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Robert L. Madden
Jeffrey G. Mulhern
Bernard J. Benedetto
Michael H. O'Shea
Michael J. Germain
Gregory L. Braden
Joan O'Shaughnessy
George S. Lipkowitz

Completely reversed acute rejection is not a significant risk factor for the development of chronic rejection in renal allograft recipients

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R.L. Madden · B.J. Benedetto
J. O'Shaughnessy · G.S. Lipkowitz
Division of Transplantation,
Department of Surgery,
Baystate Medical Center,
Tufts University School of Medicine,
Springfield, MA 01199, USA

J.G. Mulhern · M.H. O'Shea
M.J. Germain · G.L. Braden
Department of Medicine,
Baystate Medical Center,
Tufts University School of Medicine,
Springfield, MA 01199, USA

R.L. Madden (✉)
208 Ashley Avenue, West Springfield,
MA 01089, USA
Tel.: + 1-413-750-3440
Fax: + 1-413-750-3432

Abstract Although acute rejection (AR) has been shown to correlate with decreased long-term renal allograft survival, we have noted AR in recipients who subsequently had stable function for more than 5 years. We reviewed 109 renal graft recipients with a minimum of 1 year graft survival and follow-up of 5–8 years. Post-transplant sodium iothalamate clearances (IoCl) measured at 3 months and yearly thereafter were used to separate recipients into 2 groups. In 61 patients (stable group), there was no significant decrease (> 20% reduction in IoCl over 2 consecutive years) in IoCl. Forty-eight patients had significant declines in IoCl (decline group). Groups were compared for incidence, severity, timing, and completeness of reversal of AR. Rejection was considered completely reversed if the post-AR serum creatinine (Scr) returned to or below the pre-AR nadir Scr after antirejection therapy. The incidence of AR was not significantly different between groups (47% vs 52%). A trend toward a lower mean number of AR episodes per patient was noted in the stable group (0.69 vs 1.04, $P = 0.096$), but the timing of AR was not different. Steroid-resistant AR occurred in approximately 25% of both groups. A striking difference was seen in complete reversal of AR, with the stable group having 100% (42/42 episodes of AR in 29 patients) complete reversal whereas only 32% (8/25) of the patients in the decline group had complete reversal ($P << 0.001$). Of 8 declining patients with complete reversal, graft loss was due to chronic rejection (CR) in only 3. Seventeen declining patients had incomplete reversal of AR, and 82% (14/17) lost their grafts to CR. Overall, only 8% (3/37) of the recipients with complete reversal of AR developed CR. No patients with incompletely reversed AR had stable long-term function as measured by IoCl. AR is not invariably deleterious to long-term renal graft function if each episode of AR can be completely reversed.

Key words Renal transplantation · Acute rejection · Chronic rejection

Abbreviations *AR* Acute rejection · *CG* Cockcroft-Gault (method) · *CR* Chronic rejection · *CyA* Cyclosporine · *IoCl* Iothalamate clearance · *Scr* Serum creatinine

Introduction

Acute rejection (AR) has been shown to correlate with decreased long-term renal graft function, and the number, timing, and/or severity of AR episodes have been implicated as risk factors for allograft loss [2, 7, 9, 12, 13, 16–19, 23, 24]. Recent, large retrospective studies have shown that the occurrence of even one episode of AR significantly reduced long-term renal graft survival [7, 17, 19, 23]. Episodes of AR have also been shown to correlate with the development of chronic rejection (CR) [1, 2, 7, 12, 16, 17]. Conversely, other authors have reported that AR does not adversely influence long-term survival, although some found this only if AR was associated with early graft function, a serum creatinine (Scr) level of below 2.0 mg/dl at 6 months after transplantation, or no loss of graft function (as determined by pre- and postrejection Scr) [4, 10, 14, 16, 18, 24]. Against this backdrop, we have noted AR in many of our renal graft recipients who subsequently enjoyed stable, long-term function, and several of our recipients with stable function experienced multiple, early episodes of AR. We therefore performed a review of our renal graft recipients in order to further elucidate the effect of AR on long-term renal function.

