Antilymphoblast globulin for treatment of acute renal allograft rejection

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The role of heterologous antilymphocyte globulin (ALG or ATG) in clinical renal transplantation remains controversial. There have been conflicting reports on the efficacy of various ALG preparations administered prophylactically from the time of transplantation.[1–5] More recently, ALG has been used to treat acute renal allograft rejection; most reports have described its use in combination with high-dose steroids.[6–10] Two studies have suggested that ALG can successfully reverse steroid-resistant rejection episodes.[11, 12] One study of living-related graft recipients, in which ATG was used as the sole adjunctive measure to treat rejection, demonstrated both an immunologically beneficial and steroid-sparing effect.[13] We report our initial experience with antilymphoblast globulin used to treat acute rejection in 30 renal-transplant recipients. In 24 patients, ALG was used alone without high-dose steroid administration as specific therapy for an acute rejection episode. In 6 patients, ALG was given as treatment for steroid-resistant rejection.

Materials and methods

The 30 patients in this study underwent renal transplantation between May 1980 and August 1981. The post-transplant follow-up interval ranged from 5 to 20 months. There were 4 living-related and 26 cadaver-graft recipients. Twenty-nine

patients (97%) had received ≥ 2 blood transfusions before transplantation. As maintenance immunosuppression all recipients were given azathioprine, 3–5 mg/kg in the 12 hours before transplantation and were then maintained on 1.5–2.0 mg/kg/day. One gram of methylprednisolone was administered intravenously in divided doses on the day of surgery. All living-related and alternate cadaver-graft recipients were given prednisone, 2 mg/kg/day (high maintenance steroid) from the first postoperative day, which was tapered rapidly over two months to 0.6 mg/kg/day, then slowly to a maintenance dose of 0.25 mg/kg/day. The remaining cadaver-graft recipients were treated with only 30 mg of prednisone daily (low maintenance steroid) for the first two post-transplant months, which was then tapered slowly to 0.25 mg/kg/day. All cadaver-graft recipients also received equine antilymphoblast globulin (produced at the University of Minnesota) for the first 14 days following transplantation at a dose of 15–30 mg/kg/day intravenously. The preparation, testing, and administration of the latter are described elsewhere.[14]

The diagnosis of acute rejection was established in all cases by a rise in the serum creatinine level and diminished renal function on I^{131} orthoiodohippurate scintigraphy. Supportive clinical findings included fever, graft swelling or tenderness, oliguria, weight gain, and hypertension. In 16 patients, a renal transplant biopsy was done to confirm the diagnosis. Technical causes of declining graft function were ruled out in all patients with one or more pelvic imaging studies, including ultrasonography, computed tomography, cystography, or intravenous pyelography. In all patients, maintenance immunosuppression with azathioprine and prednisone was unaltered during episodes of acute rejection. When ALG was used to treat rejection, it was administered at a dose of 15–20 mg/kg/day for 10 days. Complete rejection reversal was defined as a return of the postrejection serum creatinine level to within 10% of the prerejection level. Rejection episodes not treated with ALG were managed with one gram of methylprednisolone, intravenously, in divided doses daily or on alternate days to a maximum cumulative dose of 10 g. In a few patients with repeated rejection episodes, prednisone given orally was increased to 150 mg/day and tapered rapidly over two weeks to maintenance levels.

Results

The 30 patients in this study can be categorized into three distinct groups. In Group 1 (16 patients: 14 cadaver-graft, 2 living-related) ALG was used as the only additional treatment for a first rejection episode (*Table 1*). All but two cadaver-graft recipients (patients 3 and 9) in this group received low maintenance steroid therapy. ALG was successful in reversing the first rejection episode in all 16 cases and no patient required dialytic support. A consistent fall from the peak intrarejection serum creatinine level began 1–10 days (mean, 3.0 days) after initiation of ALG treatment, whereas nadir postrejection levels were reached within 4–27 days (mean, 12.2 days). Complete rejection reversal was achieved in 12 patients (75%), and 8 patients (50%) have had no subsequent rejection. Twelve patients (75%) currently have functioning grafts with follow-up of 5–18 months. Of the 12 cadaver-graft recipients in this group on low maintenance steroid therapy, complete rejection reversal occurred in 9 (75%); 6 (50%) experienced no subsequent rejection, and 10 (83%) retain a functioning graft.

