World first use of gene-edited immune cells to treat ‘incurable’ leukaemia

The treatment, previously only tested in the laboratory, was used in one-year-old, Layla, who had relapsed acute lymphoblastic leukaemia (ALL). She is now cancer free and doing well.

This breakthrough comes from GOSH and UCL Institute of Child Health’s (ICH) pioneering research teams, who together are developing treatments and cures for some of the rarest childhood diseases.

Chemotherapy successfully treats many patients with leukaemia but it can be ineffective in patients with particularly aggressive forms of the disease where cancer cells can remain hidden or resistant to drug therapy. Recent developments have led to treatments where immune cells, known as T-cells, are gathered from patients and programmed using gene therapy to recognise and kill cancerous cells. Multiple clinical trials are underway, but individuals with leukaemia, or those who have had several rounds of chemotherapy, often don’t have enough healthy T-cells to collect and modify meaning this type of treatment is not appropriate.

A team at GOSH has now used modified T-cells from donors, known as UCART19 cells, to treat a one-year-old child with an aggressive form of ALL who had unsuccessful chemotherapy and for whom palliative care was deemed the only option left.

The treatment works by adding new genes to healthy donor T-cells, which arm them against leukaemia. Using molecular tools (TALEN®) that act like very accurate scissors, specific genes are then cut in order to make the T-cells behave in two specific ways. Firstly, the cells became invisible to a powerful leukaemia drug that would usually kill them and secondly they are reprogrammed to only target and fight against leukaemia cells.

The team at GOSH and the UCL ICH, along with investigators at University College London and biotech company Cellectis, had been developing ‘off-the-shelf’ banks of these donor T-cells and the first of which was due to be used for final stage testing ahead of clinical trials. But, after hearing about this infant, the team received special permission to try the new treatment early.

Professor Waseem Qasim, Professor of Cell and Gene Therapy at UCL ICH and Consultant Immunologist at GOSH, explains: "The approach was looking incredibly successful in laboratory studies, and so when I heard there were no options left for treating this child’s disease, I thought ‘why don’t we use the new UCART19 cells?’

"The treatment was highly experimental and we had to get special permissions, but she appeared ideally suited for this type of approach."

The patient’s parents were also keen to try the treatment. Mum, Lisa, says: "We didn’t want to accept palliative care and so we asked the doctors to try anything for our daughter, even if it hadn’t been tried before."

The treatment consisted of 1ml of UCART19 cells delivered via intravenous line in around 10 minutes. After the cells had been delivered, the patient spent several months in isolation to protect her from infections while her immune system was extremely weak. Throughout this time, the patient stayed generally well.

After several weeks there were signs that the treatment was working. Professor Paul Veys, Director of bone marrow transplant at GOSH and the patient’s lead clinician, says: "As this was the first time that the treatment had been used, we didn’t know if or when it would work and so we were over the moon when it did. Her leukaemia was so aggressive

that such a response is almost a miracle."

Once doctors were confident that the leukaemia cells had been removed, the patient was given a bone marrow transplant to replace her entire blood and immune system which had been wiped out by the treatment. The child is now recovering well at home, although she returns to GOSH regularly to check that her bone marrow cells are healthy and blood counts continuing to normalise.

Professor Qasim says: "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.

"If replicated, it could represent a huge step forward in treating leukaemia and other cancers."

Full clinical trials funded by Cellectis are now being planned to test UCART19 cells in larger groups of patients and are set to begin early in 2016.

“Cellectis main objective is to provide cancer patients with an accessible, cost-effective, off-the-shelf allogeneic CAR-T therapies across all geographies. With clinical trial for the first gene-edited UCART on the horizon, it could be the beginning of a revolution in cancer immunotherapy,” says Dr. André Choulika, Chairman and CEO of Cellectis.

