of those years [2]. One of these measures is the Quality Adjusted Life Year or QALYs, which is calculated as follows:

\[ \text{QALY} = (\text{Quality Adjustment} \times \text{Life Years}) \]

Quality Adjustment = Quality of life of patient with treatment, with 0 being death and 1 being perfect health.

Life Years = Life expectancy of a patient with this intervention.

A value 1 QALY thus represents 1 year of life in perfect health. Quantitative assessments of the quality of life are rough...
estimates at best and some have argued that certain states, such as being maintained on life support, are worse than death and more appropriately assigned a QA below 0. A major critique of the QALY-ratings system is that the scale is merely qualitative [3,4]. While the increase in life years can be roughly estimated from clinical studies, the determination of the quality adjustment portion of the equation remains highly subjective. Despite this imprecise measure, several countries with nationalized healthcare make direct comparisons of QALYs to determine whether a more expensive treatment provides a sufficient improvement in quality or quantity of life to justify coverage. While estimates of the acceptable QALY threshold in Great Britain range from $20,000-$30,000 per QALY gained, the threshold in the US was historically $50,000 per QALY with modern estimates closer to $100,000 per QALY [5].

QALY analysis favors highly expensive interventions for pediatric and young adult populations, who may lead productive lives for decades after an intervention, over costly end of life interventions. If a person has a long expected lifespan, a new highly expensive treatment that provides an improvement in quality of life over decades is more likely to meet a QALY cutoff. Regenerative medicine is unique in that many of its therapeutic targets are diseases that affect quality of life rather than causing death. As a result, very expensive treatments may actually be cost-effective in the long run, even without adjustments for quality of life.

Path to marketing approval: FDA regulation of tissue and tissue products for transplantation

The United States FDA Center for Biologics Evaluation and Research (CEBR) regulates transplant of avascular human tissues and cells, including bone marrow and stem cell transplantation in accordance with the Code of Federal Regulations Title 21 (21 CFR) Parts 1270 and 1271. Parts 1270/1271 regulates minimally manipulated tissues such as autologous or related-donor bone marrow transplants and establishes requirements to screen donors for transmissible pathogens prior to transplant. Allogenic unrelated bone marrow transplants, cord blood cells, cultured cells, and stem cell derived products are not considered minimally manipulated and are regulated as biologic products or as drugs according to Section 351 of the Public Health Service Act. Unlike minimally manipulated products, biologic products require an investigational new drug application (IND), extensive clinical trials, and issuance of a biologics license by the FDA prior to marketing. Licensure entails certification of the safety, purity, and potency of both a product and its manufacturing process in addition to clinical evidence supporting efficacy. Products classified as more than minimally manipulated, including that vast majority of anticipated stem cell products, are appropriately subjected to rigorous testing and manufacturing regulations that greatly increase production costs and thus the cost of treatment.

Search strategy

PubMed was queried for articles containing "cost" and appropriate disease specific keywords (Table 1). Citations were limited to articles published between January 2005 and December 2014.

<table>
<thead>
<tr>
<th>PubMed Keywords</th>
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<td>cost AND stem cell transplantation (10 years)</td>
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<tr>
<td>cost AND chondrocyte</td>
<td>84</td>
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<tr>
<td>cost AND islet cells</td>
<td>111</td>
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<td>cost AND ALS AND stem cell</td>
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**Table 1: Keyword Searches.**

Case Study 1: Hematopoietic Stem Cell Transplantation (HCT) as an Example of an Established Stem Cell Therapy

Though bone marrow transplants in the 1950s were characterized by dramatic failures, today bone marrow transplantation, otherwise known as hematopoietic stem cell transplantation, is the only stem cell therapy that has gained widespread acceptance or FDA approval [6]. While a recent search performed in October 2014 of clinicaltrials.gov yielded 4553 studies with the search term "stem cells" as of yet there is only one commercial stem cell product approved by the FDA. According to the consumer updates page of the FDA (www.fda.gov) at the time this manuscript was prepared, the only stem cell product currently approved by the FDA is the Hemacord cord blood cells approved for the treatment of leukemia, lymphoma, and sickle cell anemia and Wiskott-Aldrich syndrome.

