Clinical Pharmacology Update
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Cyclosporine and organ transplantation[1]

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Cyclosporine is a potent new immunosuppressive agent which is now available for use in clinical transplantation. It has a unique mechanism of action, interfering primarily with the cell-mediated response to foreign antigens. Cyclosporine has been very effective in preventing early graft loss due to rejection and has resulted in improved graft survival following kidney, heart, and liver transplants. Its major disadvantage is nephrotoxicity, which may be early (due to synergistic effects with other problems such as ischemic renal failure) or long-term (interstitial fibrosis and tubular atrophy). As cyclosporine is used more effectively, graft survival may be improved with minimal risk of toxicity.

Index terms: Clinical pharmacology updates • Cyclosporins • Transplantation

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Cyclosporine is a new immunosuppressive agent which has been approved by the Food and Drug Administration for use in human organ transplantation. It is a unique drug which holds the promise of significant improvement over conventional immunosuppressive therapy with steroids and azathioprine (Imuran, Burroughs Wellcome). Cyclosporine is a polypeptide that was isolated from a soil fungus (*Tolypocladium inflatum* Gams) by Borel et al in 1976.[1] Although it was first considered as a possible anti-fungal medication, early studies employing transplantation models in experimental animals soon documented its potent immunosuppressive activity.[2,3] Over the last six years, extensive studies in humans have also documented the effectiveness of cyclosporine in human transplantation.[4–10]

Clinical pharmacology

The cyclosporine molecule is quite insoluble in water and soluble in lipids. It comes as an oral preparation dissolved in an ethanol base at a concentration of 100 mg/mL. Before being administered, it is diluted 1:10 with another liquid (such as juice or milk). Its insolubility in water leads to variable (if any) absorption after intramuscular administration, which in turn has led to problems with its use.[11] However, it can also be given intravenously, supplied once again as a liquid preparation (50 mg/mL) in an ethanol base.

Given in liquid form, significant amounts of cyclosporine are absorbed from the gastrointestinal tract, with peak concentrations being obtained approximately two to four hours after oral administration.[12–14] It exhibits no significant

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renal excretion and is not dialyzable by either hemodialysis or peritoneal dialysis.[15] The drug is metabolized by the liver to products having uncertain biological activity and toxicity. Secretion of the active drug in the bile results in significant enterohepatic circulation, with a second peak in the blood from reabsorption of the excreted drug.[12,16] The plasma half-life varies from seven to 13 hours depending upon individual characteristics of absorption, metabolism, and enterohepatic circulation.[12] Originally, it was administered once a day; however, to minimize toxicity while maintaining clinical immunosuppression, a dosage of twice a day was believed to be more beneficial. Currently, most physicians administer it every 12 hours to avoid excessively high peaks while maintaining therapeutic trough levels throughout the day. While administration can be tailored to the individual patient, this often requires sophisticated pharmacokinetic modeling that may not be practical or available at all centers.

Cyclosporine is monitored by radioimmunoassay (RIA) or high-performance liquid chromatography (HPLC).[14] Each method has its advantages and disadvantages. RIA is a standard test that is easy to perform, and the results can be available within hours. It can be done on a batch basis, and multiple samples can be assayed within a short time. However, RIA measures not only the parent compound but also the hepatic metabolites.[17] Since it is not clear whether these metabolites are active, RIA may not necessarily correlate with therapeutic effectiveness. Also, RIA is generally performed on plasma; and depending on the temperature and the time involved in processing the sample, various amounts of cyclosporine may be taken up by the red blood cells, which may result in errors or fluctuation of results.[18] HPLC has the advantage of specifically measuring the parent compound, though the metabolites can also be measured by looking at different peaks on the chromatogram. However, HPLC is time-consuming and generally takes almost a full day. Running numerous samples is also a problem. On the other hand, since HPLC is performed on whole blood, uptake of cyclosporine by red blood cells is not a problem.

