Chronic Immunosuppression of the Renal Transplant Patient

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ABSTRACT

The advent of potent immunosuppressive drugs to prevent rejection has led to a phenomenal improvement in renal transplant results increasing spectacularly the number of transplant recipients to arrive in the transplant clinic who remain for many years. This has engendered a series of questions about the most appropriate cyclosporine dosing for these patients that prevents rejection while avoiding toxicity. Three separate issues were analyzed: the most appropriate combination strategy with cyclosporine as a base "double" or "triple" therapy; the possibility of conversion from regimens containing cyclosporine to those devoid of it; and the optimal cyclosporine dose for a maintenance regimen. A meta-analysis of seven individual prospective and randomized trials of double versus triple therapy encompassing 1,080 patients revealed no statistical difference between the two regimens in terms of graft survival at 1 or 5 yr, patient survival, the rejection rate per patient, or the infection rate. In an analysis of 17 separate studies in which conversion away from cyclosporine was attempted, in 629 individuals with 702 individuals left on cyclosporine as controls, a significant risk of acute rejection ($P < 0.001$) was found in the withdrawn group without evidence of improved graft survival. Certain factors such as previous rejection, race, and degree of reactivity predicted even more rejection in the withdrawn group. Analyzing six separate studies of renal transplant recipients maintained on cyclosporine for up to 5 yr with renal functional stability, one can conclude that a dose of approximately 4.0 mg/kg per day is optimal. Because of variant pharmacokinetics or concomitant medicines, blood levels can confirm a therapeutic concentration with this target dose. In summary, a meta-analysis of multiple studies reveals no benefit of triple therapy over prednisone/cyclosporine; no advantage to cyclosporine withdrawal, with the penalty of one third of the cases exhibiting rejection; and an optimal dose of cyclosporine for chronic immunosuppression of 4.0 mg/kg per day.

Key Words: *Immunosuppression, Cyclosporine, Steroids, Azathioprine*

With the advent of potent immunosuppressive drugs such as cyclosporine A to prevent rejection and such as monoclonal antibodies to treat rejection, early renal transplant graft survival has experienced phenomenal improvement after placement in the last decade. First-time recipients of cadaveric allografts commonly achieve 1-yr graft survivals approaching 90% and 2-yr graft survivals over 85% with low patient mortality. Such superb early graft survival results have many consequences. First, nearly twice the number of transplant recipients find their way into the transplant clinic and into the hands of referring nephrologists for chronic management. Second, a range of metabolic, electrolyte, and internal medical problems attendant to the transplant event become important. Paradoxically, however, long-term graft survival data, even in the era of potent immunosuppressive drugs, have not markedly improved (1). Chronic management strategies, then, have become paramount in terms of the numbers of patients and in terms of attempts to forestall chronic rejection and/or immunosuppressive drug toxicity. Four important issues of chronic immunosuppressive drug management are treated in this symposium. The first issue, the necessity for corticosteroids (prednisone) in cyclosporine-treated transplant recipients and the capacity to withdraw these steroid agents in such patients, is dealt with elsewhere in this symposium by Hricik *et al.* This article will handle three additional issues of chronic patient management: (*1*)

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the appropriate combination treatment strategy, "double" versus "triple" therapy; (2) the possibility of conversion strategies from regimens containing cyclosporine A to regimens devoid of cyclosporine A; and (3) the optimal cyclosporine A dose for maintenance regimen. In dealing with these three topics, it is our intention to review the published series that speak to these issues, specifically analyzing and explicating those that, in general, provide data from controlled and randomized trials rather than historical nonconcurrent data sets.

DOUBLE VERSUS TRIPLE THERAPY

The terms "double" and "triple" therapy have been used by practitioners in transplantation and clinical investigators who write about transplantation to describe the immunosuppressive regimens used to maintain renal allograft immunologic integrity in the cyclosporine era. Each specific regimen is based on cyclosporine A as an invariant element. "Double therapy" refers to regimens containing cyclosporine A and one additional immunosuppressive drug—in most studies, almost always prednisone. More recently, with the explosion of additional immunosuppressive agents, double-therapy regimens containing cyclosporine and a second agent other than prednisone are beginning to be used and reported, but these will not be the subject of this review. "Triple therapy" includes those immunosuppressive packages beginning with cyclosporine that add two additional agents, most often prednisone and azathioprine. It is in this sense that we will use the term "triple therapy" in this review.