Initially developed for the treatment of blood cancers, the applications of HCT have been expanded from blood cancers to include genetic blood diseases and severe autoimmune diseases. In general, the process involves delivery of high dose chemotherapy and or radiation to a patient to eradicate the current blood producing pool followed by reconstitution of the bone marrow via introduction of bone marrow or cord blood derived cells via intravenous infusion (Figure 1). At present, most HSC transplantation protocols involve mobilization of progenitor pools via chemical induction protocols that permit collection from peripheral blood rather than from bone marrow taps. Infused cells may be related-donor allogenic, matched allogenic, or varying combinations of mismatched donor cells [7].

While the original procedure was associated with a high mortality rate, retrospective analyses of the development of HCT indicate continuous innovation with steady improvements in safety, efficacy, and cost-effectiveness [8]. As a widely established procedure the practice of HCT has been extensively studied from a cost perspective, particularly in countries with nationalized healthcare systems where QALYs are used as a measure to determine coverage for an intervention. PubMed search for papers with the keyword "cost AND stem cell transplantation" in the 10 year period from January 2005 – December 2014 yielded 879 references. Review of abstracts and titles yielded 112 references directly addressing the costs of therapy and one study addressing out of pocket costs to patients and caregivers. Though an in depth review of the literature concerning cost-effectiveness in HSC transplantation is beyond the scope of this discussion, many of the themes are likely to affect the implementation of newer stem cell therapies. In particular, studies have examined the cost effectiveness of various regimens for prevention of fungal infections,
the cost of mobilization of progenitor pools from the marrow, and the cost-effectiveness of using HSC for the treatment of a number of indications, including anemias and multiple myeloma. Primary drivers of costs included hospital days, immunostimulant regimens for mobilization of stem cells, antifungal therapies, and readmission due to infections. According to the tri-annual Milliman report, which analyzes data published by the various organ donation registries, the 2011 cost of an autologous hematopoietic stem cell transplantation was estimated at $363,800 versus the cost of an allogenic transplant that was estimated to be $805,400 [9]. While autologous transplants incur costs related to stem cell mobilization protocols, these costs are dwarfed by the costs of immunosuppression, increased hospital days, graft versus host disease, and costs related to both prophylaxis and treatment of opportunistic infections incurred by patients receiving transplants from donors. A review of historical data, however, revealed that by 1998, the cost of allogenic HCT had reached the acceptable threshold of ~$50,000 (1996 dollars) per QALY gained, a trend which is likely to continue [10]. Thus, research focusing on bottlenecks can transform imperfect treatments into viable therapies for previously untreatable diseases.

Case Study 2: Chondrocyte Transplantation for Osteoarthritis as an Example of a Disease that is Prevalent but Not Life-Threatening

Osteoarthritis affects >20% of the adult population and is associated with a 1.5 – 2.6-fold increase in the overall cost of medical care due to loss of productivity and exacerbation of chronic diseases. Joint replacements are a cost-effective approach for end-stage arthritis despite implants that cost tens of thousands of dollars [11].

To date, autologous transplantation of chondrocytes has been achieved by harvesting non-weight bearing cartilage, expanding cells in culture, and transplanting them into weight bearing defects. A PubMed search with the keyword "cost AND chondrocyte " yielded 84 studies published between January 2005 and December 2014. As arthritis is caused by loss of a single cell type, the chondrocyte, the disease is an obvious candidate for treatment with stem cells. Transplantation of chondrocytes from stem cell sources has not yet been reported, so cost data are only available comparing autologous cell transplantation to other techniques such as microfracture [12]. QALY calculations project that the new autologous transplant...
techniques (Figure 2) would be cost effective with a 10-20% improvement in quality of life [13].

Newer techniques to generate chondrocytes via differentiation of stem cells or directly from fibroblasts may obviate the need for an extra surgery to harvest cells for expansion [14]. Although disease incurred by arthritis is not sufficiently severe to justify the risks of immunosuppression, development of approaches to induce tolerance might reduce costs by permitting the use of high throughput methods to mass-produce chondrocytes from established cell lines eliminating the need isolate and expand each patient’s cells [15].

Case Study 3: β-islet Cell Transplantation for Type I Diabetes as an Example of an Intervention for a Disease with Existing Treatments

Type I diabetes is caused by autoimmune destruction of the insulin producing β-islet cell of the pancreas. Treatment with insulin is effective but requires time-consuming self-management of blood sugar. Stricter control of blood sugar with either pancreas transplantation or more frequent monitoring may delay or prevent complications such as vision loss, peripheral neuropathy and amputation [16,17].

