

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

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ABSTRACT

BACKGROUND

Few options for transplantation currently exist for patients highly sensitized to HLA. This exploratory, open-label, phase 1–2, single-center study examined whether intravenous immune globulin plus rituximab could reduce anti-HLA antibody levels and improve transplantation rates.

METHODS

Between September 2005 and May 2007, a total of 20 highly sensitized patients (with a mean [\pm SD] T-cell panel-reactive antibody level, determined by use of the complement-dependent cytotoxicity assay, of $77\pm 19\%$ or with donor-specific antibodies) were enrolled and received treatment with intravenous immune globulin and rituximab. We recorded rates of transplantation, panel-reactive antibody levels, cross-matching results at the time of transplantation, survival of patients and grafts, acute rejection episodes, serum creatinine values, adverse events and serious adverse events, and immunologic factors.

RESULTS

The mean panel-reactive antibody level was $44\pm 30\%$ after the second infusion of intravenous immune globulin ($P < 0.001$ for the comparison with the pretreatment level). At study entry, the mean time on dialysis among recipients of a transplant from a deceased donor was 144 ± 89 months (range, 60 to 324). However, the time to transplantation after desensitization was 5 ± 6 months (range, 2 to 18). Sixteen of the 20 patients (80%) received a transplant. At 12 months, the mean serum creatinine level was 1.5 ± 1.1 mg per deciliter (133 ± 97 μ mol per liter), and the mean survival rates of patients and grafts were 100% and 94%, respectively. There were no infusion-related adverse events or serious adverse events during the study. Long-term monitoring for infectious complications and neurologic problems revealed no unanticipated events.

CONCLUSIONS

These findings suggest that the combination of intravenous immune globulin and rituximab may prove effective as a desensitization regimen for patients awaiting a transplant from either a living donor or a deceased donor. Larger and longer trials are needed to evaluate the clinical efficacy and safety of this approach. (ClinicalTrials.gov number, NCT00642655.)

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RENAL TRANSPLANTATION IS CONSIDERED the treatment of choice for patients with end-stage renal disease, since it offers improved survival and quality-of-life benefits as compared with dialysis and is considerably less costly to payers.¹⁻³ Currently, there are more than 74,275 patients with end-stage renal disease in the United States on the deceased-donor waiting list, and more than 30,000 new registrants are added each year. Despite this, there are fewer than 18,000 total kidney transplantations in the United States each year.⁴

The waiting times for kidney transplants continue to increase, owing to the limited supply. This is especially true for patients for whom matching is difficult (those considered to be highly HLA sensitized).⁴⁻⁷ Alloantibodies (anti-HLA antibodies) arise through previous transplants, blood transfusions, and pregnancy. Currently, approximately 30% of the patients on the waiting list have evidence of sensitization, and only 6.5% of highly sensitized patients (those with a panel-reactive antibody level above 80%) receive a transplant each year.⁴ Over the past several years, two regimens have evolved to help improve transplantation rates in highly sensitized patients. These are the high-dose intravenous immune globulin protocol and the plasmapheresis plus low-dose intravenous immune globulin protocol.⁸⁻¹²

Our group previously reported results of the use of the high-dose intravenous immune globulin protocol and examined its efficacy in a randomized, multicenter, placebo-controlled trial in highly HLA-sensitized patients conducted by the National Institutes of Health (NIH) (the NIH IG02 study).⁹ From the NIH IG02 study, we observed that intravenous immune globulin significantly lowered anti-HLA antibody levels ($P=0.04$) and improved rates of transplantation (primarily from deceased donors) as compared with placebo (35% vs. 17%, $P=0.02$). The projected mean waiting time to transplantation was 4.8 years for patients treated with intravenous immune globulin as compared with 10.3 years for those who received placebo ($P=0.03$). The 3-year allograft survival rate was 80% in the intravenous immune globulin group as compared with 70% in the placebo group (P not significant).⁹

A protocol for high-dose intravenous immune globulin that was similar to the protocol in the NIH IG02 trial was used at our center from 2000 until 2005¹⁰ and appears to be effective for some

patients. However, the protocol required patients to undergo a 4-month period of treatment (with monthly doses of 2 g per kilogram of body weight, for a total of four doses) and was not always effective. For these reasons, we explored other potential approaches that might be as effective, might reduce the time to desensitization, and might be less costly.