In the beginning of the basic and clinical studies that supported the new, now universal, use of cyclosporine A as the bedrock for maintenance immunosuppression, it was hoped that cyclosporine A could forestall acute allograft rejection when used as sole or monotherapy. Initial single-center trials in England and later in the European cooperative trial failed to conclusively demonstrate that monotherapy with cyclosporine A was markedly better than so-called conventional two-drug therapy with prednisone and azathioprine (2). The early trials of Kahan and colleagues using cyclosporine A with daily prednisone provided conclusive evidence for the marked graft survival advantage offered by the addition of cyclosporine A (3). Thus was born the "double therapy" approach to the chronic immunosuppressive treatment of renal transplant recipients.

It was the animal laboratory data supplied by Squifflet *et al.* that has been cited by all early authors as the laboratory support for a new approach, "triple therapy" (4). The idea advanced for the use of triple therapy flowed from the chemotherapy experience for neoplasms in which multiple drugs with variant mechanisms of action were to be used together to maximize effect and minimize toxicity. Squifflet *et al.* studied renal transplants in rats and dogs using cyclosporine at a dose that alone was ineffective to substantially prolong transplant life but to which was added a low dose of azathioprine (a dose of which was also unable alone to improve graft outcome). In rat transplant models, substantial graft prolongation was reported, whereas in five of the six studied dog transplant recipients, this combination led to severe azathioprine toxicity. Interestingly enough, there was no test of three drugs in the study nor was there a test of the notion that the combination of cyclosporine and azathioprine reduced cyclosporine A toxicity.

Despite the deficiencies in the Squifflet study, Canafax and colleagues, citing the animal experiments, reported a human trial of triple therapy (5). This trial reported 6-month data of a cohort of renal transplant recipients who received maintenance immunosuppression with cyclosporine A at 8 mg/kg per day, prednisone at 0.3 mg/kg per day, and 2.0 mg/kg per day of azathioprine and compared the results in this group with that of a historic control group that was treated with two drugs, cyclosporine A and prednisone, at quite different doses. The historic controls received 14 mg/kg per day of cyclosporine A and 0.4 mg/kg per day of prednisone. Not only were these not concurrent controls who did not receive comparable study drugs, but the subjects in the triple-therapy group also had quite a different induction strategy; to wit, all individuals in the triple-therapy group were treated with perioperative Minnesota antilymphoblast antibody, whereas none received such antibody in the historically treated, double-therapy group. Canafax *et al.* reported lower rejection rates (18 versus 23%) and a lower serum creatinine (1.4 versus 2.0 mg/dL) in the triple-therapy group compared with the double. Canafax *et al.* concluded that triple therapy was superior with respect to immunosuppression with less toxicity and improved renal function.

The Canafax study is importantly flawed. As indicated above, there were no concurrent controls and the doses of immunosuppressive drugs were quite different in the two study groups. Indeed, the dose of cyclosporine A in the double-therapy group is now known to be associated with higher rates of nephrotoxicity, likely accounting for the higher serum creatinine in the double-therapy group. Most important, this study reported only 6-month data, which reflected no statistical differences between the two groups. Nevertheless, the vogue of triple therapy in clinical transplantation was launched.

Since 1983, a multiplicity of articles have been written on the double- versus triple-therapy issue, but only a few test the two immunosuppressive approaches by an analysis using prospective and randomized study techniques. These prospective, ran-

domized trials are detailed in Table 1 and represent studies conducted throughout the transplant world from 1987 to the present. No single study demonstrates a statistical advantage of triple therapy over double therapy with respect to patient or graft survival, with respect to the number of rejection episodes per patient, or with respect to infections. These series are compiled for a clearer explication of this point in Table 2. More than 1,000 transplant recipients have been randomized into such trials of double versus triple therapy in the last 6 yr, with superb patient survival in both forms of chronic patient management at 1 yr and excellent graft survival with no differences between the two forms of management strategy (6–12).

Recently, Lindholm and colleagues have addressed this same issue with a randomized, prospective trial that provides actuarial 5-yr patient and graft survival data (13). Randomizing 229 patients into double therapy and 234 patients into triple therapy, Lindholm *et al.* concluded that there was no support for the use of triple therapy for immunosuppression in first cadaveric renal transplant because 5-yr patient survival was 80% in the double-therapy group compared with 82% in the triple-therapy group, and 5-yr graft survival was 55 versus 60%, respectively (13). The Lindholm study demonstrates that there is no statistical advantage to the use of triple therapy, chronically supporting the results in the panaply of shorter term studies compiled in Table 1.

