Effect of Increasing Baseline Immunosuppression on the Prevalence of Clinical and Subclinical Rejection: A Pilot Study

PETER NICKERSON,*† JOHN JEFFERY,* JAMES GOUGH,‡ PAUL GRIMM,†§ RACHEL MCKENNA,*† PATRICIA BIRK,§ and DAVID RUSH*

*Departments of *Medicine, †Immunology, ‡Pathology, and §Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada.*

Abstract. This group has reported that treatment of subclinical rejection in the first 3 mo posttransplant with corticosteroids decreases late clinical rejections and improves graft function at 2 yr in renal transplant recipients. The current study was performed to determine whether an increase in baseline immunosuppression would decrease the prevalence of early subclinical rejections, as well as the incidence of early and late clinical rejections. Patients received mycophenolate mofetil (MMF) and Neoral cyclosporin A (CsA) posttransplant ($n = 29$), of which 17 underwent protocol biopsies at months 1, 2, 3, and 6 (Neoral + MMF Protocol Biopsy [Bx]), while 12 declined protocol biopsies (Neoral + MMF Control). These individuals were compared with 72 historical control patients treated with Sandimmune CsA and Imuran, of which 36 had undergone protocol biopsies at months 1, 2, 3, and 6 (Sandimmune + Azathioprine [AZA] Protocol Bx), and 36 had a protocol biopsy at month 6 (Sandimmune + AZA Control). Baseline immunosuppression with Neoral + MMF decreased the incidence of early clinical rejections (0 to 3 mo) and cumulative corticosteroid exposure, but had no impact on the prevalence of early subclinical rejection. Moreover, to maximally decrease the risk of developing late clinical rejections (months 7 to 12) in Neoral + MMF patients required that protocol biopsies be done and that subclinical rejection be treated. The paradoxical finding of recent clinical trials that a reduction in acute clinical rejection has not improved long-term graft outcome may be explained in part by the failure to control subclinical rejection.

In the first 3 mo posttransplant, the Banff criteria for grade I acute rejection are present in approximately 30% of Sandimmune cyclosporine-, azathioprine-, and prednisone-treated renal transplant patients with stable graft function (1). Treatment of early subclinical rejection (months 1 to 3) with corticosteroids was associated with a decrease in early (months 2 to 3) as well as late (months 7 to 12) clinical rejection episodes, a decrease in the chronic tubulointerstitial score at 6 mo, and a lower serum creatinine at 24 mo (2). Furthermore, subclinical rejection at month 6 has been shown to be an independent predictor of an elevated serum creatinine at 24 mo posttransplant (3). The goal of the current study was to determine whether an increase in baseline immunosuppression (*i.e.*, Neoral cyclosporine and mycophenolate mofetil [MMF]) would diminish the prevalence of both clinical and subclinical rejection episodes.

Materials and Methods

Since June 1996, our center has increased baseline immunosuppression. Adult renal transplant recipients are immunosuppressed with MMF (Roche, Basel, Switzerland) in place of azathioprine (AZA), and Neoral cyclosporine (Novartis, Basel, Switzerland) in place of Sandimmune cyclosporin A (Sandoz, Basel, Switzerland). Target trough levels of cyclosporin A (CsA) were increased to 400, 375, and 350 μg/L at months 1, 2, and 3, respectively, from the previous target levels of 350, 300, and 250 μg/L. CsA levels are measured in whole blood, 12 h after dosing, using the monoclonal TDx system. Prednisone is started at 1 mg/kg per d and tapered to 15 mg/d over 2 wk, when possible. As was our previous practice, Diltiazem SR 60 mg twice a day is given to all patients from the time of transplant.

Apart from an increase in baseline immunosuppression, we have maintained all other clinical practices constant and continued our policy of protocol biopsies of the graft at 1, 2, 3, and 6 mo posttransplant after obtaining informed consent (approved by the University Medical Ethics Committee). Core renal biopsies were done in the clinical investigation unit using a spring-loaded 18-gauge gun after ultrasound localization. Acute inflammation and chronic changes were scored according to the Banff schema, 1993–1995 version (4). Two cores of tissue were obtained in most instances. Adequacy of tissue for examination was as reported previously (5). The renal pathologist reported on the biopsies, blinded to the clinical status of the patient, on the day they were done and communicated the findings to the transplant physician.