Among such treatments, we considered rituximab, a chimeric anti-CD20 monoclonal antibody that reduces B-cell and antibody levels. The role of rituximab as a desensitizing agent has not been clearly defined. This monoclonal antibody has had demonstrated efficacy in the treatment of autoimmune diseases and is reported to be effective in the treatment of antibody-mediated transplant rejection.¹³⁻¹⁶ Other groups have reported that rituximab has synergistic effects with intravenous immune globulin in autoimmune skin diseases.¹⁴

Our exploratory, open-label, phase 1-2, single-center study examined whether intravenous immune globulin plus rituximab was safe and effective in reducing the levels of anti-HLA antibodies and improving transplantation rates.

METHODS

STUDY DESIGN

The data for this investigator-initiated study were gathered, analyzed, and verified by the investigators; the manuscript, in all stages, was written by the authors. The representatives of the sponsor, Genentech, reviewed the manuscript before submission but made no substantive changes.

The study used an open-label design to examine whether human polyclonal intravenous immune globulin (10% formulation) given twice (2 g per kilogram of body weight on day 0 and day 30), plus rituximab given twice (1 g on day 7 and day 22), could reduce the rate of, or eliminate, a positive cross-match in highly HLA-sensitized patients awaiting transplantation at Cedars-Sinai Medical Center. The rituximab dose was based on data from published reports concerning rituximab use in patients with rheumatoid arthritis or autoimmune diseases.¹⁷⁻¹⁹

Donor-specific flow-cytometric cross-matching was performed at study entry, after treatment, and before transplantation. Safety data and limited data on efficacy (changes in panel-reactive antibody levels, cross-matching result, and rate of transplantation) were obtained on day 0 (the day

of infusion), at weeks 1, 2, 4, and 6, and at months 3, 6, and 12. Safety data were also obtained during and immediately after infusion, when patients were monitored for side effects such as fever, headache, and shortness of breath. In addition, patients were monitored over the course of the study for viral infections and side effects related to the central nervous system. The patients were followed to determine the proportion with reductions in anti-HLA antibody levels who subsequently obtained and retained a viable and functioning kidney allograft. All patients were evaluated on an intention-to-treat basis. To ensure the safety of all patients, the accrual rate was limited to no more than five patients per month in the first 3 months.

Written informed consent was obtained from all patients. The study was performed in accordance with the protocols approved by the institutional review board of Cedars–Sinai Medical Center. Between September 2005 and May 2007, a total of 20 patients were enrolled. All patients were highly HLA-sensitized (mean [\pm SD] prestudy panel-reactive antibody level, $77\pm 19\%$) or had donor-specific antibodies and were on the waiting list for a kidney transplant from a deceased donor or a living donor.

Rituximab was provided by Genentech. All doses of intravenous immune globulin were infused during a 4-hour hemodialysis session, as described previously.⁹ Rituximab infusions were administered in an outpatient infusion center over a 6-hour period, with frequent monitoring of vital signs. To reduce the frequency of infusion-related side effects, 30 to 60 minutes before scheduled infusions of intravenous immune globulin or rituximab, all patients were given intravenous methylprednisolone (40 mg), oral acetaminophen (650 mg), and oral diphenhydramine (50 mg).

DONOR-SPECIFIC CROSS-MATCHING, ANTI-HLA ANTIBODIES, AND TRANSPLANTATION

Donor-specific flow-cytometric cross-matching, complement-dependent cytotoxicity cross-matching, and the T-cell complement-dependent cytotoxicity panel-reactive antibody assay were performed as described previously.^{9,20} Three-color donor-specific cross-matching was performed according to the method of Bray et al.²⁰ with the use of a flow cytometer (FACScan, Becton Dickinson). T cells and B cells were stained with phycoeryth-

rin-conjugated mouse monoclonal antibody specific for human CD3 and CD19, respectively. The presence of bound antibody was determined by means of fluorescein isothiocyanate–conjugated antihuman IgG antibodies (Jackson Immuno-Research Laboratories).

After completion of the protocol, patients were eligible to receive a kidney transplant from a living or deceased donor. When donors became available, cross-matching was performed on serum samples collected after treatment, and the results were deemed acceptable or unacceptable. An acceptable cross-match was defined as a T-cell complement-dependent cytotoxicity cross-match that was negative at a 1:2 dilution of the serum in saline, a T-cell donor-specific flow-cytometric cross-match that was negative or remained positive (with a mean flow-channel shift [the number of binding fluorescent units above the background number] of <250 [normal background number, <50]), or both.