The blood levels of cyclosporine that correlate with clinical immunosuppression or toxicity with either assay are not clear. The most convenient way of monitoring the patient is to measure trough levels just prior to medication. Most centers initially set a goal of trough levels of 200–500 ng/ml; however, it now appears that ideal therapeutic trough levels may be 100–200 ng/ml for HPLC[19] and 50–200 ng/ml for RIA.[20] Although HPLC measures only the parent compound, the use of whole blood containing red cells with higher concentrations of cyclosporine accounts for the fact that desired levels are similar for the two assays. Correlation of trough levels with toxicity has been unclear, with toxicity being documented even at trough levels below 100. Since trough levels do not reflect the pharmacokinetics of the drug within the patient, some may absorb and clear it very quickly, leading to accumulation within body stores and posing the risk of potential toxicity despite low trough levels. On the other hand, patients may exhibit delayed absorption or clearance, so that trough levels remain somewhat high; yet the risk of toxicity may be no higher due to lack of accumulation of the drug within the tissues. The lipid solubility of the medication raises serious concerns about distribution into lipid compartments within the body, such as adipose tissue and the central nervous system. In addition, it may result in significant accumulation within certain renal parenchymal structures, particularly the proximal tubules.

Several significant drug interactions with cyclosporine have been noted. Concurrent use of ketoconazole increases serum concentrations of cyclosporine, probably by competing with its metabolism, and may increase the risk of toxicity.[21] It has also been suggested that aminoglycosides,[22] amphotericin,[23] and melphalan[24] may potentiate the toxicity of the drug. Nephrotoxicity has been reported following the use of trimethoprim-sulfa[25,26] in association with cyclosporine. Drugs such as dilantin which increase hepatic metabolism may result in more rapid clearance of the parent compound and decrease cyclosporine levels.[27]

Mechanism of action

Cyclosporine seems to act specifically and reversibly on the immune system, predominantly the cell-mediated component.[28,29] It seems to specifically block the generation of helper T cells and the development of cytotoxic T cells. It also inhibits the lymphokine interleukin-2, resulting in lack of proliferation of helper T cells, an integral component of the proliferative cellular response in transplant rejection.[30] Other sequelae include a tendency to reversal of the T_4:T_8 ra-

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Table 1. Cyclosporine nephrotoxicity in heart transplant recipients (one-year survivors)

	Glomerular Filtration Rate (mL/min)	Renal Plasma Flow (mL/min)	Blood Pressure (mm Hg)	CO (L/min)
Azathioprine controls	93*	480*	101†	5.8
Cyclosporine	51*	320*	111†	5.9

* $P < 0.001$
† $P < 0.1$
Data from Myers et al.[33]

tio,[31] reduced B-cell activation, and reduction of cytolytic T cells. The inhibition of the immune system is reversible with discontinuation of the drugs. Although some animal models have documented long-term donor-specific immune tolerance,[32] this has not been shown in any human studies to our knowledge. It is important to remember that cyclosporine is a nonspecific immunosuppressive agent, not a panacea for transplantation. Clearly, the ultimate goal of immunosuppression is donor-specific tolerance coupled with a normal response to other antigenic stimuli. As yet, we know of no indication that cyclosporine can be used to develop such donor-specific tolerance in man.

Of note is the absence of any cytotoxic effect on bone-marrow cells, specifically the white-cell count or the absolute lymphocyte count. The drug acts by interfering with the action of the cell and is not cytotoxic per se.

Toxicity

The side effects of cyclosporine are also unique. The most serious problem is nephrotoxicity, which may occur in as many as 90% of patients who receive medication for kidney transplants.[19,20] The nephrotoxicity may manifest itself in many forms.

