

Targeting histone deacetylases as a new strategy for graft versus host disease prevention

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New research shows that the addition of the oral anti-cancer agent vorinostat to standard therapy given before, during, and after hematopoietic stem cell transplantation (HSCT) may safely reduce the incidence and severity of a challenging complication called graft-versus-host disease (GVHD).

HSCT is the primary form of treatment for many patients with [blood disorders](#); it involves the transplantation of healthy blood-forming [stem cells](#) from the bone marrow, circulating blood, or umbilical cord blood to replace damaged, disease-causing cells in recipients. Despite the therapeutic benefits of HSCT, half of all patients who receive transplants from a related donor (allogeneic HCT) develop acute GVHD, a life-threatening condition occurring when the newly transplanted cells identify the recipient's body as foreign and attack the recipient's own cells.

Currently, HSCT patients receive prophylactic therapy before and after transplant to prepare their bodies for the procedure and to help manage their subsequent [immune response](#). While this series of drugs is designed to help reduce patients' risk of developing GVHD, it also compromises their immune systems, leaving them vulnerable to serious infections and complications. Recent research has sought to determine ways to improve patients' initial immune response to transplanted cells as well as promote faster immune recovery after transplant.

Recent early-stage studies have demonstrated that a class of anti-[cancer drugs](#) known as [histone deacetylase inhibitors](#) (HDACi) may safely reduce the risk of GVHD in patients. These drugs have demonstrated an ability to "turn off" an enzyme that leads to [inflammation](#), a major contributor to GVHD that develops as a [byproduct](#) of patients' intense immune response to HSCT. Based on those early results, researchers initiated the current study to evaluate whether one drug in this class, vorinostat, might reduce the risk of acute GVHD when added to current regimens.

To test this hypothesis, researchers enrolled 45 patients undergoing matched related donor HSCT from transplant centers at the University of Michigan in Ann Arbor, Mich. and Washington University in St. Louis to compare results of a standard regimen with vorinostat to historical controls. The primary endpoint of the single-arm, Phase I/II trial was the cumulative incidence of grade 2-4 acute GVHD (grade 1 is mildest; grade 4 is most severe). They aimed for an incidence of no more than 25 percent, compared with historical average rates of 42 percent.

Patients participating in the study received oral vorinostat daily in addition to standard preventive treatments prior to, during, and for 100 days after transplantation. After treatment, these patients had a significantly lower incidence of GVHD than their historical controls (22% vs. 42%) and had lower rates of severe (grade 3-4) GVHD (4% vs. 19% in controls) and transplant-related mortality at one year (13% vs. 19% in controls). There were no differences in rates of infectious complications or incidence of relapse, indicating that vorinostat helped reduce the risk of GVHD in patients without further compromising their immune systems.

"While GVHD remains a challenging complication that affects a large proportion of patients who receive stem cell transplants, we are

encouraged by the significant reduction in both the incidence and severity of this life-threatening condition that we observed in this trial," said Pavan Reddy, MD, senior author and Co-Director of the University of Michigan [Bone Marrow](#) Transplant and Hematologic Malignancies Program. "In order to increase the use of transplants and make them safer for more patients who need them, we need to see if this treatment approach may be successful in patients who receive stem cells from unrelated donors, and whether it may work among patients who are at high risk for severe GVHD. Moreover, we would like to confirm our findings in a larger, Phase III clinical trial."

Provided by American Society of Hematology

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