A Meta-Analysis of Immunosuppression Withdrawal Trials in Renal Transplantation

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Abstract. Since the publication of previous meta-analyses of cyclosporine (CsA) and prednisone withdrawal in renal transplant recipients, several additional randomized controlled trials with longer follow-up have been reported. Currently, in nine prednisone withdrawal trials ($n = 1461$), the proportion of patients with acute rejection was increased by 0.14 (95% confidence interval = 0.10 to 0.17, $P < 0.001$). In nine prednisone withdrawal trials ($n = 1899$), the relative risk (RR; RR = 1.0 indicates no risk) of graft failure after withdrawal was also increased (RR = 1.40; range, 1.09 to 1.70, $P = 0.012$). There was no evidence of between-study heterogeneity for either acute rejection or graft failure in the prednisone withdrawal trials by a χ^2 test ($P > 0.05$). In 10 CsA withdrawal trials ($n = 1049$), the proportion of patients with acute rejec-

tion was increased by 0.11 (0.07 to 0.15, $P < 0.001$). In 12 trials ($n = 1151$), the RR of graft failure after CsA withdrawal was 1.06 (95% confidence interval, 0.82 to 1.29, $P = 0.646$), but a χ^2 test indicated that there was study heterogeneity. However, there was no evidence of heterogeneity in the six studies ($n = 632$) with at least 4.0 yr (5.8 ± 1.7) of follow-up (RR = 0.92; range, 0.64 to 1.20, $P = 0.569$) or in the seven trials ($n = 962$) published in peer-reviewed journals (RR = 0.95; range, 0.70 to 1.20, $P = 0.682$). Finally, in three trials ($n = 259$) that compared CsA and prednisone withdrawal, there was a nonsignificant trend for less graft failure with CsA withdrawal (RR = 0.63; range, 0.08 to 1.16, $P = 0.190$). Thus, unlike prednisone withdrawal, CsA withdrawal in select patients seems to impart little risk of long-term graft failure.

Over the past two decades, new immunosuppression regimens have led to dramatic declines in the incidence of acute rejection during the first few months after renal transplantation. As a result, 1-yr graft survival has increased dramatically, and attention has shifted toward reducing the incidence of late allograft failure. Death with a functioning allograft and chronic allograft nephropathy together cause the majority of late allograft failures. Because much of the mortality in the late posttransplantation period can be directly or indirectly linked to complications of immunosuppression, a number of studies have examined whether one or more agents can be safely withdrawn. This strategy is designed to capture the early posttransplantation benefit of reduced acute rejection without paying the price of long-term toxicity.

Corticosteroids are effective in reducing the incidence of acute rejection but are a major cause of morbidity and mortality. Like all immunosuppression, corticosteroids contribute to the increased risk of infection and possibly cancer in the late posttransplantation period. In addition, corticosteroids have adverse effects on cardiovascular disease risk factors, such as

diabetes, hypertension, and hyperlipidemia. Cardiovascular disease is a major cause of death in the late posttransplantation period. As a result, a number of clinical trials have examined whether prednisone can be safely withdrawn after renal transplantation. A meta-analysis of randomized, controlled trials of prednisone withdrawal and avoidance was published in 1993 (1). However, since that time, several additional prednisone withdrawal trials have been conducted, including two large, multicenter, randomized, controlled trials (2,3).

Cyclosporin A (CsA) also adversely affects several cardiovascular disease risk factors; CsA not only may contribute to mortality after renal transplantation but also may cause nephrotoxicity that is histologically and clinically indistinguishable from chronic allograft nephropathy. A number of randomized controlled trials have been conducted to examine whether CsA can be safely withdrawn after renal transplantation. We published a meta-analysis of these trials in 1993 (4). Although CsA withdrawal caused an increased incidence of acute rejection, graft survival did not seem to be adversely affected. However, the length of follow-up was relatively short. Since that time, several groups have reported the results of long-term follow-up and several additional CsA withdrawal trials have been conducted.

Despite that a number of randomized, controlled trials have been conducted, withdrawal of either prednisone or CsA remains controversial. Therefore, we conducted a meta-analysis of randomized, controlled trials that examined either prednisone or CsA withdrawal. In addition, we included trials that

compared withdrawal of prednisone with withdrawal of CsA. Our purpose was not only to enhance statistical power by increasing sample size but also to examine possible reasons for differences in the results of the clinical trials that underlie this ongoing controversy.