Reduction in the glomerular filtration rate (GFR): Patients on cyclosporine who exhibit a decreased GFR (usually manifested as increased serum creatinine) may be undergoing nephrotoxicity from the drug. Reduction or discontinuation of the drug will almost always result in improvement of the renal function if this is indeed the case. Soon after transplantation, levels lower than the therapeutic range are often associated with rejection. Renal biopsy may be helpful in differentiating toxicity from rejection, especially in the first few months after transplantation. Since we know of no absolutely specific criteria for cyclosporine nephrotoxicity, reduction or possibly even discontinuation of the drug is warranted if toxicity is a clinical consideration. Generally, reduction is more appropriate in order to avoid interruption of the immunosuppressive effect which in turn may result in rejection. This dose-dependent effect on the GFR tends to occur over a period of days to weeks and may also reverse slowly over the same period of time. The effect of reduction of the GFR may be more chronic in patients being maintained on cyclosporine for long-term immunosuppression. Heart transplant patients who have been maintained on the drug for more than a year show a significant decrement in the GFR compared to patients not treated with cyclosporine (*Table 1*), and this has been associated with tubular atrophy and interstitial fibrosis on biopsy.[33] Two patients have progressed to renal failure and required dialysis. Thus, cyclosporine may have both an acute and chronic effect on the GFR; with the acute effect being reversible and the chronic effect being irreversible due to fibrosis and atrophy. Although the dosage was higher in these heart transplant patients than in many renal transplant recipients, this raises the possibility of irreversible toxicity in renal transplantation. In order to avoid long-term nephrotoxicity, conversion from cyclosporine to azathioprine has been attempted several months (or later) after transplantation.[34] Unfortunately, there has been a significant incidence of rejection within a few weeks of conversion, resulting in some graft loss, so that this may not be the ideal approach to long-term immunosuppression.

Synergistic toxicity with other damage to kidney: Synergistic toxicity can result in more severe acute renal failure,[35] particularly in the immediate post-transplant period when the allograft may exhibit ischemic acute tubular necrosis (ATN) and be exposed to other potential nephrotoxins, such as constrast media and antibiotics. The incidence of primary dysfunction of the allograft is probably increased in patients on cyclosporine.[36] Factors such as time of preserva-

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Table 2. Protracted dysfunction with cyclosporine

No. of patients	10
Duration of dysfunction (mean)	50 days
Improved after discontinuance of cyclosporine (mean creatinine, 2.1 mg%)	7
Continued with no function; graft lost after discontinuation of cyclosporine	3

Data from the Canadian Multicentre Transplant Study Group.[8]

tion, time of cold ischemia, time of revascularization, and donor characteristics such as hypotension and use of pressor agents may be much more important with cyclosporine due to potential synergism between nephrotoxicity and other renal trauma (*Table 2*).[8]

Hypertension: There is an increased incidence of hypertension with cyclosporine,[19] which may be mediated through salt and water retention or the renin-angiotensin-aldosterone system.[37] While the mechanism for this is not clear, it may be related to the reduction in GFR.

Hyperkalemia: There is a significant incidence of hyperkalemia associated with cyclosporine, probably related to tubular effects and decreased ability of the allograft to secrete potassium.[38] Aldosterone may also play a role.

The nephrotoxicity of cyclosporine will probably be the major problem related to prolonged use for organ transplantation, as well as limiting its use in other immunologic diseases. At present, much information is lacking regarding the nature of the nephrotoxicity and how it might be avoided. Other analogs of cyclosporin may be less nephrotoxic.

There are other adverse effects which generally do not result in discontinuation of the drug, although they may be very bothersome. These include increased hair growth, tremor, paresthesias, seizures, muscle weakness, gum hypertrophy, nausea, fluid retention, and hyperuricemia.[19] Hepatotoxicity has been described, but it is reasonably infrequent and tends to be mild and reversible.[39]

As with many nonspecific immunosuppressive agents, cyclosporine may be associated with both infection and neoplasia when used in excessive doses or coupled with other potent nonspecific immunosuppressive agents. In general, infectious complications have been less frequent in those patients treated with cyclosporine than with other immunosuppressive agents; however, a significant incidence of viral infections, particularly cytomegalovirus (CMV), Epstein-Barr virus, and other opportunistic infections (e.g., *Pneumocystis* pneumonia) have been reported in patients taking cyclosporine.[19,40,41] Bieber et al[42] reported that the early incidence of lymphoma appeared to be greater than in other immunosuppressed patients, perhaps due to overimmunosuppression with cyclosporine combined with other drugs. Lymphoma may develop in as many as 1% of immunosuppressed recipients even in the absence of cyclosporine. More recently, with more judicious use of lower doses and less utilization of other immunosuppressants, the incidence of lymphoma has not been greater than in other transplant patients and may even be somewhat less. Also, some lymphomas in patients taking cyclosporine have reversed with the antiviral drug acyclovir and discontinuation of immunosuppression, suggesting that early in their course the "lymphomas" may actually be virally mediated lymphoproliferative disorders that may not have a universally grim prognosis.[43]

