MedicalXpress

Gene therapy for blistering skin disease appears to enhance healing in clinical trial

November 1 2016

Grafting sheets of a patient's genetically corrected skin to open wounds caused by the blistering skin disease epidermolysis bullosa appears to be well-tolerated and improves wound healing, according to a phase-1 clinical trial conducted by researchers at the Stanford University School of Medicine.

The results mark the first time that skin-based gene therapy has been demonstrated to be safe and effective in patients.

The findings will be published Nov. 1 in *JAMA*. Associate professors of dermatology Peter Marinkovich, MD, and Jean Tang, MD, PhD, share senior authorship of the study. Senior scientist Zurab Siprashvili, PhD, is the lead author.

For the study, four adult patients with recessive dystrophic epidermolysis bullosa, an excruciatingly painful genetic skin disease, received the skin grafts.

"Our phase-1 trial shows the treatment appears safe, and we were fortunate to see some good clinical outcomes," said Tang. "In some cases, wounds that had not healed for five years were successfully healed with the gene therapy. This is a huge improvement in the quality of life for these people."

People with epidermolysis bullosa lack the ability to properly produce a protein called type-7 collagen that is needed to anchor the upper and

lower layers of the skin together. As a result, the layers slide across one another upon the slightest friction, creating blisters and large open wounds. The most severe cases are fatal in infancy. Other patients with recessive dystrophic EB can live into their teens or early adulthood with supportive care. Often these patients die from squamous cell carcinoma that develops as a result of constant inflammation in response to ongoing wounding.

The Stanford researchers showed that it was possible to restore functional type-7 collagen protein expression in patient skin grafts to stop blistering and allow wounds to heal. They also found that the protein continued to be expressed and that wound healing was improved during a year of follow up.

Looking to build upon results

The researchers seek to build upon these promising early results in a new trial that will include patients ages 13 and older.

"Moving into the pediatric population may allow us to intervene before serious chronic wounds and scars appear," said Marinkovich, who directs the Stanford Blistering Disease Clinic. Repeated rounds of wounding and scarring on the fingers and palms, for example, often lead to fusion of the skin and the formation of what's known as a "mitten hand."

Siprashvili used a virus to deliver a corrected version of the type-7 collagen gene into batches of each patient's skin cells that had been harvested and grown in the laboratory. He coaxed these genetically corrected cells to form sheets of skin about the size of an iPhone 5. The sheets were then surgically grafted onto the patient's chronic or new wounds in six locations.

The researchers tracked the status of the grafts at one-, three- and six-

month intervals for at least a year, checking to see if they stayed in place and caused wound closure. They also looked for any evidence of an immune reaction to the grafts, and whether the grafts continued to make the corrected type-7 collagen protein.

All 24 grafts were well-tolerated, the researchers found. Furthermore, they could detect expression of the type-7 collagen protein in the correct location of the skin in nine out of 10 tissue biopsies at three months. After 12 months, they were able to detect the collagen protein in five out of 12 biopsies.

Wound healing

Similar results were seen with wound healing. After three months, 21 of the 24 grafts were intact. This number dropped to 12 out of 24 after one year.

"Even a small improvement in wound healing is a huge benefit to the overall health of these patients," said Tang. "For example, it may reduce the likelihood of developing squamous cell carcinoma that often kills these patients in young adulthood."

Coupling grafts with hand surgery to break up scarred, fused tissue could help patients maintain the use of their hands, Marinkovich said.

Tang, Marinkovich and their colleagues will continue to monitor the patients in the phase-1 trial throughout their lifetimes to assess any long-term effects of the grafts.

The completion of the phase-1 trial and the potential to improve upon these outcomes is due to a concerted, long-term effort at Stanford to find ways to help young patients with this devastating disease.

The researchers are now starting a phase-2 clinical trial and are looking for new patients. For more information, send an email to tangy@stanford.edu or mpm@stanford.edu.

"This trial represents the culmination of two decades of dedicated clinical and basic science research at Stanford that began with the arrival of the former dean of the School of Medicine, Eugene Bauer, who set up the multidisciplinary EB Center at Stanford," said Tang. "We have been working for a long time to get to this potential therapy into patients. We had to discover the genes and proteins involved and the responsible mutations. We then had to learn to deliver the corrected gene and grow those cells into sheets suitable for grafting."

"We could not have reached this point without the support of the EB patients and their families," said Marinkovich. "Since the time of my research training in the laboratory of Robert Burgeson, PhD, who discovered type-7 collagen, I've been deeply motivated to contribute to the EB community, and it is very satisfying to be able to finally see this molecular therapy come to fruition."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Provided by Stanford University Medical Center