POST-TRANSPLANTATION INDUCTION PROTOCOL AND MAINTENANCE IMMUNOSUPPRESSIVE THERAPY

Patients who received a transplant were given a single dose of alemtuzumab (30 mg subcutaneously) as induction therapy immediately after transplantation.²¹ Subsequent maintenance immunosuppressive therapy consisted of prednisone (2 mg per kilogram, with a rapid tapering to 5 mg per day by 2 weeks after transplantation), mycophenolate mofetil (500 mg twice daily), and tacrolimus administered to maintain a target blood level of 7 to 9 ng per milliliter for the first 3 months, 6 to 8 ng per milliliter for months 3 to 6, and 5 to 7 ng per milliliter after 6 months.

TREATMENT OF ALLOGRAFT-REJECTION EPISODES

Biopsy-proven, cell-mediated rejection episodes were treated with a pulse of methylprednisolone (10 mg per kilogram per day for 3 days), as well as rabbit antithymocyte globulin (1.5 mg per kilogram per day, with the total dose not exceeding 6 mg per kilogram). Patients who had episodes of antibody-mediated rejection that were C4d+ (Banff antibody-mediated rejection grade I or II)^{22,23} were initially given a pulse of methylprednisolone (10 mg per kilogram per day for 3 days), intravenous immune globulin (2 g per kilogram once), and rituximab (375 mg per square meter of body-surface area). Patients with severe antibody-mediated rejection (Banff grade III) or thrombotic microan-

giopathy underwent plasmapheresis (three to five sessions) followed by repeat administration of intravenous immune globulin (2 g per kilogram) and rituximab (375 mg per square meter).²³

CD19+ AND CD20+ CELLS AND HUMAN ANTICHIMERIC ANTIBODIES

CD19+ cells and CD20+ cells were detected by means of flow cytometry involving a direct single-staining method. Heparinized blood samples (100 μ l each) were mixed with phycoerythrin-conjugated mouse anti-CD19 antibodies or phycoerythrin-conjugated mouse anti-CD20 antibodies (5 μ l) and were incubated at room temperature for 30 minutes in a dark room. Fluorescence-activated cell-sorting lysing solution (2 ml, BD Biosciences) was added, followed by incubation for 10 minutes. After the addition of 2 ml of buffer (0.5% bovine serum albumin in phosphate-buffered saline with 0.1% sodium azide) and centrifugation, 400 μ l of 1% paraformaldehyde was added, and within 24 hours the mixture was processed in a flow cytometer (Dako). A total of 100,000 cells were detected. Data analysis was performed with the use of Summit software (Dako). Human antichimeric antibodies were monitored, by means of an enzyme-linked immunosorbent assay, at selected time points for all patients.²⁴

INFECTION-PROPHYLAXIS PROTOCOLS

All patients who received a transplant, regardless of their cytomegalovirus status, received intravenous ganciclovir while in the hospital and valganciclovir for 6 months as outpatients, with dose adjustments for renal function. Fungal prophylaxis was accomplished with the use of nystatin (10 ml, four times daily for 1 month). Prophylaxis against *Pneumocystis carinii* and other bacteria was accomplished with the use of trimethoprim (80 mg) and sulfamethoxazole (400 mg) daily for 4 months.

MONITORING FOR VIRAL INFECTIONS AFTER TRANSPLANTATION

For all highly sensitized patients who received a kidney transplant, polymerase-chain-reaction assays for cytomegalovirus, Epstein-Barr virus, parvovirus B-19, and polyomavirus BK were performed on whole-blood specimens monthly for 6 months after transplantation. The methods used for monitoring viral replication have been described previously.²⁵

MONITORING FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

There are concerns regarding the use of rituximab, because it has been reported to induce reactivation of polyomavirus JC virus, resulting in progressive multifocal leukoencephalopathy in patients with systemic lupus erythematosus.²⁶ As part of our monitoring program, patients were questioned, after each infusion and at all follow-up visits, about the development of motor deficits, memory loss, and other neurologic symptoms. Monitoring for adverse events and serious adverse events was continued after transplantation.