Use in clinical transplantation

Numerous studies over the past five years have documented the usefulness of cyclosporine in clinical transplantation.[4–10,19,20,44] It was first used in renal allografts by Calne et al[4] in Great Britain, and subsequently numerous studies in Europe and the United States have confirmed improved graft survival after renal transplantation. Initial studies focused on comparing cyclosporine (alone or in combination with prednisone) to a conventional immunosuppressive regimen of prednisone and azathioprine. Results from a cooperative European study, a concurrently controlled study at the University of Pittsburgh, a Canadian multi-center study, and a retrospective comparison using historical controls at the University of Texas all documented significantly better graft survival with cyclosporine (either alone or combined with prednisone) compared to azathioprine and prednisone (*Table 3*). Cadaver graft survival at one year in these studies ranged from 72% to 90% using cyclosporine, compared to 50% to 64% using azathioprine and prednisone, and it is clear that the availability of cyclosporine should lead to an increase in one-year graft survival from 50% to 60% at one year to 75% to 85%.

Over the past five years, some centers have obtained 70% to 80% one-year graft survival without cyclosporine. Generally, this has re-

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Table 3. Cyclosporine in cadaver grafts

	Survival	
	Patients (%)	Grafts (%)
Starzl et al[44]		
Cyclosporine	98	90
Azathioprine	97	50
		$P < 0.05$
European Multicentre Trial Group[7]		
Cyclosporine	94	72
Azathioprine	92	52
		$P = 0.001$
Canadian Multicentre Transplant Study Group[8]		
Cyclosporine	97	84
Azathioprine	86	64
		$P = 0.003$
Azathioprine and anti-lymphocyte globulin		81
		NS
Sutherland et al[19]		
Cyclosporine	89	83
Azathioprine	94	76
		$P > 0.1$
Kahan[20]	96	81

NS = not significant.

quired the use of adjunctive immunosuppressive therapy, including anti-lymphocyte globulin (ALG), total lymphoid irradiation, thoracic duct drainage, or plasmapheresis. Comparison of cyclosporine with immunosuppressive regimens including ALG has not shown such a dramatic difference in graft survival. At the University of Minnesota, a controlled trial demonstrated 83% one-year graft survival in cadaver transplant recipients receiving cyclosporine and prednisone, compared to 76% using prednisone, azathioprine, and ALG; this difference was not statistically significant, although there was a trend toward better graft survival with cyclosporine.[10] The results of The Canadian Multicentre Transplant Study Group[8] also failed to show a significant difference in graft survival between cyclosporine-treated patients and recipients of cadaver grafts who received prednisone, azathioprine, and ALG. The Minnesota study actually showed a trend toward better patient survival without cyclosporine (94% versus 89%). However, these same studies have documented fewer episodes of rejection with cyclosporine, even if overall graft survival was not significantly different. Patients who received conventional immunosuppressants even with ALG have a 50% to 80% incidence of at least one episode of rejection; with cyclosporine, the incidence of rejection is probably 25% to 30%.[10] Some studies[7,8] have not documented decreased rejection with cyclosporine. However, the problem of differentiating rejection and toxicity (with subsequent overdiagnosis of rejection) makes these data less reliable. On the other hand, it is unlikely that episodes of rejection are underdiagnosed. If rejection goes untreated, it will likely worsen and not go undetected. Also, infection seems to be reduced using cyclosporine, especially viral infections such as CMV[19,4] (*Table 4*); however, the difference is small, and more data will be needed to confirm these observations.