Acute rejections were classified as "clinical" or "subclinical." A clinical rejection could be diagnosed at the time of, or between, protocol biopsies. At the time of protocol biopsy, a diagnosis of clinical rejection required an acute inflammatory score ≥ 4 (acute rejection $\geq$ grade I) and an increase in the serum creatinine $>10\%$ from the baseline of the preceding 2 wk (months 1 to 3), or the preceding month (month 6). Between protocol biopsies, clinical re-

Received March 26, 1999. Accepted April 15, 1999.

Correspondence to Dr. Peter Nickerson, Department of Medicine, GG549-820 Sherbrook Street, Winnipeg, Manitoba, Canada, R3A 1R9. Phone: 204-787-7251; Fax: 204-783-6780; E-mail: pnickerson@hsc.mb.ca

1046-6673/1008-1801

Journal of the American Society of Nephrology

jection was defined by an increase in the serum creatinine >10% from the baseline for which an alternative diagnosis was excluded (*e.g.*, obstruction). The diagnosis of clinical rejection was supported either by a biopsy or by a subsequent decrease in the serum creatinine in response to an increase in steroids, or OKT3 (Ortho Biotech, North York, Ontario, Canada) administration. A diagnosis of subclinical rejection required an acute inflammatory score ≥4 in a protocol biopsy and an increase in serum creatinine <10% from the defined baseline. Rejection, defined either on clinical grounds or by pathologic criteria, occurring at any time posttransplant, was treated with a 2-wk tapering course of high-dose steroids (starting either at 1000 mg of intravenous Solumedrol or 200 mg of oral prednisone, with taper).

In the current study, we compared the prevalence of early and late rejections in patients who received Neoral, MMF, and prednisone ($n = 29$) to individuals that we have previously reported as part of a randomized control study treated with Sandimmune, AZA, and prednisone ($n = 72$) (2). Within both of these groups there were patients that had undergone protocol renal allograft biopsies at 1, 2, 3, and 6 mo.

Statistical Analyses

Values reported are mean ± SEM or, where indicated, as medians and ranges. P values ≤0.05 were considered statistically significant. Analysis was conducted using SAS software (version 6.12) in conjunction with the Biostatistical Consulting Unit of the University of Manitoba. Comparison of treatment groups used ANOVA or Wilcoxon rank sum tests. Testing for correlation between clinical and histologic parameters was done by Pearson correlation analysis or, where appropriate, Spearman rank correlation test. Backward stepwise logistic regression modeling was applied to late clinical rejections from months 7 to 12 posttransplant.

Results

Comparisons between the entire group of patients on Neoral + MMF and the Sandimmune + AZA group are shown in Table 1. Transplant recipients in the Neoral + MMF group had significantly higher pretransplant panel reactive antibody levels and older donors than those in the Sandimmune + AZA group. However, the cold ischemic time and the incidence of delayed graft function were similar in both groups. As expected, transplant recipients in the Neoral + MMF group had significantly higher CsA levels in the first 3 mo posttransplant than those in the Sandimmune + AZA group.

The incidence of clinical rejection episodes was significantly reduced in the first 3 mo posttransplant in the Neoral + MMF group, with the major benefit being a reduction in the frequency of individuals with ≥2 clinical rejection episodes (months 0 to 3: 51% *versus* 28%, $P = 0.04$) (Table 1). Moreover, the increase in baseline immunosuppression decreased the cumulative prednisone dose administered in the early posttransplant period (*i.e.*, months 0 to 3: 6.0 ± 0.3 g *versus* 4.7 ± 0.4 g, $P = 0.02$). The incidence of clinical rejections was similar between the groups during months 4 to 6 posttransplant (P = NS). From 7 to 12 mo, there was a trend toward fewer clinical rejection episodes in the Neoral + MMF group compared to the Sandimmune + AZA group (10% *versus* 23%, $P = 0.26$).

We attempted to separate the beneficial effects of increasing baseline immunosuppression from the beneficial effects of treating subclinical rejection detected by protocol biopsy on the incidence of clinical rejection episodes. The patients were therefore separated into those who had undergone protocol biopsies and compared with those that had declined or had been randomized to no protocol biopsies (Table 2). The subgroup that had both an increase in the baseline immunosuppression and underwent protocol biopsies (Neoral + MMF + Protocol Biopsy [Bx]) had the greatest reduction in clinical rejection episodes during the first 2 mo posttransplant ($P = 0.03$ *versus* Neoral + MMF Control, $P = 0.007$ *versus* Sandimmune + AZA + Protocol Bx, $P = 0.004$ *versus* Sandimmune + AZA control), with the major benefit being a reduction in the number of individuals with ≥2 clinical rejection episodes. Increasing baseline immunosuppression alone tends to increase the number of individuals who remained free of clinical rejection episodes in the first 3 mo posttransplant (25% Neoral + MMF Control *versus* 8% Sandimmune + AZA control, $P = 0.16$). There was no difference in the incidence of clinical rejection episodes during months 4 to 6 posttransplant between any of the subgroups. However, the subgroup with both an increase in baseline immunosuppression and protocol biopsies (Neoral + MMF + Protocol Bx) had no clinical

