Mycophenolate Mofetil Treatment of Severe Renal Disease in Pediatric Onset Systemic Lupus Erythematosus

SILVIA BURATTI, ILONA S. SZER, CHARLES H. SPENCER, SHARON BARTOSH, and ANDREAS REIFF

ABSTRACT. ***Objective***. To report the first clinical experience with mycophenolate mofetil (MMF, CellCept®) in children with lupus nephritis.

Methods. Eleven children with various forms of lupus nephritis were treated with oral MMF at a mean dose of 22 mg/kg/day (range 17-42) for a mean of 9.8 months (range 3-17). All children received concomitant prednisone and 7/11 were taking concomitant hydroxychloroquine. Indications for MMF included treatment refractory nephritis despite high dose oral or IV prednisone, azathioprine, and/or cyclophosphamide. Treatment outcome was monitored through assessment of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, renal function, and serologic markers such as complement and anti dsDNA antibodies.

Results. While renal function normalized in 4/4 patients with membranous glomerulonephritis, little effect was observed in children with proliferative glomerulonephritis. Ten children experienced a marked reduction in SLEDAI score. Anti-dsDNA antibody and serum complement levels improved or remained stable in 80% of the children. Concomitant prednisone was decreased in 6/11 patients (55%) without deterioration of renal function. Adverse events, observed in 8 patients (73%), were not dose dependent, and included infections, leukopenia, nausea, pruritus, headache, and fatigue.

Conclusion. MMF may represent a valuable alternative to traditional cytotoxic agents for children with class V lupus nephritis, but was less effective in attenuating disease progression in class IV glomerulonephritis. MMF had a steroid sparing effect and appeared to be effective in controlling serologic disease activity in pediatric onset SLE. Adverse events such as infections may limit its use and remain a concern. (J Rheumatol 2001;28:2103–8)

Key Indexing Terms:
MYCOPHENOLATE MOFETIL NEPHRITIS SYSTEMIC LUPUS ERYTHEMATOSUS
CHILDREN TREATMENT

Systemic lupus erythematosus (SLE) is the prototype of a multisystem autoimmune disease. The disease incidence in children is estimated at 0.4 per 100,000, of which two-thirds develop renal involvement, manifesting mainly as diffuse proliferative glomerulonephritis (DPGN) or, less commonly, as membranous glomerulonephritis[1,2].

From the Divisions of Rheumatology, Department of Pediatrics, University of Southern California, Keck School of Medicine, Childrens Hospital Los Angeles, Los Angeles; Childrens Hospital San Diego, UCSD School of Medicine, San Diego, CA; La Rabida Childrens Hospital, University of Chicago, Chicago, IL; Children's Hospital University of Wisconsin-Madison, Madison, WI, USA.

S. Buratti, MD, Research Fellow, University of Pavia, and Childrens Hospital Los Angeles; I.S. Szer, MD, Clinical Professor of Pediatrics, UCSD School of Medicine, and Director, Pediatric Rheumatology, Childrens Hospital San Diego; C.H. Spencer, MD, Associate Professor of Clinical Pediatrics University of Chicago, La Rabida Childrens Hospital Chicago; S.M. Bartosh, MD, Associate Professor of Pediatrics, and Chief, Section of Pediatric Nephrology, University of Wisconsin Children's Hospital; A. Reiff, MD, Assistant Professor of Pediatrics, University of Southern California, Keck School of Medicine, Childrens Hospital Los Angeles.

Address reprint requests to Dr. A. Reiff, Division of Rheumatology, Mailstop 60, Childrens Hospital Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027. E-mail: reiff@hsc.usc.edu

Submitted June 7, 2000; revision accepted March 21, 2001.

Without aggressive treatment DPGN can have a devastating disease course, resulting in end stage renal disease or death[3,4]. Children with membranous glomerulonephritis on the other hand may develop nephrotic syndrome with persistent proteinuria and increased risk of cardiovascular events[5]. Aggressive management is therefore indicated to prevent or delay progression in either form of childhood lupus nephritis.

Traditional treatment of severe DPGN in children includes the use of corticosteroids, often in combination with cytotoxic agents such as azathioprine or intravenous (IV) cyclophosphamide (CyP). Controlled studies from the National Institutes of Health have concluded that parenteral CyP is the current gold standard for DPGN since it is superior to corticosteroids in preventing irreversible renal damage and end stage renal disease[6-9]. Therefore, CyP protocols for lupus nephritis have been adopted by most pediatric rheumatology centers[10].