Materials and methods

Patients

The records of 109 consecutive recipients of renal transplants performed from November 1988 to December 1992 with a minimum graft survival of 1 year and a 5–8 year follow-up were reviewed. All transplants were performed at Baystate Medical Center, Springfield, Mass. by two transplant surgeons using the same clinical protocol. Both living related and cadaveric graft recipients were included. All recipients had a negative T cell crossmatch using current sera, and cadaveric kidneys were preserved by cold storage methods. Recipients of combined kidney-pancreas transplants were excluded.

Immunosuppression

Immunosuppression was prospectively tailored for each recipient based upon an assessment of immunologic risk. Recipients considered to be at a low immunologic risk (panel reactive antibody < 20%) and who experienced good initial graft function (average urine output > 100 ml/h and Scr decrease > 2 mg/dl in the first 24 h) received dual therapy with cyclosporine (CyA) and corticosteroids. If the initial graft function was less than good, azathioprine was added to the regimen (triple therapy). Immunologically sensitized patients, repeat transplant recipients who had lost their first graft in less than 6 months, and/or those with no initial graft function were treated with sequential, quadruple therapy with OKT-3 induction, CyA, azathioprine, and corticosteroids. CyA was dosed to maintain whole blood trough levels at 300–400 ng/ml during the first 3 months, 250–300 ng/ml from months 4–12, and 200–250 ng/ml thereafter as measured by TDX assay. Azathioprine was given at 2 mg/kg per day and reduced if necessary to keep the white blood cell count at more than 4.0 K/mm^3. Methylprednisolone was given intraoperatively (500 mg), and oral corticosteroids were tapered to a level of 7.5 mg/day by 4 months.

Creatinine clearance

All patients were evaluated with IoCl at 3 months after renal transplantation and yearly thereafter. Glofil (Isotex, Friendswood, Tex.) was mixed with 0.1 ml of 1:1000 epinephrine and was given subcutaneously in the upper arm. Three urine collections were obtained through voluntary voiding, with blood samples drawn after each time of collection. I^{125} activity in the urine and serum was determined by counting 0.5 ml samples for 2 min on a Tracor analytic gamma counter, model 1197 (Tracor Analytical, Des Plaines, Ill.). IoCl was calculated using the UV/P formula, in which U and P are urine and serum counts and V is the volume of urine per minute. The mean clearance was calculated from three consecutive values. For comparison purposes, the creatinine clearances of all patients were calculated using the Cockcroft-Gault (CG) method at 3 months after transplantation and yearly thereafter [3].

Rejection

AR was diagnosed based upon clinical criteria (≥ 25% rise in Scr creatinine that was unresponsive to a reduction in CyA dose) and Doppler ultrasound resistive indices (resistive index > 0.8 or a ≥ 20% increase in resistive index above baseline) [8]. In the majority of cases (72%), AR was confirmed by percutaneous core biopsy. Methylprednisolone (500 mg/day × 3 days) followed by recycling of oral corticosteroids was used as initial treatment for AR, and steroid-resistant AR was treated with OKT-3 (5 mg/day × 10–14 days) or a polyclonal antilymphocyte preparation. A diagnosis of CR was made solely on the basis of percutaneous core biopsy as interpreted by 2 independent nephropathologists. Percutaneous core biopsies were performed on most patients (84%) with a significantly decreasing IoCl and/or the development of proteinuria.

The histologic criteria used to diagnose CR, including the criteria for a differential diagnosis with chronic CyA nephropathy, have been described previously [15]. Briefly, concentric intimal thickening of arterioles and larger arteries without hyalinosis, patchy interstitial fibrosis, and glomerular changes (nonspecific ischemic changes or chronic transplant glomerulopathy) were used to diagnose CR. Although interstitial fibrosis may be seen with chronic CyA nephropathy, this diagnosis was based primarily on vascular changes. Circumferential hyalinosis of arterioles (especially if identified in a nodular pattern within the vessel wall) with relative sparing of larger arteries, and/or subendothelial mucoid changes in arterioles were used as criteria for a diagnosis of chronic CyA nephropathy.