A PubMed search for “cost AND islet cells” published from January 2005–December 2014 yielded 193 results, however, data are derived from transplants with allogeneic or porcine sources as the first IND for transplants with islet cells was approved in August 2014. Successful β-islet cell transplantation via the portal vein was first reported in 2000, however, only 20% of transplant recipients are insulin independent compared with 65% of pancreas transplant patients (Figure 3) [17,18]. A recent health economics analysis indicates that compared to no treatment, traditional insulin therapy costs approximately $71,000 per QALY while islet cell transplantation costs $47,800 per QALY over 20 years [19,20]. Despite the apparent cost effectiveness of islet cell transplantation and the limited interval over which the cells function, the widespread use of the treatment is hindered by the supply of donor pancreata. The median time on the waitlist for pancreas transplantation ranged from 260 days to 436 days in recent years [9]. In part due to scarcity of donor tissue, candidates for islet transplantation are those who exhibit “hypoglycemia unawareness” and are a risk of death due to inability to recognize signs of hypoglycemia. At $120,000–$150,000, islet cell transplants are far more expensive than a $40,000 pancreas transplant and typically fail within a few years likely due to the same immune mediated mechanisms that destroyed the patient’s original islet cell population [17]. Steady improvements in immunosuppressive regimens and islet cell isolation techniques have been slowly improving the graft survival rates as well as the 5 year success rate for achieving insulin independence [21]. Advances required to make this approach a reality on a broader scale include high throughput production of β-islet cells from stem cells and development of improved immunosuppression protocols or encapsulation techniques.

Over the past 2 years, great strides have been made on the stem cell front, including high throughput generation of human β-islet cells from iPSCs and ViaCyte’s recently approved IND for the transplantation of encapsulated embryonic stem cell derived β-islet cells into patients with type 1 diabetes [22,23].

Case Study 4: Amyotrophic Lateral Sclerosis (ALS) as an Example of a Fatal Orphan Disease with no Treatment

ALS is a rare disorder of motor neuron loss that results in progressive weakness, paralysis, and death [24]. With a prevalence of 2–4 per 100,000 in North American and Europe, ALS is considered an orphan disease with special status for funding of both more expensive treatments and disease-specific research [25–27]. A PubMed search for “cost AND ALS” during the period from January 2005–December 2014 yielded 189 results, however, as there are no FDA approved stem cell therapies for ALS a search for “cost AND ALS AND stem cells” yielded 2 results. In theory, replacement of lost motor neurons with stem cell derived motor neurons might improve quality of life, productivity, and reduce or postpone caregiving needs. While it is difficult to imagine cell transplant procedures that would allow replacement of upper and lower motor neurons (Figure 4), the results of a recent Phase 1 clinical trial of neural stem cells in the lumbar spinal cord showed unexpected benefits in one patient despite dosing for safety rather than therapeutic effects [28,29]. A follow-up Phase
A trial involving transplantation into the cervical spinal cord also did not show harm and yielded results suggestive of a slowed rate of decline [30]. Justification of the cost to extend the life of ALS patients, however, should be carefully weighed against measures of the quality of life gained, as there is a risk of prolonging a state of existence that some would consider unacceptable.

Detailed Case Study: Spinal cord injury (SCI) as an Example of a Disease with Significant Morbidity but Near-Normal Lifespan.

**Therapeutic target**

As impairments associated with spinal cord injury are caused by loss of cell types with limited regeneration potential, spinal cord injury has been routinely cited as a promising target of stem cell-based therapy. Injured tissue includes neuron cell bodies and glia at the injury site in addition to descending and ascending axon tracts. Potential sources for stem cell transplantation into the central nervous system include embryonic or induced pluripotent stem cell derived products, fetal neural stem cell products, and newer potential sources such as directly reprogrammed neurons or neural stem cells (Figure 5) [31-36].

