REVIEW

Complications of Spinal Cord Stem Cell Injections for ALS

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a progressively fatal neurodegenerative disorder that destroys motor neurons and, in most cases, inevitability leads to death from respiratory failure within five years post-diagnosis. The pathogenesis of the disease is poorly understood and, the sole FDA-approved anti-ALS drug, riluzole extends one's lifetime by only a few months. In recent years, researchers have shifted their focus towards implementation of stem cell therapy in ALS patients i.e. intrathecal injection of four different stem cell types: neural stem cells (NSC), embryonic stem cells (ESC), mesenchymal stromal cells (MSC), or induced pluripotent stem cells (iPSC). Although reported to be well-tolerated and effective in multiple trials, stem cell injection may provide varying degrees of complications depending on the surgical technique and the type of transplanted cell. We aim to explore the potential complications of this novel intervention under the subheadings: iatrogenic pain syndrome, immunosuppressant toxicity, and tumorigenesis. The complications of stem cell therapy, regardless of the severity, must not be overlooked by physicians due to the significant social, financial, and emotional burden that ALS bestow on the patients and their relatives. The patient must be provided with a thorough examination and in-depth information about possible complications prior to the intervention to reduce their disease burden and improve, or at the very least, not exacerbate one's quality of life. Spine Scholar 1:80-83, 2017

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive, lethal neurodegenerative disorder that causes destruction of upper and lower motor neurons. ALS manifests as muscle weakness, atrophy, fasciculation, and spasticity and, in a later stage, with bulbar symptoms such as problems with the speech (Caroscio et al., 1987). Patients typically die three to five years post-diagnosis from loss of respiratory muscle control and subsequent respiratory failure (Mao et al., 2015). Approximately 90-95% of all cases of ALS are sporadic and the remaining 5-10% are familial (fALS) (Mao et al., 2015).

To date, nearly 60 genetic mutations are identified in fALS and are associated with glutamate toxicity, protein structural defects and loss, impaired axonal transport, endoplasmic reticulum and mitochondrial dysfunction, damage by free radicals, and inflammatory responses (Lu et al., 2016; Millar and Appel, 2017). However, the exact pathogenesis of ALS remains unknown, posing a significant challenge in developing the ideal targeted therapy (Lu et al., 2016).

The pharmacological agent riluzole, the first FDA-approved drug for treatment of ALS, has shown to prolong survival by three months (Traynor et al., 2003). It is described to block activated sodium channels, preventing overstimulation of post-synaptic glutamatergic receptors and, hence, protecting against neuronal degeneration (Traynor et al., 2003). Several studies attest to the efficacy of riluzole. For instance, Bensimon et al. (1994) and Hugon (1996) established riluzole's efficacy in prolonging survival up to 12 months. Bensimon et al. (1994) showed that the greatest effect was observed in bulbar-onset participant group, though Hugon (1996)'s results for the limb-onset and the bulbar-onset groups showed no significant difference. More recently, Zoccolella et al. (2007) confirmed significant survival rates only in bulbar-onset participants and in older patients, but not in the limb-onset group. Despite its documented efficacy, riluzole utilization is not without controversy e.g., there is only a small increase in survival duration and it may not have a real value regarding the disability itself and/or the quality of life of the patients

(Turner, 2003). Hence, several recent studies have shifted their focus away from drug therapy and on to the use of stem cells (Thomas, 2014).

Types of Stem Cells Utilized in Cell Therapy

A cellular therapy for ALS has recently gained attention. This approach involves replacing the diseased motor neurons or introducing exogenous cells to support the growth of new cells. There are four different kinds of stem cells used in this therapy: neural stem cells (NSC) derived from fetal brain tissues or fetal spinal cord, embryonic stem cells (ESC) derived from the inner cell mass of the blastocyst, mesenchymal stromal cells (MSC), which are multipotent adult stem cells easily extracted from connective tissue such as the bone marrow, and induced pluripotent stem cells (iPSC), which are genetically engineered adult somatic cells.

Although the utilization of NSCs and ESCs entails ethical and immune rejection concerns (Mao et al., 2015), Wyatt et al. (2011) demonstrated beneficial effects of NSC in ALS rats and the capacity of transplanted human ESCs to survive, differentiate, and secrete neurotrophic factors in animal models. Transplanted NSCs can also differentiate into neurons and form synaptic connections with the host tissue, delaying disease progression and, consequently, prolonging the survival of the experimental animals (Xu et al., 2006).

MSCs also have their own unique characteristics e.g., just like NSCs, they have been described to generate immunomodulatory cells, growth factor-releasing cells, functional support cells such as glia, or GABAergic interneurons to modify motor neuron survival and activity (Thomsen et al., 2015). Minguell et al. (2013) showed that after 18 months of intrathecal injection of bone marrow-derived MSC, patients became significantly stable with an appreciably improved quality of life.

iPSCs injection has unparalleled advantages over the other stem cell types used in this therapy as it circumvents the problem of transplant rejection with its autologous nature (Dimos et al., 2008). For instance, Dimos et al. (2008) successfully produced pluripotent stem cells from an elderly woman with chronic ALS and directed their differentiation into motor neurons. Further, Mao et al. (2015) reviewed several studies and documented improved clinical symptoms and prolongation of survival via injection of NSCs derived from purified human iPSC.

