

IN THE LITERATURE

New Approaches For Desensitization Strategies Prior to Kidney Transplantation

Commentary on Vo AA, Lukovsky M, Toyoda M, et al: Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med* 359:242-251, 2008.

Kidney transplantation is the treatment of choice for patients with chronic kidney failure. Not only does kidney transplantation prolong survival, but it also improves overall quality of life.¹ Unfortunately, due to the shortage of kidney donors in the United States, the waiting time for a deceased donor kidney has increased to several years (up to 7 years in some parts of the country). To complicate matters further, for many patients, sensitization to human leukocyte antigens (HLAs) severely restricts the donor pool. One approach is donor exchange programs, where an ABO- or crossmatch-positive incompatible donor donates to another recipient so that his or her intended recipient potentially receives a kidney from another living donor (ie, paired donation) or the deceased donor pool (ie, list donation).² Unfortunately, many patients do not have any potential donors and are reliant on receiving a deceased donor kidney. Desensitization protocols that allow highly sensitized patients to receive a deceased donor kidney could fill this gap.

Approximately one-third of patients awaiting a deceased donor kidney transplant have circulating anti-HLA antibodies, and almost 15% have a high degree of sensitization to potential kidneys.^{3,4} Anti-HLA antibodies result from exposure to nonself HLA antigens, usually from previous transplants, blood transfusions, and/or pregnancies.⁵ Because a failed kidney transplant is an increasingly common cause for incident kidney failure, it is expected that the population of highly sensitized patients will continue to increase. In recent years, desensitization of highly sensitized patients has been increasingly utilized

to allow transplantation in this patient population. This is most commonly attempted in patients who have a defined anti-HLA antibody response against a potential living donor. In a recent issue of the *New England Journal of Medicine*, Vo and colleagues apply a new method for desensitization for recipients of kidneys from deceased or living donors.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Vo and colleagues administered intravenous immunoglobulin (IVIG) and rituximab (a chimeric anti-CD20 antibody targeting B cells) to 20 highly sensitized patients with a mean panel reactive antibody (PRA) level of 77% ± 19%.⁶ Patients had a mean time on dialysis of 12 years and were at the very top of the deceased donor list, only being delayed by their sensitized status, and hence were likely to receive a transplant offer if desensitization succeeded. The desensitization protocol included 2 g/kg IVIG on days 0 and 30 and 1 g rituximab at days 7 and 22. Following the second infusion of IVIG, the mean PRA decreased to 44% ± 30%, and 16 of 20 patients (80%) received a transplant, 6 and 10 from living and deceased donors, respectively. The mean time to transplantation was 5 ± 6 months (range of 2 to 18 months) after desensitization. Following transplantation, 30 mg alemtuzumab (also known as campath, an anti-CD52 monoclonal antibody that targets lymphocytes amongst other cells) was given subcutaneously for induction therapy, while prednisone (5 mg, once daily), mycophenolate mofetil (500 mg, twice daily), and tacrolimus were used for maintenance immunosuppression. Acute rejection occurred in 50% of the patients, 31% being antibody-mediated rejections, mostly in the first months after transplant. Acute rejection was treated with a pulse of methylprednisolone (10 mg/kg/d for 3 days), as well as rabbit antithymocyte globulin (1.5 mg/kg/d). Patient and graft

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0272-6386/09/5303-0004\$36.00/0
doi:10.1053/j.ajkd.2009.01.012

survival were 100% and 94%, with all patients having at least 12 months of follow up.

