

New protocol streamlines therapy that makes more kidney transplants possible

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A new therapy developed at Cedars-Sinai Medical Center improves transplant rates and outcomes for patients awaiting living- and deceased-donor kidney transplantation, according to a study published in the July 17 issue of the *New England Journal of Medicine*.

The therapy may provide an option for many patients "sensitized" to transplant antigens (human leukocyte antigens, or HLA) who previously would not have been candidates for transplantation because of their intense immune response to these HLA targets.

HLA exposure can come through blood transfusions, previous transplantation or pregnancy. Once exposed, the immune system is sensitized to those antigens and develops antibodies to fight them. If a donor organ with the antigens is later transplanted, the antibodies respond, increasing the risk of rejection and loss of the organ. Antibodies to HLA were previously considered an absolute contraindication to transplantation – the risk was too high for transplantation to be an option.

About 30 percent of the 74,000 patients on the transplant waiting lists for a deceased-donor kidney are sensitized, and those with exceptionally high antibody levels are considered especially poor candidates for transplantation. In fact, each year only 6.5 percent of highly sensitized patients receive a transplant. Most remain on dialysis indefinitely, without hope for a life-saving transplant.

"From a quality-of-life perspective, as well as from the financial standpoint, transplantation is a much better option than years of dialysis," said Stanley C. Jordan, M.D., director of the Division of Nephrology and medical director of the Renal Transplant Program at Cedars-Sinai. The senior author of the journal article, Jordan developed high-dose intravenous immunoglobulin (IVIG) therapy to "desensitize" highly sensitized patients and increase their chances of successful transplantation. The approach became a Medicare-approved therapy in 2004 at the conclusion of a National Institutes of Health-funded multicenter study.

Cedars-Sinai is a national leader in desensitization for the highly HLA sensitized patient, offering therapy for those awaiting both living-donor and deceased-donor transplantation.

The *New England Journal* article describes a Phase I/II safety and limited efficacy trial of a combination of IVIG and rituximab, a monoclonal antibody – an antibody engineered to bind to a specific protein. The combination of IVIG and rituximab appears to offer superior benefits to IVIG alone, improving transplant rates to 80 percent of treated patients. The one-year patient and graft survival rates were 100 percent and 94 percent, respectively.

Based on these results, the new protocol is less costly than IVIG alone yet appears to be highly effective in reducing antibody levels and improving transplantation rates. Larger, multicenter trials are necessary to confirm these findings.

Because nearly one-third of kidney failure patients are highly sensitized and few transplant centers specialize in desensitization therapy, many potential candidates are told that a transplant simply is not possible.

"Patients who are on dialysis and those who are progressing toward renal

failure should be considered for a kidney transplant. Ideally, they would be referred to a transplant center for evaluation even before they start dialysis because data show that those who get transplanted before starting dialysis do better," Jordan said. "However, for the highly sensitized patient, transplantation is not an option unless desensitization therapies are used."

Jordan estimates that about 40 percent of Cedars-Sinai's kidney transplant patients are highly sensitized and are referred or self-referred to the program because of their highly sensitized state. For many patients, especially those awaiting a deceased-donor transplant, the combination of IVIG and rituximab appears to offer an alternative to ongoing dialysis.

The *New England Journal of Medicine* article is accompanied by an editorial written by Ron Shapiro, M.D., of the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh. He concludes his comments by saying, "As the authors note, their observations need to be confirmed and validated by other centers and in larger numbers of patients and during longer periods of follow-up. However, their approach may represent a breakthrough in the care of sensitized patients awaiting transplantation and may have the potential to help thousands of patients who are languishing on waiting lists around the world."

Source: Cedars-Sinai Medical Center

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