Complications of Stem Cell Transplantation

Most studies agree with the safety of stem cell injections. For Example, Mazzini et al. (2016) conducted a long-term safety study of MSC transplants in ALS patients. Although the therapy neither positively nor negatively affected the disease progression, the participants had no adverse effects during a nine-year follow-up period post-therapy (Mazzini et al., 2016). Thomsen et al. (2014) also draw a firm conclusion that the therapy is safe and well-tolerated from their extensive pre-clinical and clinical trials. Although the injection is regarded as a safe procedure, patients may experience complications.

Iatrogenic Pain Syndrome

Pain is one of the most common complications of stem cell transplantation. Glass et al. (2012) present a phase 1 trial of intra-spinal NSC injection, after which several patients experienced transient radicular-type pain and/or sensory abnormalities associated with the procedure. The study also reports a case of a severe bilateral groin pain, which required opioid analgesia (Glass et al., 2012). Furthermore, Thomsen et al. (2014) describe transient pain experienced by some patients associated with the injection procedure.

In the follow-up study by Glass et al. (2016), whose objective was “to test the safety of spinal cord transplantation of human stem cells in patients with amyotrophic lateral sclerosis (ALS) with escalating doses and expansion of the trial to multiple clinical centers,” two patients suffered life-threatening complications from the therapy. Following 10 bilateral cervical injections, on postoperative day (POD) two, one of the patients had reduced sensation to pinprick stimuli below the neck, severe neck pain, burning sensation in both arms, and episodes of myoclonus in legs bilaterally (Glass et al., 2016). Cervical MRI revealed spinal cord edema and some of the symptoms i.e. impaired bowel and bladder control and inability to walk independently persisted until POD 22 (Glass et al., 2016). Infection and transplant rejection were ruled out and the cause of the edema remained unknown. A surgical intervention was conducted and the patient partially regained strength in his legs and the bowel and bladder functions were completely restored after five months of rehabilitation (Glass et al., 2016). However, a moderate neck pain persisted (Glass et al., 2016). The study reports another patient who developed central pain syndrome i.e. thigh pain following a lumbar injection and severe neuropathic pain in both arms following a cervical injection (Glass et al., 2016).

However, it is important to acknowledge that pain can be a complication of any intrathecal injection, owing to the delicate nature of the manipulated organ, and is not unique to patients receiving ALS therapy. For instance, a 66-year-old male who received intrathecal NSC injection to treat residual damage from an ischemic stroke reported progressive lower back pain, paraplegia, and urinary incontinence (Galvin, 2015). In addition, Glass et al. (2012)’s MRI scans also showed consistent accumulation of extradural fluid only at the surgical entry site.

Immunosuppressant Toxicity

NSCs and ESCs carry the potential to trigger a transplant rejection and, therefore, recipients must be placed under a strict immunosuppression regimen. Glass et al. (2012) claim that such patients suffer less from opportunistic infections and more from the toxicity of the drugs, most commonly tacrolimus and mycophenolate mofetil, utilized. The immunosuppressants induce gastrointestinal symptoms (diarrhea, nausea, and/or anorexia), which can be intolerable enough to stop drug regimen altogether (Glass et al., 2012). Most patients were unable to tolerate either one or both of the drugs and required dose adjustment (Glass et al., 2012). Glass et al. (2012) also report cases of minor tinea cruris and basal cell carcinoma associated with the immunosuppression.

Tumorigenesis

Unlike NSCs and ESCs, iPSCs and MSCs do not carry the risk of immune rejection but may proliferate in an uncontrolled manner, forming a tumor. Mao et al. (2015) claim such tumorigenesis is possible but rare since very small proportion of iPSC grafts remain positive for neural progenitor marker genes.

Galvin et al. (2015) presents a case of a 66-year-old who underwent intrathecal infusion of iPSCs as part of post-stroke care. The patient developed a rapidly growing primary neoplasm of the thoracic spinal cord (Galvin et al. (2015). The neoplasm resembled a malignant glioma histologically with nuclear atypia and high proliferative index (Galvin et al. (2015). However, genetic studies of the mass showed an absence of typical mutations found in glioma (Galvin et al. (2015). Thonhoff et al. (2009) agree that this can be a drawback of iPSC therapy and attributes it to the lack of control on the gene delivery method. Mao et al. (2015) claim that the lack of control over the number and differentiation of the transplanted cells is also responsible for the tumorigenesis.

CONCLUSION

The study of ALS management has progressed a long way, from molecular studies to discover the probable pathophysiology, to genetic studies to spot potential treatments targets, and now to a more invasive and direct surgical approach to generate new motor neurons and replace the diseased cells with new ones. Although stem cell therapy has been proven to be effective and safe, healthcare providers must not undermine its novelty i.e. more research to elucidate its full potential is required and still ongoing. Patients must be thoroughly examined and should be made aware of all the possible adverse effects prior to the intervention. Any form of complication, regardless of the severity, must not be overlooked since the slightest addition to the tremendous social, financial, and emotional burden that ALS patients and their families are already under can significantly impair one's quality of life.

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