



Role of cyclosporine in glomerular diseases

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- **BACKGROUND** Clinical researchers are beginning to use the immunosuppressive agent cyclosporine to treat a variety of immunologically mediated diseases.
- **PURPOSE** To review the clinical experience with cyclosporine in the nephrotic syndrome and in lupus nephritis.
- **SUMMARY** Most studies to date have been small or uncontrolled, or both. Nevertheless, cyclosporine appears to produce remissions in adults and children with the nephrotic syndrome with minimal histologic changes ("minimal-change disease"). It also appears to produce remissions in children with focal and segmental glomerulosclerosis; it is less effective in adults and in individuals with focal and segmental glomerulosclerosis that is resistant to steroids. It appears to reduce proteinuria and to slow the progression of renal insufficiency in membranous glomerulonephritis but has little beneficial effect in IgA nephropathy. Anecdotal experience in patients with lupus nephritis suggests cyclosporine produces an improvement in symptoms, a decrease in protein excretion, and improvement in renal function when other treatments have failed. Cyclosporine's pharmacokinetic properties vary widely with the age of the patient and the presence of concomitant diseases and drugs. Relapses are common after the drug is stopped, and nephrotoxicity is a real risk with prolonged treatment.
- **CONCLUSIONS** Cyclosporine shows promise in treating immunologically mediated glomerular diseases, but larger randomized studies will be needed to define its role in this setting. Physicians should become more familiar with this drug as its indications increase.

■ **INDEX TERMS:** CYCLOSPORINE; NEPHROTIC SYNDROME; LUPUS NEPHRITIS
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THE UNIQUE immunosuppressive properties of cyclosporine were first recognized by Borel and colleagues in 1977.¹ Since then, more than 17 000 publications have examined the diverse facets of cyclosporine's pharmacology and clinical use. In addition to being used to prevent rejection in transplantation of the kidney, heart, lung, liver, bone marrow, and pancreas, cyclosporine has been used to treat a variety of diseases.

As of 1993, reports have appeared describing the use of cyclosporine in more than 90 different diseases, including approximately 15 renal diseases. These include studies of patients with the nephrotic syndrome (caused by minimal histologic changes ["minimal-change disease"], focal and segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, and immunoglobulin A [IgA] nephropathy), and with the acute nephritic syndrome (caused by systemic lupus erythematosus, Goodpasture's disease, Wegener's granulomatosis, and microscopic polyarteritis). Much of the literature consists of brief reports involving small numbers of patients treated in an uncontrolled fashion and fol-

lowed up for short periods of time. A few randomized controlled trials have been published, and many more are in progress.

The interpretation of results of these studies is confounded by variation in dosages employed, vagaries of bioavailability and pharmacokinetics of cyclosporine, concomitant use of other agents, (eg, glucocorticoids and cytotoxic drugs), heterogeneity of disease in patients undergoing therapy, and lack of controls. Nevertheless, cyclosporine in dosages of 4 to 6 mg/kg/day appears to reduce protein excretion, albeit temporarily, in many patients. Lasting remission of clinical manifestations of renal disease is uncommon, and relapses frequently occur after cyclosporine is stopped. Furthermore, covert or overt nephrotoxicity is a real risk, particularly after prolonged treatment. This review will analyze current results of cyclosporine therapy in glomerular disease, including minimal-change disease, focal and segmental glomerular sclerosis, membranous glomerulonephritis, IgA nephropathy, and lupus nephritis.

PHARMACOKINETICS

Much of the data regarding the pharmacokinetics of cyclosporine have been derived in patients undergoing organ transplantation. The applicability of these data to patients with glomerular disease who are not undergoing transplantation may be questioned. Clinicians need to take into account cyclosporine's remarkable variability in pharmacokinetic properties when applying this drug.

