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A Hallmark Clinical Study of Cord Blood Therapy in Adults with Ischemic Stroke

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Commentary

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A Hallmark Clinical Study of Cord Blood Therapy in Adults with Ischemic Stroke

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Abstract

The therapeutic application of human umbilical cord blood cells has been an area of great interest for at least the last 25 years. Currently, cord blood cells are approved for reconstitution of the bone marrow following myeloablation in both young and old patients with myeloid malignancies and other blood cancers. Translational studies investigating alternative uses of cord blood have also shown that these cells not only stimulate neurogenesis in the aged brain but are also potentially therapeutic in the treatment of adult neurodegenerative disorders including amyotrophic lateral sclerosis, Alzheimer's disease, ischemic stroke, traumatic brain injury, and Parkinson's disease. Recent advances in the clinical application of cord blood cells by Dr. Joanne Kurtzberg and colleagues have found that non-HLA matched allogeneic banked cord blood units in immunocompetent patients with ischemic stroke are safe and well tolerated. Although the exact mechanism(s) of action that provide the beneficial effects observed from a cord blood cell-based therapy are currently unknown, several studies using models of neurodegenerative disease have shown these cells are immune-modulatory and anti-inflammatory. Thus, any future clinical studies investigating the efficacy of this cord blood cell therapeutic would strongly benefit from the inclusion of methodologies to determine changes in both markers of inflammation and the response of immune tissues, such as the spleen, in subjects receiving cell infusion.

Keywords

cord blood, ischemic stroke, non-HLA matched

A recent clinical study by Joanne Kurtzberg with her colleagues at Duke University, and the University of Texas has opened the door for further clinical investigation into the application of cord blood cells as a therapeutic treatment for adult neurodegenerative disorders[1]. The study, titled "Allogeneic Umbilical Cord Blood Infusion for Adults with Ischemic Stroke: Clinical Outcomes from a Phase I Safety Study," is a hallmark clinical study using non-human leukocyte antigen (HLA) matched cord blood units for the treatment of ischemic stroke in immunocompetent adult patients (CoBIS).

The therapeutic application of human umbilical cord blood cells has been an area of great interest for at least the last quarter of a century, with the first clinical infusion of cells derived from cord blood being used to treat juvenile Fanconi's anemia in 1988[2], to more current applications to treat myeloid malignancies in children. Recent clinical studies have investigated the alternative application of cord blood to treat other childhood-related neurological disorders such as cerebral palsy[3,4], autism spectrum disorder[5], and lysosomal or peroxisomal storage diseases[6]. Early basic research and translational studies from our group, which date back almost two decades, have also shown that cord blood cells can not only stimulate neurogenesis in the aged brain[7] but are also potentially therapeutic in the treatment of adult neurodegenerative disorders including amyotrophic lateral sclerosis (ALS)[8,9], Alzheimer's disease (AD)[10,11], ischemic stroke[12–14], traumatic brain injury (TBI)[15–17], and Parkinson's disease (PD)[18]. In addition, many of these studies have highlighted a unique property that exists for cord blood cell-based therapies in neurodegenerative diseases: the non-necessity for HLA matching or immunosuppression. Many

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early studies exploring the therapeutic potential of cord blood cells in animal models of neurodegenerative disorders employed cyclosporine or some other immunosuppressant to reduce the probability of developing of graft versus host disease (GvHD), and graft rejection[8,9,19]. Later studies found this practice to be unnecessary, with reports showing that the therapeutic effects of cord blood cell infusion remained the same with no incidence of GvHD in animals where immunosuppression was omitted[10,11]. The lack of need for HLA matching and low immunogenicity of this particular cell population results in the ability to treat cord blood cell therapy in the same regard as a simple blood transfusion. This phenomenon is mostly due to the relative immaturity of these cells in relation to inflammation and the immune response, and makes them good candidates to treat many of the aforementioned neurodegenerative diseases[20]. While a decade has passed since much of this original work was performed, it has provided the foundation for this clinical study as well as others which have aided in furthering the development of cord blood cells as a therapy for neurological disorders.

CoBIS is a phase I open-label study which investigates the safety and tolerability of non-HLA matched allogeneic banked cord blood units in immunocompetent patients of ischemic stroke. The study enrolled 10 male patients who were infused with cord blood cells at 3–9 days post the stroke event, and monitored for 12 months post treatment. Each participant completed the study with no apparent incidence of GvHD or other unexpected adverse reactions that could be directly attributed to the infusion of cord blood. In addition, all participants displayed improvement in the modified Rankin Score and the National Institutes of Health Stroke Scale, indicating a recovery of both neurological and physical function. Overall the study found that infusion of non-HLA matched allogeneic cord blood in adults that have been recently experienced ischemic stroke is safe and well tolerated.

