Low-dose treatment with Il2 across studies shows benefits in chronic graft-versus host

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Daily low doses of the immune signaling protein interleukin-2 (IL-2) can safely benefit patients who develop chronic graft-versus-host disease following stem cell transplants, including particular benefit in pediatric patients in one small study, report scientists from Dana-Farber Cancer Institute.

Dana-Farber researchers, who have pioneered the use of IL-2 in post-transplant patients, presented four related abstracts at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition in Atlanta. IL-2 is a signaling molecule that regulates the activity of white blood cells in the immune system and plays a key role in immunity (helping the body fight infections) and tolerance (protecting the body from its own defensive attacks). In the latter situation, IL-2 stimulates the production and activity of white blood cells called T-regulatory (or Treg) cells that dampen the inflammatory response caused by immune activation.

Graft-versus-host disease (GVHD) is a common and sometimes severe complication in which immune cells from a transplant donor attack and injure normal tissues in the recipient, including the skin, lining of the gastrointestinal system, the liver, and the lungs. Standard treatment for chronic GVHD includes steroid drugs, which have serious side effects of their own.

Because IL-2 boosts the production of inflammation-damping Treg cells, "we've been using it in the post-transplant setting - we've treated more

than 100 patients in Phase 1 and 2 trials," said John Koreth, MBBS, DPhil, senior physician, Adult Stem Cell Transplantation Program, Dana-Farber Division Cancer Institute. "We are reporting on several of these chronic GVHD trials at ASH, including the very dramatic response rates in pediatric patients who have not been helped by standard therapies."

Abstract #3248

The trial he referred to is a Phase 1 study led by Jennifer Whangbo, MD, PhD, Dana-Farber/Boston Children's Cancer and Blood Disorders Center. It involved 10 adults and eight pediatric patients (ranging in age from five to 22) with chronic GVHD that was not responding to steroid treatment. The patients underwent daily subcutaneous injections of IL-2 for eight weeks.

At eight weeks, seven of the eight pediatric patients (88 percent) had clinical benefit while only one of eight adult patients (13 percent) evaluated saw benefit. The eight pediatric patients continued to receive IL-2 therapy for up to 120 weeks.

"We demonstrate for the first time that low-dose IL-2 is safe in children with advanced, steroid refractory chronic GVHD and results in a high clinical response rate," said the researchers, who also include Koreth and Robert J. Soiffer, MD, chief of the Division of Hematologic Malignancies at Dana-Farber.

As to why the pediatric patients fared better with IL-2 therapy, despite receiving lower doses than the adults, Whangbo says it's not yet known. "We are doing studies in the lab to compare thymic function and T-cell receptor (TCR) diversity between the pediatric and adult cohorts," she said.

Abstract #74

Another study looked in molecular detail at how low doses of IL-2 tweak the transplanted, foreign immune system so that it tolerates, rather than attacks, the recipient's normal tissues. It's not only immune T cells that are involved in chronic GVHD; another type of immune defender, B cells, are also part of the problem. B-cell activity is regulated by T follicular helper (TFH) cells, which direct B cells against the recipient patient's normal tissues, and T follicular regulatory (TFR) cells, which suppress the B-cell response.

In the study led by Yusuke Kamihara, MD, PhD, the Dana-Farber scientists looked at the effects of IL-2 therapy on TFH and TFR cells in the blood circulation of patients with steroid-resistant chronic GVHD. They observed that daily low-dose IL-2 therapy selectively activated the immune-dampening TFR cells and proteins associated with them, while simultaneously suppressing the injurious TFH cells and their associated proteins. This selective function of IL-2, they said, "provides a mechanism whereby low-dose IL-2 therapy can promote B-cell tolerance as well as T-cell tolerance in patients with chronic GVHD."

Senior authors of the study are Soiffer and Jerome Ritz, MD, executive director of the Connell and O'Reilly Families Cell Manipulation Core Facility at Dana-Farber.

Abstract #511

Investigators in another study tested a hypothesis that IL-2 therapy for chronic GVHD might be even more effective if the transplant recipient were given an infusion of fresh Treg cells from the original donor prior to treatment with IL-2. In a previous trial, low-dose IL-2 treatment alone produced clinical improvement in 50 to 60 percent of patients with

chronic GVHD. Adding fresh Treg cells, the researchers suggested, could increase that percentage.

In this Phase 1 trial, 25 transplant patients who had steroid-refractory chronic GVHD were given escalating doses of Treg cells, followed by eight weeks of daily doses of IL-2. At eight weeks, the rate of clinical benefit was 56 percent and the rate of complete plus partial responses was 16 percent. By six months, the median steroid dose the patients were on was reduced by half. Laboratory studies to determine persistence of freshly infused donor Tregs, TCR diversity, and impact on long-term outcomes are underway.

The researchers, led by Sarah Nikiforow, MD, PhD, Associate Medical Director, Connell and O'Reilly Families Cell Manipulation Core Facility and Technical Director, Immune Effector Cell Therapy Program at Dana-Farber, and senior author Koreth, concluded that giving Tregs plus IL-2 is safe and has clinical efficacy in steroid refractory chronic GVHD, "including in those with inadequate responses to IL-2 alone."

Abstract #515

Because chronic GVHD is such a big problem in stem cell transplants, a variety of experimental treatments have been tried. In what's known as extracorporeal photopheresis (ECP), about a pint of the transplant recipient's blood is removed and treated with a chemical that makes it sensitive to ultraviolet (UV) radiation. Then the blood is zapped with UV, which stuns the immune cells so they can't multiply, and the blood is returned to the body, which "has a calming influence on the immune system," Koreth said.

He and Soiffer led a Phase 2 trial that combined ECP with low-dose IL-2 therapy to treat patients with chronic, steroid-refractory GVHD. A total of 25 patients underwent twice-weekly ECP sessions for 16 weeks,

with daily IL-2 added in weeks nine through 16.

Initially, there was a drop in immune-dampening Treg and other cells during ECP-alone treatment; when the IL-2 treatment kicked in, the Tregs went up by an average of five-fold. The researchers noted partial responses in up to 60 percent of the patients. However, they concluded, "the overall clinical efficacy of ECP plus IL-2 did not appear markedly higher than low-dose IL-2 alone."

Provided by Dana-Farber Cancer Institute