Factors which are important in improving graft survival with conventional immunosuppressive therapy may have less significance when cyclosporine is administered. HLA typing (AB and DR) has shown a definite effect on cadaver graft survival with conventional therapy but seems to be relatively unimportant when cyclosporine is used;[7] however, recent data from larger series

Table 4. Infection treated with cyclosporine versus conventional therapy

	Anti-Lymphocyte Globulin and Azathioprine (%)	Cyclosporine (%)
Cytomegalovirus	25	8
Herpes simplex virus	20	13
Cytomegalovirus viremia	20	0
Cytomegalovirus viruria	20	0
Bacterial	16	2
Fungal	6	6

Data from Sutherland et al.[19]

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Table 5. One-year graft survival with cyclosporine

Perfusion time >24 hours	70%	P < 0.005 (versus < 24 hours)
Anastomosis time >45 minutes	60%	P < 0.002 (versus < 45 minutes)
Perfusion time <24 hours and Anastomosis time <45 minutes	96%	

Data from the Canadian Multicentre Transplant Study Group.[8]

have shown a small benefit to typing.[45] It may be that the more potent immunosuppressive effect of cyclosporine tends to mask any minor effect of matching in the short run. Pretransplant blood transfusions have been shown to be a significant determinant of graft survival with conventional immunosuppressive therapy: the greater the number of transfusions, the better the graft survival. With cyclosporine, there may be a beneficial effect of blood transfusions prior to transplantation, but this effect is less than with conventional immunosuppressive therapy.[46] Other factors which have not been significant with conventional immunosuppressive therapy may be more important with cyclosporine. Because of its nephrotoxicity, other trauma to the kidney, such as ischemia and nephrotoxic drugs, may increase the risk of post-transplant failure. A long perfusion or preservation time (greater than 24 hours),[45] a long anastomosis time (greater than 45 minutes), and the presence of post-transplant oliguria, anuria, or ATN have all been associated with an increased risk of graft loss when using cyclosporine from the time of transplantation[8] (*Tables 5 and 6*). It may be necessary to minimize other damage to the kidney in order to avoid serious nephrotoxicity with cyclosporine.

Table 6. Effect of cold ischemia on one-year graft survival

	0–24 hours	25–36 hours	37–48 hours
Cyclosporine (N = 600)	87%	72%	66%
Prednisone and azathioprine (N = 2,700)	64%	64%	69%

Data from Opelz.[45]

Table 7. Results with cyclosporine in other organs

	One-Year Patient/ Graft Survival
Liver	60%–70% (Starzl et al[47])
Heart	75%–85% (Oyer et al[48])
Pancreas	31%–48% (Goetz et al[49])

Cyclosporine has also been used for other organ transplants, including the liver,[47] heart,[48] pancreas,[49] and heart and lung. Reduced graft loss due to rejection has been documented with these organs as well (*Table 7*), which will undoubtedly result in a significant increase in the number of transplants performed. Cyclosporine has also been used successfully to treat rejection,[50] although it has generally been reserved for rejection which fails to respond to steroids.

Currently, several new protocols are being considered to try to improve the results with cyclosporine. One technique involves low doses of azathioprine combined with prednisone and cyclosporine,[52] based on the theory that use of three drugs having different mechanisms of action may result in synergistic immunosuppressive activity. However, they all have different toxicities and side effects, and since lower doses of each individual medication are used, toxicity may be minimized or eliminated. With another protocol, therapy with ALG is employed until the allograft begins to function, followed by conversion to cyclosporine;[53] thus potentiation of the ischemia present at the time of transplantation is averted by avoiding cyclosporine and its nephrotoxicity until after the graft has recovered.

Conclusion

There seems to be little doubt that cyclosporine is the most potent immunosuppressive agent currently available. Almost all studies have documented reduced graft loss due to rejection, and some have shown subgroups of patients with very high graft survival (95% to 100%); these are generally patients with immediate graft function, without other medical problems that may lead to death, and in whom other trauma to the kidney has been minimized. Thus, cyclosporine could possibly eliminate rejection as a cause of graft failure in more than 90% of cadaver graft recipients. With more judicious use of cyclosporine and better overall immunosuppressive protocols, this promise may be realized.

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