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New approach to graft-versus-host treatment results in improvement for some patients

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In a study that seems to pivot on a paradox, scientists at Dana-Farber Cancer Institute have used an immune system stimulant as an immune system suppressor to treat a common, often debilitating side effect of donor stem cell transplantation in cancer patients. The effect, in some cases, was profound.

The phase I study, published in the Dec. 1 issue of the New England Journal of Medicine, involved allogeneic (donor) stem cell transplant patients with chronic graft-versus-host disease (GVHD), a multi-system inflammatory condition that arises when donor immune system cells launch an attack on a patient's own tissues, leading to varied symptoms such as skin rash and thickened or scarred skin, lung inflammation, or hepatitis, among others. The patients received once-daily injections of interleukin-2 (IL-2), a drug traditionally used to spur an immune system attack, but which, at low doses, investigators had reason to believe, could have the opposite effect in this case: blunting a harmful activation of the immune system and subduing GVHD.

After eight weeks on the regimen, 12 of 23 participants showed clear physical benefits, including softened skin and underlying tissue, reduced redness of skin, improved mobility and gait, improved liver function, and resolution of neuropathy, a degenerative nerve condition. The responding patients who went on to receive longer-term daily IL-2 continued to show improvements, including alleviations of skin conditions that had previously been considered irreversible in chronic GVHD, while simultaneously reducing their other immune-suppressing

medications. In fact, four of 10 patients on longer-term IL-2 treatment have completely tapered off glucocorticoids (steroid hormones), and two of them have stopped all other immune suppression medications as well. This group of patients has been able to reduce the use of glucocorticoids by an average of 60 percent.

None of the patients in the trial had their chronic GVHD progress while taking IL-2 and none had a relapse of their original cancer. None of the patients contracted opportunistic viral or fungal infections while on the IL-2 therapy, suggesting their immune system remains functional.

"More than half of patients who successfully undergo hematopoietic stem cell transplants [in which the blood-making tissue in the bone marrow is wiped out with chemotherapy and replaced with blood-forming stem cells from a donor] develop chronic GVHD," says the study's lead author, John Koreth, MBBS, DPhil, of Dana-Farber. "The conventional treatment, glucocorticoids, are limited in their effectiveness and can produce significant side effects."

He adds that the findings show that low-dose IL-2 is both safe for patients with active, chronic GVHD and it can produce powerful immunological effects – reversing, in some cases, some of the most severe symptoms of GVHD. "This technique not only offers a new way of treating GVHD but possibly also of approaching a range of inflammatory conditions that result from an imbalance in the immune system," says Koreth.

The technique focuses on regulatory T cells (T-reg), which normally act to control the immune system and prevent a harmful immune cell attack on bodily tissue. Deficient T-reg cells are thought to play a role in GVHD and autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, among others, which result from a hazardous immune assault on normal

tissue. Scientists have shown that growing T-reg cells in a lab and infusing them into animals with GVHD or other autoimmune disorders can improve the animals' condition, but applying this technique to humans has been difficult.

IL-2 represented another potential way to boost T-reg numbers. A natural protein that was identified in the 1970s, IL-2 is considered to be a critical growth stimulant for T-reg cells, helping them mature, multiply, survive, and function effectively. In an earlier clinical trial designed to enhance immune system function, the Dana-Farber team found that low-dose IL-2 safely boosted T-reg levels in stem-cell transplant patients with no GVHD. The new study was designed to see if low doses also could serve as a treatment for patients with active GVHD.

There was an element of uncertainty in this approach, for even as IL-2 bolsters the immune-suppressing effect of T-reg cells, it might also spark the growth of immune-stimulating natural killer (NK) cells and conventional T cells (T-con), both of which lead the immune system's assault on disease. In fact, the primary Food and Drug Administration-approved use of IL-2 is in cancer treatment and involves administering high doses to patients with advanced kidney cancer or melanoma in hopes of provoking a powerful immune attack on the cancer cells. The high-dose IL-2 treatment often produces harsh side effects, but occasionally induces complete and long-lasting remissions. The question in the new study was whether low-dose IL-2 could have, in treating GVHD, the opposite effect of the high doses used in treating cancer.

"We had good reason to believe this low-dose approach would be safe, based on our previous experience," Koreth says, "but the irony is that it represents a complete reversal of the rationale on which IL-2 therapy was originally based."

The reduction in GVHD symptoms experienced by half the study

participants is mirrored in the results of lab tests on participants' blood. Levels of T-reg cells that were low at the start increased rapidly and substantially in all study members without adversely affecting the level of T-con cells, resulting in a sustained correction of the imbalance between immune-suppressive and immune-active cells.

Investigators are not certain why only about half the participating patients had a reduction in symptoms, even though all patients had substantial increases in T-reg cells. They speculate that it might be due to differences in the starting level of T-reg cells or to differences in the extent of T-reg cell increase during treatment.

"This study demonstrates that daily injection of low-dose IL-2 is safe for patients with active, chronic GVHD and can restore the balance between pro- and anti-inflammatory immune system cells in their bodies. It shows that, in some patients, this approach can reverse the most severe manifestations of the disease, while also allowing them to reduce their use of glucocorticoids," Koreth says. "These findings may have implications for a variety of diseases resulting from immune system imbalances. This approach deserves further study in larger numbers of GVHD patients, as well as in other autoimmune diseases and solid organ transplants."

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