Isoniemi and colleagues have approached the long-term effects of various immunosuppressive regimens in a different way, exploring morphologic consequences as well as patient and graft survival results with four different chronic immunosuppressive strategies (14). The Helsinki group found no differences in patient or graft survival, similar to the studies shown in Table 1, but suggested that less chronic allograft damage was recognized by biopsy in the triple-therapy group. It remains to be seen whether the Helsinki findings will have clinical import as patients continue to be monitored beyond 5 yr.

TABLE 2. Summary of prospective trials of double versus triple therapy

	Totals	
	Double	Triple
N	498	572
Graft Survival	87	83
Patient Survival	96	92
Rejection Rate		
Patient	0.8	0.6
Infection	30	38

Regardless of morphologic changes, there is no evidence of physiologic advantage of triple versus double therapy, as revealed in a 3-year follow-up of the cohort of randomized subjects originally reported by Brinker and colleagues (12) and studied for an additional 2 yr (K. Brinker, personal communication). Measuring renal function as serum creatinine and GFR by iothalamate clearance and controlling for cyclosporine dose and blood level, Brinker finds no advantage for either treatment strategy.

One can safely conclude that there is no advantage for the first 5 yr after engraftment of a triple-therapy regimen in terms of graft outcome, rejection rates, or infection rates. For those centers whose routine protocol uses triple therapy as cyclosporine, prednisone, and azathioprine, it is strongly suggested that azathioprine be discontinued if any evidence of azathioprine toxicity is encountered because little immunosuppressive advantage accrues from the addition of this drug. It remains to be tested whether triple-therapy regimens containing a different mix of immunosuppressive drugs added to the backbone of cyclosporine can offer the patient an important advantage in the face of the explosion of alternative

TABLE 1. Prospective trials of double versus triple therapy[a]

	Hardie 1993 (6)		Salamon *et al.* 1987 (7)		Lundgren *et al.* 1987 (8)		Pontichelli *et al.* 1983 (9)		Kootte *et al.* 1986 (10)		Restito *et al.* 1989 (11)		Brinker *et al.* 1990 (12)	
	D	T	M	T	D	T	D	T	D	T	D	T	D	T
N	142	141	28	27	124	136	43	43	40	40	50	75	99	110
Graft Survival (%)	86	85	78	75	80	80	91	86	90	92	90	89	75	75
Patient Survival (%)	98	91	96	78	92	95	93	100	98	98	100	92	90	93
Rejections (%)	0.9	1.0	1.3	0.1	0.8	0.7	1.1	1.3	0.4	0.6	1.2	0.3	0.2	0.2
Infections (%)	30	30	0	27	25	25	58	56	29	29	14	65	25	30

[a] D, double; T, triple; M, monotherapy.

immunosuppressive drugs to prednisone and azathioprine.

CYCLOSPORINE CONVERSION

"Cyclosporine conversion" is the conventional language used to indicate the discontinuance of cyclosporine A from the immunosuppressive package after successful engraftment in patients whose initial regimen included that drug. This strategy was initially designed in response to the fear that chronic cyclosporine nephrotoxicity would itself lead to late losses of renal allografts. This has been one of the most studied issues of chronic immunosuppressive management. This having been said, however, only a few groups have performed randomized, prospective trials. An analysis of these data has been made more difficult by the wide range of protocols used, each one variant in terms of baseline immunosuppression and the time posttransplant at which the "conversion" was attempted. In one of the first reports of conversion, Rocher and colleagues withdrew cyclosporine from a cohort of stable patients at 4 to 6 months posttransplantation with an abrupt change in immunosuppressive medications to a prednisone/azathioprine regimen (15). Temporally related to this abrupt conversion, the Brigham team noted a 28% rejection rate with 84% graft survival after treatment and only a 16% graft loss. Serum creatinine was reduced by 20%, allowing for the conclusion by the investigators that such conversion led to improved GFR and reduced acute cyclosporine effects, inferred from the serum creatinine measurement alone. Rocher and colleagues concluded that conversion was a potentially safe maneuver; despite an increased risk of an acute rejection episode temporally related to conversion, graft loss was uncommon. Twenty-two additional studies can be found in the literature looking at conversion regimens, with the time of conversion ranging from 3 months to 1 yr postsurgery. In these studies, 349 individuals experienced a rejection episode of the more than 1,000 individuals who have been converted, for a rejection rate of one third.

