



## IVIG Rescue Therapy in Renal Transplantation

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**I**NTRAVENOUS immunoglobulin (IVIG) has been used to treat autoimmune disorders,<sup>1</sup> as well as infectious diseases in immunosuppressed patients.<sup>2</sup> It has been used in transplantation to prevent graft versus host disease (GVHD) in bone marrow transplant recipients<sup>3</sup> and reduce anti-HLA antibodies in presensitized patients awaiting organ transplantation.<sup>4</sup> There is also preliminary evidence that it can be used as an induction agent<sup>5</sup> and may be able to reverse antibody-mediated rejection in the early post-transplant period.<sup>6</sup> However, the data regarding IVIG rescue therapy are limited.<sup>7,8</sup> In this study, we report the University of Pittsburgh experience with IVIG in reversing steroid- and anti-lymphocyte antibody-resistant rejection in renal transplant recipients.

### PATIENTS AND METHODS

Between September 1996 and March 1999, 25 patients received IVIG for steroid- or anti-lymphocyte antibody-resistant rejection. Eight patients were excluded from analysis because of concurrent administration of anti-lymphocyte antibody therapy; thus, a total of 17 patients were analyzed. All patients had biopsy-proven rejection. Thirteen patients (76%) were treated for steroid-resistant rejection and 4 patients (24%) were treated for anti-lymphocyte antibody-resistant rejection.

Sixteen patients (94%) had received tacrolimus-based immunosuppression. The remaining patient received microemulsion cyclosporine. Six (35%) patients received mycophenolate mofetil maintenance therapy and 6 (35%) patients had been weaned off corticosteroids prior to the development of refractory rejection. A total of 2 g/kg of IVIG was administered over 2 to 10 days during each treatment course, according to the fluid balance status of each patient. Four (24%) patients required two courses of IVIG, and 3 patients had three or more IVIG treatment courses. The mean tacrolimus dose was increased by  $1.5 \pm 2.4$  mg/d as part of the treatment for refractory rejection. The IVIG course was accompanied by a steroid recycle in 10 patients, and in 7 patients, mycophenolate mofetil was added (mean dose  $1143 \pm 690$  mg/d, range 500 to 2000 mg/d).

### RESULTS

After a mean follow-up of  $21.5 \pm 9.5$  months from the initiation of IVIG therapy, the patient survival rate was 95% (16/17), and the graft survival rate was 71% (12/17). Renal allograft function was well maintained after IVIG therapy. The baseline serum creatinine level prior to development of rejection was  $2.2 \pm 0.7$  mg/dL, and rose to  $3.3 \pm$

$1.1$  mg/dl during the refractory rejection episode. IVIG therapy reduced mean creatinine level in 11 patients 2 weeks after the conclusion of therapy ( $2.8 \pm 1.1$  mg/dL in all patients). The current creatinine level in patients with functioning grafts is  $2.8 \pm 1.6$  mg/dL.

Prior to the initiation of IVIG therapy, 47% (8/17) of patients had Banff Ia, 29% (5/17) had Banff Ib, and 24% (4/17) had Banff II rejection. By the conclusion of IVIG therapy, 53% of allograft biopsies (9/17) demonstrated complete resolution of rejection, and 29% (5/17) demonstrated reduced rejection severity. Overall, 82% of allograft biopsies had a reduction in rejection severity. In a subset of patients who received IVIG without a steroid recycle or mycophenolate mofetil, 86% (6/7) of post-IVIG allograft biopsies demonstrated reduction or resolution of rejection.

A total of four patients received IVIG to reverse anti-lymphocyte antibody-resistant rejection. Three patients had failed OKT3 therapy, and one patient failed anti-thymocyte globulin (ATG) therapy for either steroid-resistant or Banff II rejection. IVIG was able to completely reverse rejection in one patient and reduce rejection severity to borderline rejection in two other patients. Overall, IVIG rescued three of four patients with anti-lymphocyte antibody-resistant rejection.

IVIG was very well tolerated. Although one patient developed symptomatic cytomegalovirus infection 5 months after IVIG therapy and one patient developed fungal endocarditis 13 months post-IVIG, these complications were attributed to intensive long-term immunosuppression, and were not likely directly related to IVIG therapy.

### DISCUSSION

Previously, Casadei et al<sup>7,8</sup> showed that IVIG was able to rescue 82% of renal allografts with steroid-resistant rejection. Our data support their findings. After a follow-up of 21.5 months, we established that both graft and patient survival were relatively good, and stable renal graft function was maintained as well. For the first time, we also demon-

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strated that IVIG is able to reverse anti-lymphocyte antibody-resistant rejection.

A number of patients in our study were treated concomitantly with a steroid recycle and initiation of mycophenolate mofetil, confounding our ability to assess the efficacy of IVIG in reversing rejection. However, in a subgroup of patients who did not receive additional concurrent anti-rejection therapy, rejection was completely eliminated or markedly reduced in six of seven patients. Therefore, IVIG therapy by itself appears to be able to reverse steroid-resistant rejection.

It appears that the efficacy of IVIG therapy in the treatment of steroid-resistant rejection may be similar to that of OKT3 or ATG. The main advantage of IVIG over anti-lymphocyte therapy is the relative paucity of side-effects. In addition, its inherent anti-viral properties make IVIG an attractive agent in treating rejection in patients who harbor (or are at high risk for) immunosuppression-related viral infections, such as CMV, Epstein Barr Virus, or parvovirus.

## CONCLUSION

IVIG rescue therapy for steroid-resistant rejection is associated with histologic resolution or improvement of rejection severity, maintenance of renal function, and long-term graft survival. In addition, it appears that IVIG is capable of reversing anti-lymphocyte-resistant rejection.

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