Groups and definitions

The IoCl results were used retrospectively to divide the patients into 2 groups. The stable group included patients with no significant decrease in IoCl at any time after transplantation. A significant decrease was defined as a more than 20% reduction in IoCl over 2 consecutive years. Patients experiencing a significant decline in IoCl were included in the decline group. Groups were compared for the incidence, severity, timing, and completeness of reversal of AR. An episode of AR was considered completely re-

Table 1 Mean sodium iothalamate (IoCl) and Cockcroft-Gault (CG) clearances

Renal function	3 months	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8 year
No. of Patients	61	61	61	61	61	61	46	28	18
Stable IoCl	61 ± 22	65 ± 22[a]	65 ± 23[b]	66 ± 24[b]	65 ± 25[b]	66 ± 24[b]	63 ± 18[b]	68 ± 22[a]	61 ± 18[a]
CG	59 ± 14	68 ± 21	73 ± 20	70 ± 22	72 ± 24	74 ± 25	71 ± 27	70 ± 26	58 ± 15
No. of Patients	48	48	44	39	35	30	22	10	7
Declining IoCl	63 ± 18	54 ± 24[a]	50 ± 24[b]	49 ± 23[b]	41 ± 22[b]	43 ± 18[b]	42 ± 18[b]	33 ± 17[a]	39 ± 18[a]
CG	60 ± 18	54 ± 17	49 ± 17	50 ± 20	47 ± 18	46 ± 18	44 ± 19	34 ± 18	39 ± 19

[a]Significant difference in IoCl ($P < 0.01$) between stable and decline groups
[b]Significant difference in IoCl ($P < 0.001$) between stable and decline groups

versed if the post-AR Scr returned to or below the pre-AR nadir Scr after antirejection treatment. For recipients with more than 1 episode of AR, all of the episodes had to be completely reversed for them to be considered patients with complete reversal.

Statistical analysis

Groups were compared using χ^2- and Student's t tests where appropriate. Patient and graft survivals were evaluated by Kaplan-Meier survival analysis and compared for significant differences with the log-rank test. Results were considered significant at P values of less than 0.05. Arithmetic means are expressed as mean ± SD.

Results

Patient groups, IoCl, and characteristics

Of the 146 transplant procedures performed during the 4-year period, 37 recipients were excluded from this analysis because of a graft survival of less than 1 year, patient refusal to undergo IoCl, follow-up at different institutions, or kidney-pancreas transplantations, leaving 109 patients available for study. Using IoCl as an assessment of renal graft function, 61 recipients had no significant deterioration and were included in the *stable* group. Forty-eight patients experienced significant decreases in IoCl and were placed in the *decline* group. The mean IoCls and CG clearances are shown in Table 1. The mean IoCls of the stable group remained at a mean of 64.2 ± 2.6 ml/min over the 8-year follow-up period. In contrast, the mean IoCls of the decline group fell significantly starting at 1 year after transplantation. Mean IoCl between groups was not different at 3 months. The mean CG clearances varied from the mean IoCls with an overall mean difference of + 7% and a range from + 15% to −5%.

As shown in Table 2, the groups were similar with respect to age, sex, diabetes, repeat transplants, panel reactive antibodies, HLA mismatch, and donor source. The only significant difference in group demographics was race. The decline group had a significantly higher percentage of nonwhite patients ($P < 0.03$). There was no significant difference in the proportion of patients treated with dual, triple, or sequential, quadruple immunosuppressive therapy between groups.

Table 2 Patient characteristics

	Stable n (%)	Decline n (%)
Number	61	48
Age (mean)	42.6 ± 13.3	45.7 ± 13.0
Sex (M/F)	35/26	25/23
Diabetes	11 (18)	11 (23)
Donor source:		
Cadaver	49 (80)	37 (77)
Living	12 (20)	11 (23)
PRA	5.1 ± 9.1	4.4 ± 8.8
HLA mismatch	4.1 ± 1.8	3.7 ± 2.1
Transplant number:		
1st	49 (80)	43 (90)
2nd	11 (18)	5 (10)
3rd	1 (2)	0 (0)
Race[a]:		
Caucasian	53 (87)	32 (67)
AfroAmerican	5 (8)	11 (23)
Hispanic	2 (3)	5 (10)
Asian	1 (2)	0 (0)
Immunosuppression:		
Dual	26 (43)	26 (54)
Triple	19 (31)	12 (25)
Sequential, quadruple	16 (26)	10 (21)

[a]Significant difference ($P < 0.03$) between stable and decline groups

Rejection

The overall incidence of AR for the entire cohort of 109 recipients was 49.5%. There was no significant difference in the incidence of AR between the stable (47.5%) and the decline (52.1%) groups (Table 3). To assess the timing of AR, the groups were evaluated in the following time periods after transplantation: 0–1 months, 1–6 months, 6–12 months, and after 12 months. Although no significant differences were found in the timing of AR, there was a trend toward more late (> 12 months) AR in the decline group. Similar results were noted with respect to the number of ep-