Three stem cell-based clinical trials for SCI have been initiated in recent years. The Geron SCI trial, which transplanted five of eight planned patients before its suspension due to business considerations, aimed to transplant embryonic stem cell-derived oligodendrocytes into patients with new (<14 days) injuries in hopes of remyelinating axons that had lost their myelin sheaths, and thus enhancing action potential transmission. The company Asterias obtained the stem cell IP from Geron and in 2014, launched a follow-up trial that uses the stem cell product developed by Geron. The Stem Cells, Inc. trial, which has transplanted nine patients to date, is investigating the use of fetal derived neural stem cells into patients with "chronic"...
spinal cord injuries, with chronic being defined as >6 weeks from the date of injury. The Stem Cells Inc. trial began in Switzerland, and is now approved for enrollment in Canada, and the United States. A third trial has been launched by Neuralstem, which also involves transplantation of a product of fetal-derived neural stem cells.

**Epidemiology**

Nearly 1.3 million Americans are affected by spinal cord injury and an estimated 12,000 civilian Americans sustain spinal cord injuries annually [37-39]. Estimates of the incidence vary widely across the globe with an estimated incidence of 40 per million in North America, 16 per million in Western Europe, and 15 per million in Australia. Estimates of prevalence vary widely with the US having an estimated 721-4187 spinal cord injured people per million, Western Europe reporting an estimated 316 per million in Western Europe, and Australasia reporting 681 per million [40]. At least half of all spinal cord injuries are at the cervical level of the spinal cord. While the average age of newly diagnosed spinal cord injured people is 37.6, the distribution is bimodal with younger individuals sustaining injuries through accidents and older individuals sustaining SCIs through falls [38]. Spinal cord injured individuals live a near normal lifespan, incurring decades of healthcare costs.

**Current medical and surgical management**

Treatment for spinal cord injury is mainly supportive [41]. Spinal cord injury is more accurately described as a condition that is managed rather than treated – a distinction that may be critical when seeking to incorporate a new therapy into practice. Though administration of corticosteroids to prevent secondary degeneration was previously advocated, secondary analysis of data suggests that treatment is at best modestly effective [42,43]. More recently, the sodium channel blocker Riluzole and Rho inactivating agent Cethrin have shown potential benefits in Phase I and Phase I/IIa trials, respectively [44,45]. Early surgical intervention is emerging as a critical player in outcome, but likely reduces secondary injury rather than treating the primary neurological injury [46,47]. Most treatments in the clinical pipeline target either acute (< 48-72 hours post-injury) or sub-acute (< 2-3 weeks) injuries [42,43,48,49]. An exception is the experimental use of epidural stimulation for people with chronic injuries, which has been reported to enable some voluntary movement in people previously diagnosed as motor complete [50].

**Functional outcome and long term quality of life with current management**

The long term functional outcome for spinal cord injured individuals varies greatly with the level and severity of injury. Individuals with thoracic or lumbar level injuries lose voluntary control of the lower limbs, bowel, and bladder and may develop permanent life-threatening autonomic instability known as autonomic dysreflexia. Individuals with thoracic or lumbar level injuries generally retain the capacity for independent living, self-care, and the potential for full employment.

High cervical injuries may result in permanent respirator dependence, whereas individuals with lower cervical injuries may retain partial hand function. While a respirator-dependent individual may require 24-hour nursing care, an individual with a lower cervical injury may be able to live independently or with part-time home care. Of special importance for independent living is function of the triceps muscle, which permits un-aided transfer for activities of daily living. Long-term complications include pressure ulcers, pneumonia, pathological fractures from disuse osteopenia, and Charcot neuroarthropathies.

A broad set of literature has been published about Quality of Life (QoL) after spinal cord injury with reported satisfaction scores ranging from 10-70% lower for spinal cord injured individuals versus uninjured individuals [51]. Physical limitations and a lack of gainful employment are particularly significant contributors [52,53]. At 10 years post-injury, fewer than 35% of individuals with SCI are gainfully employed [54]. These individuals frequently live for decades after their injuries. As a result, even a highly expensive intervention that leads to a small improvement in quality of life, the “Quality Adjustment,” is likely to be cost effective because the cost would be spread across several decades with an improved quality of life.

