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Her Journey with Lupus

STEM cell TRANSPLANTATION

BY JENNY ALLAN

Experts weigh in on this potentially life-saving treatment for lupus

STEVE ALLEN/GETTY IMAGES

Corrina Vigil lived a normal life, with an older brother and sister and a twin sister in Arvada, Colo., until she was nearly 15 years old. It was during ninth grade that her knees began to feel weak. Bending down became difficult. She developed flu-like symptoms, along with swelling in her fingers and joints. Her pediatrician ordered a variety of tests, and in a few weeks Corrina had an answer: systemic lupus. "From the time of that diagnosis," she says, "I knew my life would never be the same."

Corrina recalls spending most of the next few years trying to get well, and watching her identical twin enjoy normal activities that seemed like impossible chores because of her constant weakness and pain.

"My goal at this time was just to get my [high school] diploma and attend graduation," Corrina recalls. "I remained determined to finish school even on mornings when getting out of bed was nearly impossible." By March of 1999, her senior year, she had lost kidney function and was developing heart complications. By 2002, she was bedridden and had open wounds (calciphylaxis) caused by her kidney failure.

But in September 2002, Corrina became one of the few people in the United States to receive a hematopoietic stem cell transplant at Northwestern University in Chicago. In this dramatic, experimental procedure, the stem cells that give rise to all blood cells are withdrawn from a patient's bone marrow and sustained outside the body in a disease-free environment. Then, most of the immune-system cells in the patient's body are destroyed. Finally, the harvested stem cells are reimplanted—theoretically, cleansed of lupus.

A Lifesaving Treatment for Lupus

Although still considered an experimental treatment for lupus, hematopoietic stem cell transplantation (HSCT) has been undertaken in about 100 individuals in the U.S. and Europe who have systemic lupus that has proved unresponsive to all the usual drugs and drug combinations.

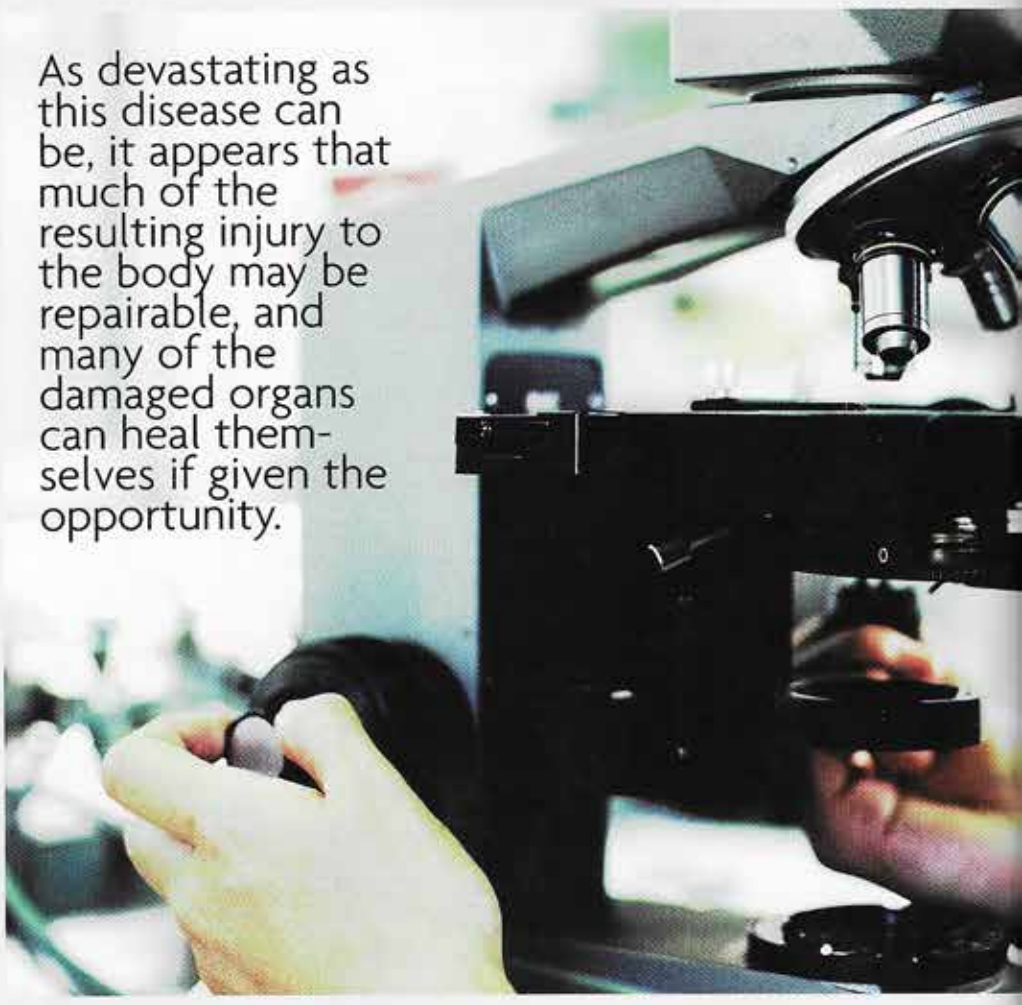
The concept underlying the use of HSCT for lupus is that for most people, lupus is not a straightforward inherited disease. If this is true, then the body's blood stem cells are not inevitably programmed to produce lupus. A person may have a genetic predisposition to developing lupus, but the disease occurs because certain factors in that person's environment and hormonal makeup compound that risk.