While the primary endpoint of this phase I trial was to determine the safety of cord blood infusion in subjects with ischemic stroke, the authors do suggest several potential mechanisms for the efficacy that was also observed. They refer to animal studies that have shown the migration of infused cells to sites of injury in the central nervous system (CNS) and the production of trophic factors that aid in repair[21], but fail to address a key factor where cord blood therapy has shown to have a significant impact: the migration of endogenous immune cells from the periphery and resultant inflammation. This phenomenon occurs shortly after the stroke event, and ultimately leads to exacerbation of both neurological and physical disability. Translational studies in animals using a middle cerebral artery occlusion (MCAO) model of ischemic stroke have shown that the efficacy of cord blood primarily stems from peripheral anti-inflammatory effects that reduce cell death and disease pathology within the CNS[13,22]. These studies have shown significant reduction in infarct volume, mainly due to the prevention of cell loss within the penumbral tissue surrounding the core of the stroke. Without therapeutic intervention the tissue in the penumbra becomes hypoxic and extremely sensitive to inflammatory insult, which can result in cell death occurring days to weeks after the ischemic event. Vendrame et al.[23] were the first to detail that the anti-inflammatory effects of cord blood therapy in ischemic stroke are primarily due to inhibition of the peripheral splenic immune response to the damage that has occurred in the CNS. This study observed a significant reduction in spleen volume occurring shortly after the ischemic insult in untreated animals. Another cohort receiving an intravenous injection of cord blood cells, after MCAO, resulted in retention of the normotypic spleen size and shape with significant reduction in neurodegeneration in the penumbra. Since this dynamic change in spleen size has also been observed in patients of ischemic stroke[24], the inclusion of this phenomenon as a secondary outcome in future clinical studies might be beneficial in determining efficacy of the cord blood infusion. This could be easily documented using either ultrasound or CT technologies, and could potentially provide additional clinical evidence of the anti-inflammatory nature of the cord blood cell-based therapy.

In addition, even though the inclusion criteria of this phase I study did allow for female subjects to participate, it seems somewhat odd that only male patients were enrolled. This is not necessarily a fault of the current study, since it is only determining the overall safety of cord blood therapy in ischemic stroke, but could be a detriment in future clinical studies if they are unable to enroll a representative population of female participants. Translational studies have reported significant differences in sex-specific responses to ischemic injury, with alterations in inflammation and potential regeneration between males and females[25].

There have been a number of studies that have also investigated a combination of cord blood cells with blood brain permeabilizers, such as mannitol, in attempts to increase the efficacy of this particular therapy. One pre-clinical study in particular has shown that co-administration of cord blood with mannitol has shown greater efficacy compared with cord blood infusion alone[26]. This therapeutic combination results in not only the ability to reduce the cell dose while increasing therapeutic efficacy, but also results in a significant increase in the number of stem cells that enter the brain to promote regeneration and repair[27]. In addition, this combinatorial infusion of cord blood cells and mannitol increases the effective therapeutic window of cord blood cell infusion and allows for the treatment of chronic cases of ischemic stroke[26]. Future clinical work that employs this combination may show improve the therapeutic efficacy and, due to lower cell numbers needed per infusion, allow for multiple doses to be provided from the same cord blood unit to treat a patient with ischemic stroke.

Overall, this recent clinical study (Laskowitz et al.[1]) shows that the infusion of non-HLA matched allogeneic cord blood is safe and well tolerated in patients of ischemic

stroke. Future studies investigating the efficacy of this cord blood therapeutic would strongly benefit from the inclusion of methodologies to determine changes in the spleen size of ischemic stroke patients. Determining this outcome could provide significant clinical evidence to one of the potential mechanisms of action for cord blood therapy. In addition, the inclusion of a representative population of female participants is needed to fully ascertain the therapeutic efficacy for both sexes. The therapeutic efficacy observed from cord blood cells in this clinical trial makes it a good candidate to help individuals impacted by hemorrhagic stroke as well[28]. While this study is the most recent step in the clinical advancement of cord blood therapy for age-related neurodegenerative disorders, additional clinical studies may now be possible to test the safety and potential efficacy in a wide range of other indications such as ALS, AD, TBI, and PD. A phase II double-blind placebo-controlled study investigating non-HLA matched cord blood therapy in ischemic stroke (CoBIS 2 - NCT03004976) is currently underway and we are anxiously awaiting the results[29].

Ethical Approval

Ethical Approval is not applicable for this article.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Disclosure

PRS is co-founder of Saneron CCEL Therapeutics, Inc., and holds patents with the University of South Florida, for the use of human umbilical cord blood as a cell therapy for several disorders. JE is the Director of Research and Development for Saneron CCEL Therapeutics, Inc.

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