**Cost Bottlenecks in SCI**

The cost of medical management for SCI is staggering with a total annual burden approaching $10 billion in the United States alone. Global estimates are hindered by a paucity of data on the prevalence of SCI in developing nations. Indeed, in developing nations, a spinal cord injury is often a death sentence due to the lack of management of secondary complications, especially bladder dysfunction. Anyone with a spinal cord injury requires daily care of some sort for decades. To date, there are no accepted therapies for spinal cord injury, stem cell or otherwise, however, limited data are available for the costs to manage spinal cord injuries of different severities. While a PubMed search for “cost AND spinal cord injury” during the period from January 2005–December 2014 yielded 939 results, a search for “cost AND spinal cord injury AND stem cell” yielded 31 results, 10/31 results were editorial pieces about the Gerion trial. If we were to hypothesize that a stem cell therapy which permitted a patient with a high cervical injury to become ventilator independent represented a quality of life (QoL) improvement of 10% over 10 years or 0.1 QoL * 10 years = 1 QALY, then we would be left with a rather insignificant budget of 1 QALY which ranges from $30K to $100K depending on the country. A crude cost projection based on published data from the National Spinal Cord Injury Statistical Center database (Figure 6) suggests that the cost of care for an individual with a high cervical injury would exceed that of a lower cervical injury by nearly 1 million dollars at 10 years post-injury and more than 1.5 million dollars at 20 years post-injury [55]. Thus, even without QALY adjustment, the break-even point for therapeutic interventions that could convert upper cervical injuries into lower cervical injuries would approach

[Figure 6: Project Accrual of Medical Costs for SCI Individuals by Level and Severity of Injury. Projections based on 2012 National Spinal Cord Injury Statistical Center Report https://www.nscisc.uab.edu]
1 million dollars, comfortably exceeding the generally accepted maximum QALY of $50,000 per life year gained.

Limits to commercialization for stem cell-based therapies

The commercialization of a stem cell-based therapy is an extraordinarily costly process. First, the product must be produced according to Good Manufacturing Practices (GMP) and shown to have efficacy in a reasonable animal model. Briefly, GMP guidelines include strict adherence to Standard Operating Procedures (SOPs) during manufacturing, careful lot tracking, and extensive quality control (QC) measures. The cost of development was likely amplified for the first few stem cell-based therapies approved for Phase I trials as FDA guidelines had yet to be established for cells that undergo more than minimal manipulation prior to transplant. The field may be further strengthened by the preliminary demonstration of safety in a Phase I trial involving the transplantation of neural stem cells into the CNS [28]. Final cost will depend on a number of variables including whether or not there is a requirement for stringent safety tests of each batch of cells. Requirements for batch control could make stem cell products both impractical from the timing standpoint (if cells have to be delivered at short post-injury intervals), and prohibitively expensive.

Tremendous and prolonged development costs made the Geron SCI trial a liability to its investors, leading to the suspension of a trial regarded as promising from a scientific standpoint. It remains to be seen how Asterias will weather the economic seas during the new trial of the Geron product. On the other hand, StemCells, Inc. is developing their fetal neural stem cell product as a platform technology for the treatment of multiple neurologic diseases. Successful completion of a Phase I safety trial in Batten’s disease provided critical safety data to reduce development costs for other interventions, including chronic SCI. Development of therapies for SCI, is hindered not by the absence of a societal need for such treatments, but by the limits to commercialization of such a therapy. SCI represents a relatively small target patient population, which reduces the likelihood that a publicly traded entity will recoup the costs required to bring a treatment to market.

Limitations to commercialization vs. limits to widespread implementation

It is critical to distinguish between limits to commercialization and limits to implementation. Limits to commercialization include the cost of development, manufacturing, and clinical trials, which must be fronted by a company prior to recouping of costs via sale of a product. Limitations to implementation are encountered in the setting of care delivery. These include the case with which a new therapy fits into the existing medical treatment paradigm and the willingness of insurers to cover the cost of therapy. The required specialization of the health care providers, i.e. technical proficiency of the surgeon, and delivery setting, i.e. community versus tertiary care center, also impact implementation.

Cost analysis of acute vs. chronic stem cell transplantation

Though surgical stabilization is a critical component of acute SCI care, a search of the National Trauma Database, maintained by the American College of Surgeons (www.facs.org/trauma/ntdb/index.html) revealed that only 66% of the 5562 acute adult isolated SCI admissions recorded in between 2008-2011 were treated surgically [2]. After controlling for patient demographics, injury characteristics, and hospital factors, the likelihood of receiving surgical intervention was significantly influenced by insurance status with 68.3% of insured patients vs. 57.6% of uninsured patients treated surgically (OR 1.46, 95% CI 1.23-1.72, p=0.001). These data indicate that financial considerations likely play a role in modern medical decision-making Table 2 [56].