Materials and Methods

Search Strategy

We searched (1) Medline, (2) bibliographies from recent, pertinent publications, and (3) abstracts from scientific meetings conducted in 1998 and 1999. Key words in our Medline search included "prednisone" or "corticosteroids" combined with "withdrawal" or "discontinue" or "conversion" as well as "cyclosporine" or "cyclosporine A" combined with "withdrawal" or "discontinue" or "conversion." We searched abstracts from international transplantation society meetings published in 1998 or 1999 in either *Transplantation Proceedings* or *Transplantation*. Included in these were abstracts from meetings of the International Transplantation Society, the American Society of Transplant Surgeons, and the American Society of Transplantation.

Study Selection

We included only published, randomized, controlled trials in which either prednisone or CsA was withdrawn or randomized trials comparing prednisone withdrawal with CsA withdrawal. We included only trials that reported the incidence of acute rejection and/or renal allograft failure. All end points were analyzed by intent to treat. We did not exclude reports on the basis of language, but all studies were published in English. In several instances, results from some or all patients in a clinical trial were reported more than once. In these instances, we extracted data on end points from the publication with the longest duration of follow-up. We did not include studies of prednisone or CsA avoidance, *i.e.*, studies in which patients in one arm never received prednisone or CsA. Studies that compared prednisone withdrawal or CsA withdrawal with the withdrawal of other immunosuppression, *e.g.*, azathioprine, also were excluded.

Data Extraction

Two investigators (B.L.K. and H.A.C.) independently reviewed all studies. We extracted data on study quality, including whether (1) the study was published in a peer-reviewed journal, (2) it had been stated that institutional review board approval had been obtained, (3) the source of funding was indicated, (4) the study design included a statistical assessment of the sample size needed, (5) inclusion and exclusion criteria were clearly stated, (6) possible differences in patients allocated to treatment and control were examined, (7) a placebo was used to mask investigators and subjects, (8) the allocation process was truly random (compared with a pseudo-random allocation whereby, for example, every other patient was allocated to treatment or control), (9) the randomization technique was clearly described (envelopes, central randomization, etc.), (10) the statistical methods used to analyze the results were described, (11) patient withdrawals were described, (12) results were analyzed by intention to treat, and (13) the study end points were clearly defined. We derived an arbitrary quality index using a formula whereby each of the above quality indices were given one point if the criterion was completely fulfilled, one half of a point if the criterion seemed to be only partially fulfilled, or (in the case of publication in a peer-reviewed journal) two points. The composite study quality index was the total number of points (maximum = 14).

We also extracted data on the proportion of study patients who

were first transplants, the proportion who were recipients of cadaveric donor kidneys, whether patient selection was based on the absence of acute rejection and/or stable graft function, and what other immunosuppressive agents were used, *e.g.*, azathioprine and mycophenolate mofetil. In addition, we tabulated the time withdrawal was begun, the time it was completed, and the duration of follow-up (from the time of transplantation to the time of last follow-up or loss of the allograft).

Statistical Techniques

For acute rejection, the duration of follow-up was often relatively short, because most acute rejection episodes occurred soon after withdrawal. Indeed, some studies failed to report the exact duration of follow-up. Therefore, we examined the difference in the proportion of withdrawal and control patients who had acute rejection following randomization: $D_i = P_{ti} - P_{ci}$, where $P_{ti} = r_{ti}/n_{ti}$, $P_{ci} = r_{ci}/n_{ci}$, r_{ti} and r_{ci} are the number of patients with an acute rejection episode, and n_{ti} and n_{ci} are the numbers of patients allocated to the treatment and control groups respectively for the ith study. The variance of D_i was calculated as

$$\mathrm{Var}(D_i) = P_{ti} \cdot (1 - P_{ti})/n_{ti} + P_{ci} \cdot (1 - P_{ci})/n_{ci}.$$

Weighted means and confidence intervals (CI) were then calculated for the combined differences between treatment and control groups using a fixed-effects model. The weighted mean treatment effect was calculated as

$$\bar{D}_w = \sum (w_i \cdot D_i)/\sum w_i,$$

where D_i is the difference between treatment and control for the ith study and $w_i = 1/\mathrm{Var}(D_i)$. The 95% CI of this weighted mean treatment effect was calculated as

$$\bar{D}_w + \sqrt{1/\sum w_i} \cdot t_{df},$$

where t_{df} is the 97.5th percentile of the t distribution for $df = 100$. We used 100 for estimating the degrees of freedom, *i.e.*, an order of magnitude larger than the number of studies and an order of magnitude smaller than the total number of patients in the combined studies so that $t = 1.984$.

