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Update on Nate – will Bone-Marrow transplants ‘cure’ E

The story of Nate, the young boy in the USA who has recessive dystrophic epidermolysis bullosa (RDEB), and received a bone-marrow transplant from his healthy unaffected brother Julian, continues.

Because Nate has RDEB, he lacks the correct version of the gene which codes for the collagen VII protein: this protein is essential for holding together the outer epidermis and deeper dermis layers of the skin. The aim of the transplant surgery was that stem cells derived from his brother's donated bone marrow would travel in Nate's body to his fragile skin, and produce collagen. One hundred days after the transplant, Nate is reported to have been making collagen derived from the transplant, and this collagen is making the anchoring fibrils that tether the two layers of skin together.

Good progress so far....

Some six months on since he received the transplant at the age of 18 months, Nate's progress looks promising. It is reported that his skin has fewer blisters, and he is able to be more active and, for a few hours each day, to wear fewer bandages. Whereas, previously, eating anything but babyfood was painful and damaging to his esophagus, he is now reportedly eating biscuits and other food enthusiastically, and has put on weight since the surgery.

If the treatment is successful in the longer-term, Nate should, with fewer wounds, have a lower risk of infection, and be at a lower risk of the aggressive skin cancers that are a frequently fatal complication affecting people with RDEB in their twenties and older. If the epithelium lining his digestive system is also improved, his nutrition should also be better, and he is more likely to continue to thrive. Not insignificantly, with fewer wounds and the scarring that are characteristic of RDEB, he should suffer far less pain, and have better mobility and general quality of life.

Professor John McGrath, of Guy's Hospital and Kings College London has commented that this is a "potentially significant new treatment for some people with RDEB and perhaps other forms of EB". However, as he notes, it is still early days, and results to date should be viewed with very cautious optimism.

Early big risks overcome

The first hurdle, of surviving the bone marrow transplant procedure, has been overcome: in itself, this is a risky procedure because Nate's own bone marrow had to be destroyed by intensive chemotherapy to prevent his body rejecting the transplanted bone marrow. This was necessary to reduce the risk of transplant rejection, even though his brother was a perfect tissue match. And, until the transplanted bone marrow created a new immune system for Nate, this would leave him open to infection.

The main measure of success of the trial was that Nate would have some detectable collagen derived from the transplanted cells after about 3 months. He did, but his skin still shows considerable fragility and is thus not normal – he cannot yet be said to be

cured. Full details of the trial, the techniques used, and the clinical and scientific analysis of the results, have yet to be published in a peer-reviewed journal.

Of mice and men....

Nate is the first child to receive a bone-marrow transplant to attempt to treat EB. What is the evidence that this type of cell therapy might work?

Mice that mimic human RDEB had been created in the laboratory – these mice lack functional collagen VII protein and show all the characteristic signs of RDEB, including a lack of anchoring fibrils holding the dermis and epidermis together, extensive blistering and fusion of toes, and a very short lifespan. These mice were created specifically for the purpose of testing novel RDEB therapies, by the laboratory of Jouni Uitto (Professor and Chair of the Department of Dermatology and Cutaneous Biology, Thomas Jefferson University in Philadelphia), a member of DEBRA's Medical and Scientific Advisory Panel.

Extensive research was then carried out by University of Minnesota researchers Jakub Tolar, and Bruce Blazar. Injections of various types of stem cells were tried with the RDEB mice while they were still in the uterus, but all the treated mice still died within two weeks of being born. Only one type of stem cell, derived from bone marrow, seemed to have any benefit: of thirteen mice treated, three were born with healing blisters and survived for more than 2 months. Although it seemed to work in only around one-quarter of the mice treated, this was the proof-of-principle that transfer of bone marrow could correct the clinical condition, in mice at least.

Angela Christiano (Professor of Dermatology and Genetics, Columbia University Medical Center, New York), who has worked on RDEB genetics for some 15 years, much in collaboration with Jouni Uitto, first put forward the idea of using stem cells to treat Nate, to his family. She was also involved in carrying out the detailed genetic analysis of Nate's mutation to find out whether he was suitable for this type of treatment. Christiano and Uitto's work together has included identification of the human and mouse type VII collagen genes, establishing type VII collagen gene mutations as the molecular basis for dystrophic forms of EB, leading to the development of DNA-based diagnostic tests for EB and eventually to pre-clinical animal models, through research supported by DEBRA.