Table 1. Comparison of pretransplant and posttransplant characteristics[a]

Characteristic	Sandimmune + AZA ($n = 72$)	Neoral + MMF ($n = 29$)	P Value
HLA matching[b]	2 (0,5)	2 (1,4)	NS
PRA (%)	0.8 ± 0.5	7.2 ± 3.1	0.004
Donor age (yr)	33 ± 2	41 ± 2	0.03
Cold ischemia (min)	989 ± 54	914 ± 81	NS
Delayed graft function	22% (16 of 72)	27% (8 of 29)	NS
CsA level (μg/L)			
mean 1 to 2 mo	313 ± 7	374 ± 9	<0.0001
mean 1 to 3 mo	307 ± 5	359 ± 7	<0.0001
Corticosteroid dose (g)			
1 to 3 mo	6.0 ± 0.3	4.7 ± 0.4	0.02
4 to 6 mo	2.3 ± 0.2	2.6 ± 0.3	NS
Clinical rejection[c]	(0, 1, ≥2)[c]	(0, 1, ≥2)	
0 to 2 mo	16, 42, 42	24, 62, 14	0.03
0 to 3 mo	14, 35, 51 (0, ≥1)[d]	24, 48, 28 (0, ≥1)	0.03
4 to 6 mo	67, 33	64, 36	NS
7 to 12 mo	77, 23	90, 10	0.26
Creatinine (μmol/L)			
6 mo	136 ± 6	143 ± 9	NS
12 mo	143 ± 9	136 ± 7	NS

[a] AZA, azathioprine; MMF, mycophenolate mofetil; PRA, panel reactive antibody; CsA, cyclosporin A.
[b] Values represent median (minimum, maximum).
[c] Values are expressed as percentage of individuals experiencing 0, 1, or ≥2 rejection episodes.
[d] Values are expressed as percentage of individuals experiencing 0 or ≥1 rejection episode.

Table 2. Subgroup analysis of pretransplant and posttransplant characteristics[a]

Characteristic	Sandimmune + AZA		Neoral + MMF	
	Protocol Bx (n = 36)	Control (n = 36)	Protocol Bx (n = 17)	Control (n = 12)
HLA matching[b]	2 (0,4)	2 (0,5)	2 (1,4)	2 (1,4)
PRA (%)	1.0 ± 0.9	0.5 ± 0.3	7.6 ± 5.0[c]	6.6 ± 4.2[d]
Donor age (yr)	30 ± 3	36 ± 3	39 ± 3[c]	42 ± 4
Cold ischemia (min)	963 ± 76	1015 ± 77	904 ± 88	928 ± 156
Delayed graft function	19% (7 of 36)	25% (9 of 36)	29% (5 of 17)	25% (3 of 12)
CsA level (μg/L)				
mean 1 to 2 mo	318 ± 11	309 ± 7	380 ± 5[c]	366 ± 21[d]
mean 1 to 3 mo	308 ± 8	305 ± 6	365 ± 8[c]	351 ± 11[d]
Corticosteroid dose (g)				
1 mo	2.9 ± 0.3	2.6 ± 0.3	2.2 ± 0.3	2.4 ± 0.5
2 to 3 mo	3.6 ± 0.3	2.8 ± 0.3	2.6 ± 0.3	2.0 ± 0.3
4 to 6 mo	2.4 ± 0.3	2.4 ± 0.4	2.9 ± 0.6	
Clinical rejection	(0, 1, ≥2)[e]	(0, 1, ≥2)	(0, 1, ≥2)	(0, 1, ≥2)
0 to 2 mo	22, 39, 39	11, 45, 44	24, 76, 0	25, 42, 31
0 to 3 mo	20, 33, 47	8, 36, 56	23, 59, 18	25, 33, 42
	(0, ≥1)[f]	(0, ≥1)	(0, ≥1)	(0, ≥1)
4 to 6 mo	69, 31	64, 36	71, 29	58, 42
7 to 12 mo	89, 11	67, 33	100, 0	75, 25
Subclinical rejection				
1 mo	43%		38%	
2 mo	32%		25%	
3 mo	27%		31%	
6 mo	15%		25%	
	(0, 1, ≥2)[e]		(0, 1, ≥2)	
0 to 3 mo	31, 44, 25		41, 35, 24	
Creatinine (μmol/L)				
6 mo	135 ± 10	137 ± 7	136 ± 14	151 ± 12
12 mo	136 ± 12	151 ± 13	126 ± 7	149 ± 14