Cyclosporine is a lipophilic cyclic polypeptide composed of 11 amino acids; it was originally isolated from the soil fungus *Tolypocladium inflatum* Gams. It is erratically absorbed, primarily from the small intestine. Bile salts enhance absorption; therefore, anything that interferes with the presence of bile acids, such as the concomitant use of cholestyramine or colestipol, will reduce the absorption of cyclosporine, the peak levels that will be achieved, and the bioavailability. The bioavailability is approximately 30%, but this may range from 5% to 70% depending on absorption. Bioavailability tends to be lower in children than in adults. It is also lower in patients with small-bowel disease and perhaps in patients with severe nephrotic syndrome who have concomitant edema of the intestine. This topic has been reviewed in detail by Faulds and colleagues.²

Following absorption, cyclosporine is initially distributed in the intravascular compartment: 60% in erythrocytes, 30% in lipoproteins, and 10% in leukocytes. Only small amounts are found free in the plasma. In patients with hyperlipoproteinemia, a higher fraction of the ingested cyclosporine may distribute within the lipoproteins, leaving less available for concentration in the leukocytes and thus decreasing its effectiveness.³ Conversely, in patients with aplastic anemia, the relative paucity of erythrocytes causes an increased shift of cyclosporine to other cells.

Cyclosporine is distributed throughout the body except in the brain, with an apparent volume of distribution of 4 to 8 L/kg. The volume of distribution is higher in children than in adults. The tissue levels of cyclosporine correlate well with the lipid and cyclosporine-binding protein content of specific tissues. Peak blood levels are found at 2 to 3 hours after an oral dose. The elimination half-life is approximately 19 hours, but ranges from 3 to 27 hours. Cyclosporine is metabolized by the P-450III_A system, predominantly in the liver. More than 30 metabolites, most with little or no immunosuppressive activity, have been described. The toxicity of cyclosporine is primarily due to the parent molecule rather than to its metabolites.²

The apparent clearance of cyclosporine varies widely from 0.4 to 3 L/hr/kg. It is higher in children and in patients with markedly elevated lipoprotein levels and lower in older subjects, patients with liver disease, and those with reduced low-density lipoprotein (LDL) levels. Several drugs affect clearance, largely through an influence on hepatic metabolism. Erythromycin, ketoconazole, diltiazem, nicardipine, verapamil, and even grapefruit juice reduce clearance and increase trough levels. More than 90% of cyclosporine is excreted in the bile, and very little is found in the urine. Carbamazepine, phenytoin, and rifampin increase clearance and reduce trough levels. Amphotericin B, gentamicin, tobramycin, and trimethoprim enhance its nephrotoxicity without an apparent effect on its metabolism.²

This analysis of pharmacokinetics suggests that the dosage required to achieve a desired effect will be increased in children, patients with severe nephrotic syndrome with hyperlipidemia, and patients with concomitant small-bowel absorption problems. The dosage required to achieve a desired effect is likely to be reduced in the elderly and in patients with accompanying liver disease.

EFFECT ON THE IMMUNE SYSTEM

The immunosuppressive properties of cyclosporine are only partially selective but largely due to an influence on the function of the CD4⁺, CD3⁺ helper T cells (both TH1 and TH2 subsets). Cyclosporine inhibits synthesis of interleukin 2, interferon gamma, and other lymphokines, and to a lesser degree inhibits the expression of the proto-oncogenes *c-myc* and *c-fos*. It also has an effect on macrophages and on antigen-presenting cells, but only at very high dosages. It has little or no effect on B cells or upon the bone-marrow production of granulocytes or platelets.

The immunosuppressive effects of cyclosporine occur within the cytoplasm of the affected cell populations. Cyclosporine passes across cell membranes due to its lipophilic character. Within cytoplasm, it binds to a cytoplasmic receptor called cyclophilin. This binding protein is a rotamase that catalyzes the *cis-trans* isomerization of proline-imido peptide bonds necessary for protein folding.