We looked for homogeneity of treatment effects with the test statistic:

$$Q = \sum_i w_i \cdot (D_i - \bar{D}_w)^2$$

where Q is approximately a X^2 statistic with k-1 degrees of freedom, where k was the number of studies. Q was used to test whether the variance of the treatment effect from the population mean of treatment effects was significantly different from 0 (the null hypothesis).

We also examined the relative risk (RR) of graft failure (defined as either return to dialysis or death with a functioning allograft) between immunosuppression withdrawal and nonwithdrawal control groups. Some studies reported results over a specific time interval, *e.g.*, the proportions of patients with graft survival in withdrawal and control groups after an exact (or mean) period of follow-up. In other words, these studies reported two proportions—the proportion of patients who survived in the withdrawal group and the proportion of patients who survived in the control group—and reported the exact (or mean) duration of follow-up. For these studies, we estimated the RR of graft survival between withdrawal and control as

$$R_i = \log(S_{ti}(x))/\log(S_{ci}(x)),$$

where S_{ti} and S_{ci} are the survival probabilities at time x for the withdrawal and control groups, respectively, for the ith study. Variance of R_i was calculated as $Var(R_i) = 1/d_{1I} + 1/d_{2i}$, where

$$d_{ti} = -n_{ti} \cdot \log(S_{ti}(x))/(1 - \log(S_{ti}(x))/2), \text{ and}$$

$$d_{ci} = -n_{ci} \cdot \log(S_{ci}(x))/(-\log(S_{ci}(x))/2)$$

For other studies, data were presented in more detail using tables and/or figures that indicated the proportions of the withdrawal and control groups that survived after two or more discrete time intervals. For these studies, we estimated the RR of graft failure as

$$R_i = \sum_j [d_{tji} \cdot (n_{cji} - d_{cji})/(n_{tji} + n_{cji})]/\sum_j [d_{ctji} \cdot (n_{tji} - d_{tji})/(n_{tji}$$

$$+ n_{cji})], \text{ and } Var(R_i) = 1/\sum_j [d_{cji} \cdot (n_{tji} - d_{tji})/(n_{tji} + n_{cji})],$$

where d_{tji} and d_{cji} were the numbers of grafts lost in the withdrawal and control groups, respectively, in the jth follow-up interval of the ith study. Weighted means, 95% CI, and a χ^2 test for homogeneity were calculated as described above.

We also examined potential reasons for heterogeneity in study results using linear regression analysis weighted by inverse variance. In this analysis, differences in the proportions of patients with acute rejection and differences in the RR for graft failure were used as dependent variables. Study quality and other study characteristics were used as independent variables. All differences were considered significant for $P < 0.05$ (two-tail). Analysis was carried out using the Statistical Package for the Social Sciences.

Results

Prednisone Withdrawal

We included 10 studies that examined prednisone withdrawal (Table 1) (2,3,5–18). Seven had been published in a peer-reviewed journal. Nine studies that examined the effects of prednisone withdrawal on acute rejection included 1461 patients (mean ± SD, 162 ± 147) with 29 ± 19 mo of follow-up. Nine studies that examined the effects of prednisone withdrawal on graft survival included 1899 patients (mean ± SD, 211 ± 186) with 28 ± 19 mo of follow-up.

For acute rejection, the pooled mean difference between treatment and control was 0.14 (95% CI = 0.10 to 0.17, $P < 0.001$), indicating that the proportion of patients with acute rejection after prednisone withdrawal was significantly greater compared with controls (Figure 1). The test for homogeneity ($\chi^2 = 13.7$, $P > 0.05$) indicated that the individual studies were relatively homogeneous. The RR for graft failure was 1.40 (1.09 to 1.71, $P = 0.012$), indicating that significantly more patients lost their grafts in the prednisone withdrawal group compared with controls (Figure 2). The test for homogeneity ($\chi^2 = 12.0$, $P > 0.05$) indicated that the individual study results were relatively homogeneous. Although the results were relatively homogeneous, we nevertheless sought possible reasons for differences in results using regression analysis. There were no statistically significant correlations between the differences in acute rejection and any of the study or patient characteristics. None of the patient or study characteristics correlated with the effect of prednisone withdrawal on graft survival.