Therapy for pure membranous glomerulonephritis on the other hand is more controversial. Various treatment regimens, such as monotherapy with corticosteroids or combinations of cyclosporin A, cyclophosphamide, azathioprine,

and chlorambucil have been proposed[11]. However, the efficacy of these regimens has not been evaluated in controlled clinical trials and remains anecdotal.

The impact of prolonged steroid treatment on growth and development and the increased risks of infection, infertility, and the longterm risk of malignancy limits the use of CyP or other immunosuppressive agents in the management of pediatric SLE[12]. In addition, a substantial portion of children have an inadequate response or relapse taking traditional therapy, underscoring the need for therapeutic alternatives[13–14].

Mycophenolate mofetil (MMF) is a new xenobiotic immunosuppressive agent. Its active metabolite, mycophenolic acid, is a reversible inhibitor of inosine monophosphate dehydrogenase, which functions as a critical rate limiting enzyme in the *de novo* pathway of purine biosynthesis. MMF also inhibits the formation of antibodies and the generation of cytotoxic cells *in vitro*[15-17]. In addition, MMF inhibits T and B lymphocyte proliferation and downregulates the expression of adhesion molecules on lymphocytes, impairing their ability to bind to endothelial cells. In a murine model of lupus nephritis, MMF delayed deterioration of renal function and prolonged survival[18]. MMF has been shown to be safe and efficacious in extensive clinical trials in transplant patients[19-21]. Recent evidence in adult patients with treatment resistant lupus nephritis suggests that MMF in lower doses may be a safe and well tolerated alternative to traditional chemotherapy[22-23]. Moreover, MMF has been investigated and found beneficial in the treatment of rheumatoid arthritis, psoriasis, autoimmune hemolytic anemia, antineutrophil cytoplasmic antibody-associated vasculitis, and IgA nephropathy[24-26].

Our study describes the first clinical experience with mycophenolate mofetil in 11 children with various forms of severe lupus nephritis.

MATERIALS AND METHODS

Patient selection. Eleven children from 4 pediatric rheumatology centers, who fulfilled the classification criteria for SLE[27], were included in the study and followed for a mean of 9.8 months (range, 3 to 17). The patient population included 9 females and 2 males with an average age at disease onset of 12.3 years (range 9 to 15.3). There were 4 Hispanic, 4 Afro-American, and 3 Caucasian patients. The mean disease duration was 2.9 years (range 0.8 to 7.8).

All patients had undergone renal biopsies at disease onset in order to establish a histologic diagnosis (Table 1). Criteria for starting MMF included (I) inadequately controlled nephritis despite aggressive treatment with longterm steroids and/or cytotoxic drugs (iv or oral cyclophosphamide, azathioprine) and/or (II) inability to taper steroids below 0.5 mg/kg/day including ongoing need of IV methylprednisolone pulses.

Therapy. Prior to treatment with MMF, 5 children (patients 1–3,7,11) had received IV cyclophosphamide (mean cumulative dose 9.32 g; range, 2 to 17.1) and one child (patient 1) had received oral cyclophosphamide. Three children (patients 2,3,7) had been treated with azathioprine, and another (patient 8) with oral methotrexate (Table 1). Five children had been treated with steroids alone but not with cytotoxic agents. Four children (patients 8–11) had received numerous pulses of IV methylprednisolone.

MMF (CellCept®, Roche Laboratories, Nutley, NJ, USA) was administered twice daily at a dose range from 17 to 42 mg/kg/day (median 22) or 1.25 to 2.25 g qd (median 1g bid) total dose. The mean duration of therapy was 9.8 months (range 3–17). During the study all children received concomitant prednisone in various doses and 7/11 were on concomitant hydroxychloroquine (Table 2).

All parents and patients were informed that MMF, a US Food and Drug Administration approved drug, was used off label for a non-approved indication.

Clinical and laboratory assessment. In order to assess treatment outcome all patients had regular complete clinical evaluations using the SLE Disease Activity Index (SLEDAI)[28] and serial measurements of complete blood cell counts to monitor drug toxicity, chemistry panel, serum antinuclear antibodies by immunofluorescence, anti-dsDNA antibodies and complement fractions C3-C4 (mg/dl). Anti-dsDNA antibodies were measured by a modified Farr assay, while complement levels were determined by radial immunoelectrophoresis. Renal function was monitored through 24 h urine protein excretion (g/24 h), timed 24 h creatinine clearance (ml/min), and serum creatinine (mg/dl).

A positive response to treatment was defined as improvement of at least 2 points in the SLEDAI score, reduction of more than 0.5 g/24 h in proteinuria, reduction in serum creatinine of more than 0.2 mg/dl, increase of at least 10 ml/min in creatinine clearance, reduction of at least 50 IU/ml in the serum anti-dsDNA titer, and improvement of more than 10 mg/dl in one or both complement fractions.