STATISTICAL ANALYSIS

Paired t-tests were used to analyze patient and graft survival rates, mean serum creatinine level, transplant status (single vs. multiple), type of acute rejection episode (C4d- vs. C4d+), the interaction of transplant status and cross-match result, and panel-reactive antibody status. Reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The 20 highly sensitized patients, all of whom were older than 18 years of age, underwent desensitization with intravenous immune globulin and rituximab, each over a 4-week period. Of the 20 patients, 16 (80%) subsequently underwent successful transplantation (with 6 receiving a kidney from a deceased donor and 10 receiving a kidney from a living donor). Of the remaining four patients, three were still awaiting a transplant from a deceased donor at the time of this writing, but all have panel-reactive antibody levels that were greater than 50%.

The mean follow-up time was 22.1 \pm 6.0 months, and 100% of patients had at least 12 months of follow-up (Table 1). All 16 patients who received a transplant were deemed to have a high immunologic risk (63% had received one or more previous transplants and 69% had evidence of a positive cross-match on flow cytometry at the time of transplantation). Ten of the 16 patients receiving transplants (62%), 6 from a living donor and 4 from a deceased donor, had panel-reactive antibody levels above 50%. Survival of patients and

Table 1. Baseline Characteristics of the 20 Study Patients.

Characteristic	Value
Sex — no. (%)	
Male	7 (35)
Female	13 (65)
Receipt of transplant during the study — no. (%)	16 (80)
From deceased donor	6 (38)
From living donor	10 (62)
Age range at time of transplantation — yr	22–61
Mean duration of follow-up after treatment ≥ 12 mo — %	100
Race or ethnic group — %*	
White	26
Black	11
Hispanic	58
Other	5
Cause of end-stage renal disease — %	
Diabetes or hypertension	32
Focal or segmental glomerulosclerosis	16
Systemic lupus erythematosus	16
Other (glomerulonephritis, Alport's syndrome, obstructive uropathy, or chronic interstitial nephritis)	36

* Race or ethnic group was self-reported.

grafts, acute rejection episodes, infectious complications, and renal function were monitored. Tables 1 and 2 summarize the baseline characteristics, immunologic profiles, and infectious complications of the patients.

Patients who received a transplant from a deceased donor were on the waiting list for 144 ± 89 months (range, 60 to 324) before receiving intravenous immune globulin and rituximab for desensitization but had to wait only an additional 5 ± 6 months (range, 2 to 18) after this treatment for a transplant. These patients did not receive additional United Network for Organ Sharing points toward transplantation for participation in this study.

IMMUNOLOGIC FACTORS

All patients had reduced numbers of CD19+ cells after rituximab infusion (mean percentage of total lymphocytes that were B cells, $6.12 \pm 0.18\%$ before treatment vs. $0.90 \pm 0.02\%$ after treatment; $P < 0.001$). Human antichimeric antibodies did not develop in any patient during the study. Panel-reactive antibody levels were significantly reduced

after treatment with intravenous immune globulin and rituximab ($77 \pm 19\%$ before the first infusion of intravenous immune globulin, vs. $44 \pm 30\%$ after the second infusion; $P < 0.001$) (Fig. 1). T-cell flow-cytometric cross-matching was performed on samples obtained before treatment, after treatment, and immediately before transplantation (Fig. 2). The mean channel shifts were 212 ± 95 before treatment, 245 ± 104 after treatment, and 149 ± 97 before transplantation ($P = 0.02$ for comparison of the channel shifts before treatment and before transplantation).

SURVIVAL RATES OF PATIENTS AND GRAFTS

The 12-month patient and allograft survival rates among the 16 patients receiving a transplant were 100% and 94%, respectively. All 16 of these patients have had at least a year of follow-up. The single allograft that was lost was from a living donor in a recipient with stable renal function 1 year after transplantation who had a severe rejection episode after her immunosuppressive therapy was reduced at an outside hospital. From an immunologic standpoint, 62% of the patients who

Table 2. Immunologic Findings and Infectious Complications of the 16 Patients Who Received a Transplant.*

Characteristic	Patients no. (%)
Panel-reactive antibody level at study entry	
<20%	4 (25)
Transplant from deceased donor	1
Transplant from living donor	3
20–50%	2 (13)
Transplant from deceased donor	1
Transplant from living donor	1
>50%	10 (62)
Transplant from deceased donor	4
Transplant from living donor	6
Previous transplants	
0	6 (38)
1	6 (38)
≥2	4 (25)
Cross-match at time of transplantation†	
CDC+, FCMX+	3 (19)
CDC+, FCMX–‡	2 (12)
CDC–, FCMX+	8 (50)
CDC–, FCMX–	3 (19)
Complications of infection	
Viral	
Polyomavirus BK	0
Cytomegalovirus	0
Parvovirus B-19	0
Epstein–Barr virus	0
Bacterial (asymptomatic urinary tract infection)	7 (44)
HLA mismatches	
6-Antigen mismatch	4 (25)
5-Antigen mismatch	3 (19)
≤4-Antigen mismatch	9 (56)

* CDC denotes complement-dependent cytotoxicity assay, and FCMX flow-cytometric cross-matching.