CsA Withdrawal

Thirteen studies examined CsA withdrawal (Table 2) (5–7,19–36). Seven had been published in peer-reviewed journals, and six had not. The 10 studies that examined the effects of CsA withdrawal on acute rejection included 1049 (mean, 105 ± 83) patients with 50.7 ± 33.9 mo of follow-up. The 12 studies that provided adequate data on graft survival after CsA withdrawal included 1151 (mean, 96 ± 80) patients with 45.1 ± 32.9 mo of follow-up.

For acute rejection, the pooled mean difference between CsA withdrawal and control was 0.11 (0.07 to 0.15, $P < 0.001$), indicating that the proportion of patients with acute rejection after CsA withdrawal was 11% higher than that of controls (Figure 3). The test for homogeneity ($\chi^2 = 64.9$, $P < 0.001$) indicated that the individual study results were heterogeneous. To explore possible reasons for this heterogeneity in

Table 1. Studies comparing prednisone withdrawal with continued prednisone

| First Author (reference) | Year(s) Published | Follow-Up (mo) | Number Studied | Peer Reviewed | End Point | |
					Acute Rejection	Graft Survival
Isoniemi, H.M. (5–7)	1990, 1991, 1993	48	64	Yes	Yes	Yes
Maiorca, R. (8,9)	1987, 1988	27	66	No	Yes	Yes
Schulak, J.A. (10,11)	1990, 1992	18	67	Yes	Yes	Yes
Hollander, A.A. (12)	1997	14	84	Yes	Yes	Yes
Gulanikar, A.C. (13)[a]	1991	60	85	No	Yes	Yes
Ratcliffe, P.J. (14,15)	1993, 1996	12	100	Yes	Yes	Yes
Ponticelli, C. (16,17)	1997	48	229	Yes	Yes	Yes
Ahsan, N. (3)	1999	12	266	Yes	Yes	Yes
Lebranchu, Y. (2)	1999	12	500	No	Yes	Yes
Sinclair, N.R. (18)[a]	1992	60	523	Yes	No	Yes

[a] The report by Gulanikar *et al.* (13) included patients also reported by Sinclair *et al.* (18). The former report provided detailed information on acute rejection and was used in the analysis of acute rejection. The latter report provided data on graft survival (but not acute rejection) and was used in the analysis of graft survival.
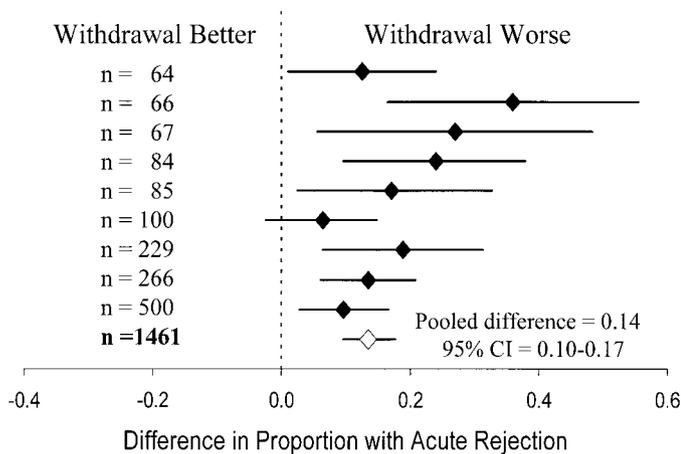
Figure 1. Effects of prednisone withdrawal on acute rejection. Shown are weighted differences in the proportion of patients with acute rejection between withdrawal and control for individual studies (♦) and the pooled results of all studies (◇). The area to the right of the vertical dashed line indicates a greater proportion of patients with acute rejection after withdrawal compared with control. Horizontal lines indicate 95% confidence intervals (CI), and failure of 95% CI to cross the vertical dashed line indicates $P < 0.05$. The number of patients uniquely identifies each study (see Table 1).
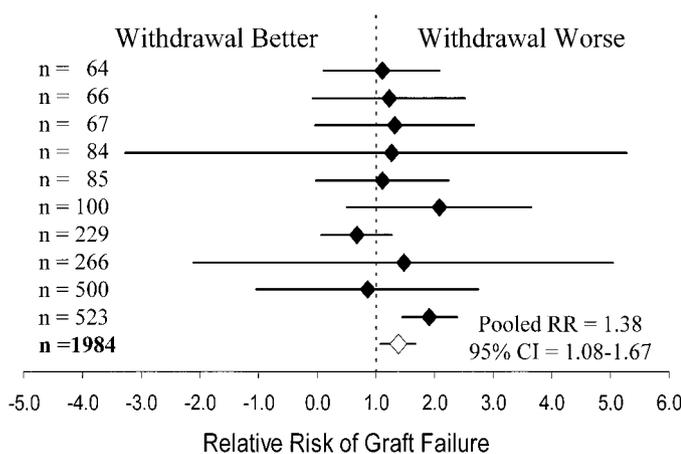