A recent meta-analysis of elective cyclosporine withdrawal has just been completed by Kasiske and colleagues in which 10 randomized and 7 nonrandomized trials were combined and carefully analyzed (16–33) (see Table 3). There was a highly significant risk of acute rejection in the cyclosporine-withdrawn group ($P < 0.001$). Most of those patients were able to have their allografts rescued because there were no differences in graft loss or mortality attributable to the cyclosporine withdrawal. In addition, there was no evidence for improved graft survival, at least in the short run, in the withdrawn group. Kasiske and colleagues concluded that there was an increased incidence of acute rejection after elective cyclosporine withdrawal and that this increased risk of rejection, although leading to the need for acute high-dose immunosuppressive therapy, hospitalization, and increased cost, did not have a short-term effect on graft or patient survival. Those investigators queried whether such conversion could improve more long-term outcomes but had no data to speak to such times. Indeed, with increasing evidence that acute rejection episodes may be predictive of decreased long-term results, one might actually conclude that conversion approaches can be harmful.

A carefully controlled study at the University of Texas Health and Science Center Southwestern Medical School attempted to maximize potential success by a study design in which putative design errors of previous studies were carefully taken into account (25). Thus, only patients with stable renal allograft function at 1 or more years postsurgery were entered into the trial. All patients entered into the trial had to have had no difficulties with cyclosporine with respect to toxicity or other side effects. These stable patients on a double-therapy regimen were randomized by computer to receive cyclosporine at a dose that was tapered by protocol to be approximately 4 mg/kg per day or to undergo a slow conversion. This slow conversion was effected by the addition of azathioprine to the regimen and then the withdrawal of cyclosporine over a 6-week period. Outcome variables included acute rejection, azathioprine toxicity, and GFR as measured by the isotopic clearance of iodothalamate (glofil). Stop points were designed into the trial. For the cyclosporine taper group, a reduction in

TABLE 3. Studies of cyclosporine conversion[a]

Author (Ref. No.)	Converted	Controls
Hall *et al.* (17)	141	138
Delmonico *et al.* (18)	47	45
Sweny *et al.* (19)	33	44
Spielberger *et al.* (20)	28	40
Kootte *et al.* (21)	32	34
Hiesse *et al.* (22)	30	34
Isoniemi (23)	32	32
Busing *et al.* (24)	22	22
Sagalowsky *et al.* (25)	10	9
Land *et al.* (26)	9	9
Woodle *et al.* (27)	46	110
Venning *et al.* (28)	70	68
Veitch *et al.* (29)	42	44
Oka *et al.* (30)	39	22
Maddux *et al.* (31)	21	21
Kaiser *et al.* (32)	11	12
Gonwa *et al.* (33)	16	18
Total	629	702

[a] Adapted from Kasiske *et al.* (16).

the GFR of 20% or more was considered a stop point, with patients then converted away from cyclosporine under the umbrella of a triple-therapy regimen. Such patients were taken to be cyclosporine failures. The stop points for the conversion arm of the protocol included acute rejection rates and azathioprine toxicity. Such patients were returned to cyclosporine. Despite an initial intention to randomize 50 patients, the Southwestern study was terminated after the first 19 entrants because six acute rejection episodes were experienced in the 10 converted patients as compared with no acute rejection episodes in the 9 patients left on relatively low-dose cyclosporine A. Indeed, there was one graft loss in the 10 converted individuals. GFR rose in both groups by 20%, interestingly enough.

Another instructive single-center study examined the fate of stable renal transplant recipients who have been converted from cyclosporine A for financial reasons. Three groups fell out—a "no" dose group, a low-dose group, and a "therapeutic" dose group. Late rejections were encountered in the "no" dose group, which led to graft losses in previously stable patients, especially among African-American recipients (34). This single-center experience taken together with the meta-analysis of 17 prospective and/or randomized trials reviewed by Kasiske leads to the important conclusion that there is a substantial risk of acute rejection after attempts at cyclosporine withdrawal in patients who are stable. Such episodes, which require increased immunosuppressive reserve therapy, potential risk, hospitalization, and increased cost, argue against attempts at cyclosporine conversion in patients who are stable and who have no problems with the side effects of that immunosuppressive drug. Because the graft half-life after the first year in cyclosporine A treated patients is similar to the half-life of graft survival in the precyclosporine era, one does not have evidence for an over-arching problem of graft loss owing to chronic cyclosporine nephrotoxicity. This observation undermines the necessity for conversion away from cyclosporine A of stable patients on relatively low doses of that drug (1). On the other hand, it is possible to conclude from an analysis of these studies that it is safe to convert two thirds of the patients, but the long-term effect of this conversion remains to be studied. Finally, one can also conclude that conversion can be a useful strategy for those individuals with important cyclosporine side effects because it can be done relatively safely in most patients without consequence, in the short term, to the graft or to the patient.