Layla's story

Layla was born healthy at 7lb 10 in June 2014. There were no problems during pregnancy and when she was born she was happy and content. At three months old, Layla was taken to the doctors as she was off her milk crying lots and her heart beat was fast. At first doctors suspected a tummy bug but after a blood test a few days later, it was confirmed that Layla had Infant Acute Lymphoblastic Leukaemia (ALL.) Layla was just 14 weeks old.

The family were immediately sent to GOSH in a CATS ambulance and Layla was taken to intensive care with what doctors described as "one of the most aggressive forms of the disease we have ever seen." The next day Layla was moved to Elephant Ward where chemotherapy started straight away. She had several rounds of treatment to try and get rid of the cancer and was then given a bone marrow transplant (BMT) so her damaged blood cells could be replaced.

Seven weeks later the family were told that despite the transplant Layla’s cancer had returned. As the strong doses of chemotherapy that Layla had already received hadn’t killed off the cancer cells, a second round of treatment wasn’t an option. After travelling to Sheffield and taking part in an experimental treatment that sadly didn’t work for Layla, the family returned to London the day before her first birthday.

Doctors at GOSH explained that there were no treatment options left for Layla that would cure her and suggested palliative care. Mum, Lisa, says: "Doctors don’t want to say that there’s nothing we can do and offer palliative care but sometimes that’s the only option.

"We didn’t want to accept palliative care and give up on our daughter though so we asked the doctors to try anything."

The family were then told that a very recent and experimental treatment, which had only been trialled in mice, was being developed in the hospital and could be used to try and treat the aggressive form of cancer that Layla had. Only

one vial of the treatment was available for Layla but in order for that to be given, an emergency ethics committee meeting had to be called to discuss whether it was the right thing to do for her. Dad, Ashleigh, says: "It was scary to think that the treatment had never been used in a human before but even with the risks, there was no doubt that we wanted to try the treatment. She was sick and in lots of pain so we had to do something.

"Doctors explained that even if we could try the treatment, there was no guarantee that it would work but we prayed it would."

After ethical approval was gained, doctors explained to mum and dad what the treatment would involve, consent forms were signed and treatment could begin. Treatment involved Layla being given a small 1ml infusion of genetically engineered cells through her Hickman line, which took a couple of minutes followed by a five minute flush. "Layla didn't notice anything was going on, and was bouncing around her cot all the way through!"

Ashleigh says: "We thought that the little bit of liquid in the syringe was nothing, and asked 'what is that going to do when bags and bags of chemo haven't worked.' The nurse said this was about quality and not quantity though."

Within one to two weeks doctors expected to see an immune response – usually in the form of a rash or a fever – to show that the treatment was working but when there was no change in Layla at two weeks, medical staff were unsure whether it had been successful. Doctors were preparing to send Layla home when she got 'the rash'. Something seemed to be happening.

The rash got worse but aside from that Layla remained well. Lisa says: "We didn't know she was going to be so well. We were preparing ourselves for her to be in intensive care and were constantly waiting to pull the crash bell.

"It was terrifying because you think that if she hasn't gone to intensive care then it's not working. When she didn't, we couldn't believe it."

A few weeks later, Lisa was picking up her elder daughter from school when Ashleigh called. "He said that the consultants had been in with results of the treatment and told me to sit down.

"I thought it was bad news but then he said ' it's worked' and I just cried happy tears."

Around two months later and cancer free, Layla came back to GOSH for a second BMT to replace her bone marrow which had also been affected by the treatment. Her blood cell numbers increased from that point and one month after the transplant, she was well enough to go home.

Ashleigh says: "Even though she is well at the moment, we still don't know what the future holds. She will still have monthly bone marrow checks for now and might be on some medicines for the rest of her life.

"It's always at the back of your mind. It's not like chickenpox that clears away, this is constant. You always have doubts."

But Lisa says: "I consider ourselves lucky that we were in the right place at the right time to get a vial of these cells. We always said that we had to try new things as we didn't want to be saying 'what if?

"Hopefully Layla will stay well and lots more children can be helped with this new treatment."

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