Figure 2. Effects of prednisone withdrawal on graft failure. Shown are weighted relative risks (RR) of graft failure after withdrawal *versus* control for individual studies (♦) and the pooled results of all studies (◇). The area to the right of the vertical dashed line indicates a greater RR of graft failure after withdrawal *versus* control. Horizontal lines indicate 95% CI, and failure of 95% CI to cross the vertical dashed line indicates $P < 0.05$. The number of patients uniquely identifies each study (see Table 1).

results, weighted, univariate regression analysis was carried out to determine which, if any, patient or study characteristics correlated with the effect of CsA withdrawal on acute rejection. The study quality index ($r = -0.698$, $P = 0.025$), whether the study was published in a peer-reviewed journal ($r = -0.696$, $P = 0.025$), and the number of patients studied ($r = -0.823$, $P = 0.003$) each correlated inversely with the difference in the rate of acute rejection. However, these characteristics were significantly correlated with each other. It is

difficult to tell whether study quality and sample size were independent correlates to the study results. However, in a multivariate analysis, sample size was a better predictor and study quality did not correlate with differences in acute rejection once sample size was taken into account (data not shown).

The RR for graft failure was 1.06 (0.82 to 1.29, $P = 0.646$), indicating no difference in the risk for graft failure in the CsA withdrawal group compared with controls (Figure 4). However, the test for homogeneity ($\chi^2 = 43.0$, $P < 0.001$) again indicated that the individual study results were heterogeneous. In an unweighted regression analysis, the study quality index was inversely proportional to the RR for graft failure ($r = -0.645$, $P = 0.024$), suggesting that in studies of lower quality, CsA withdrawal had a more adverse effect on graft survival. Whether studies were published in peer-reviewed journals also correlated inversely with the RR of graft failure from CsA withdrawal ($r = -0.721$, $P = 0.008$) in unweighted regression analysis. However, when the regression analysis was weighted by inverse variance, neither study quality ($r = -0.367$, $P = 0.241$) nor peer review ($r = -0.416$, $P = 0.178$) significantly influenced the results of studies that examined the effects of CsA withdrawal on graft survival. Thus, it seems that the influence of study quality and peer review on the results was largely abolished when the variability in results was accounted for by weighting with inverse variance.

Studies that were or were not peer-reviewed were combined separately (Figure 5). The pooled RR for graft failure among five studies ($n = 189$ patients) that were not published in peer-reviewed journals was 2.07 (1.30 to 2.83, $P = 0.006$; χ^2 test for homogeneity = 39.4, $P < 0.001$), indicating that these study results were heterogeneous. In contrast, the pooled RR for graft failure among the seven studies ($n = 962$ patients) published in peer-reviewed journals was only 0.95 (0.70 to 1.20, $P = 0.682$). The χ^2 test for homogeneity = 3.5 ($P > 0.05$), indicating that the results in these seven studies were more homogeneous. Thus, the heterogeneity in results seemed to be found in studies that were not published in peer-reviewed journals, which also correlated with a low study quality index.

We also compared the pooled results of studies with less than 48 or more than 48 mo of follow-up. The pooled RR of graft failure for the six studies ($n = 519$ patients) with less than 48 mo (17 ± 7 mo) of follow-up was 1.43 (0.97 to 1.89, $P = 0.066$). The χ^2 was 34.9 ($P < 0.001$), indicating significant heterogeneity. The pooled RR of graft failure for the six studies ($n = 632$ patients) with at least 48 mo (70 ± 20 mo) of follow-up was 0.92 (0.64 to 1.20, $P = 0.569$). The χ^2 was 5.1 ($P > 0.05$), indicating that these studies with longer follow-up were relatively homogeneous. Thus, the studies of short duration seemed to contribute to the heterogeneity of results and were more likely to report that CsA withdrawal negatively influenced graft survival compared with studies of longer duration.