[a] Bx, biopsy. Other abbreviations as in Table 1.
[b] Values represent median (minimum, maximum).
[c] ANOVA $P < 0.05$ Sandimmune + AZA + Protocol Bx *versus* Neoral + MMF + Protocol Bx.
[d] ANOVA $P < 0.05$ Sandimmune + AZA Control *versus* Neoral + MMF Control.
[e] Values are expressed as percentage of individuals experiencing 0, 1, or ≥2 rejection episodes.
[f] Values are expressed as percentage of individuals experiencing 0 or ≥1 rejection episode.

rejection episodes during months 7 to 12 posttransplant (P = 0.06 *versus* Neoral + MMF Control, P = 0.29 *versus* Sandimmune + AZA + Protocol Bx, P = 0.005 *versus* Sandimmune + AZA Control).

The prevalence of subclinical rejection episodes was unchanged despite an increase in baseline immunosuppression. Indeed, subclinical rejection was detected in 38, 25, 31, and 25% of protocol biopsies at 1, 2, 3, and 6 mo, respectively, in the Neoral + MMF + Protocol Bx group compared with 43, 32, 27, and 15% in the Sandimmune + AZA + Protocol Bx group. Moreover, the frequency of recurrent subclinical rejection episodes in the first 3 mo posttransplant was not significantly different between the aforementioned groups (24% *versus* 25%) (Table 2).

We have reported previously that one of the strongest risk factors for a decline in renal function beyond 6 mo, or the absolute creatinine at 24 mo, was the occurrence of a clinical rejection episode during months 7 to 12 posttransplant (2). Therefore, to determine the relative impact of increasing baseline immunosuppression *versus* conducting protocol biopsies on clinical rejection episodes during months 7 to 12, we applied logistic regression analysis to the entire group of patients. Variables examined in the model were HLA matching, pretransplant panel reactive antibody levels, donor age, cold ischemic time, delayed graft function, early posttransplant CsA levels, MMF *versus* AZA, and protocol biopsies *versus* no protocol biopsies. The adjusted odds ratio (OR) and 95% confidence intervals (CI) for a clinical rejection episode occurring during months 7 to 12 posttransplant increased if delayed graft function was present (OR 7.2; 95% CI, 1.8 to 28.5). Matching for one or both HLA-A loci decreased the risk of having a clinical rejection from months 7 to 12 (OR 0.25; 95%

CI, 0.07 to 0.98). Moreover, for every increase in the mean 1 to 2 mo CsA level of 1.0 μg/L (range, 198 to 606), the relative odds of having an acute rejection episode during months 7 to 12 decreased by 2.0% (OR 0.98; 95% CI, 0.96 to 0.99). Finally, serial protocol biopsies with the treatment of subclinical rejection decreased the relative risk of having a clinical rejection episode from months 7 to 12 posttransplant (OR 0.19; 95% CI, 0.05 to 0.80).

Discussion

The principal findings of this study are that an increase in baseline immunosuppression with Neoral CsA and MMF tends to reduce the incidence of early clinical rejection episodes and leads to a reduction in the total exposure to corticosteroids early posttransplant. However, the prevalence of subclinical rejection in protocol biopsies remains unchanged from that observed under a less intense immunosuppressive protocol with Sandimmune CsA and AZA. Subclinical rejection that occurs under Neoral CsA and MMF is nevertheless important, as underscored by the finding that its treatment reduces the risk of having a late clinical rejection episode (*i.e.*, months 7 to 12), which in turn is one of the strongest markers for poor graft function at 2 yr posttransplant (2).