Table 3 Characteristics of acute rejection episodes (*AR* acute rejection)

	Stable *n* (%)	Decline *n* (%)
Number	61	48
Patients with AR	29 (47)	25 (52)
Number of AR episodes: 0	32 (52)	23 (48)
1	19 (31)	10 (21)
2	6 (10)	10 (21)
> 2	4 (7)	5 (10)
Mean *n* AR/patient	0.69 ± 0.9	1.04 ± 1.3
Patients with completely reversed AR[a]	29 (100)	8 (32)
Timing of AR: 0–1 months	23 (55)	27 (54)
1–6 months	16 (38)	13 (26)
6–12 months	3 (7)	4 (8)
> 12 months	0 (0)	6 (12)
Steroid resistant AR	10 (24)	13 (26)

[a]Significant difference ($P << 0.0001$) between stable and decline groups

isodes of AR. Though not quite reaching statistical significance, there was a trend toward a higher number of episodes per patient in the decline group (0.69 vs 1.04, $P = 0.096$). Severity of AR was evaluated in terms of steroid resistance, and the percentage of steroid-resistant AR was similar in both groups (24% vs 26%).

The groups were compared for the completeness of reversal of AR as measured by Scr. In the stable group, all 29 recipients experiencing AR had complete reversal of all episodes of AR. In sharp contrast, only 8/25 patients (32%) in the decline group experienced complete reversal of all episodes of AR. This difference was found to be highly significant ($P << 0.0001$). Episodes of AR in the stable group were also evaluated for the amount of time required to achieve complete reversal. Figure 1 shows the number of days for each AR episode to be reversed. The mean time to complete reversal was 15.6 ± 16.1 days, and the median was 11.0 days with a range of 2–79 days. Seventy percent, 80%, and 90% of the episodes were completely reversed by 15, 18, and 24 days, respectively. In addition, the pre-AR Scr, the post-AR Scr and the Scr at 6 months after transplantation were also compared between groups. The mean pre-AR Scr was similar in both groups (stable: 1.69 mg/dl, and decline: 1.75 mg/dl), but the mean post-AR Scr in the stable group (1.25 mg/dl) was significantly ($P < 0.001$) lower than the mean post-AR Scr (1.85 mg/dl) in the decline group. The mean Scr at 6 months after transplantation was also significantly lower in the stable group vs the decline group (1.57 vs 1.90 mg/dl, $P < 0.03$).

The groups were also evaluated for CR. Again, significantly more CR was seen in the decline group compared to the stable group (56.2% vs 1.6%, $P << 0.0001$). In the decline group, only 3/8 (38%) with complete reversal of AR developed CR, while 14/17 (82%) with incompletely reversed AR lost their grafts to CR. Ten patients in the decline group with no history of AR were diagnosed with CR on biopsy. Overall, looking at the groups together, only 3/37 (8%) patients with completely reversed AR developed CR.

Patient and graft survival

The actual 5-year patient and graft survivals were 100% in the stable group, and 88% and 61% in the decline group, respectively. Actuarial patient and graft survivals in both groups with a follow-up of 5–8 years are shown