RESULTS

Treatment response. After a mean of 10 months of treatment we observed a marked reduction of disease activity in 80% of the children as determined by SLEDAI score, which decreased from a mean of 9.6 at baseline to 3.4 (mean change of –6.3) (Table 3). Serum C3 and C4 levels increased in 3/6 children (patients 4–6) with low values at baseline (patients 3–6,8,11) and decreased below normal in one patient whose levels were normal at study entry (patient 10). Anti-dsDNA levels decreased in 3/4 children (patients 2,5,8) with elevated titers at baseline (patients 2,3,5,8) and increased in one child (patient 10). Patient 6 who was negative for anti-dsDNA showed a significant drop in previously elevated Sm antibodies (Table 3).

Out of 8 children with baseline proteinuria ≥ 0.5 g/24 h, we observed decreased proteinuria in 5/8 children (patients 4–7, 11), unchanged values in 1/8 (patient 2), and increased proteinuria in 2/8 children (patients 1,3). Three children had less than 0.5 g protein/24 h at baseline (patients 8–10). Creatinine clearance increased in 6/11 children (patients 2,4–6,8,9), decreased in 2/11 (patients 1,3), and remained stable in 3/11 (patients 7,10,11). Among the 6 children with a serum creatinine ≥ 1.2 mg/dl at baseline, levels increased in 3/6 (patients 1–3), remained stable in 1/6 (patient 11) and decreased in 2/6 (patients 4,9) (Table 4).

Four children (patients 4–7) had an overall excellent response to MMF, with normalization of serum creatinine, proteinuria, SLEDAI score (≤ 2), anti dsDNA antibodies and increased C3 and C4 serum levels. Three of these children had membranous glomerulonephritis and the fourth had mixed features of membranous and proliferative nephritis by renal biopsy. Concomitant prednisone was discontinued in 1/11 children, tapered in 9/11 (mean drop 0.5 mg/kg/day, range 0.2 to 1) and remained unchanged in

Table 1. Demographic and baseline clinical variables of study cohort.

Study No./ Patient-Center	Gender	Race	Age, yrs	Age at Onset, yrs	Disease Duration, yrs	Renal Biopsy, (WHO Class)	Previous Cytotoxic Therapy
1/CHLA	F	AA	16.0	12.3	3.7	IV	Oral and IV CyP
2/CHLA	F	AA	16.4	12.2	4.2	IV	AZA-IV CyP
3/CHLA	F	AA	17.0	10.8	6.2	IV	AZA-IV CyP
4/CHSD	M	H	16.1	15.3	0.8	V	—
5/CHSD	F	H	13.3	11	2.3	V	—
6/CHSD	F	H	14.2	13.4	0.8	V	—
7/LRCH	M	AA	16.8	9	7.8	V+III	AZA-IV CyP
8/LRCH	F	W	14.3	12.8	1.5	III	Oral MTX
9/LRCH	F	W	13.8	12.9	0.9	Interstitial nephritis	—
10/LRCH	F	H	14.4	13	1.4	III	—
11/CHUWM	F	W	15	12.8	2.2	Diffuse sclerosis	IV CyP

W: white; AA: Afro-American; H: Hispanic; CyP: cyclophosphamide; AZA: azathioprine; MTX: methotrexate. CHLA: Children's Hospital Los Angeles; CHSD: Children's Hospital San Diego; LRCH: La Rabida Children's Hospital; CHUWM: Children's Hospital University of Wisconsin-Madison. WHO: World Health Organization.

Table 2. Treatment during the study.

Study No./ Patient-Center	MMF Dose (mg/kg/day and total dose)	Treatment Duration, months	Cumulative Dose, Total g	Concomitant Medications	Prednisone Starting Dose, mg/day	Prednisone Ending Dose, mg/day
1/CHLA	19.4 (1 g bid)	15	900	Pred-HCQ	10	0
2/CHLA	17.6 (1 g bid)	(2)[a] 3	180	Pred-HCQ	15	5
3/CHLA	20.6 (1 g bid)	13	780	Pred-HCQ	10	10
4/CHSD	35 (1.25 g+1 g)	11	743	Pred-HCQ	100 qod	7.5 qod
5/CHSD	35 (1 g bid)	10	600	Pred-HCQ	120 qod	30 qod
6/CHSD	42 (1 g bid)	9	540	Pred-HCQ	70 qod	15 qod
7/LRCH	22 (0.75 g bid)	8	360	Pred	30	15
8/LRCH	21.7 (0.25 qd to 0.75 bid)	17	600	Pred-HCQ	20+ weekly MP pulses	5+ monthly MP pulses
9/LRCH	20.0 (0.75 bid)	6	270	Pred	30	15
10/LRCH	17.5 (0.75 bid)	7	315	Pred	20+ weekly MP pulses	5+ monthly MP pulses
11/CHUWM	17.1 (0.75 g+0.5 g)	7	262.5	Pred	15	2.5