Table 1. Clinical data on patients who received ALG for treatment for first rejection episode

Patient	Donor source	Days to rejection	Prerejection serum creatinine (mg/dl)	Peak intrarejection serum creatinine (mg/dl)	Nadir postrejection serum creatinine (mg/dl)	Subsequent rejection (IVMP, g)	Current serum creatinine (mg/dl)	Follow-up (mo)
1	LR	10	0.8	1.4	0.8	No	1.1	18
2	LR	18	0.9	1.9	1.3	No	1.3	13
3	CAD	30	2.6	5.1	1.5	Yes(6)	Graft loss due to rejection 14 mo posttransplant	
4	CAD	20	1.7	7.5	3.0	Yes(3)	2.6	15
5	CAD	22	0.9	3.0	1.0	No	1.1	15
6	CAD	86	1.3	2.3	1.4	Yes(3)	2.0	15
7	CAD	16	4.6	5.4	3.7	Yes(3)	Graft loss due to rejection 2 mo posttransplant	
8	CAD	44	1.2	3.5	1.8	Yes(3)	2.0	13
9	CAD	22	0.8	2.5	0.9	Yes(8)	Graft loss due to rejection 7 mo posttransplant	
10	CAD	20	1.0	4.0	1.3	Yes(9)	Graft loss due to rejection 2 mo posttransplant	
11	CAD	26	1.0	2.1	0.9	No	0.9	7
12	CAD	27	1.1	2.2	1.2	No	1.1	6
13	CAD	22	1.2	1.5	1.2	No	1.2	6
14	CAD	104	1.9	2.7	2.0	No	2.0	5
15	CAD	22	1.3	2.0	1.4	Yes(3)	1.8	5
16	CAD	17	1.3	2.6	1.3	No	1.3	5

IVMP = methylprednisolone, administered intravenously; LR = living related; CAD = cadaver.

Group 2 (*Table 2*) includes 8 patients (6 cadaver-graft, 2 living-related) who received ALG as treatment for a second or third rejection episode. Earlier rejections in these patients had been partially or completely reversed with 4–10 g of methylprednisolone. All but one cadaver-graft recipient (patient 22) in this group received high maintenance steroid therapy. Although ALG succeeded in reversing all of these rejection episodes, complete rejection reversal was accomplished in only 4 patients (50%). The time to initial reversal was again short, ranging from 1 to 5 days (mean, 2.7 days), and postrejection nadir serum creatinine levels were reached within 6–15 days (mean, 11.1 days). However, 5 patients (63%) experienced subsequent rejection, including 3 in whom graft loss ultimately resulted. Of the 5 patients who retain a functioning graft in this group, 4 have a current serum creatinine level > 3 mg/dl and the long-term prognosis is therefore guarded.

Group 3 (*Table 3*) includes 6 cadaver-graft recipients in whom ALG was employed to treat a steroid-resistant rejection episode. These patients received high-maintenance steroid therapy. In these patients, despite methylprednisolone, 3–10 g, given intravenously over the previous 5–21 days, renal function continued to deteriorate and 2 patients required dialysis. In all cases, within 3–21 days of initiating treatment with ALG, a fall from the peak intrarejection serum creatinine level was observed al-

Table 2. Clinical data on patients who received ALG as treatment for second or third rejection episode

Patient	Donor source	Prior rejections No. (IVMP, g)	Prerejection serum creatinine (mg/dl)	Peak intrarejection serum creatinine (mg/dl)	Nadir postrejection serum creatinine (mg/dl)	Subsequent rejection (IVMP, g)	Current serum creatinine (mg/dl)	Follow-up (mo)
17	LR	2 (9)	3.4	5.8	4.4	No	4.7	20
18	LR	2 (10)	2.4	4.0	2.6	Yes(*)	3.3	17
19	CAD	2 (10)	3.6	4.5	3.6	Yes(0)	Graft lost to rejection 7 mo post-transplant	
20	CAD	2 (4)	1.6	3.0	2.2	Yes(6)	Graft lost to rejection 6 mo post-transplant	
21	CAD	1 (5)	1.5	2.8	1.6	No	1.5	13
22	CAD	1 (9)	1.0	5.5	2.4	Yes(*)	3.7	8
23	CAD	1 (5)	3.4	5.7	3.7	No	3.7	9
24	CAD	1 (6)	1.5	5.4	2.5	Yes(2)	Graft lost to rejection 3.5 mo post-transplant	

* Increased prednisone, administered orally.

though complete rejection reversal occurred in only 2 patients. Nadir postrejection serum creatinine levels were attained in 12–38 days (mean, 23.2 days). Three patients experienced a subsequent mild rejection episode that responded to additional steroid therapy. One patient died of overwhelming bacterial infection 10 weeks after transplantation. Currently, 5 patients in this group (83%) retain a functioning graft with serum creatinine levels ranging from 1.1 to 3.6 mg/dl (mean, 2.4 mg/dl).

