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Induced Pluripotent Stem Cells and CRISPR-Cas9 Gene-Editing on Transthyretin Amyloid Cardiomyopathy

By Caden L. Reedy

Abstract- Transthyretin amyloid cardiomyopathy is a fatal disease of the myocardium causing a protein buildup of Transthyretin. Over 120,000 people in the United States suffer from transthyretin amyloid cardiomyopathy, and half of those diagnosed will die within four years of the onset of symptoms. However, applying CRISPR-Cas9 gene editing will reduce amounts of transthyretin produced by the liver by up to 96% and minimize transthyretin expression by 91%. Induced Pluripotent Stem Cell therapy shows signs of at least 20 years or greater in life expectancy. It puts 39% of recipients into complete remission. Using CRISPR-Cas9 technology, an IV is placed and lipid nanoparticles deliver mRNA with Cas9 production and a single guide RNA for targeting the transthyretin production in hepatocytes. Gathering stem cells has never been easier, using adult somatic cells and returning them to an embryotic state is more efficient and ethical than ever.

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I. Introduction

Over 120,000 Americans have Transthyretin Amyloid Cardiomyopathy (ATTR-CM), one in 2700 Americans, 5000-7000 new cases a year, men seven more times likely than women. (Institute for Clinical and Economic Review, 2024). A haunting disease with an extremely poor prognosis, but usually goes undiagnosed and leads to heart failure. (*Transthyretin Cardiac Amyloidosis | ATTR-CM for HCPs | Therapy Area*, n.d.) When a patient in the past was given a diagnosis, it was usually a liver or heart transplant, and sometimes an LVAD (Left Ventricle Assisting Device) which are all surgical and extremely high risk. In the four years after the onset of symptoms, half of the patients will die. To explore treatments and possibly cures, I have looked at one of the leading treatments that show extreme recovery and remission and a new promising gene editing drug. I saw the existence of both treatments to be together and work hand in hand. The disorder thickens the wall of the left ventricle, making it harder for adequate pumping function, reducing ejection fraction rate, and being put at risk for heart failure. The main risk factor for developing ATTR-CM is HCM (Hypertrophic Cardiomyopathy), this genetic condition causes the wall of the heart to become thickened as well and can cause heart failure. Induced Pluripotent Stem Cells (IPSCs) as well as new CRISPR gene editing can completely eradicate the symptoms and possibly even the disease entirely; both treatments are showing promising signs separately and together they could work together in unison without any negative interactions or interferences. 39% of patients who received stem cells alone were in total remission (*BU Study: Stem Cell Transplantation for AL Amyloidosis Leads to Long-term Survival and Possible Cure in Selected Patients | Clinical & Translational Science Institute*, 2022). I hypothesized that two treatments with good outlooks can work together and treat transthyretin amyloid cardiomyopathy.

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II. Materials and Methods

a) Study Design

Patient statistics were monitored with IPSCs and without them as well as monitoring patient statistics and outcomes with CRISPR-Cas9 and without from 1994-2024. The two treatments were never given to the same patient in the same care plan but were compared from treatment to treatment. Statistics were monitored and documented from outside sources in citations. Patients received one dose of CRISPR gene editing through IV between November 2020 and April 2021. Patients were either given 0.1mg per kg or 0.3mg per kg of RNA dose. Patients were aged 18-80, with a range of weight between 50-90kg (Gillmore et al., 2021). IPSCs were given to specific patients and statistics were done on life expectancy, state of disease, and prognosis. This study was conducted in Auckland, New Zealand. (*BU Study: Stem Cell Transplantation for AL Amyloidosis Leads to Long-term Survival and Possible Cure in Selected Patients | Clinical & Translational Science Institute*, 2022).

b) Ethics Review

Ethics are usually a sensitive topic in stem cell research because they are derived from a human embryo, Induced Pluripotent Stem Cells are adult somatic cells taken from skin or blood (not embryotic) but were taken to the lab and going through cellular reprogramming by erasing and reshaping and remodeling the cells "differentiation memory". This can happen by expressing four transcription factors: Oct4, Sox2, Klf4, and c-Myc. This brings the cells into an undifferentiated embryotic form without using or being an embryo. The main disadvantage of this on the ethical side would be that this could turn into an actual embryo if exposed to the correct conditions.

III. Results

An induced knockout was the result of the CRISPR-Cas9 gene editing. Patients who received 0.1mg per 1kg had a reduced transthyretin concentration of 52%, and patients who received 0.3mg per 1kg had a reduced transthyretin concentration of 87%. Over 95% of transthyretin production was halted, 91% of transthyretin expression was reduced and showed few adverse effects. 12 months after the mRNA was delivered to the hepatocytes the production and expression of transthyretin was still maximally suppressed (Gillmore et al., 2021). Boston University researchers say hematologic complete remission was achieved in 39% of patients with a median survival of 15 years and 30% of those patients survived longer than 20 years (after onset of symptoms). A permanent reduction of transthyretin production and concentration was claimed. (*BU Study: Stem Cell Transplantation for AL Amyloidosis Leads to Long-term Survival and Possible Cure in Selected Patients | Clinical & Translational Science Institute*, 2022).

IV. Discussion

The results show a promising future and do support my hypothesis that the two treatments together would be beneficial and treat patients with ATTR-CM better than they have ever been. Patients going into remission, living longer, and having a better quality of life is something we all should strive for. Results show that separately the treatments are working extremely well. The growing understanding of gene editing, stem cells, and diseases, will come up with new treatment plans and objectives, where we once wanting to give medications for symptoms to go away, to now giving stem cells and CRISPR gene editing and truly having hope for remission in people suffering from this. Using the two treatments in unison as one treatment plan will save lives and be revolutionary to the treatment of cardiomyopathy. 39% of patients in remission with one of the treatments alone is incredible, this fully supports my hypothesis, there is no room for misunderstanding when numbers like these are being produced. Stopping the production of transthyretin proteins with CRISPR-Cas9 will cause the protein to be restricted and the stem cells will repair and enhance cardiac tissue in need.

Past treatments have never come close to the current treatments. With current technology, we can access and do things we have never imagined happening. Once we used stem cells from embryos and now, we can derive stem cells from skin and blood cells. Our technology and field have grown tremendously. Treatments for transthyretin cardiomyopathy have never been better. This is the first time we have seen patients completely cured of the disease. Not being on lasting drugs, having impairments, symptoms, and living restricted lives. When these two treatments are used together, they will without a doubt change the course of treatment for ATTR-CM.

V. Conclusion

The results of the two studies support my hypothesis undoubtedly. I can see a future where we have cures for diseases like this one, where a diagnosis is not a sentence, where we have a chance. These treatments open a window for that opportunity.

VI. Declaration

I, Caden L. Reedy declare that research 'Induced Pluripotent Stem Cells and CRISPR-Cas9 Gene-Editing on Transthyretin Amyloid Cardiomyopathy' has not been published nor is being reviewed elsewhere.

I, Caden L. Reedy declare all the following:

Ethics Approval: Yes.

Consent for publication: Yes.

Availability of Data and Materials: Yes.

Funding: None.

Authors Contributions: Author took lead in writing all manuscript, gathered and organized all data, and came up with the research idea.

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