† The CDC+ result was at a 1:1 dilution, and the CDC– result was at a 1:2 dilution, of the serum in saline.

‡ The cross-match result reflects a probable IgM donor antigen.

underwent desensitization and transplantation had panel-reactive antibody levels that were greater than 50%, 63% had had one or more previous transplants, and 69% of patients had a positive cross-match on flow cytometry at the time of transplantation.

ACUTE REJECTION EPISODES

Acute rejection episodes occurred in 50% of patients who received a transplant, and 31% of these

episodes were C4d+ antibody-mediated rejections. Most rejection episodes occurred within the first month after transplantation and were reversible with treatment. However, two patients had late antibody-mediated rejection episodes (more than 6 months after transplantation) that were related to subtherapeutic immunosuppressive drug levels. Donor-specific antibody levels were monitored after transplantation in four patients with antibody-mediated rejection. Three of the four had increases

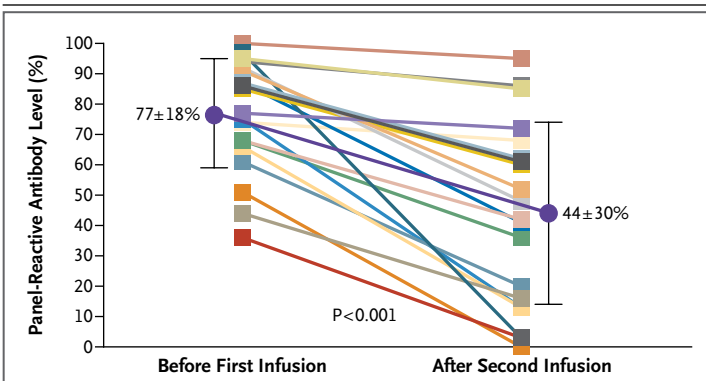


Figure 1. Panel-Reactive Antibody Levels in the 20 Study Patients.

Individual data are shown for patients before the first infusion of intravenous immune globulin and after the second infusion. The pretreatment and post-treatment means are also shown, as determined with the T-cell complement-dependent cytotoxicity panel-reactive antibody assay. The means were significantly different ($P<0.001$). I bars denote standard deviations.

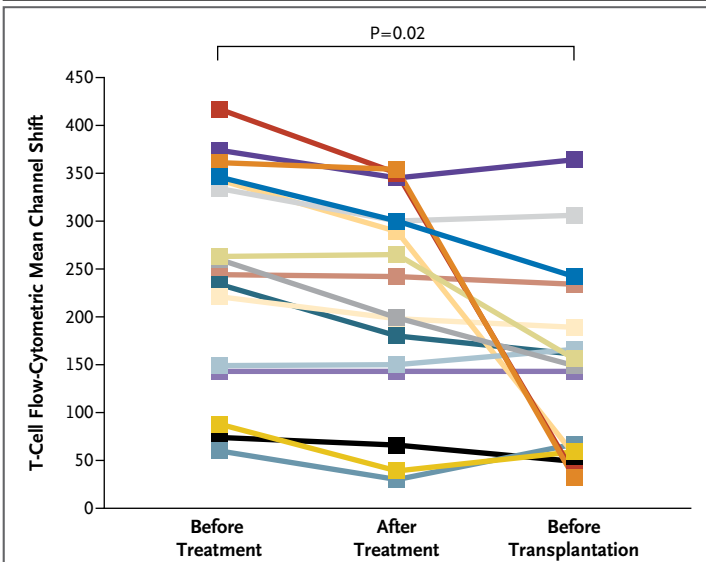


Figure 2. Mean Channel Shifts from T-Cell Flow-Cytometric Cross-Matching of the 16 Study Patients with Donors.

The mean (\pm SD) channel shifts (the numbers of binding fluorescent units above the background number) were 212 ± 95 before treatment ($P=0.30$), 245 ± 104 immediately after treatment ($P=0.15$), and 149 ± 97 immediately before transplantation.

in donor-specific antibody levels in association with the antibody-mediated rejection. New donor-specific antibodies were not detected, and antibody levels decreased after treatment.