If this theory is correct for most people with lupus, it follows that, if their stem cells are allowed to develop outside their bodies, in a safer environment, a normal immune system should emerge when damaged cells in their bodies are destroyed and healthy blood stem cells are reinfused into their bone marrow. Lupus may not redevelop at all, or may not redevelop for many years, unless or until the same risk factors come together again in the same manner.

Body, Heal Thyself

The U.S. physicians with the most experience in the HSCT procedure practice today at the Division of Immunotherapy for Autoimmune Diseases of Northwestern University/Northwestern Memorial Hospital (NWU/NMH) in Chicago. Over the past six years, Richard Burt, M.D., and his colleagues have performed hematopoietic stem cell transplants on 40 people with life-threatening lupus, mostly young women in their teens and early twenties. Besides lupus, their team also has performed the first stem cell transplants in America for a variety of other autoimmune diseases.

Of the 40 individuals who received HSCT for lupus, Burt notes, three people died following the transplant. "They died of relapsed aggressive lupus; they did not die of the procedure," he says. In addition, three others developed renewed lupus activity following the transplantation. Burt says that, although all the follow-up data are not in yet, he anticipates relapse in 40 to 50 percent of the NWU lupus transplant cases.



As devastating as this disease can be, it appears that much of the resulting injury to the body may be repairable, and many of the damaged organs can heal themselves if given the opportunity.

However, instead of being resistant to available treatments, such as Cytoxan (also known as cyclophosphamide) the bodies of lupus transplant patients are much more responsive to these medications.

"Almost everyone gets benefit and marked improvement, and more than 60 percent have been in complete remission for years. For people who have failed every other therapy, stem cell transplantation has shown very promising results," Burt says.

The patients who have most benefited from hematopoietic stem cell transplants have had very active lupus, involving the kidneys, brain, spinal cord, lungs or heart. And it appears that the greater the degree of inflammation prior to the transplant, the better the outcome will be. This highlights one of the remarkable aspects of lupus: as devastating as this disease can be, it appears that much of the resulting injury to the body may be repairable, and many of the damaged organs can heal themselves if given the opportunity.

New Lupus Clinical Trial Underway

The stem cell transplantations for lupus that have been performed worldwide so far have had varying degrees of success, according to Steven Pavletic, M.D., head of the Graft-Versus-Host and Autoimmunity Unit, Experimental Transplantation and Immunology Branch of

the National Cancer Institute of the National Institutes of Health (NIH). He explains that these were pilot studies whose primary aim was to assess feasibility and tolerance of the stem cell transplant for severe lupus.

"But now," Pavletic says, "an intramural study at NIH takes this research a step further."

Researchers at NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) are preparing to subject the procedure to the rigorous criteria of clinical trials. Recruitment is underway for 14 lupus patients, and the study will be conducted at the NIH Clinical Center, in Bethesda, Md. (See sidebar on page 28 for explanation of criteria.)

"This is the first lupus transplant study in the world that is using carefully and rigorously defined entry and response criteria," notes Pavletic.

"The unique aspects of what we are doing in this study are several-fold," says Barbara Mittleman, M.D., director of the NIAMS Office of Scientific Interchange. Most important, she says, "We are setting out careful and well-defined entry criteria for neuropsychiatric SLE, hematologic SLE, renal SLE and pulmonary SLE. This level of definition has not been used before."

Mittleman says that the NIAMS treatment plan, too, is somewhat different from treatments that have been used elsewhere. In other centers, the patient is given medicine to stimulate the bone marrow to make high numbers of stem cells, which are then collected and purified for later re-infusion.

The preparative regimen used at the NIH involves two drugs, cyclophosphamide and fludarabine, along with an antibody to the disease-causing B lymphocytes. These will be given in order to empty the bone marrow of all B lymphocytes, but not other necessary white blood cells or platelets. Specifically getting rid of B lymphocyte cells may be very important in SLE, since B cells make the autoantibodies that occur so typically in this disease. Selective targeting of lymphocytes and not other cells helps prevent infection, and allows the blood counts to return to normal more rapidly after the transplant.

"A unique feature of the NIH is our ability to do clinical studies and intensive basic science investigations at the same time," Mittleman says. "We plan to determine which cells are present and active in lupus patients prior to the transplant, and then see what we have gotten rid of, which cells come back and when. We will then correlate this information with the patient's clinical status."

Finally, says Mittleman, the NIH is planning careful and controlled follow-up of the patients, with defined rules for re-starting or tapering corticosteroids or immunosuppressive agents, if such measures become necessary. "Careful follow-up, and the same rules for treatment for all patients, will make it possible to know what has happened and why.