Unlike ALS, transplantation of stem cells for the treatment of spinal cord injury is likely to involve transplantation into a localized surgical site. As management of acute spinal cord injury frequently includes surgery, the added risk of transplanting cells during the initial surgery is arguably smaller than for an intervention requiring an additional surgery, such as transplantation at a chronic time point. In the former case, many of the costs and risks inherent in spinal surgery are already accounted for due to the need to decompress the spinal cord and obtain spinal column stability. In the latter case, the cost and risks of an additional, invasive procedure are also incurred. Additionally, transplantation at acute time points is likely to be a revision of procedures performed in the acute setting, which is a more technically challenging surgery.

At our own tertiary care facility, the average cost of each additional hour of operating room time is ~$1500 while the average hospital cost of a separate laminectomy is >$14,000 (~$6000 operating room costs). Thus, the cost of adding an additional step to a planned operation (i.e. surgery for acute SCI) is nearly 1/10 the cost of adding a new procedure to the standard of care (i.e. surgical intervention to treat chronic SCI). Note that these costs are relatively inexpensive in comparison to lifetime costs associated with managing SCI.

Cost analysis of immunosuppression needs in acute vs. chronic transplants

Functional recovery after SCI plateaus after the first several months. A therapy targeting the acute phase of a spinal cord injury must be ready for near off-the-shelf administration to allow intervention in the early weeks after injury when the spinal cord presumably has greater plasticity. With current technology, an off-the-shelf cell-based therapy would have to be allogenic and may require immune suppression at least until the re-establishment of the blood brain barrier, if not for life. In the case of Geron’s human embryonic stem cell derived oligodendrocytes, the product was only weakly immunogenic on T cell proliferation assays, so a six month immunosuppression protocol was implemented in their Phase I trial [57].

The limited existing clinical data for transplant of neural stem cells indicates that there may be significant difficulty with adherence to immunosuppression protocols. In one report, only 7/12 patients tolerated the immunosuppression protocol. Thus far, surrogate markers of immune response do not indicate a development of an immune response to transplants [28].

The chronically injured spinal cord has reduced plasticity, due in part to the development of an extensive scar at the site of injury. Thus, people with chronic SCI whose recoveries have plateaued may be able to wait for autograft-based approaches, which would not require immunosuppression. One promising avenue is the use of induced pluripotent stem (iPS) cells, which can be generated by “reprogramming” fibroblasts from a skin biopsy from the patient via genetic modifications involving transfection with transcription factors to generate cells similar to embryonic stem cells [58]. Similar approaches are under development for direct reprogramming into the cell type of interest [34-36]. There is hope that this rapidly evolving technology may be adapted to produce patient-specific stem cells, however, current production methods require months rather than weeks, and iPS cells derived through genetic modifications may
require additional tests of safety. In this regard, recent reports of the generation of iPS cells using simple chemical/physical manipulations generated huge excitement, but unfortunately, the veracity of this report has been brought into question by the author’s institution reports of scientific misconduct [59-61]. An unresolved question is whether each “batch” of iPS-derived cells would have to undergo safety testing prior to transplantation. If so, this could require months of testing, adding greatly to the cost of iPS-based therapy.

The blood brain barrier is acutely disrupted post-SCI, but is re-established by a few weeks post-injury. Nevertheless, it is not clear whether a chronic injury will retain the immunologic privilege attributed to the native CNS and may depend on into the injury site or the intact parenchyma. Transplantation into a chronic injury will open the blood brain barrier, so it is assumed that immune suppression will be required for at least some time after transplantation. In a subset of patients transplanted with fetal dopaminergic cells, functional decline was noted following withdrawal of immunosuppression [62]. Postmortem analysis of the transplanted patients revealed signs of microglial activation at short intervals (4 years) after transplant, however, similar numbers of cells were observed at longer time points (11-16 years) without long term immunosuppression [62,63]. It is not yet known whether these findings will extend to cells transplanted into patients with acute spinal cord injury, which is a far more inflammatory environment than in Parkinson’s disease. Transplantation of a small number of foreign cells into non-CNS locations, as with β-islet cell transplants, has been associated with a more robust rejection response than transplant of whole organs as in pancreas transplants [17]. It has been proposed that the increased size of the whole organ transplant induces tolerance to the foreign antigens. Whether this observation will extend to the transplant of a small number of stem cells into the CNS remains to be seen.

