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SCIENCE SPOTLIGHT

New Immunosuppressive Drug Regimen Reduces Complications after Transplant

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Hematopoietic stem cell transplantation (HCT) is used to treat patients with blood cell malignancies. Before receiving a transplant, patients first must undergo treatment regimens to remove diseased bone marrow and to create an immunosuppressive environment that allows engraftment of donor stem cells and reconstitution of a normal blood system. Although the outcomes for HCT have improved, graft-versus-host-disease (GVHD) and relapse of the malignancy remain the main causes of morbidity and mortality. GVHD results from transplanted donor immune cells recognizing recipient cells as foreign and attacking them, however these same donor immune cells can prevent relapse by attacking diseased cells. The most optimal immunosuppressive drug regimen that balances dampening the risk of GVHD while preventing relapse is still under investigation. In a phase II clinical trial report published in *Haematologica*, lead author and visiting investigator Dr. Brian Kornblit in the laboratory of Dr. Brenda Sandmaier of the Clinical Research Division reports the safe addition of sirolimus to the immunosuppressive regimen after transplant.

Eleven different transplant centers treated patients prior to transplant with a reduced-intensity regimen, using low-dose total body irradiation and fludarabine, a cytotoxic purine nucleoside analog. This nonmyeloablative regimen allowed for the treatment of patients who cannot tolerate traditional high-dose conditioning regimens, such as older patients and those with comorbidities (Storb *et al.*, 2012). These reduced-intensity regimens promote engraftment through immunosuppression, but result in less tissue damage, inflammation, and lower rates of GVHD than traditional myeloablative regimens that aim to remove all diseased cells. After receiving transplants from unrelated matched donors, patients were randomized to three immunosuppressive drug regimens: arm 1, the standard regimen of tacrolimus and mycophenolate mofetil for 180 and 95 days respectively (n=69); arm 2, an experimental regimen of tacrolimus and mycophenolate mofetil for 150 and 180 days respectively (n=71), or arm 3, the same treatment as arm 2 with the addition of sirolimus for 80 days (n=68).

Both mycophenolate mofetil and tacrolimus are commonly used post-HCT, while sirolimus is traditionally used in solid organ transplants to prevent rejection. Each drug functions by inhibiting different pathways that control immune cell function. Mycophenolate mofetil blocks the growth of T and B cells by inhibiting a specific enzyme involved in recycling purine nucleotides for DNA

synthesis. Tacrolimus inhibits calcineurin, an enzyme necessary for activation of T cell function. Sirolimus inhibits the mTOR cell signaling pathway, blocking the response of immune cells to cytokines.

Patients in all three arms of the study sustained donor engraftment with no significant differences in relapse or overall survival rates. The non-relapse mortality at 2 years was comparable among the three arms at 26%, 23%, and 18% respectively. While toxicity rates were similar, the rate of acute GVHD at day 150 was 64%, 48%, and 47% for the three arms respectively (arm 3 vs. arm 1 hazard ratio 0.62, $p=0.04$). Since the incidence of acute GVHD was lower, fewer steroids were administered to patients in arm 3 versus arm 2 and arm 1 (32% vs. 49% vs. 55%, $p=0.009$). The rate of cytomegalovirus (CMV) reactivation was also lower in arm 3 (22%) versus arm 2 (47%) and arm 1 (22%). The mechanism of decreased viral reactivation by sirolimus is unknown, but could be due to either reduced steroid use or antiviral activity of the drug. Taken together, the study demonstrated that the combination of the three immunosuppressive drugs is safe and reduces post-transplant complications.

"This study, which tests a new combination of immunosuppressive drugs, lowers the risk of acute GVHD and thus, reducing the secondary complications of steroid treatment and infections such as CMV, which contribute to morbidity and mortality. This allows the curative approach of HCT to be applied to a bigger group of patients with hematologic malignant and nonmalignant disorders," according to Dr. Sandmaier. A phase III randomized trial is ongoing to further investigate the efficacy of sirolimus after nonmyeloablative-conditioned HCT.