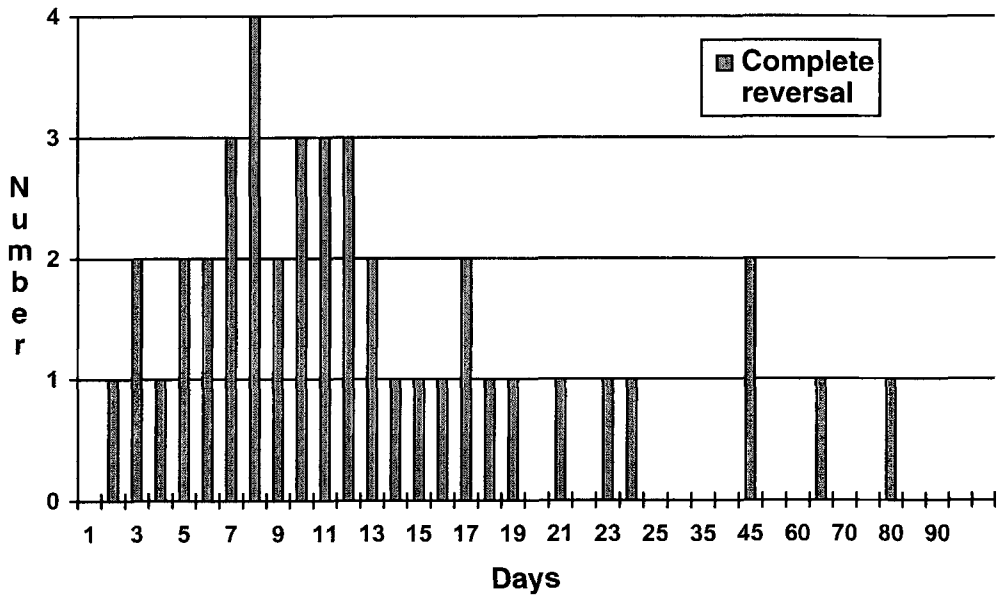

Fig. 1 Number of days for each episode of acute rejection ($n = 42$) in the stable group of patients to be completely reversed

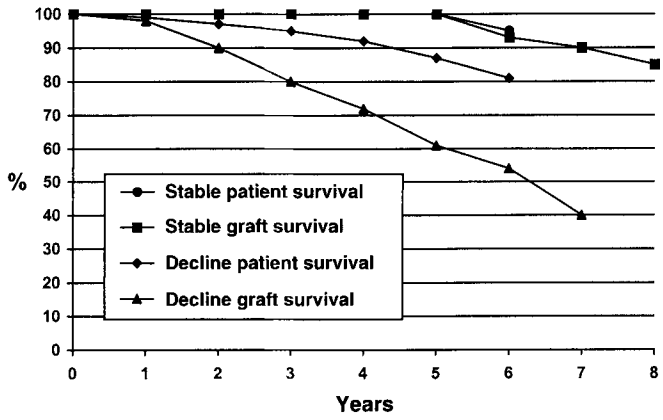

Fig. 2 Actuarial patient and graft survival curves ($P = 0.01$ and $P << 0.0001$ between stable and decline groups, respectively)

Table 4 Causes of graft loss

Cause	Stable (n)	Decline (n)
Death with function	3	4
Chronic rejection[a]	1	14
Glomerulonephritis[b]	1	7
Cholesterol emboli	0	2

[a]Significant difference ($P < 0.001$) between stable and decline groups.
[b]Significant difference ($P < 0.03$) between stable and decline groups

in Fig. 2 and were significantly worse in the decline group compared to the stable group ($P = 0.01$ and $P << 0.0001$, respectively). Reasons for graft loss are shown in Table 4. Notably in the decline group, of patients with completely reversed AR, 62% (5/8) lost their grafts to biopsy-proven, nonimmunologic causes (2 due to cholesterol emboli and 3 due to glomerulonephritis).

Discussion

AR has been implicated in numerous recent studies as a significant risk factor for the development of CR and decreased long-term renal graft survival [1, 2, 7, 9, 12, 13, 16, 17–19, 23, 24]. Our clinical research interest has been focused on chronic CyA toxicity, which we have evaluated by studying serial IoCl on our renal graft recipients. Interestingly, we noted episodes of AR that were at times multiple and severe in many of our recipients who went on to enjoy very stable, long-term renal graft function. In other recipients, however, episodes of AR did seem to lead to CR and graft loss. Review of the literature pointed to differences in AR in terms of number, timing, and/or severity as etiologies of the different long-term results of AR [1, 2, 7, 9, 12, 13, 16, 17–19, 23, 24]. Utilizing an accurate assay (IoCl) for the assessment of renal function, the goal of our study was to identify what differences, if any, existed in episodes of AR that led to CR versus those in which AR did not seem to affect long-term function.