Most published data involving transplants of human cells is from xenograft models, which provide limited insight into the need for immunosuppression in humans. Due to the cost of immunosuppression, the necessity for and duration of therapy may be a critical determinant of the cost-benefit ratio of any stem cell therapy.

The Framework: Critical Components in the Construction of a Viable Stem Cell Therapy

Analysis of the above case studies highlights the following major contributors to the cost effectiveness of a stem cell based therapy:

Existing treatments

The adoption of a new therapy that is more expensive than current therapies would require demonstration of a sufficiently improved outcome. Some treatments may initially have a higher cost but result in substantial improvements in QALYs, decreases in lifetime medical costs, and/or transform the individual into a productive member of the workforce.

Method of transplantation

Methods exist for single site transplantation of chondrocytes, β-islet cells, and bone marrow cells, albeit with variations in cost and risk to the patient. On the other hand, treatment of ALS is likely to require injections into multiple sites in the brain and spinal cord using recently pioneered instrumentation [29]. Costs for and risks of surgical procedures will depend on whether the procedure is part of a currently indicated procedure or an additional operation.

Potential for improvements in Quality and Quantity of Life

Adoption of a more expensive treatment can be justified if it results in either a prolonged life of the same quality (i.e. higher “Quality Adjustment”) or an equivalent lifespan with a higher quality of life (i.e. greater “Life Years”).

Need for immunosuppression

Pending the development of methods to induce tolerance, the $5,000-$13,000 cost of life-long immunosuppression per year must be factored into cost analyses as immunosuppression is associated with significantly increased costs including those related to immunosuppressive drugs, infection prophylaxis, related lymphoproliferative disorders, and admissions for life-threatening opportunistic infections. Additionally, immunosuppression has been shown to play a major role in the success of a transplant and inclusion of lifelong immunosuppression coverage in Medicare benefits has been associated with an increase in the lifespan of kidney grafts [64]. An estimate of the difference in cost between an autologous bone marrow transplant that does not require immunosuppression and an allogenic bone marrow transplant that requires immunosuppression indicates outpatient medication costs in the first 6 months after transplantation to be $23,300 and $7,100 respectively. Overall, the cost of an autograft is estimated to be $363,800 versus the cost of an allograft which is estimated to be $805,400 [9]. Currently, $400,000 is a common cutoff for lifetime medical expenses covered by insurance plans, so the difference between the two can have significant implications for both societal and individual medical costs.

Single administration or repeat treatments

β-islet cell transplants are typically rejected within several years and must be repeated every couple of years at a cost of $120,000 per transplant. Similar effects were seen with transplants of fetal dopaminergic cells into Parkinson’s patients [65]. Repeated administrations will be required if transplants succumb to the underlying disease with multiplicative effects on the costs of therapies. The recent approval of the IND for ViaCyte’s encapsulated β-islet cell technology is an example of a focusing technology at a bottleneck; in this case the intention is that encapsulating the β-islet cell population will protect the transplant from immune destruction and prevent the need for repeat administrations seen with infusion of islets through hepatic vasculature.

Marketing Approval and Costs for the End User

Unlike many countries with nationalized healthcare where the cost of a therapy plays a role in the decision to provide coverage, in the United States the decision to cover a treatment is based on safety and efficacy alone. In general, once a product receives FDA approval, applications are issued for coverage by major insurers such as Medicare and private insurers [66]. Currently, expensive therapies that meet the criteria of “necessary and reasonable” are covered, and the American Recovery and Reinvestment Act of 2009 is the first national attempt at conducting comparative effectiveness research.

Published data estimating costs of transplantation to the end user (patient) come from surveys of out-of-pocket costs for hematopoietic stem cell transplant patients and caregivers; estimates range from $199-$13,769. Of the patients surveyed, the 48% who had to relocate to the transplant center incurred higher out of pocket costs (median $5247 vs. $716) than those who did not require relocation [67].
In an effort to control costs, insurers implement cost saving measures such as prior authorization, annual deductibles, copays, annual caps, and lifetime caps. Historically, after an annual deductible was met, a patient would pay a fixed portion of the costs of treatment, typically 10-20% up to an annual or lifetime deductible after which the patient is responsible for all costs. If stem cell transplantation therapies are sufficiently efficacious to be classified as an “essential benefit” under the provisions of the Affordable Care Act (ACA), the treatments may become exempt from annual and lifetime maximums. Prior to the ACA, patients receiving therapies would be responsible for any costs beyond annual and lifetime maximums, whereas under the ACA, out of pocket costs for “essential benefits” would limit annual expenditures. While society or insurers would bear the full cost of a therapy, an insured patient’s out of pocket costs would be limited to an annual maximum. For 2015, the maximum out of pocket costs are limited to $6000 per individual plan and $13,000 per family plan [68].