[Kornblit, B, Maloney, DG, Storer, BE, Maris, MB, Vindelov, L, Hari, P, Langston, AA, Pulsipher, MA, Bethge, WA, Chauncey, TR, Lange, T, Petersen, FB, Hubel, K, Woolfrey, AE, Flowers, MED, Storb, R, Sandmaier, BM](#). 2014. A randomized phase II trial of tacrolimus, mycophenolate mofetil and sirolimus after nonmyeloablative unrelated donor transplantation. *Haematologica* Epub ahead of print, doi:10.3324/haematol.2014.108340

See also: [Storb R, Gyurkocza B, Storer BE, Sorrow ML, Blume K, Niederwieser D, Chauncey TR, Pulsipher MA, Petersen FB, Sahebi F, Agura ED, Hari P, Bruno B, McSweeney PA, Maris MB, Maziarz RT, Langston AA, Bethge W, Vindeløv L, Franke GN, Laport GG, Yeager AM, Hübél K, Deeg HJ, Georges GE, Flowers ME, Martin PJ, Mielcarek M, Woolfrey AE, Maloney DG, Sandmaier BM](#). 2013. Graft-versus-host disease and graft-versus-tumor effects after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 31:1530-1538.

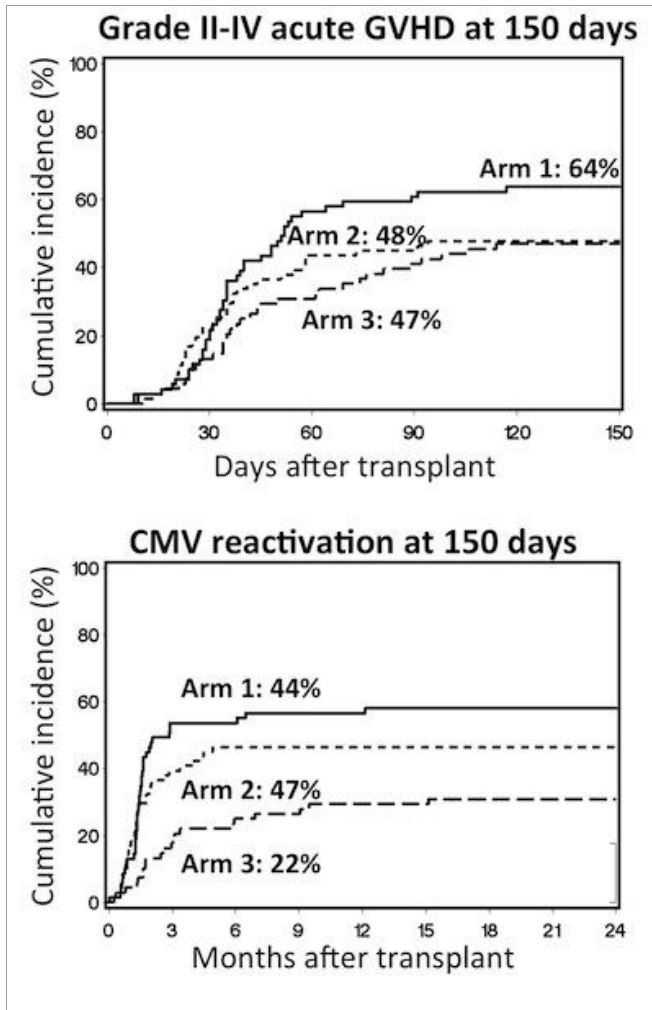


Image provided by Dr. Brian Kornblit

A phase II trial of immunosuppressive drug regimens after hematopoietic stem cell transplant demonstrates safety of sirolimus addition with reduced post-transplant complications of acute GVHD (top) and CMV reactivation (bottom). Patients were randomized to: arm 1, tacrolimus 180 days and mycophenolate mofetil 95 days (n=69); arm 2, tacrolimus 150 days and mycophenolate mofetil 180 days (n=71), or arm 3, tacrolimus 150 days, mycophenolate mofetil 180 days, and sirolimus 80 days (n=68).