**Gene Therapy: A New Advancement in Stopping Disease**

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Researchers are recently proposing that the best way to fight a disease may just be to alter our genes. Gene therapy could be the new method for fighting large B-cell lymphoma. The newly discovered CAR-T therapy (chimeric antigen receptor T-cell therapy) is the first gene therapy to be approved by the FDA. There are currently two-products available on the market, tisagenlecleucel and axicabtagene ciloleucel. While this treatment has only been used on patients that are nonresponsive to any of the normal treatments, there has been an overall success. Even with these remarkable results, there are still problems that arise. First, treatment is very expensive due to the extensive testing. Also, there are various unpredictable side effects that researchers are not clear on the origin of. Lastly, precision in therapy delivery is a rising problem. Researchers are searching for cheaper and safer ways to test and modify genes. While the side effects are unpredictable, researchers have found them to be treatable. Since these trials have had substantial results compared to others and considering how fast CAR-T therapy has progressed, it is becoming well recognized and trusted treatment method.

**Introduction**

Gene therapy is a treatment that uses genes to help prevent, slow, and stop diseases. It includes inserting new healthy genes, stopping a misfunctioning gene, or replacing a gene altogether (U.S. 2019). This method is still being tested due to the risk factor and side effects that it involves. Since a gene will not function if inserted directly into a cell, a common method to deliver the gene to the cell, is by a vector (U.S. 2019). These vectors are sometimes viruses so that they can infect the cell, but they are altered so that the virus will not cause additional diseases (U.S. 2019). Normally, the vector is inserted by IV, or cells can be removed, treated, and returned if treatment is successful (U.S. 2019). Human trials are now being conducted, but only when a patient has gone through normal treatments, in which all are ineffective (U.S. 2019). For treatments to become more regularly used, new delivery methods are being researched to find better cell targeting and a more predictable outcome.

**Recent Progress**

New progress has developed within gene therapy. According to an article by Nogrady (2018), the first FDA approved gene therapy is now on the market, known as CAR-T therapy. The article states that CAR-T therapy is used to treat B-cell lymphoma. The research shows that treatment uses the T-cells in patients to target and destroy malignant B cells, the target site being CD19. This target is chosen due to the fact that the B-cell needs CD19 to survive. It can also be found on the surface of the cell, so the T-cell can easily attack (Nogrady, 2018). For the research, T-cells are programmed by taking a sample of the patients’ cells, obtained through a blood sample, and separating them by apheresis, a mechanical process. A gene that codes for CAR is inserted into the T cell by an inactivated virus (lentivirus or retrovirus) (Nogrady, 2018). A problem that arises during research is that CD19 is also present on healthy B cells, meaning they get targeted and destroyed as well. Even so, these healthy B-cells are able to regenerate within a couple of months (Nogrady, 2018).

In this study, the treatments only consist of a single infusion. There are currently two forms of this treatment in the market, tisagenlecleucel and axicabtagene ciloleucel (Nogrady, 2018). Tisagenlecleucel is used to treat acute B-cell lymphoma in pediatric and young adults. This product became FDA approved in August 2017 (Nogrady, 2018). Axicabtagene ciloleucel is used on adult patients with large B-cell lymphoma. This product became FDA approved on October 2017 (Nogrady, 2018). Unlike other gene therapy treatments, CAR-T therapy is one of the first products with a fast progression (Nogrady, 2018). Through this treatment, patients have seen remarkable results. Phase II of these trials have shown remission for 30% using tisagenlecleucel, and 54% for axicabtagene ciloleucel (Nogrady, 2018). For the study, these results were taken 6 months into treatment. The patients that underwent this trial all had B-cell lymphoma and were not responding to the normal treatment (chemotherapy and stem-cell transplants) (Nogrady, 2018). After 18 months, 52% of the patients that used the axicabtagene ciloleucel were still living (Nogrady, 2018).

While this is an effective treatment, there are still some problems that need to be fixed. Researchers are still trying figure out what the ideal target on the malignant B-cells would be. Researchers want to be able to have a specific target, in order to avoid causing severe damage to other cells when the T-cells attack (Nogrady, 2018). Since this treatment is still new, the side effects are very unpredictable. One concerning side effect is neurotoxicity. This leads to patients having confusion, difficulty speaking, and sleepiness (Nogrady, 2018). While these are concerning side effects, they are temporary and non-harmful, lasting only up to a couple of weeks (Nogrady, 2018). Another side effect in this study was cytokine release syndrome. A trial where axicabtagene ciloleucel was used, 93% of patients saw this side effect (Nogrady, 2018). When tisagenlecleucel was used, 58% of patients saw this side effect (Nogrady, 2018). Symptoms included low blood pressure, low oxygen, and fever (Nogrady, 2018). Cytokine release syndrome is treatable with medication and steroids (Nogrady, 2018).

Another problem to consider is the tremendous cost of the treatment. The cost is due to the need for the inactivated virus, known as a vector, so that the T-cells can be primed for attack (Nogrady, 2018). Another reason is that extensive testing is required in order to make the therapy safe for human trials (Nogrady, 2018). Since gene therapy is still in the experimental stage of research, there is extra caution that is needed to be taken when running tests. There is still a lot of unpredictability. Researchers are looking into cheaper methods in order to lower costs. Some ideas include using electric shock on T-cells (Nogrady, 2018). This causes holes to arise in the T-cells membrane, which means inactivated viruses will no longer be needed (Nogrady, 2018). Transposons (jumping genes) could be used as a tool to cut DNA and insert CAR into the T cells DNA (Nogrady, 2018). This method is known as piggyBac, and is tremendously cheaper due to the fact that making the transposons are easy (Nogrady, 2018).

This transposon-based CAT-T therapy is even in phase I testing in patients with lymphoma, as well as leukemia (Nogrady, 2018). These trials are using T-cells from matched sibling donors, rather than the patients themselves. Results from these trials have been promising, and while some patients are having disease recurrence, it is only in the early stages of trials. Different doses are being experimented with to see if they have effect on those with disease reoccurrence (Nogrady, 2018). Other targets are now being focused on to see if this therapy can be effective with other lymphomas, one being CD30, which is a protein associated with tumor growth. (Nogrady, 2018). Past research has led current researchers to believe that this could be the next target to analyze (Nogrady, 2018).

**Discussion**

Looking at the results, it is clear to see that researchers are making a step in the right direction. For gene therapy to be able to extend the life of an otherwise untreatable patient is remarkable. These results are proven to be valid in the fact that these trials are now on a third phase of clinicals, and treatment is now FDA approved (Nogrady, 2018). While there are side effects, they are being proven to be treatable and temporary (Nogrady, 2018). While results are promising, there are still unanswered questions. Researchers are still trying to figure out if there are cheaper and safer ways to conduct this therapy, and if this therapy can be extended to other diseases (Nogrady, 2018).

There are still some boundaries that researchers face since they are experimenting on humans. Since there is a question of ethics when experimenting, researchers must be very careful on where they go with these experiments. I believe one thing that benefits these researchers is that they are dealing with people who have failed to be responsive to the normal treatments (Nogrady, 2018). I think this leads people to be more open and willing to participate in this study.

Through this experiment, researchers have been able to make a solid case for why gene therapy is working, but now they must fine tune the process in order to make things more efficient, and safer. I believe that if these two problems are solved, then CAR-T therapy might come to be the most effective way to treat B-cell lymphoma, as well as lead researchers to expand to other diseases.

**References**

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