Limitations of this study include a relatively small number of patients, short follow-up time, and a high rate of early rejection; however, the implications for the future are important. Even though there was a high rate of rejection in early posttransplantation, this was reversible, and the 1-year patient and graft survival were excellent, without a higher-than-usual rate of infectious complications.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

The goal of desensitization protocols is to reduce or neutralize circulating anti-HLA antibodies. Past therapeutic approaches include plasmapheresis, IVIG, B-cell specific agents, or combinations of these. The majority of successful protocols can basically be divided into 1 of 2 approaches. One utilizes a “high-dose IVIG” (2 g/kg/dose)^{7,8} and the other utilizes the combination of plasmapheresis and “low-dose IVIG” (100 mg/kg/dose).⁹ These protocols have been used mostly with living donation so the antibody response against donor tissue can be monitored and transplantation surgery proceeds only if antibody levels are low.

The timing of deceased donor transplantation is more difficult than for transplantation with a living donor. Even though potential recipients may be at the top of the deceased donor list, it is uncertain in any individual case as to when they will actually get a transplant offer. Thus, to stand a realistic chance of getting a deceased donor organ offer, the effects of desensitization must last longer. Accomplishing and maintaining a low anti-HLA response through regular plasmapheresis is expensive and often impractical. A regimen such as high-dose IVIG, which inhibits antidonor antibody levels without the need for continuous plasmapheresis, is clearly more attractive for patients awaiting a deceased donor kidney. The cost of therapy has to be weighed against the potential efficacy of treatment in enabling transplantation and thus avoiding dialysis.

Most of the previously published studies of desensitization prior to kidney transplantation have focused on donor-specific desensitization

for living donor transplantation. Some studies have been able to show that use of high-dose IVIG can lead to successful transplantation of a deceased donor kidney.¹⁰⁻¹² All of these studies used a combination of high-dose IVIG and variety of induction agents. While they were able to show effectiveness, they were not truly controlled studies, and modifications in patient selection or treatment were required during them.

The study by Vo and colleagues builds on their original controlled clinical trial of desensitization therapy, the National Institutes of Health IGO2 Study, which was conducted between 1997 and 2000. A controlled, clinical, multi-center, double-blinded trial of IVIG versus placebo in highly sensitized patients who were awaiting kidney transplantation, IGO2 was designed to determine whether IVIG could reduce PRA levels and improve rates of transplantation without concomitantly increasing the risk for graft loss in this difficult-to-transplant group. The study found that IVIG was superior to placebo in reducing anti-HLA antibody levels and improving rates of transplantation, but did not cause patients to experience excessive allograft loss.⁷ Compared with this original study, which showed the significant benefits of IVIG alone in desensitizing highly HLA-sensitized patients for transplantation, the recent report in the *New England Journal of Medicine* found that combining high-dose IVIG with an anti-CD20 antibody reduced the total amount of IVIG given, increased the effectiveness of treatment, and reduced the overall time to transplantation. These observations need to be confirmed in larger studies.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The results of this study are fascinating and potentially represent the beginning of a change in our current standard of care in the management of the sensitized patients with kidney failure for whom there are limited options at present. Desensitization is still a relatively new procedure for transplant patients and, at most centers, is a relatively infrequent occurrence. As highly sensitized patients will likely have other significant comorbid conditions associated with long-term dialysis, it is probably wise to limit desensitization to a smaller number of transplantation units

that can develop expertise in this area. The cost of desensitization is also significant, especially because of the use of IVIG. While it has been argued that treatment is cost effective, there is no universal mechanism to pay for desensitization protocols, although there are some states where this is covered. As a group concerned with care for patients with kidney failure, we need cost-benefit analyses to design a more rational and universal approach for paying for all treatments, including desensitization. Researchers need to show that this protocol is broadly applicable and is safe in the longer term. The addition of rituximab to alemtuzumab is a very powerful combination of nonspecific immunosuppression and the consequences in terms of infection and malignancy may not be apparent for several years. The development of more specific immunosuppression that would precisely target circulating HLA antibodies as well as a memory T-cell response is also an area that would make the approach of desensitization more applicable.

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ACKNOWLEDGEMENTS

Financial Disclosure: Dr Chandraker serves as the Study Chair for the "Rituximab in Kidney Transplantation" trial, which is sponsored by National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health.

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