RENAL FUNCTION

Serum creatinine values for individual patients and mean serum creatinine values are shown in

Figure 3. Mean serum creatinine values 1 month, 3 months, 6 months, and 12 months after transplantation were 1.3 ± 0.9 , 1.2 ± 0.4 , 1.3 ± 0.6 , and 1.5 ± 1.1 mg per deciliter (115 ± 80 , 106 ± 35 , 115 ± 53 , and 133 ± 97 μ mol per liter), respectively.

ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND INFECTIONS

No patients to date have had neurologic symptoms suggestive of progressive multifocal leukoencephalopathy. No viral infections were seen after transplantation in patients who were treated with intravenous immune globulin and rituximab for desensitization. Urinary tract infections developed in 7 of the 16 patients who received a transplant, who were then treated with oral antibiotics (Table 2). No patients required hospitalization, and the rate of urinary tract infection was not greater than that among transplant recipients who are not highly sensitized. No other important infectious complications were noted. No infusion-related side effects were noted in study patients, probably owing to the medication regimen used before infusion and the long infusion times. Our previous work⁹ showed that the rates of adverse events and serious adverse events did not differ significantly among highly sensitized patients treated with intravenous immune globulin during hemodialysis as compared with those who received placebo.

DISCUSSION

Among patients with high levels of preformed anti-HLA antibodies (i.e., high panel-reactive antibody levels), who are thus highly sensitized, renal-transplantation rates are low because of the additional immunologic barrier. When transplantation is performed in such patients, the incidence of antibody-mediated rejection is high, with unacceptable rates of graft loss.⁴⁻⁷ Thus, the highly sensitized patient is destined to remain on the waiting list for extended periods of time while undergoing dialysis, an additional risk factor for death and graft loss.^{4,9} Thus, early transplantation would result in considerable cost savings, reduced morbidity and mortality, and improved quality of life.

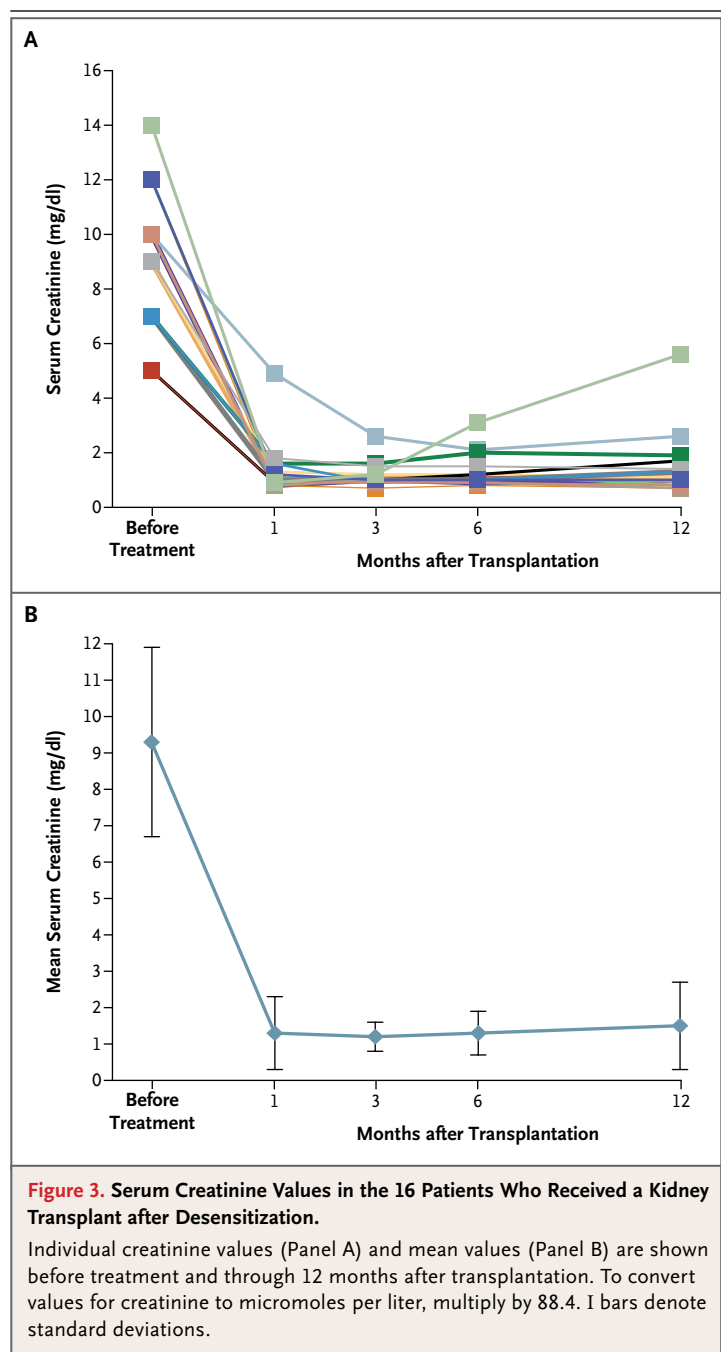
Intravenous immune globulin products are known to have powerful immunomodulatory effects.²⁷ There are compelling clinical and laboratory data that suggest that intravenous immune