Upon binding to cyclophilin, cyclosporine becomes more polar, and the cyclophilin-cyclosporine complex binds and subsequently inhibits calcineurin in a calcium-dependent fashion. Calcineurin is a calcium- and calmodulin-dependent serine-threonine phosphatase. The inhibition of calcineurin phosphatase activity is responsible for the immunosuppressive properties of cyclosporine. This inhibition prevents the activation of nuclear factors that are involved in the transcription of genes encoding for interleukin 2 and other cytokines. These include nuclear factors AT-1, AP-3, and kB. These nuclear activating factors bind to and activate the promoter-enhancer elements in the interleukin gene.²

As a consequence of its partially selective immunomodulating properties, cyclosporine has its principal effect on cellular immunity. It is quite potent in inhibiting the allograft rejection response and in *in vitro* models of cellular immunity. However, it is not clear whether its beneficial effect in glomerular diseases is due to its action on the T cells or on the secretion of a permeability factor⁴; at least some of its immediate and short-term effects on protein excretion could also be mediated by a hemodynamic influence on the glomerular capillary circulation and barrier function.⁵

While many glomerular diseases are thought to be pathogenetically linked to humoral immunity (eg, antibody formation and immune complexes), it

TABLE 1
CYCLOSPORINE IN EXPERIMENTAL RENAL DISEASE*

Model	Prophylactic effect	Therapeutic effect
Acute serum sickness	Beneficial	Beneficial
Chronic serum sickness	Beneficial	Beneficial
Anti-glomerular basement membrane nephritis	Beneficial	None or harmful
Aminonucleoside nephritis	None	Beneficial
HgCl ₂ -induced nephritis	Beneficial	Beneficial
Murine lupus nephritis	Beneficial	Beneficial

*Data summarized from reference 2

is increasingly evident that cellular immunity also contributes to renal injury in many instances and may be the primary initiating factor in some circumstances. These observations implicating cellular immunity in glomerular disease provide a rationale for the use of cyclosporine as a therapeutic agent.

CYCLOSPORINE IN EXPERIMENTAL RENAL DISEASE

The effect of cyclosporine has been examined in a wide variety of animal models of disease (Table 1), both of the spontaneous and induced character. The protocols have involved the administration of cyclosporine as a prophylactic agent (eg, before or at the time the disease is induced) and as a therapeutic agent (eg, after full expression of the disease). In general, favorable effects have been seen, with occasional exceptions. Under certain experimental circumstances, the effect of cyclosporine in the thymus may interfere with the acquisition of self-tolerance and thus promote rather than impede the development of autoimmunity.

CYCLOSPORINE IN HUMAN RENAL DISEASE

Minimal-change disease

Cyclosporine in a dosage of 4 to 6 mg/kg/day can induce remission in 80% to 85% of children and adults with minimal-change disease that frequently relapses and is "steroid-dependent" (ie, relapses when the steroids are withdrawn).^{2,6-13} However, withdrawal of cyclosporine will often be associated with a relapse within a few days to several weeks. Prolonged cyclosporine treatment at a low dosage (1 to 3 mg/kg/day) may maintain a remission, but covert, slowly progressive nephrotoxicity may occur. Renal biopsy specimens from patients who have mini-

TABLE 2
EFFECTS OF CYCLOSPORINE IN MINIMAL-CHANGE DISEASE IN CHILDREN*

Type	N	Complete response	Partial response	No response	References
Steroid-dependent	110	85% (93)	11% (12)	5% (5)	4, 15-21
Steroid-resistant	52	67% (35)	2% (1)	44% (23)	5, 16, 17, 19
Total	162	79% (128)	8% (13)	13% (28)	

*Adapted from reference 2

TABLE 3
EFFECTS OF CYCLOSPORINE IN MINIMAL-CHANGE DISEASE IN ADULTS*

Type	N	Complete response	Partial response	No response	References
Steroid-dependent	53	79% (42)	0% (0)	21% (11)	3, 18, 22-25
Steroid-resistant	41	61% (25)	20% (8)	20% (8)	3, 22-27
Total	94	71% (67)	9% (8)	20% (19)	

*Adapted from reference 2

mal-change disease and who receive low-dosage cyclosporine as maintenance therapy have shown the development of small areas of tubular atrophy and interstitial fibrosis over time.¹⁴ Monitoring of renal function with measurements of the serum creatinine concentration or creatinine clearance may be insufficient to detect subtle degrees of nephrotoxicity when low-dosage cyclosporine therapy is used for prolonged periods of time. Because of the high rate of relapse after cyclosporine is reduced or stopped, this agent is not recommended for the primary treatment of frequently relapsing disease. Remissions induced by cyclophosphamide or chlorambucil in patients with minimal-change disease that frequently relapses are likely to be longer-lasting.