CsA Versus Prednisone Withdrawal

Three studies compared CsA withdrawal with prednisone withdrawal, and two of these were published in peer-reviewed journals (Table 3) (5–7,37,38). The three studies included 259

Table 2. Studies comparing cyclosporine withdrawal with continued cyclosporine

First Author (reference)	Year(s) Published	Follow-Up (mo)	Number Studied	Peer Reviewed	End Point	
					Acute Rejection	Graft Survival
Land, W. (19)	1983	12.0	18	No	No	Yes
Sagalowsky, A.I. (20)	1988	N.A.	19	No	Yes	No
Saadi, M.G. (21)	1997	60.0	26	No	No	Yes
Heering, P. (22,23)	1994, 1995	12.0	35	No	Yes	Yes
Büsing, M. (24)	1989	12.0	46	No	Yes	Yes
Hiesse, C. (25)	1991	28.6	64	No	Yes	Yes
Isoniemi, H.M. (5–7)	1990, 1991, 1993	48.0	64	Yes	Yes	Yes
Sweny, P. (26,27)	1990, 1997	12.0	77	Yes	No	Yes
Delmonico, F.L. (28,29)	1990, 1994	83.0	92	Yes	Yes	Yes
Pedersen, E.B. (30)	1993	60.0	106	Yes	Yes	Yes
Kootte, A.M.M. (31–34)	1988, 1989, 1995	96.0	128	Yes	Yes	Yes
MacPhee, I.A.M. (35)	1998	93.0	216	Yes	Yes	Yes
Hall, B.M. (36)	1988	24.0	279	Yes	Yes	Yes

Table 3. Studies comparing cyclosporine withdrawal with prednisone withdrawal

First Author (reference)	Year(s) Published	Follow-Up (mo)	Number Studied	Peer Reviewed
Isoniemi, H.M. (5–7)	1990, 1991, 1993	48	64	Yes
Spielberger, M. (37)	1988	37	68	No
Hillbrands, L.B. (38)	1996	48.6	127	Yes

(86 ± 35) patients who were followed for 43.9 ± 6.0 mo. Each examined both acute rejection and graft survival. There was no difference in the proportion of patients with acute rejection between CsA and prednisone withdrawal; pooled difference = 0.04 (-0.07 to 0.144, $P = 0.516$). The χ^2 was 6.2 ($P > 0.05$), indicating that the results were homogeneous. There was a nonsignificant trend for graft failure to be less for CsA withdrawal compared with prednisone withdrawal (0.63 [range, 0.08 to 1.18], $P = 0.190$; $\chi^2 = 3.5$, $P > 0.05$).

Discussion

Most of the improved renal allograft survival from immunosuppressive agents seems to result from the prevention of early, acute rejection. However, much of the risk of immunosuppression is manifest in the late posttransplantation period. Therefore, many investigators have attempted to use multiple immunosuppressive agents early after renal transplantation to reduce the risk of acute rejection, then withdraw one or more agents to reduce the risk of long-term complications. Both prednisone and CsA withdrawal strategies have been studied in randomized controlled trials. Earlier meta-analysis of these trials has been criticized because the length of follow-up of the studies has been relatively short (1,4). Therefore, we reexamined the issue with additional trials and longer follow-up.

The results of prednisone withdrawal trials have suggested not only that the risk of acute rejection after withdrawal is high (Figure 1) but also that the risk of graft failure tends to be increased (Figure 2). The results seem to be fairly homogeneous, at least by a crude statistical test of homogeneity. It was hoped that the use of mycophenolate mofetil would allow prednisone to be discontinued safely. Mycophenolate mofetil seems to be more effective than azathioprine in preventing acute rejection early after renal transplantation, so it is possible that withdrawal of prednisone may be more successful in patients who are treated with mycophenolate mofetil than in patients who receive azathioprine. Two of the prednisone withdrawal trials used mycophenolate mofetil (2,3). In both trials, the difference in acute rejection between withdrawal and control did not seem to be different compared with trials that did not use mycophenolate mofetil (Figure 1). Both trials reported only 12 mo of follow-up to date, so it may be too early to tell whether the effect of prednisone withdrawal on graft survival will be different in these studies.