Based on the RDEB mouse studies, John Wagner, a hematologist at the University of Minnesota Medical School, put together a team at the University of Minnesota and designed the clinical trial to test this type of stem cell therapy for humans. His team were able to proceed with this experimental procedure because bone-marrow transplantation is an accepted, though risky, medical procedure, and the University of Minnesota Medical School has a track record of successful use of bone-marrow transplantation for treating various diseases.

But, is it a long-term 'cure'?

The big question is whether the skin stem cells derived from the transplanted bone marrow survive and reproduce, and continue to give Nate an adequate supply of collagen to hold his skin together for the rest of his life. A further question is whether the transplanted bone-marrow cells will also persist and continue to provide him with an immune system.

This is why the clinical trial will continue to monitor Nate's progress over the next two years. This will involve blood sampling and skin biopsies at intervals to measure, for example, the recovery of his immune system, and any signs of rejection of the

transplanted cells, and any incidence of potentially serious 'graft-versus-host' disease after one year.

Furthermore, the continued production of new collagen will be monitored, as will the relative proportion of his skin cells that are derived from the transplant – this will give an indication of whether the transplanted cells are likely to continue to survive and make a significant contribution to skin strength. (Nate's skin is still 'chimeric' i.e. his skin is made up of some of his own skin cells, and some skin cells derived from his brother's bone marrow stem cells – if the transplant is successful long-term, it will be because Nate's skin is derived in large part from stem cells from the donated bone marrow.) As John Wagner, who oversaw Nate's therapy, reportedly says, he hopes Nate's body will continue to make more collagen VII over time - this is essential if Nate is to continue to make good progress.

Should insufficient levels of collagen type VII be produced by the donor cells to prevent the blistering and other problem of RDEB, it's thought that the bone-marrow transplantation might have made Nate's immune system able to accept grafts of skin cells from his brother - as a back-up strategy, this could improve his quality of life and chance of survival.

Even after completion of the two years of the current treatment study, Nate will be followed periodically for at least 5 years: it will be some time before the long-term outcomes will be known.

What are the prospects for other patients with RDEB?

Nate is very young and so, if the treatment is successful, he may avoid much of the skin damage and scarring accrued over time by RDEB patients. This trial will eventually recruit 10 patients, under the age of 8 years. It is likely that patients for this trial will be recruited from US patients, and over 100 enquiries have already been received. If this trial proves successful, similar trials may well be developed internationally in the not too distant future.

Nate's parents and doctors have reportedly already decided that Nate's 5-year-old brother, Jake, who also has RDEB, will also undergo a bone-marrow transplant. However, the stakes are higher for Jake, as it was not possible to find a perfectly matched tissue donor, so he is receiving a transplant from an unrelated donor. Because Jake is older, he has already accumulated significant scarring, with fusion of his fingers. If the transplant proves successful, surgeons will reportedly try to repair the damage – indeed, if his skin recovers some of its healing ability, such hand surgery may stand a greater chance of success.

Still more research needed to make therapy safe and effective

Even if Nate's story is a success, there needs to be further research before this approach can be regarded as likely to be appropriate for many more RDEB patients: it only worked for one-quarter of the mice tested.

Issues concerning how safe and effective the technique is, and how it might be improved, have already been identified: it is important to know exactly which cells are responsible for any benefits, and what effects that laboratory manipulation might have on the cells. There's also a need to reduce the risks of using cells from a donor, such as chronic immune rejection, or infection. Research in these areas will enable the design of improved 'second-generation' trials, for further patients.

The preliminary pre-clinical work took three years, from 2004 to 2007, and this included not only the research on the mouse RDEB model, but also writing the

protocol for the clinical trial, taking the trial through the different US regulatory agencies, ethics panels, securing funding approval from health insurance companies and putting together the clinical-care team. These procedures will vary in detail from country to country, but the same issues need to be addressed. So far, it is estimated that the costs for Nate's treatment reach about \$500,000, met in part by university research funding, part by insurance, and in part by fund-raising by Nate's family.

DEBRA International is currently engaged in discussions with the EB research and clinical community, including through Task Forces specifically set up to address such issues. Through our expert advisors, we are looking at how we can help to expedite delivery of treatments while at the same time helping to ensure, through funding of further fundamental and preclinical research, that questions of safety and efficacy are thoroughly investigated for a wide range of candidate therapies.

For further information from other sources see:

Clinical and scientific detail on trial:

<http://www.cancer.gov/clinicaltrials/UMN-MT2006-15>

University press releases:

http://cumc.columbia.edu/news/press_releases/stemcell-collagen-vii-RDEB-angela-christiano.html

<http://www.ahc.umn.edu/eb/>

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