The response rate of children and adults with minimal-change disease that is initially steroid-resistant is less than that seen in patients with steroid-responsive disease (Tables 2 and 3).^{3-5,15-27} Although results vary, the initial response rate is approximately 60% to 65%, and relapses frequently occur when cyclosporine is discontinued. There are few side-by-side comparisons of cyclosporine with an alkylating cytotoxic agent such as cyclophosphamide or chlorambucil in steroid-resistant minimal-change disease. Cyclosporine appears to be more effective when it is used with modest dosages of glucocorticoids.

Therefore, cyclosporine may be useful in the management of minimal-change disease when patients continue to have relapses following appropriate therapy with glucocorticoid and cytotoxic

agents. Many nephrologists would prefer to treat such patients with at least two courses of cyclophosphamide or chlorambucil before resorting to cyclosporine-based management protocols. At present, it is unclear whether cyclosporine, cyclophosphamide, or chlorambucil is the preferred agent for the management of truly steroid-resistant minimal-change disease.

Focal and segmental glomerulosclerosis

Children with biopsy-proven focal sclerosis that relapses when steroids are withdrawn will respond to cyclosporine in a manner very similar to those with minimal-change disease; however, adults with focal sclerosis and steroid dependency do not fare as well as children (Tables 4 and 5).^{2,3,5,6,10,15-19,21,23,24,27-34}

Children with focal sclerosis that is resistant to steroids have a poor response to cyclosporine, with at least 50% demonstrating no reduction in proteinuria. Adults with steroid-resistant focal sclerosis fare even worse, with 70% showing no response at all to cyclosporine.^{2,6,10}

Overall, only 35% of children and 20% of adults with focal sclerosis that is steroid-resistant have a complete remission with cyclosporine therapy. There have been no side-by-side comparisons of cyclosporine with cytotoxic agents. As in minimal-change disease, relapses following withdrawal of therapy are common. Renal functional impairment at the time cyclosporine is introduced appears to reduce the likelihood of a response and enhance the risk of nephrotoxicity. Serial biopsies in patients receiving cyclosporine for focal sclerosis have demonstrated continued progression of the glomerular lesions and the occurrence of interstitial fibrosis, especially if chronic tubulointerstitial lesions antedated the exposure to cyclosporine.

Membranous glomerulonephritis

There is a paucity of information regarding the effect of cyclosporine on idiopathic membranous glomerulonephritis. A large number of small uncon-

trolled trials have been conducted, and preliminary results of small controlled trials have been recently reported.³⁵⁻³⁸ Overall, approximately 20% of patients have had a complete remission, with an additional 20% to 30% having a significant reduction in protein excretion.³⁵⁻³⁸ Many of these patients had disease that failed to respond to either glucocorticoids or combinations of glucocorticoids and cytotoxic agents. Whether this response rate is different from the rate of spontaneous remission that would be expected from the natural history of the disease cannot be ascertained from published reports.

Nevertheless, careful longitudinal studies have strongly suggested that cyclosporine exhibits an antiproteinuric effect in membranous glomerulonephritis.^{35,38} If this antiproteinuric effect can be sustained with dosages that are not associated with progressive nephrotoxicity, then it would be reasonable to conclude that these patients would be partially protected from the later development of progressive renal insufficiency. Preliminary data from prospective controlled trials in progress support the view that cyclosporine may have a beneficial effect on progression of renal insufficiency.³⁸

Nevertheless, these trials have involved only small numbers of patients followed for short periods of time. We do not yet know whether the cumulative nephrotoxic effects of cyclosporine will counterbalance any putative beneficial effect based on its reduction of protein excretion. Similarly, there are no side-by-side comparisons between cyclosporine and other agents commonly used in the treatment of membranous glomerulonephritis, such as combinations of glucocorticoids and cyclophosphamide or chlorambucil.