"This approach may help us identify which patients can benefit most from such an intervention, as well as help us refine our regimen to get the maximal good response with the least toxicity and morbidity," she says.

As with all investigational studies, the Food and Drug Administration will have to review and approve the protocol—the set of procedures for the trial—before the clinical trial can begin. "The FDA is an important partner with investigators at the NIH and elsewhere, to develop safe and effective treatments," Mittleman says.

Mittleman acknowledges that it's hard to know just how long the study may take. "It depends on how rapidly we are able to recruit patients, and whether this approach succeeds.

"The initial period will involve a stay at the Clinical Center and in the local area for frequent evaluation and close follow-up; after that, we will follow up at least every month to three months. This depends somewhat on how the patient is doing from a clinical standpoint, but study evaluation points are at least every three months for most measures," she says.

She adds, "If lupus recurs in a patient, we will consider that they have failed this trial, which is looking for 'cure'—meaning a disease-free, treatment-free response to the intervention. If lupus does not recur, we will wait a reasonable time to feel confident that this is the case, and evaluation will go on for one to two years after the transplant."

"We cannot promise a cure, but this is our long-term goal with using stem cell transplantation for autoimmune disease," Pavletic says. "We want to answer more precisely the question 'Does this therapy help these patients?'"

Who Pays?

As always with new and emerging therapies, cost is an issue. The HSCT proce-

dure can cost $150,000—not counting housing and living expenses incurred during the treatment, and required follow-up visits to monitor and report information for the trial. Many insurance companies consider it experimental and refuse to pay for it.

"Insurance companies are getting better at covering the procedure," notes Burt. "Many states do pay with Medicaid, but usually the patient will have to go through an appeals process."

Certainly, a huge benefit of participating in the NIH-run clinical study, Mittleman points out, is that expenses are covered.

"No patients are charged for NIH studies," she stresses, "not for lab tests, not for imaging, not for medications or treatments, not for hospitalizations."

In addition, she says, travel and lodging assistance may be available to patients who do not live in the Bethesda/Washington area. But, while that is good news for the 14 participants who go to the NIH Clinical Center, many people can't afford to take advantage of an expensive experimental therapy such as stem cell transplantation.

Fortunately for Corrina Vigil, her older sister, Julie, and Julie's husband were in a financial position to spend the thousands of dollars necessary to temporarily relocate Corrina and her mother from Arvada to Chicago, and to cover the cost of staying there for several months during the transplant and follow-up visits. They also made her mother's house payments, which saved the home from certain foreclosure.

"Today Corrina is walking around, she's driving—she's doing all the things she was never supposed to be able to do," Julie says.

But the distress over what her family went through still lingers. Julie knows that many patients, who are as sick as Corrina was, do not have the financial resources that Julie and her family had.

"My mother lost both her jobs after the 13-week unpaid family leave ran out," Julie relates. "But what was she supposed to do? Say to her child, 'Well, I have to go back to work now,' and leave the hospital and maybe never see her daughter alive again?"

BraveWings Reaches Out

The harrowing experiences of Corrina's illness and recovery led Julie, her husband, and several friends and business colleagues to start a nonprofit fundraising charity called The BraveWings Foundation, in honor of Corrina's inspiration and courage. In partnership with Northwestern Memorial Hospital and Northwestern Memorial Foundation, The BraveWings Foundation helps families pay for the two- to three-month stay in Chicago when a family member is undergoing the stem cell transplant procedure for lupus or other autoimmune diseases.

Corrina turned 23 on December 29, 2003, but considers September 2002 the date of her rebirth. She has no signs or symptoms of the diseases that nearly took her life in 2002—lupus, colitis, renal disease and calciphylaxis—and she has received a kidney transplant, a gift from her twin sister, Ericka. She says she has never felt better.

"At one point I wanted to die because of the pain from the calciphylaxis, but I have a twin sister, and I didn't want to leave her, or my family," Corrina remembers.

"There is still so much in life left for me, and I would tell other young people with lupus, 'Just don't give up.'" ■

Gabor Illei, M.D., Principal Investigator/Rheumatology at NIAMS, explains the protocol and criteria for the lupus clinical trial:

"Eligible candidates will have therapy-resistant, severe active lupus with the potential of a long-term response to HSCT. Eligible patients must have either kidney, lung, severe hematologic [blood] or nervous system manifestations that are associated with signs of inflammation," he says.

He explains that therapy-resistant disease is defined as 'worsening of disease despite immunosuppressive therapy or the inability to taper prednisone below 0.5 mg/kg.' "The minimum length of immunosuppressive therapy will be defined based on the organ involved," Illei says.

He adds that active disease will be differentiated from permanent damage: "For example, proteinuria would be regarded as active only if it is supported by an active urine sediment or a biopsy."

In addition to fulfilling these criteria, enrolled subjects must have acceptable major organ functions (lung, heart, liver, kidney). Illei adds that some other exclusion criteria also apply, and that there is no control group, as the study is not blinded.

Corrina's journal can be read in its entirety at **www.bravewings.com**.