The need for long-term follow-up was demonstrated when decreased graft survival after prednisone withdrawal first became evident after 5 yr of follow-up (18). Although this trial has been criticized because of the large number of crossovers and other design flaws, it is nevertheless the largest randomized controlled trial of prednisone withdrawal published to date. Because the mean follow-up of all of the prednisone withdrawal trials is only 28 mo, it is important for investigators to report long-term follow-up results (>5 yr) in the future.
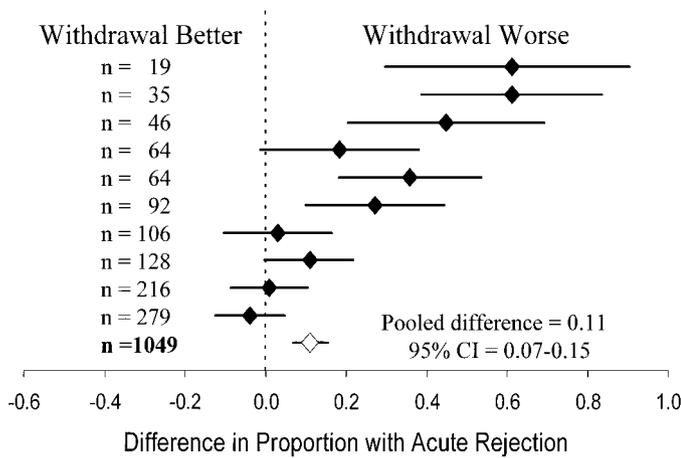
Figure 3. Effects of cyclosporine withdrawal on acute rejection. Shown are weighted differences in acute rejection between withdrawal and control for individual studies (♦) and the pooled results of all studies (◇). The area to the right of the vertical dashed line indicates a greater proportion of patients with acute rejection after withdrawal compared with controls. Horizontal lines indicate 95% CI, and failure of 95% CI to cross the vertical dashed line indicates $P < 0.05$. The number of patients uniquely identifies each study (see Table 2), except for the two studies with $n = 64$, which are in the same top-to-bottom order as in Table 2.

Figure 5. Study quality and the effects of cyclosporine withdrawal on graft failure. Shown are weighted RR of graft failure after withdrawal *versus* control for individual studies that were (♦) or were not (◇) published in a peer- reviewed journal. The area to the right of the vertical dashed line indicates a greater RR of graft failure after withdrawal *versus* control. Horizontal lines indicate 95% CI, and failure of 95% CI to cross the vertical dashed line indicates $P < 0.05$. The number of patients uniquely identifies each study (see Table 2), except for the two studies with $n = 64$, which are in the same top-to-bottom order as in Table 2.
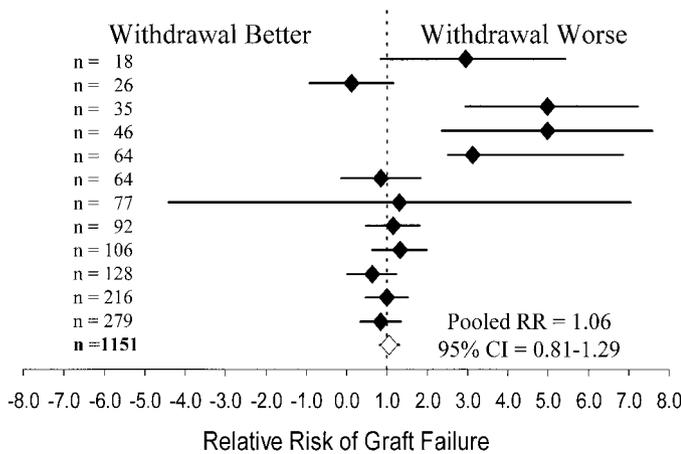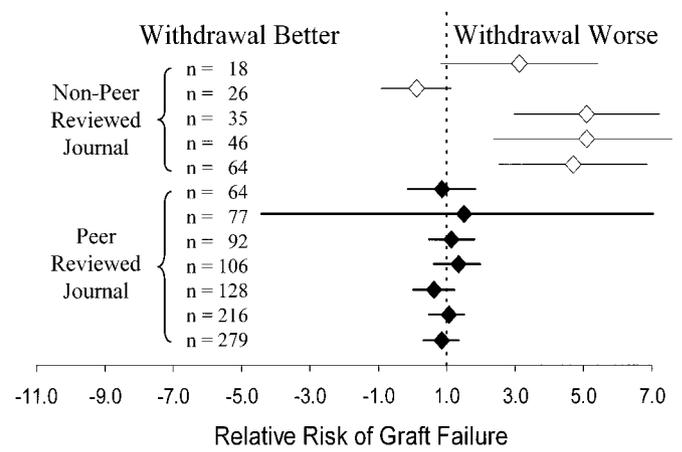

