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Citation: *Journal of the American Society of Nephrology*, December 2004, "Evaluation of Intravenous Immunoglobulin (IVIG) As an Agent To Lower Allosensitization And Improve Transplantation In Highly-Sensitized Adult ESRD Patients: Report of the NIH IGO2 Trial."

HIGHLIGHTS:
An immune-modulating therapy improves kidney transplantation rates, even among "highly sensitized" patients whose immune systems have prevented them from receiving donated organs. Results of a government-supported study appear in the December 2004 issue of the *Journal of the American Society of Nephrology*.

MULTI-CENTER STUDY FINDS THERAPY BOOSTS KIDNEY TRANSPLANTS IN "HIGHLY SENSITIZED" PATIENTS

LOS ANGELES (Dec. 7, 2004) – Although transplantation is by far the preferred treatment option for patients with end-stage renal disease (ESRD), those with high levels of "anti-donor" antibodies have had little hope of receiving a donated organ. Among the relatively few who have undergone transplantation, rejection rates have been very high.

Because the immune systems of "highly sensitized" individuals initiate a rejection response against the tissue of the majority of the population, these patients typically spend the rest of their lives undergoing kidney dialysis several times a week – a painful, costly process that extends life but usually results in a diminishing quality of life.

Now, a 12-center study, funded in part by the National Institutes of Health and reported in the December 2004 issue of the *Journal of the American Society of Nephrology*, found that an immune-modulating therapy pioneered for transplant patients at Cedars-Sinai Medical Center reduced high antibody levels and improved transplantation rates. The analysis was based on the experiences of 98 highly sensitized patients who were administered either the medication, called intravenous immunoglobulin (IVIG), or a placebo while awaiting transplantation.

"The study showed that there was a significant benefit of IVIG over placebo. In fact, the rates of transplantation for the IVIG group were more than double that for the placebo group. And for patients who had had a previous transplant – which is a very big risk factor for not being able to have another one – the IVIG group's transplant rate was triple that of patients on placebo," said Stanley C. Jordan, MD, director of Pediatric Nephrology & Transplant Immunology and medical director of the Renal Transplant Program at Cedars-Sinai.

"Most other anti-rejection drugs can make the patient more susceptible to infectious complications because they are globally immunosuppressive," said Dr. Jordan, the study's principal investigator, the article's senior

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author and a professor of pediatrics at the University of California, Los Angeles. "The good thing about IVIG is that it modulates the immune system, it doesn't suppress it. It appears to 'turn off' deleterious immune responses without damaging the immune system, and in fact, it strengthens the immune system because it provides antibodies to infectious agents as well."

Although tissue compatibility issues exist for all patients receiving transplanted organs, rejection risks are especially high for a patient who has the added barrier of an immune system that has been exposed to "non-self" human leukocyte antigens (HLAs). Exposure may occur through blood transfusions, earlier organ transplantation or even pregnancy, when the mother is exposed to antigens from the father expressed in the cells of the developing baby. The immune system is then "sensitized" to those antigens – primed with antibodies to attack, even if the antigens arrive in the form of a potentially life-saving donated organ.

The degree of sensitization is measured in terms of "panel reactive antibody" or PRA levels. For a non-sensitized patient with end-stage renal disease, the wait time for a cadaveric transplantation averages four to five years. For sensitized patients, the odds of being transplanted drop. According to the article, "the higher the PRA, the more difficult it becomes to find an immunologically compatible match. Transplant rates are lower for sensitized patients and the waiting times for a compatible crossmatch are longer. Furthermore, while many of these patients may have living donors, transplantation cannot proceed …."

In 2000, fewer than 3 percent of all kidney transplants were performed in patients with PRAs higher than 80 percent at the time of transplant, despite the fact that these patients represent about 20 percent of those on the waiting list. In fact, transplant rates for these patients have gone down over the past decade as antibody detection techniques improved and waiting lists for the limited number of donor organs grew.

Dr. Jordan began to develop the concept of using immunoglobulins in a transplant environment in the late 1980s as IVIG was becoming established as a therapy for immune system disorders. The proteins, naturally produced in the body, can act as antibodies – natural defenses against invading organisms called antigens. A processed form of immunoglobulin made from blood plasma can be administered to boost the body's natural levels.

Researchers led by Dr. Jordan have published several studies showing that IVIG therapy increases success rates for patients receiving cadaver organs as well as organs donated by relatives or friends. They also have developed a lab test that enables them to predict which patients will most likely benefit from IVIG. If IVIG changes a poor match into a more compatible one in the lab, it likely will help the patient's immune system accept a transplanted organ.

The new study results showing that IVIG can make transplantation available to many patients who previously would have lingered on dialysis comes just months after some Medicare and other insurance providers began offering coverage for IVIG therapy in certain situations. Using IVIG to get even half of the sensitized patients transplanted and off of long-term dialysis would bring huge savings, according to cost analyses.

"From a financial standpoint and from a quality of life standpoint, there is no question that IVIG therapy and transplantation have more to offer than years of dialysis," Dr. Jordan said.

The study was supported by grants 1UO1-AI40129 and 1UO1-AI37313 from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and a grant from the Rebecca Sakai Memorial Fund. Bayer Corp. co-sponsored the study by providing medication and placebo.

A Magnet Nursing facility, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For the fifth straight two-year period, it has been named Southern California's gold standard in health care in an independent survey. Cedars-Sinai is internationally

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renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. It ranks among the top 10 non-university hospitals in the nation for its research activities and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at www.cedars-sinai.org.

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