A major cause of late renal transplant loss is chronic rejection (6), which has been consistently correlated with acute rejection episodes (7–10). Indeed, the major goal of recent clinical trials, which increased baseline immunosuppression, has been the reduction of early acute clinical rejection episodes (11–14). Paradoxically, although a reduction in acute clinical rejection episodes was reported, the increase in baseline immunosuppression has not improved long-term graft outcome (11–14). The principal impact of these trials was on early clinical rejection episodes (*i.e.*, $\leq$3 mo posttransplant). However, late clinical rejection episodes, which are widely accepted as being one of the best markers predictive of a poor graft outcome, were not affected (3,7,10,15,16). Indeed, in our previous study, clinical rejection episodes that occurred from 7 to 12 mo were strong independent predictors of both the serum creatinine at 24 mo, and the stability of renal function from 6 to 24 mo (2). In the current study, by logistic regression analysis, both an increase in the 1 to 2 mo CsA trough level and the detection and treatment of the early subclinical rejection independently reduced the risk of late clinical rejection. This study and our previous randomized study are the first, to our knowledge, that demonstrate that the attainment of sufficient CsA levels and the treatment of subclinical rejection in the early posttransplant period can affect late clinical rejections (2).

It should be noted that the rates of clinical rejection in our protocol biopsy studies are higher than those reported in the literature (1–3,11–14). This is true for patients on either Sandimmune CsA + AZA or Neoral CsA + MMF-based therapy. Although the explanation for this is likely multifactorial (*e.g.*, limited HLA matching, no induction therapy, high levels of surveillance posttransplant), we hypothesize that this is primarily due to the lower threshold used to suspect clinical rejection (*i.e.*, $\geq$10% change from the baseline serum creatinine). In most centers, and in clinical trials, a $\geq$20% rise in serum creatinine is required before a diagnosis of acute rejection is considered. Interestingly, Colvin *et al.* demonstrated that the agreement rates between a clinical and a pathologic diagnosis of rejection were the same regardless of whether the increase in serum creatinine from baseline was set at 5 or 30% (17). Moreover, our group has shown that the histologic criteria for rejection are prevalent even with a $<$10% change in the baseline serum creatinine (*i.e.*, "subclinical rejection"). Together, these studies demonstrate that the serum creatinine is an insensitive marker of inflammation in the renal allograft and suggest that the threshold required for the diagnosis of acute rejection has been set too high. By setting a lower threshold, one would expect the rates of clinical rejection to increase relative to other centers. Nevertheless, despite a higher reported rate of clinical rejection, our data are consistent with the reported literature (11–14): An increase in baseline immunosuppression decreases the prevalence of clinical rejection.

Although the prevalence of early clinical rejection episodes tended to be reduced with an increase in baseline immunosuppression, there was no impact on the incidence of subclinical rejection episodes. It is possible that the pathogenesis of subclinical rejection is different from that of clinical rejection, thereby explaining the differential effect. However, in our studies to date, the molecular programs detected during clinical and subclinical rejection are qualitatively similar (18). A more likely explanation is that under increased baseline immunosuppression, clinical rejections have been decreased in intensity and become subclinical. Indirect evidence supporting this contention comes from our randomized study, which found a decrease in the number of early clinical rejection episodes in those patients treated for early subclinical rejection compared to the control group, suggesting that if left untreated, subclinical rejection may evolve into clinical rejection (2).

The fact that subclinical rejection has not been affected would suggest that baseline immunosuppression is still inadequate in the early posttransplant period. Although a further increase in baseline immunosuppression may reduce subclinical rejection, as well as decrease the exposure to steroids early posttransplant, this may come at the risk of infection and/or lymphoproliferative disorders. Importantly, not all individuals are at the same risk to develop graft dysfunction; the majority of patients are stable from 6 to 24 mo (3). Thus, it may be more prudent to use protocol biopsies to identify patients who are insufficiently immunosuppressed rather than exposing all patients to the risks associated with a further increase in baseline immunosuppression.

In summary, this study suggests that an increase in baseline immunosuppression, while tending to decrease the frequency of early clinical rejection episodes, has failed to decrease the prevalence of subclinical rejection. This may explain the paradoxical findings of recent clinical trials that have significantly decreased clinical rejection while having no effect on the long-term outcome. Indeed, an increase in baseline immunosuppression and the treatment of subclinical rejection were required to maximally decrease the incidence of late clinical rejection episodes, one of the strongest markers of individuals

at risk for a poor outcome. Therefore, frequent surveillance of the allograft with protocol biopsies may be required in the early posttransplant period until noninvasive tests to detect subclinical inflammation are developed.

Acknowledgments

We are indebted to the clerks and nurses of the Transplant Clinic, the technologists of the Transplant Laboratory, and most of all to our patients.