Figure 4. Effects of cyclosporine withdrawal on graft failure. Shown are weighted RR of graft failure after withdrawal *versus* control for individual studies (♦) and the pooled results of all studies (◇). The area to the right of the vertical dashed line indicates a greater RR of graft failure after withdrawal *versus* control. Horizontal lines indicate 95% CI, and failure of 95% CI to cross the vertical dashed line indicates $P < 0.05$. The number of patients uniquely identifies each study (see Table 2), except for the two studies with $n = 64$, which are in the same top-to-bottom order as in Table 2.

The results of CsA withdrawal seem to be different from those of prednisone withdrawal. Like prednisone withdrawal, acute rejection is increased after withdrawing CsA (Figure 3). However, unlike prednisone withdrawal, CsA withdrawal does not seem to increase the rate of graft failure (Figure 4). The results of the prednisone withdrawal trials seem to be homogeneous, whereas those of CsA withdrawal are relatively het-

erogeneous. In particular, CsA withdrawal trials of lower study quality (indicated by failure to publish results in a peer-reviewed journal) seem to report a higher incidence of graft failure than trials of higher study quality (Figure 5). Studies of longer duration (>4 yr of follow-up) also tended to be studies of higher quality and reported no adverse effect of CsA withdrawal on graft survival.

We can only speculate on why the increased rate of acute rejection after CsA withdrawal did not produce an increased incidence of graft failure. Acute rejection, especially acute rejection occurring more than 3 to 6 mo posttransplantation, has been linked to graft failure in several observational studies (39,40). However, we are not aware of studies comparing the effects on graft survival of acute rejections that occur on regular maintenance immunosuppression *versus* acute rejections that occur after CsA withdrawal. It is possible that acute rejections that occur after CsA withdrawal resemble those that occur in the early posttransplantation period and have minimal effect on graft survival. It is also possible that the deleterious effects of acute rejection after CsA withdrawal are balanced by the beneficial effects of reduced nephrotoxicity. In fact, it is tempting to speculate that the difference in the effects on graft survival of prednisone *versus* CsA withdrawal may be due to the fact that CsA is nephrotoxic, whereas prednisone is not. In any case, it is possible that the results with both prednisone and CsA withdrawal may be different with longer follow-up, and it is hoped that investigators will continue to report long-term follow-up results of these trials.

For both prednisone and CsA withdrawal, we could find no effects on acute rejection or graft survival attributable to whether withdrawal was early or late after transplantation. Similarly, we could find no effects on outcomes attributable to

how patients were selected, *e.g.*, whether only "stable" patients were selected for withdrawal. However, the numbers of patients studied were relatively small, so it is possible that an effect of the timing of withdrawal or of how patients were selected for withdrawal could have gone undetected in our analysis. Similarly, the duration of the taper period did not seem to influence the results, but the small numbers and differences in how prednisone and CsA were withdrawn may have precluded our ability to detect significant differences.

No two clinical trials are the same. Many reported and unreported differences in patient populations and/or study design may have influenced these results. For example, uncontrolled observations have indicated that CsA withdrawal may be associated with a higher rate of graft failure in black patients compared with Caucasian patients (41). Race also influenced the rate of acute rejection after prednisone withdrawal (11). Individuals with a greater degree of major histocompatibility mismatching and individuals who were younger tended to have a higher incidence of acute rejection after CsA withdrawal (42). The real possibility that these or other risk factors can help in determining patients in whom CsA or prednisone can be safely withdrawn has not been adequately studied in controlled trials.

In summary, the results of this meta-analysis indicate that prednisone withdrawal after renal transplantation is associated with a higher incidence of acute rejection and graft failure. A higher incidence of acute rejection is also seen after CsA withdrawal, but CsA withdrawal does not adversely affect graft survival, even in studies with long-term follow-up. Some of the controversy over the results of CsA withdrawal may be due to differences in trial results attributable to a greater incidence of postwithdrawal graft failure in studies of low quality and/or shorter duration of follow-up.

Acknowledgments

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