There were no serious side effects observed during the course of ALG therapy for acute rejection. Febrile reactions were common, particularly after the initial dose, but these invariably abated after the first few days of treatment. Leukopenia requiring temporary discontinuation of azathioprine occurred in 15 patients; in all cases, it was possible to reinstitute azathioprine administration either during or immediately following treatment with ALG. Nonfatal infectious complications included herpeslike lesions in 4 patients, oral moniliasis in 2, asymptomatic bacteriuria in 2, and staphylococcal pneumonia in one patient. All of the latter resolved without sequelae either spontaneously or following appropriate treatment. The only death occurred three days after completion of ALG therapy for steroid-resistant rejection because of overwhelming bacterial sepsis.

Discussion

Most prior studies of ALG for treatment of rejection have involved its use with increased steroid dosages.[6–12] The only report of ALG employed as the sole treatment for established allograft rejection was in recipients of kidneys from living-related donors.[13] This study compared ALG with high-dose steroids and found the former to be effective, safe, and steroid-sparing. There are no published reports on the use of ALG alone for treatment of rejection of cadaver transplants. The data reported herein are not the result of a prospective randomized comparison of ALG with an-

Table 3. Clinical data on patients who received ALG as treatment for steroid-resistant rejection

Patient	Donor source	Prior rejections No. (IVMP, g)	Prerejection serum creatinine (mg/dl)	IVMP, g (days)	Peak intrarejection serum creatinine (mg/dl)	Nadir postrejection serum creatinine (mg/dl)	Subsequent rejection (IVMP, g)	Current serum creatinine (mg/dl)	Follow-up (mo)
25	CAD	0	1.0	6 (13)	3.0	2.1	Yes(*)	2.3	14
26	CAD	1 (3)	2.1	4 (6)	Dialysis	2.0	No	2.0	13
27	CAD	0	1.5	3 (5)	5.2	1.4	No	1.1	8
28	CAD	0	1.1	10 (21)	6.9	4.4	No	*Died 2.5 mo post-transplant*	
29	CAD	0	0.8	5 (7)	Dialysis	3.2	Yes(2)	3.1	6
30	CAD	1 (4)	1.7	3 (4)	3.8	2.4	Yes(*)	3.6	5

* Increased prednisone, administered orally.

other antirejection treatment method and it is therefore not possible to comment on the relative efficacy of this particular protocol. Nevertheless, several conclusions may be drawn from this preliminary report.

ALG alone was effective in reversing first acute rejection episodes with minimal morbidity and excellent short-term graft success; e.g., the 12 patients in Group 1 managed with prophylactic ALG, low maintenance steroid therapy, and a second course of ALG to treat first rejection. The two sequential courses of ALG were well tolerated in all cases. Six of these patients (50%) experienced no subsequent rejection and were thereby spared the potential morbidity of increased maintenance and antirejection steroid dosages. Methylprednisolone, given intravenously, was used to treat subsequent rejections that occurred in the remaining 6 patients, of whom 4 currently retain a well-functioning graft. Perhaps, as has been suggested,[15] ALG prophylaxis resulted in rejections of diminished severity that were more easily treated. Nevertheless, these initial results suggest an approach to maintenance and antirejection immunosuppressive therapy that may be both efficacious and steroid-sparing.

The results of ALG alone for treatment of second or third rejections were not as encouraging. Complete rejection reversal was achieved in only half of these patients and the current serum creatinine levels suggest a guarded prognosis for most of these grafts still functioning. Finally, as Hardy et al[12] and Light et al[11] have indicated, ALG appeared to be effective in treating steroid-resistant rejections. One of our patients treated with ALG for rejection died after undergoing heavy immunosuppression with methylprednisolone (10 g intravenously) and a 10-day course

of ALG during a 32-day period. The latter case suggests that if steroid-resistant rejections are to be treated with ALG, the recognition of these episodes and the decision to change therapy should be made early.

In summary, initial results in 30 renal transplant patients suggest that ALG alone can provide safe and effective treatment for acute renal allograft rejection, particularly first rejection episodes. The use of ALG, both prophylactically and as therapy for initial rejection, may possibly achieve satisfactory cadaver graft survival with reduced steroid dosages. ALG also appears to be useful in the management of steroid-resistant rejection episodes.

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