References

1. Rush DN, Henry SF, Jeffery JR, Schroeder T, Gough J: Histological findings in early routine biopsies of stable renal allograft recipients. *Transplantation* 57: 208–211, 1994
2. Rush D, Nickerson P, Gough J, McKenna R, Grimm P, Cheang M, Trpkov K, Solez K, Jeffery J: Beneficial effects of treatment of early subclinical rejection: A randomized study. *J Am Soc Nephrol* 9: 2129–2134, 1998
3. Nickerson P, Jeffery J, Gough J, McKenna R, Grimm P, Cheang M, Rush D: Identification of clinical and histopathologic risk factors for diminished renal function 2 years posttransplant. *J Am Soc Nephrol* 9: 482–487, 1998
4. Solez K, Benediktsson H, Cavallo T, Croker B, Demetris AJ, Drachenberg C, Emancipator S, Furness P, Gaber LW, Gibson IW, Gough J, Gupta R, Halloran P, Hayry P, Kashgarian M, Marcussen N, Massy Z, Mihatsch M, Morozumi K, Noronha I, Olsen S, Papadimitriou J, Paul LC, Picken M, Racusen LC, Ramos E, Randhawa P, Rayner DC, Rush D, Sanfilippo F, Taskinen E, Trpkov K, Truong L, Yamaguchi Y, Yilmaz S: Report of the third Banff conference on allograft pathology on classification and lesion scoring in renal allograft pathology. *Transplant Proc* 28: 441–444, 1996
5. Rush DN, Jeffery JR, Gough J: Sequential protocol biopsies in renal transplant patients: Clinico-pathologic correlations using the Banff schema. *Transplantation* 59: 511–514, 1995
6. Paul L: Chronic renal transplant loss. *Kidney Int* 47: 1491–1499, 1995
7. Flechner S, Modlin C, Serrano D, Goldfarb D, Papajcik D, Mastroianni B, Goormastic M, Novick A: Determinants of chronic renal allograft rejection in cyclosporine-treated recipients. *Transplantation* 62: 1235–1241, 1996
8. Almond P, Matas A, Gillingham K, Dunn D, Payne W, Gores P, Gruessner R, Najarian J: Risk factors for chronic rejection in renal allograft recipients. *Transplantation* 55: 752–757, 1993
9. Tesi R, Henry M, Elkhammas E, Ferguson R: Predictors of long-term primary cadaveric renal transplant survival. *Clin Transplant* 7: 345–352, 1993
10. Massy Z, Guijarro C, Wiederkehr M, Ma J, Kasiske B: Chronic renal allograft rejection: Immunologic and nonimmunologic risk factors. *Kidney Int* 49: 518–524, 1996
11. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C: Mycophenolate mofetil in renal allograft recipients: A pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 63: 39–47, 1997
12. Mathew TH, for the Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group: A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: Results at three years. *Transplantation* 65: 1450–1454, 1998
13. Bjorn N, Moore R, Amiot P, Schmidt A-G, Abeywickrama K, Soulillou J-P, for the CHIB 201 International Study Group: Randomized trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 350: 1193–1198, 1997
14. Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P, Neylan J, Wilkinson A, Ekberg H, Gaston R, Backman L, Burdick J, for the Daclizumab Triple Therapy Study Group: Interleukin-2-receptor blockade with Daclizumab to prevent acute rejection in renal transplantation. *N Engl J Med* 338: 161–165, 1998
15. Basadonna G, Matas A, Gillingham K, Payne W, Dunn D, Sutherland D, Gores P, Gruessner R, Najarian J: Early versus late acute renal allograft rejection: Impact on chronic rejection. *Transplantation* 55: 993–995, 1993
16. Leggat JE Jr, Ojo AO, Leichtman AB, Port FK, Wolfe RA, Turenne MN, Held PJ: Long-term renal allograft survival: Prognostic implication of the timing of acute rejection episodes. *Transplantation* 63: 1268–1272, 1997
17. Colvin RB, Cohen AH, Saiontz C, Bonsib S, Buick M, Burke B, Carter S, Cavallo T, Haas M, Lindblad A, Manivel JC, Nast CC, Salomon D, Weaver C, Weiss M: Evaluation of pathologic criteria for acute renal allograft rejection: Reproducibility, sensitivity, and clinical correlation. *J Am Soc Nephrol* 8: 1930–1941, 1997
18. Lipman ML, Shen Y, Jeffery JR, Gough J, McKenna RM, Grimm PC, Rush DN: Immune activation gene expression in clinically stable renal allograft biopsies: Molecular evidence for subclinical rejection. *Transplantation* 66: 1673–1681, 1998