IgA nephropathy

Relatively few patients with IgA nephropathy have been treated with cyclosporine. Most patients considered for such therapy have had severe prote-

TABLE 4
EFFECT OF CYCLOSPORINE IN FOCAL
AND SEGMENTAL GLOMERULOSCLEROSIS IN CHILDREN*

Type	N	Complete response	Partial response	No response	References
Steroid-dependent	11	91% (10)	9% (1)	0 (0)	5, 17, 21
Steroid-resistant	93	32% (30)	12% (11)	56% (52)	5, 15-17, 19, 21, 30-32
Total	104	38% (40)	12% (12)	50% (52)	

*Adapted from reference 2

TABLE 5
EFFECT OF CYCLOSPORINE IN FOCAL
AND SEGMENTAL GLOMERULOSCLEROSIS IN ADULTS*

Type	N	Complete response	Partial response	No response	References
Steroid-dependent	10	50% (5)	10% (1)	40% (4)	3, 23
Steroid-resistant	64	14% (9)	19% (12)	67% (43)	3, 17, 18, 23, 24, 30, 33, 34
Total	74	19% (14)	18% (13)	64% (47)	

*Adapted from reference 2

inuria and evidence of progressive renal insufficiency. Although the experience is small, preliminary data suggest that cyclosporine aggravates the tendency to progressive renal insufficiency while having only modest effects on protein and erythrocyte excretion.³⁹ Because of the indolent and often unpredictable nature of IgA nephropathy and the propensity for cyclosporine to aggravate renal insufficiency, there is little current enthusiasm for the use of cyclosporine in IgA nephropathy.

Lupus nephritis

It is not surprising that cyclosporine has been used to treat lupus nephritis when one considers its beneficial effects in experimental models of lupus nephritis, the possible involvement of cell-mediated immunity in the pathogenesis of this disease, and the lack of any agreed-upon protocol for its management. To date, there have been no controlled trials; however, several centers have accumulated a rather large experience in the use of cyclosporine in lupus nephritis in an uncontrolled fashion.⁴⁰⁻⁴³ Most patients who have been treated with cyclosporine have had disease that failed to respond to other therapies or that was severe and progressive, often complicated by multiple organ involvement.

A high percentage of patients with lupus nephritis treated with cyclosporine have demonstrated a

diminution in the clinical signs of disease activity, often despite little change in serologic abnormalities (anti-dsDNA, C3, C4). Fever, arthralgias, skin rash, and even central nervous system abnormalities have abated concomitantly with the use of cyclosporine. In addition, a high percentage of patients have demonstrated a decrease in protein excretion, sometimes accompanied by improvement in renal function. Patients with membranous glomerulonephritis secondary to systemic lupus erythematosus rather consistently demonstrated a decline in protein excretion and improved or stabilized renal function.

Because of the anecdotal nature of this experience, it is difficult to conclude whether there is a role for cyclosporine in the management of lupus nephritis. Nevertheless, it would not seem unreasonable to use cyclosporine in a patient whose condition is deteriorating despite other aggressive therapeutic approaches. Controlled trials are needed to evaluate the beneficial effects of cyclosporine in membranous glomerulonephritis; however, preliminary results are quite encouraging.

SUMMARY

Cyclosporine shows promise in renal disease, but randomized controlled trials are needed to better define how and when it should be used. Wide variations in absorption, bioavailability, and clearance of cyclosporine occur among patients. Furthermore, this potent immunosuppressive drug has serious side effects, including toxicity to the kidney. Progressive interstitial fibrosis may occur, even when the creatinine clearance rate and serum creatinine concentration remain normal. Other problems are reversible when the drug is discontinued or controllable if the dosage is kept low.

Cyclosporine appears to be effective in selected patients with minimal-change disease, focal sclerosis, and membranous glomerulonephritis, and in some patients with lupus nephritis. It appears to be either ineffective or unsafe in IgA nephropathy. Although cyclosporine is approved in Europe to treat the nephrotic syndrome, its safety profile may pose a barrier to its approval for this indication in the United States. When beneficial effects occur, they usually are seen within the first 3 to 4 months of therapy. Relapse occurs frequently when cyclosporine therapy is withdrawn.

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