

HIV drug reduces graft-vs.-host disease in bone marrow transplant patients

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An HIV drug that redirects immune cell traffic significantly reduces the incidence of a dangerous complication that often follows bone marrow transplants for blood cancer patients, according to research from the Perelman School of Medicine at the University of Pennsylvania that will be published today in the *New England Journal of Medicine*. The findings represent a new tactic for the prevention of graft-versus-host disease (GvHD), which afflicts up to 70 percent of transplant patients and is a leading cause of deaths associated with the treatment.

Allogeneic [bone marrow transplantation](#) – also known as stem cell transplantation – involve the transfusion of a matched donor's blood stem cells to rebuild the patient's [bone marrow](#) after treatment has eliminated both the defective blood cells associated with their cancer and their healthy blood cells.

"It appears that our new approach allows us to prevent some [patients](#) from developing [GvHD](#) by redirecting [immune cells](#) away from certain sensitive organs that they could harm," says lead author Ran Reshef, MD, an assistant professor in the division of Hematology-Oncology and a member of the Hematologic Malignancies Research Program at Penn's Abramson Cancer Center. "This is a novel way for us to try to decrease treatment-related complications among bone marrow [transplant patients](#) without also reducing their new immune system's ability to attack their cancer."

Typically, patients receive immunosuppressive drugs following their

transplant to lower the risk of developing graft-versus-host disease (GvHD), which occurs when the newly transplanted immune cells attack healthy tissue they perceive as foreign. But since patients' own immune systems must be wiped out in order to receive their transplants, those drugs leave patients even more vulnerable to life-threatening infections and to a relapse of their cancer. The Penn team found that treatment with the [HIV drug](#) maraviroc dramatically reduced the incidence of GvHD in organs where it is most dangerous – the liver and gut -- without compromising any other function of the immune system.

The findings, which involved repurposing maraviroc -- approved for [HIV](#) treatment in 2007 -- could represent a breakthrough for prevention of GvHD. Reshef and his co-authors showed that the drug is safe in BMT patients who receive stem cells from a healthy donor, and that a brief course of the drug led to a 73 percent reduction in severe forms of GvHD in the first six months after transplant, compared with the incidence rate typically seen in similar patients who do not receive maraviroc.

"Just like in real estate, immune responses are all about location, location, location," Reshef says. "Cells of the immune system don't move around the body in a random way. There is a synchronized and well orchestrated process whereby cells express particular receptors on their surface that allow them to respond to small proteins called chemokines, which direct the immune cells to specific organs where they are needed -- or in the case of GvHD, to where they cause damage. We're using maraviroc, which was initially designed to prevent certain types of HIV from entering healthy cells in the body, as a traffic signal to direct the donor's immune cells away from those places in the body where they might cause GvHD."

Thirty-eight patients with blood cancers, including acute myeloid leukemia, myelodysplastic syndrome, lymphoma, myelofibrosis and

others, were enrolled in the trial. All patients received the standard GvHD prevention drugs tacrolimus and methotrexate, plus a 33-day course of maraviroc that began two days before transplant. In the first 100 days after transplant, none of the patients treated with maraviroc developed GvHD in the gut or liver, which are the most severe forms of the illness. At six months, only six percent of patients treated with maraviroc had severe graft-versus-host disease, only three percent had it in their liver, and nine percent had it in their gut. Among similar patients who receive standard drugs without maraviroc, rates of severe GvHD six months after transplant are 22 percent, with liver and gut involvement seen in 15 and 27 percent of patients, respectively. At one year, the benefit of maraviroc appeared to be partially sustained, with a cumulative incidence of severe GvHD of only 15 percent, as opposed to 29 percent in patients who receive standard therapy.

Based on these data, the research team plans to try a longer treatment regimen with maraviroc in future studies, to see if they could prolong the protective effect.

The differential impact of maraviroc on the liver and gut indicates that the drug is working as expected, by limiting the movement of immune cells called T lymphocytes to specific organs in the body. Maraviroc works by blocking the CCR5 receptor on lymphocytes, preventing the cells from trafficking to certain organs. The researchers saw no effect on skin GvHD, so they theorize that the CCR5 receptor might be more important for recruiting lymphocytes into the liver and the gut than for the skin.

Maraviroc treatment did not appear to increase treatment-related toxicities in these patients, nor did it alter the relapse rate of their underlying disease or risk of infection, and it did not slow the amount of time it took for patients' new immune systems to engraft in their bodies.

Provided by University of Pennsylvania School of Medicine

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