

# Stem Cell Transplants for PIDDs



By Ronale Tucker Rhodes, MS

Better gene sampling and newer transplant regimens are making stem cell transplantation possible for a host of disease states that previously were rarely considered for this procedure.

**O**n April 4, a group of physicians at the 37th annual meeting of the European Group for Blood and Marrow Transplantation in Paris, France, reported that they believe hematopoietic stem cell transplants (HSCTs) are feasible in patients with common variable immune deficiency (CVID) and that it can result in an improvement of the immunodeficiency. Their conclusion was a result of a cohort of four CVID patients who underwent HSCTs with peripheral stem cell grafts. All four of the patients presented with a host of other medical issues, in addition to CVID. In all, no graft failure occurred. Two of the patients had normal values for T and NK cells two years after HSCT, while only one patient showed normal B cell subsets resulting in independence of IG substitution.



One patient died three months after HSCT due to infectious problems.<sup>1</sup>

Transplants are controversial for patients with CVID, one of the more common primary immunodeficiencies (PIDDs), because there are no published data that prove they are effective. In contrast, transplants are very common in a lot of the genetic immune deficiencies, such as severe combined immunodeficiency (SCID) and Wiskott-Aldrich syndrome (WAS). But that is slowly starting to change. Not only are transplants becoming more and more successful in curing genetic immune deficiencies, but better gene sampling and newer transplant regimens are now making transplants possible for other immune and autoimmune disease patients.

### How Transplants Work

There are two forms of stem cell transplants: autologous and allogeneic. In an autologous transplant, patients receive stem cells from their own blood. In an allogeneic transplant, the stem cells come from a donor, which can be a sibling, family member or unrelated individual. Since immunodeficient patients have abnormal function of B cells and T cells, the very cells that are being replaced by a transplant, an allogeneic stem cell transplant is the only option.

The first successful allogeneic HSCTs in PIDD patients occurred in 1968 when three patients received grafts from human leukocyte antigen (HLA)-matched siblings — two with SCID and one with WAS. Since then, significant progress has been made in correcting PIDDs due to four factors: 1) the ability to phenotype and quantitate hematopoietic stem cells, 2) the advent of high-resolution tissue typing, 3) the availability of closely matched unrelated donor bone marrow, peripheral blood stem cells and

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cord blood and 4) the application of reduced-intensity conditioning regimens pre-transplant. In addition, the genetic basis of many PIDDs is now being identified, allowing for earlier transplantation that provides a much greater success rate.<sup>2</sup>

With HSCT, a patient's cells are replaced with the donor's. Donor cells are collected in one of three ways: bone marrow, peripheral blood and cord blood. In a bone marrow transplant, stem cells are collected through a surgical procedure conducted in a hospital. This procedure involves inserting a needle into the donor's hip bone to remove the stem cells from the marrow. A peripheral blood or cord blood stem cell transplant is conducted in an outpatient setting. In the peripheral blood cell transplant, a donor is given medicine to increase the number of stem cells in the bloodstream. Then, much like a blood transfusion, blood is collected from the donor, stem cells are separated from the blood and collected, and the blood is returned to the donor.<sup>3</sup> In a cord blood stem cell transplant, umbilical cord blood is collected from the umbilical cord

and placenta after a baby is born. Donated cord blood, which is rich in blood-forming cells, is tested, frozen and stored at a cord blood bank for future use.<sup>4</sup> In all three procedures, most patients receive a preparatory regimen of doses of chemotherapy, radiation or both to destroy their existing immune system. While high doses of chemotherapy were once the norm, some patients today are getting lower doses, known as reduced-intensity (nonmyeloablative), or “mini,” transplant. After the preparatory regimen, the donated stem cells are injected into the patient through a tube that goes into a vein in the chest, and the stem cells find their own way to the marrow space.<sup>3</sup>

According to Troy Torgerson, MD, PhD, attending physician at Seattle Children’s Hospital, who specializes in the clinical care of patients with immune deficiency and autoimmune disorders and who coordinates care for patients treated by HSCTs, the determination of how cells are collected really depends upon what the patient’s needs are, and there are different advantages to using one or another. In addition, he says, it depends on the site where the transplant is being conducted, as some facilities do only certain types of transplants.

