Medical first use of gene editing in humans, reversing leukemia, points to promising future

These are heady days for gene editing now that physicians at the Great Ormond Street Hospital in London have reversed a severe form of cancer in a baby girl using gene edited immune cells.

The patient, baby girl Layla, had been steadily deteriorating from acute lymphoblastic leukemia (ALL) and running out of treatment options when as a last ditch approach, her parents decided to try the gene-edited cells that were being prepared for a clinical trial next year. Regulators gave special permission to use the treatment on the grounds of compassion as Layla had not been responding to any of the traditional therapeutic approaches.

Now, Layla's cancer has been in remission for a few months and the 'off-the-shelf' gene-edited cells appear, for the moment, to have saved her life. This is only the second time that gene-editing has been tested in a clinical setting and the first using TALENS. Immune cells taken from a donor were first modified to seek out and destroy cancer cells and then its genes were edited to prevent it from being attacked by the patient's body.

"We didn't know if or when it would work and so we were over the moon when it did. Her leukemia was so aggressive that such a response is almost a miracle," said Professor Paul Veys, director of bone marrow transplant at GOSH and the patient's lead clinician,

What does this portend for the future of using genetic editing on humans? Researchers are cautiously optimistic. Professor Wasim Qasim, a professor at University College London and one of the physicians who treated Layla:

> We have only used this treatment on one very strong little girl, and we have to be cautious about claiming that this will be a suitable treatment option for all children. But, this is a landmark in the use of new gene engineering technology and the effects for this child have been staggering.

Researchers contacted by the Genetic Expert News Service, a project that connects scientists directly with journalists on breaking science stories, were quick to commend the team for their efforts while also being cautious about the findings. According to Stephen Grupp, professor of pediatrics at the University of Pennsylvania:

> It is extremely important to see the first patient ever has been treated with this sort of genetically engineered T cell product. It is something we've been waiting for. The innovation here is gene-editing T cells so that one person's T cells could be given to another even if they are not a donor match. This is a very exciting first effort and the authors imply that they are taking this to wider trial. More patients treated will give us a better idea of what the true impact

these genetically engineered T cells will have on leukemia.

Interestingly, Grupp also pointed out that it was difficult to pinpoint whether the gene edited cells had directly contributed to the remission as the hospital claimed without further information.

> In what is described in the abstract, the authors show that their approach is safe, but is not possible to conclude whether the cells provided clinical benefit to the patient. The reason why gets technical, but basically the patient had a high leukemia burden after failing a newer leukemia treatment called blinatumomab, but then got two rounds of standard chemotherapy and the amount of leukemia dropped to a very low level. This means at the time of receiving the T cells the patient was technically already in remission.
>
> The authors were able to detect very small amounts of leukemia immediately before the patient received the T cells and then at the end were not able to detect any leukemia. Since the patient was responding to chemotherapy just before the infusion of these T cells, it is impossible to separate between what the chemotherapy did and what the T cells did.

Mark Osborn, assistant professor, Department of Pediatrics, Division of Blood and Marrow Transplantation, University of Minnesota said,

> This first in-human use of TALEN engineered cells is designed to fill a critical gap for the treatment of acute lymphoblastic leukemia, the most common type of childhood cancer that has a poor prognosis. The employment of engineered nucleases can result in so called ‘off-target’ effects where similar sequences in the genome to the intended targets are also cleaved. Rigorous assessment of off-target effects will be needed to streamline further patient application. In an elegant approach to account for any deleterious effects of the engineering process, the authors included a ‘suicide gene’ that allows for selective removal of the TALEN/CAR modified cells.
>
> This ‘off the shelf’ approach allows for the generation and banking of a population of cells that can be delivered to any patient for widespread and urgent use. This approach resulted in molecular remission of the leukemia in this patient and serves as a springboard for clinical trials.

Gene-editing gathering steam

The success comes on the heels previous trials conducted by Sangamo Biosciences last year who used ZFNs (Zinc Finger Nucleases), another gene editing technique, to alter immune cells and make them resistant to HIV in 12 patients. The difference in that case was that the patient’s own cells were used unlike the off-the-shelf donor cells in Layla’s case which are far more broadly applicable in a clinical setting.

Celltics, the company that worked with physicians to provide the edited cells is on course for a larger

clinical trial next year while also monitoring Layla closely to look for any signs that the therapy is unsafe or ineffective in the long run.

Several other companies in the space are also planning clinical trials according to reports in *Nature* and STAT, including Sangamo which is looking to test a treatment for hemophilia and Editas Biosciences, the company co-founded by Feng Zhang and Jennifer Doudna, pioneers of the newest gene editing technique, CRISPR. Not to mention, industry giants like Novartis and Pfizer which are also in the space through deals made with startups like Cellectis.

Even as experts are urging a cautious approach, there are high hopes for gene-editing with millions of dollars are being invested and many promises of cures and treatments.

Arvind Suresh is a science media liaison at the Genetic Expert News Service. He is also a science communicator and a former laboratory biologist. Follow him @suresh_arvind.