Genetic Silencing of BCL11A for Sickle Cell treatment Summary

Sickle cell anemia is a genetically inherited disorder that alters the shape of red blood cells. The sickle cell mutation is located on the hemoglobin beta gene. To clinically present with the disease, an individual must carry both copies of the mutation. Those who carry one copy of the mutation are said to have sickle cell trait, however, they do not experience the complications of the disease, making the disease a recessive one. Sickle cell anemia can be extremely painful causing bouts of pain referred to as "sickle cell crisis", anemia from the early death of red blood cells caused by their abnormal shape, and organ damage (1). As a result, researchers have worked endlessly to find ways to mitigate the effects that this genetic mutation has on individuals.

In the article, "Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease," a clinical trial that took place at Harvard Medical School to find new therapeutic options for mitigating the effects of sickle cell is detailed (1). The trial is a single-center open-label pilot study which means it was a smaller trial in preparation for a larger study where both the patients and providers know exactly what treatment they are receiving (opposite of a blind study). The article was published in the online peer-reviewed journal called The New England Journal of Medicine.

In the trial, researchers tested the use of BCL11A, a protein-coding gene that acts as a repressor of HbF, or fetal hemoglobin, production. Individuals with sickle cell disease have a higher concentration of fetal hemoglobin than adult hemoglobin, making it more difficult for sickle cells to bind together. The purpose of the trial was to test the hypothesis that BCL11A would repress the expression of HbF genes enough to prevent sickle cell anemia complications. The test subjects were infused with CD34+ cells which were transduced with a BCH-BB694 lentiviral vector, or retrovirus that can invade both dividing and nondividing cells, to produce a short hairpin RNA (shRNA) which then targets the mRNA of BC11A. Erythroid, or red blood cell, lineage-specific knockdown occurs, repressing the expression of HbF. The patients were monitored and assessed for clinical responses to treatment (1).

After the completion of treatment, six of the patients were then followed for two years and then offered enrollment into a 13-year-long study. Patients reported feeling adverse side effects similar to those of preparative chemotherapy including hair loss, vomiting, lack of appetite, and skin rashes. Regardless of the adverse reactions, all the patients who returned for follow-up evaluation achieved stable and robust HbF induction, and HbF was broadly distributed throughout red blood cells. Any clinical manifestations of sickle cell anemia were completely absent or greatly reduced upon clinical assessment following the infusion treatment (1). This leaves the question of outweighing the risk vs. benefit of the treatment contingent on individual patient health profiles.

In conclusion, the single-center open-label pilot study conducted by Harvard Medical School confirmed the hypothesis of BCL11A gene repression being effective at targeting HbF induction. It also showed evidence that the shRNA-base gene knockdown can be an effective treatment for sickle cell anemia. During the study, each patient knew exactly what treatment they were receiving, and each provider knew which patients were the test subjects. Even though there are a few adverse reactions notated in the study, the results of the preliminary study are promising for the treatment of sickle cell anemia. Further research can assist patients and providers in making treatment plans using this technology with a risk-benefit analysis formed with evidence-based decision-making.

References

1. Esrick, E. B. et al. Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease. *The New England Journal of Medicine;* https://www.nejm.org/doi/full/10.1056/NEJMoa2029392 (2021).