### **Donor Matching**

The closer the tissue type match between the patient and the donor, the better the chance of the transplant being a success. Donors are matched to patients through a process called HLA matching. HLAs are proteins found on the surface of most cells, and make up a person’s tissue type. Each person has a number of pairs of HLA antigens that are inherited from their parents. The best match is when all of the major HLA antigens are the same — a six out of six match. However, for bone marrow and peripheral blood stem cell transplants, sometimes a donor with a single mismatched antigen is used — a five out of six match. For cord blood transplants, a perfect HLA match isn’t as crucial, and even a sample with a couple of mismatched proteins may be OK.<sup>5</sup>

Related donors have had better success rates. “In general, the order of preference from lowest to highest risk is a matched sibling [matched related donor] is the best, followed by a matched unrelated [donor],” says Dr. Torgerson. “Next in line is a cord blood transplant, which works very well in a lot of patients. With cord blood, you can be a little more flexible in matching. And, then, the worst is a half-match [haploidentical donor].” Today, an HSCT from an HLA-matched sibling donor offers a 90 percent chance of a cure for certain PIDD patients, such as

those with SCID, WAS and other prematurely lethal X-linked immunodeficiencies. And, in some conditions, the availability of closely matched unrelated donors (adult marrow or umbilical cord blood) can provide similar results. For patients with genetically determined immune/inflammatory disorders such as hemophagocytic lymphohistiocytosis (HLH) and other disorders of immune homeostasis, the results with HSCT are less favorable, with five-year disease-free survival rates closer to 60 percent to 70 percent.<sup>2</sup>

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In the past, SCID patients typically received either haploidentical or cord blood transplants because there was a rush to transplant since the children had infections and the parents were readily available, says Dr. Torgerson. But now that SCID tests are done routinely at birth in many states, early diagnosis while the child still has protection from the mother’s antibodies allows a wait of a month or two so a well-matched donor can be located. One of the problems with haploidentical donors, explains Dr. Torgerson, is that some patients lose their grafts later in life and they have to be retransplanted.

In a study of 89 children with SCID who received transplants at Duke University Medical Center in North Carolina between 1982 and 1998, only 12 had a matched related donor, while the others had a partly matched related donor. All 12 of the children with a matched related donor were alive, while only 60 of the 77 children with a partly matched donor were alive. In another European multicenter study of 475 children with SCID who received a transplant between 1968 and 1999, 153 had a matched related donor, 11 had an unrelated donor and 294 had a partly matched related donor. The three-year survival rate was 77 percent for those with a matched donor (either related or unrelated), while it was only 54 percent for those who had a partly matched related donor.<sup>6</sup>

Because there are thousands of different combinations of possible HLA types, an exact match is hard to come by. Finding a donor usually begins with siblings who have a one out of four chance of being a perfect match. If a good match is not found in a sibling, the search moves to other relatives, such as parents, half-siblings, and extended family. Then, the search widens to the general public. Bone marrow registries serve as matchmakers between patients and volunteer donors. The largest registry in the United States is the National Marrow Donor Program, which lists the tissue types of approximately nine million possible donors and nearly 145,000 cord blood units. The Caitlin Raymond International Registry is another agency that has access to millions of international records. Each year, the chances of finding a matched unrelated donor improve, and today, about half of white people who need stem cell transplants can find a perfect match, while this drops to about one out of 10 people in other ethnic groups due to their diverse HLA types.<sup>5</sup>

Because of the ability to better identify a donor match, as well as the improved pre-transplant treatment that mostly destroys the immune system, the chance of problems is much lower than before. However, there can be complications. First, if the donor is not a good match, it's possible that the patient's immune system will recognize the new stem cells as foreign and destroy them. This is known as graft rejection. Another problem occurs when the donor stem cells make their own immune cells and the new cells see the patient's cells as foreign and turn against their new home. This is known as graft-versus-host disease.<sup>5</sup> "[A] bone marrow [transplant] is typically associated with lower graft versus host disease rates than [a] peripheral [blood transplant]," says Dr. Torgerson. "But, peripheral allows us to isolate more cells and give a higher cell dose."

### **Transplant Candidates**

"Transplant is a big deal," says Dr. Torgerson. "I tell families that a bone marrow transplant is the surest way for your child to be dead by Christmas. But it's also the surest way for your child to be alive 20 years from now." In short, it's a balancing act. And, it all comes down to the individual patient.