CYCLOSPORINE A DOSE

The general use of cyclosporine A as part of the immunosuppressive regimen for the maintenance of a renal transplant has raised an important clinical and intellectual dilemma. Despite the clear advantages with respect to 1-yr graft survival and reduced infection rates, the acute dose-related and reversible nephrotoxicity of cyclosporine A has engendered the question as to whether prolonged use of this agent will lead to detrimental renal effects. These effects may be reflective either at the level of morphology or in terms of long-term graft outcome or survivals. The question that is posed, then, is whether there is an optimal safe dose for prolonged administration that prevents organ rejection while avoiding toxicity. In this section of the review of chronic immunosuppressive management, we would like to argue that such a safe and effective dose of cyclosporine A may be found for renal transplant patients that forestalls rejection while generally avoiding chronic nephrotoxicity.

The dilemma concerning prolonged cyclosporine A use stems from the original observations of Brian Myers and his group at Stanford (35). Myers and colleagues reported on a group of cyclosporine/prednisone-treated cardiac transplant recipients compared with a cohort treated historically with imuran and prednisone. Regardless of whether the reciprocal of serum creatinine or isotopic GFR were analyzed, the cardiac recipients receiving cyclosporine demonstrated progressively worse function when compared with historical controls. Indeed, several patients lost intrinsic renal function and required renal replacement merely as a function of cyclosporine usage (35). These appeared to be an initial substantial reduction in GFR of as much as 50 mL/min that was sustained over many months, regardless of cyclosporine dosage or blood level, as shown in Table 4 in this group of heart transplant recipients (36). In those patients, confounding interpretive variables such as renal rejection to explain the renal anatomic or morphologic change thought to be related to cyclosporine A were absent. In contrast to the heart transplant experiences, the kidney transplant imposes potential toxicity of the drug or acute immunologic attack of the

TABLE 4. Renal function in cardiac transplant recipients treated with cyclosporine A at Stanford (36)

	Months		
	12–24	36	48
Cyclosporine Dosage (mg/kg per day)	6.8 ± 0.6	4.5 ± 0.5	3.1 ± 0.6
Cyclosporine Trough Levels (ng/mL)	175 ± 23	118 ± 21	66 ± 16
GFR (mL/min per 1.73 m^2)	56 ± 4	54 ± 7	55 ± 5

transplanted organ, confounding an etiologic understanding of morphologic and/or functional changes in the transplanted organ. Myers *et al.* argued, and the transplant community accepted the notion, that cyclosporine nephrotoxicity as demonstrated in the heart transplant environment was clearly a proven entity in any cyclosporine-treated patient population.

More recently, a number of analyses of the cyclosporine chronic nephrotoxicity issue have led to a more balanced view of the role of cyclosporine in chronic renal injury. Lewis and colleagues examined renal function in cardiac transplant recipients for 3-yr duration and found an initial reduction in GFR that occurred in the first 6 months, followed by 2.5 yr of stable renal function (37). Lewis *et al.* argued that the initial very high-dose cyclosporine use that characterized the early Stanford experience set in motion intrarenal scarring, which culminated in reduced renal function and even renal failure, as reported by Myers *et al.* The use of lower cyclosporine doses (8 to 12 mg/kg) is associated with an initial, early, small but fixed loss of renal function without further damage, Lewis *et al.* argued. Thus, one cannot conclude, they would suggest, that the prolonged use of effective cyclosporine is a continued renal injurant. (This issue is handled in greater detail in another article in this symposium.) Suffice it to say that Lewis and the Houston group and many other authors examining chronic or long-term usage of cyclosporine in renal transplant patients in both cadaver and living related donor recipients support the stability of renal function over time (37). Lindholm and colleagues found stable renal function in the largest group of renal transplant recipients on prolonged cyclosporine A studied to date, with a follow-up of longer than 3 yr (13). Furthermore, Burke *et al.* demonstrated superb graft and patient survival data without reduction in renal function (38), analyzing 1,663 renal transplant recipients over 3 yr from surgery. All authors emphasized that optimal dosing of cyclosporine A is the key to avoidance of nephrotoxicity (early with respect to preventing the basal spastic renal effects of the drug and late in terms of reducing the fibrotic changes with long-term usage).