Although not reaching statistical significance, our results are consistent with previous studies that have shown an increasing number of AR episodes and later episodes of AR to be risk factors for graft loss [2, 7, 9, 13, 17, 19, 23]. We found a trend ($P = 0.096$) toward an increased number of AR episodes per patient in those that developed deteriorating function. Indeed, with larger numbers, this may well have reached significance. Albeit a weaker trend, we also saw a larger number (12% vs 0%) of late (> 12 months) AR episodes in recipients in the decline group. These findings seem compatible with a hypothesis that those with decreased long-term function may be stronger immune responders who would experience more AR for a longer time and be more likely to develop CR. These results could also implicate noncompliance as an etiology for CR and graft loss [5, 6, 19, 20]. We suspect that subclinical noncompliance was a contributing factor in many of our decline recipients with CR who never experienced AR and in the single stable patient who went from an IoCl that was stable over 6 years to graft loss resulting from CR in a 7-month period. Conversely, we did not find that resistance to steroid therapy was a risk factor for loss of function as previously reported [9, 23]. Our results indicate that the response to treatment rather than the severity of AR is more important in determining long-term function.

Regardless of long-term graft function, fully one half of the patients included in this study experienced AR. This rate of AR is consistent with the results of other transplant centers in the United States [2, 19, 23]. Although the differences in number and timing of AR episodes did not reach significance, the one clearly striking difference between the groups was the completeness of reversal of rejection. All patients that experienced AR and went on to have stable long-term graft function had their AR completely reversed. In sharp contrast, only one third of the patients whose function declined significantly over time showed complete reversal of AR. Logically, this reduction of long-term function should correlate with decreased long-term graft survival. Our results indeed show a marked diminution in graft survival in the decline group, which is in agreement with previous studies. Vereerstraeten et al. examined the effect of reversal of AR and noted that a completely reversed ("benign") episode of AR was not deleterious on long-term graft survival. AR that was incompletely reversed, however, resulted in significantly worse graft survival [24]. Cosio et al. found that AR predicted poor renal graft survival only when associated with graft dysfunction (Scr > 2 mg/dl at 6 months after transplantation) [4]. The mean 6 months post-transplant Scr in our

decline group did not reach 2 mg/dl, but was significantly higher than that of the stable group (1.90 mg/dl vs 1.57 mg/dl, respectively). Similarly, Opelz reporting for the Collaborative Transplant Study found that cadaver kidney recipients who were treated for AR during the first year after transplantation and who attained a 1-year Scr of less than 130 μmol had only a slightly lower long-term graft survival rate compared to patients who experienced no AR during the first year. Those recipients with a 1-year Scr of more than 130 μmol had a significant decrease in long-term graft survival [18].

In addition to diminished long-term function and reduced graft survival, AR has also been found to correlate with an increased rate of CR [1, 2, 7, 12, 16, 17]. Our study showed that the risk of CR is much greater in recipients with incompletely reversed AR compared to those with complete reversal. Of the patients in the decline group with incompletely reversed AR, most (82%) lost their grafts to CR. On the contrary, only 3 patients in this group with complete reversal suffered from CR. Furthermore, in the declining patients with completely reversed AR, the majority (5 of 8 patients) of graft loss was due to nonimmunologic causes (biopsy-proven glomerulonephritis in 3 patients and cholesterol emboli in 2). Finally, considering the entire cohort of recipients, only 8% of the recipients with completely reversed AR developed CR.

Clearly, reversing the immunologic process that leads to long-term dysfunction and/or CR is of paramount importance. In some recipients, the completeness of reversal seems easy to assess because the post-AR Scr quickly returns to or drops below their pre-AR nadir and remains stable. The reversal in other patients is difficult to judge and can be a very gradual process, as shown by the broad range of time to complete reversal seen in our data. It can be extremely difficult to ascertain whether an episode of treated AR with a slowly falling Scr is being completely reversed or whether a second antirejection agent should be used. Repeating an IoCl as opposed to following the Scr would give a more accurate estimate of function, but that would not be much better than Scr in deciding whether function was at a steady state or still improving. Perhaps treating all AR more aggressively would result in a higher percentage of episodes with complete reversal, and some authors have recommended treating all episodes of AR with OKT-3 [11, 21, 22]. We have not followed these recommendations, fearing increased rates of infectious and malignant complications, antimurine antibody formation, and higher costs.

In conclusion, we believe that AR is not invariably deleterious to long-term renal graft function if each episode of AR can be completely reversed as measured by pre- and postrejection Scr. Moreover, completely reversed AR does not often lead to the development of CR. Incomplete AR reversal, however, frequently leads to CR, decreased long-term graft function, and significantly reduced graft survival.

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