There are three factors that determine whether a transplant is viable for a patient. First is whether the benefits outweigh the risks. "In a CVID patient, one of the things we look at is they're living into the 50s and beyond," explains Dr. Torgerson. "Do we want to risk killing them in their 20s with a bone marrow transplant?" But, some of

these patients also present with a lot of comorbidities, and Dr. Torgerson recommends transplanting these patients because they are not going to live healthy lives and they are likely to be heavy users of the medical system. What's needed is a set of predictors to see which patients are going to be high risk versus low risk with just treatment, says Dr. Torgerson. For instance, X-linked agammaglobulinemia patients just don't experience as many comorbidities, so they do better with just treatment.

Second is whether the insurance company will pay for a transplant. The problem is that there is a lack of literature that shows that a transplant will work. "When there's no literature, insurance companies don't want to pay for it," explains Dr. Torgerson. "The last one I did took just over a year to get the insurance to cover it, and many hours of my life. The patient eventually got it by going to the press." Yet, while expense is a factor, many insurance companies are starting to realize that for patients who have a host of other autoimmune diseases that need to be treated with IVIG, as well as a whole lot of other drugs, the cost of the transplant might be cheaper in the end.

Third is whether this is a genetic defect. It's known that patients with a genetic defect are not going to do well, and many die by the time they are 20 years old. So, in those cases, a transplant makes sense. But, CVID patients don't have a genetic defect, at least any that are the cause of the disease. "So, you watch the patients and as they get down the road, now they've got lung disease and gut disease and type 1 diabetes," says Dr. Torgerson, "so now, we have to think about transplanting these patients. It's based on clinical picture."

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Dr. Torgerson believes that we are at the point now where transplants should be considered for patients who have a host of comorbidities, such as the more severe CVID patients. He estimates that about 20 percent of CVID patients have autoimmune disorders. And, based on his patient cohort at Seattle Children's Hospital, just more than

5 percent of his patients would “fall into the category that they would have so many problems that a transplant would be a reasonable thing to think about.”

### **The Future of Transplantation**

Many PIDD patients are hanging their hopes on a transplant to cure them. But not all PIDD patients are transplant candidates. “As good as medicine is now, I am still humbled,” says Dr. Torgerson. “Sometimes, we get a little cavalier that it’s ‘just’ a transplant.” Regardless, the number of transplants has increased quite a lot for two reasons, says Dr. Torgerson: “safer transplant regimens and finding genetic disorders in disease where we hadn’t really thought about them before.”

Many studies to determine who are good transplant candidates are going around in different centers around the world. Dr. Torgerson’s center has a study for transplant in nonmalignant diseases, like immunodeficiencies. His facility has developed an integrated transplant program that operates like a tumor board format.

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A patient being considered for transplant who has a nonmalignant disease meets with the providers on the board, which include a neurologist and two transplant infectious disease doctors. The board examines the patient’s records and decides whether transplant is advisable, which regimen should be used and which kind of donor should be used. A protocol and document are then developed, which go into the patient’s chart. When it comes time for the transplant, the immunologists step into a consultative role and the transplant specialists take over. If all goes well after the transplant, the patient’s care transitions back to the immunologists and the transplant specialists take on the consultative role.

The future of HSCT looks very promising, especially for PIDD patients, because of increased successes and, now, genome sequencing. “There’s going to be an explosion of identification of new gene defects that will allow us to put a genetic label to predict in a more definitive way how they’re going to do in the future,” explains Dr. Torgerson. “It’s going to do two things: 1) help to identify new gene defects that we hadn’t known before, and in some disorders like CVID, it’s going to give us some answers, 2) help to expand the phenotypes. Maybe five to 10 years from now, people are going to show up in a clinic with their genome on a disk, and they’re going to ask the doctors: ‘Is there anything there that could cause the symptoms I’m having?’”

### **A New Beginning for Many**

“There will never be a transplant that is 100 percent safe,” says Dr. Torgerson. “But we are approaching the point at which the balance of the risk-to-benefit ratio might tip in favor and become safe enough even for disorders like CVID. The risk-to-benefit ratio will be equivalent, especially as we do more transplants and we see how successful they are.” ■

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