Under the ACA, Bronze, Silver, Gold and Platinum plans must cover 60%, 70%, 80%, and 90% of total healthcare costs for any of the ten “essential benefits” until the maximum out of pocket cost for the year is reached [68]. Costs in excess of the maximum out of pocket costs are borne by the insurer. Should cell transplantation therapies be sufficiently efficacious to be included as one of the “essential benefits,” most likely under the category of “hospitalization” with transplantation of solid organs, then patients receiving treatment would only be expected to cover costs up to the annual maximum for the year. Given that the median household income was $51,939 in 2013, the most recent date for which data are available, the costs would still represent a significant burden to the patient [69]. Under pre-ACA rules, however, many stem cell treatments would be likely to exceed annual and possibly even lifetime maximums. As seen in Table 3, which projects the costs of several stem cell therapies according to the four “metal” categories of ACA compliant health care plans, should stem cell therapies be excluded from the list of “essential benefits” under the ACA, severely ill patients would be left with medical bills in excess of the median household income.

**Discussion**

Stem cell transplantation for blood dyscrasias is a time-tested reality, and data are available for extension of lifespan, quality of life, cost-effectiveness, and even end user costs. These data span decades and provide insight into the evolution of a therapy from a cost perspective as cost data is available for multiple generations of the interventions as well as for out of pocket costs to the patients and their families.

Similarly, data concerning the costs and efficacies of cell transplantation for the treatment of osteoarthritis (autograft) and diabetes (allograft) are becoming available though comparison of costs are limited by small samples sizes, regional cost variability, and variability in methods used to estimate costs. Regardless, for these two conditions the primary unknown from a cost perspective will be the cost of manufacturing stem cell products to substitute for the existing tissue-derived products.

Transplantation into the central nervous system is a new horizon, however, and will require extensive clinical validation before costs of treatment can be reasonably assessed. A simple analysis of health costs, such as provided in this manuscript for spinal cord injuries of varying severity, may be used to provide a rough estimate of the costs to care for patients with CNS injuries. While these analyses may not provide an estimate of the cost of a stem cell therapy, they may be used to estimate the costs. As described above, the cost of treating a high cervical injury (ventilator dependent) is approximately $1 million greater than the cost of treating a lower cervical injury over 10 years. It is difficult to estimate the actual cost of treatment from the current literature, but a therapy that transitioned a patient from ventilator dependent to ventilator independent would provide savings over current medical therapy if it cost less than $1 million.

**Conclusion**

While stem cell based therapies hold tremendous promise for improving both the quality and the quantity of human life, the suspension of the Geron trial for financial reasons is a sobering reminder that for a treatment to be medically viable, it must be both scientifically and economically viable. It may be in the best interest of society to underwrite the development of therapies that have poor commercial viability but have relatively few limits to widespread implementation or a significant impact on future medical costs and productivity. We encourage investigators seeking to develop a stem cell-based therapeutic intervention to analyze their proposed therapy in great detail, as shown in the above case study of spinal cord injury, in order to identify critical bottlenecks a priori as well to develop approaches with a reasonable chance of deployment in the medical environments of developed countries. Funding agencies that award large sums for translational activities should not only encourage, but also require those seeking support to provide a detailed analysis such as that shown above to document the viability of the proposed therapy in light of the existing medical delivery system. Additionally, proposed treatments should be assessed continuously as improvements in technology, particularly with regards to immunosuppression, may improve the cost effectiveness of a previously non-viable treatment. Although a broad spectrum of diseases are targeted for stem cell-based therapies, existing data and methods of cost analysis may be used to direct research dollars towards the development of the most cost-effective treatments for tomorrow. In any case, there is no time like the present for an honest discussion about the economic models used for the funding of translational science.

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