The identification of optimal cyclosporine dosing is a dialectic between enough to prevent rejection but without too much in order to avoid toxicity. Dosing regimens that underdose the drug or target subtherapeutic blood concentrations may avoid toxicity but expose the patient to late acute or chronic rejections. For example, Wrenshall *et al.* demonstrated that a low mean daily dose of the drug under the aegis of so-called triple therapy (cyclosporine, azathioprine, and prednisone) led to more than a fourfold increase in the number of late rejection episodes—consequences of which are increased graft loss (39). Indeed, a similar point was emphasized by Roth and colleagues when they examined their double versus triple-therapy data (40). In triple-therapy patients, when cyclosporine dosing was 2.6 mg/kg per day, 35% of the cohort experienced a late acute rejection, whereas patients whose cyclosporine dose was on the order of 5 mg/kg per day had many fewer rejections (40). A few late rejection episodes had a paradoxically lower serum creatinine, reflective of the absence of renal dysfunction on an immune basis. In an analysis of a large group of patients, Ben-Maimon and colleagues revealed that a daily dose of approximately 4.0 mg/kg per day in more than 500 patients was associated with the absence of rejection episodes and stable renal function, whereas doses below 3.5 mg/dL per day in 542 subjects was associated with at least one rejection episode and a reduced renal function, as evaluated by the 1/creatinine paradigm (41). One can conclude from these and the other analyses reviewed in Table 5, with follow-up ranging from 1.5 to 5 yr, that an optimal maintenance dose of cyclosporine is approximately 4 to 5 mg/kg per day.

One can further conclude that, by using targeted daily doses with measurements of blood levels to ensure absorption and avoid drug-drug interactions, it is possible to effect excellent long-term graft survival with long-term results not worse than those of historical controls with other agents that are not deemed nephrotoxic. Equally important is the possibility that such optimal dosing can avoid late rejections and avoid the chronic scarring phenomenon

TABLE 5. Optimal dosing provides stable renal function

Author (Ref. No.)	Measured Maintenance Dose (mg/kg per day)	Length (yr)	Conclusions
Lewis *et al.* (37)	4.3	5	Stable renal function
Canafax *et al.* (42)	≥4.0	5	"Stable and excellent" renal function
Roth *et al.* (40)	4.0	4	Better renal function than <4.0
Perez *et al.* (43)	4.0	3.5	Stable serum creatinine
Canafax *et al.* (44)	4.3	1.5	No significant reduction in renal function
Ben-Maimon *et al.* (41)	4.0	3	No rejections and stable function

within the kidney taken to be cyclosporine nephrotoxicity. Corollary to this conclusion are several important rules of the maintenance use of cyclosporine. In order to avoid late rejections, programmed cyclosporine dosage unrelated to target blood levels or targeted optimal dosing levels risks late rejections. The maintenance of subtherapeutic cyclosporine doses or blood concentrations out of the fear of chronic nephrotoxicity can culminate in the late rejections and hasten graft loss on an immunologic basis. Finally, the use of multiple immunosuppressive drugs to cover the underdosing of cyclosporine A may avoid cyclosporine fibrosis while risking enhanced graft loss to rejection. Taken together with the comments concerning the late withdrawal of cyclosporine A, one can conclude that the prolonged or chronic use of cyclosporine A is effective and safe, undermining the suggestion in stable patients to attempt cyclosporine conversion.

SUMMARY

This review dealing with strategies for the maintenance use of cyclosporine A has analyzed three important issues: (*1*) the use of double versus triple immunosuppressive drug therapy, (*2*) the utility of and risk of conversion away from cyclosporine A, and (*3*) the optimal cyclosporine A dosing. Until a new class of immunosuppressive agents is introduced into the clinic that supersedes cyclosporine A or, importantly, synergizes with cyclosporine A, one may safely conclude that cyclosporine A should be the mainstay of the maintenance immunosuppression of the renal transplant recipient at an optimal dose of between 4 and 5 mg/kg per day, which effectively forestalls rejection while avoiding fibrotic nephrotoxicity. Attempts to delete cyclosporine A from the maintenance regimen should only occur in the setting of drug intolerance.

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