globulin therapy administered to highly sensitized patients may reduce allosensitization and acute rejection episodes and result in better long-term outcomes for recipients of cardiac or renal allografts.^{9,11,12,28-31} However, in spite of the efficacy of intravenous immune globulin, its use in these patients is not completely effective. In fact, patients with high anti-HLA antibody titers, detected with the use of complement-dependent cytotoxicity cross-matching and flow-cytometric cross-matching, have only a partial response or none at all. Other investigators have shown that plasmapheresis and administration of intravenous immune globulin may also improve the success of transplantation in this group. However, the rejection rates are high, and this approach is effective only in patients awaiting transplants from living donors.^{11,12}

The use of rituximab, which is directed against the CD20 antigen, would seem to be a logical strategy, since reduction or elimination of B cells that express CD20 and make anti-HLA antibodies should have a beneficial effect. However, there are problems with this concept. First, anti-CD20 activity has no effect on plasma cells, which are the primary source of acute antibody production. Second, rituximab has no immediate effect on circulating antibody levels. These problems might limit the benefit of rituximab if it were used as the sole treatment.¹³ However, it appears that the use of rituximab in combination with other treatments (e.g., plasmapheresis, intravenous immune globulin, or both) might constitute an improved approach for the management of allosensitization. Vieira et al. performed a small phase 1 study using rituximab alone as a desensitization agent; there were no significant reductions in the panel-reactive antibody levels or antibody specificity in most of the patients.¹³ Other investigators have demonstrated that rituximab treatment for antibody-mediated rejection results in the reduction or elimination of donor-specific antibodies.^{15,16}

The use of rituximab may also lead to prolonged and substantial interference with both flow-cytometric cross-matching and complement-dependent cytotoxicity assays for B cells, complicating its use in desensitization protocols and analysis of B-cell cross-match results for patients awaiting a transplant from a deceased donor.

We believe that the data presented here, reflecting the use of a combination of intravenous



immune globulin and rituximab, are encouraging and may support further analysis of this approach. There are potential advantages for the use of intravenous immune globulin and rituximab as compared with currently accepted approaches to desensitization. For example, protocols for plasmapheresis and low-dose intravenous immune globulin are suitable only for recipients of

transplants from living donors. High-dose intravenous immune globulin has been shown to be effective as a desensitization agent for patients receiving transplants from either living or deceased donors,⁹ but it requires monthly infusions over a 4-month period for optimal results.

Although transplantation was not a primary end point in the NIH IG02 study,⁹ 35% of the patients underwent transplantation during a 2-year observation period, as compared with 17% in the placebo group. In our smaller, nonrandomized study, transplantation was accomplished in 80% of the patients, and treatment time was reduced from 16 weeks to 5 weeks. In addition, our patients who received a transplant from a deceased

donor had been on a waiting list for a mean of 12 years (range, 5 to 27) but received transplants within 5 to 6 months after treatment with intravenous immune globulin plus rituximab. These observations might have important implications for highly sensitized patients awaiting transplants from deceased donors. Larger and longer trials are needed to assess the safety of this approach.

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Dr. Reinsmoen reports receiving lecture fees from Cylex; and Dr. Jordan, receiving consulting fees and grant support from Talecris and Bristol-Myers Squibb and lecture fees from Genentech and owning a patent entitled "Use of IVIG in Desensitization," issued on January 9, 2001 (6171585B1, with co-owner Dr. Dolly Tyan; application filed in 1994). No other potential conflict of interest relevant to this article was reported.

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