[a] Patient 2 temporarily discontinued treatment due to herpes zoster virus cerebritis (see side effects). CHLA: Childrens Hospital Los Angeles; CHSD: Children's Hospital San Diego; LRCH: La Rabida Children's Hospital; CHUWM: Children's Hospital University of Wisconsin-Madison. Pred: prednisone; HCQ: hydroxychloroquine. MP: IV methylprednisolone.

1/11 (0.10). Patients 8 and 10 were able to decrease weekly methylprednisolone treatment to monthly pulses (Table 2).

Adverse events. MMF was overall well tolerated and only one patient discontinued MMF due to an adverse event. The most frequent adverse events included infections: one (patient 2) became leukopenic after 2 months of treatment (white blood cell count, WBC, 1100/mm^3) and developed a herpes zoster virus infection with cerebritis. MMF was discontinued. The patient recovered and MMF was restarted 5 months after the infection with no further complications. A second patient (patient 8) presented with oral thrush in the context of leukopenia (WBC 2400/mm^3) and required a gradual taper of MMF from 0.75 bid to 0.25 g qd. Infections possibly related to MMF were reported in 2 other children. One had necrotizing lymphadenitis and another a re-infection of a jaw cyst.

In addition, 4 children complained of nausea, one child complained of itching and fatigue, one complained of headaches, and another of transient generalized body aches.

In general the adverse events did not seem to be dose related.

DISCUSSION

Traditional treatment of children with severe lupus glomerulonephritis combines corticosteroids with immunosuppressive drugs such as azathioprine and cyclophosphamide. Despite clinical effectiveness in most children, potential serious toxicity and longterm adverse events limit the use of

Table 3. Disease activity variables at start of MMF therapy and at last followup.

Study No./ Patient-Center	Anti dsDNA[a]*		C3/C4 (mg/dl)[b]		SLEDAI Score[c]	
	Start	End	Start	End	Start	End
1/CHLA	Neg	Neg	122/28	165/26	6	4
2/CHLA	156	66	128/30	189/37	2	2
3/CHLA	> 590	> 590	112/17	75/10	30	12
4/CHSD	Neg	Neg	49/9	117/28	10	0
5/CHSD	160	Neg	60/< 10	79/12	8	2
6/CHSD	Neg Sm > 100	Neg Sm Neg	23/< 10	88/15	10	2
7/LRCH	Neg	Neg	120/41	163/52	5	0
8/LRCH	551	Neg	93/13	101/18	12	2
9/LRCH	Neg	Neg	138/25	97/24	6	0
10/LRCH	Neg	160	121/23	83/11	11	11
11/CHUWM	Neg	Neg	114/16	98/19	6	2

[a] Modified Farr assay (< 50 = negative); Sm: anti-Smith antibodies
[b] Serum complement (normal values: C_3 86–184 mg/dl, C_4 22–59 mg/dl)
[c] SLEDAI: 24 descriptors grouped into 9 organ systems, each descriptor ranging from 1 to 8, with a total maximum possible score of 105.
CHLA: Childrens Hospital Los Angeles; CHSD: Children's Hospital San Diego; LRCH: La Rabida Children's Hospital; CHUWM: Children's Hospital University of Wisconsin-Madison.

Table 4. Renal function at the start of MMF therapy and at last followup.

Study No./ Patient-Center	24 h Urine Protein g/24 h		Creatinine Clearance, ml/min		Serum Creatinine, mg/dl	
	Start	End	Start	End	Start	End
1/CHLA	3.4	6.1	72.9	58.2	1.4	1.7
2/CHLA	0.5	0.5	12	30.2	1.8	2.3
3/CHLA	2.6	3.7	84	72	1.2	1.4
4/CHSD	2.6	0.1	90	120	1.4	0.7
5/CHSD	1.4	0.3	70	88	0.8	0.6
6/CHSD	3	0.2	80	120	1.0	0.6
7/LRCH	6.4	0.3	71	73	0.8	0.8
8/LRCH	0.2	0.2	92	142	0.3	0.5
9/LRCH	0.16	0.16	40	107	1.3	0.9
10/LRCH	ND	0.17	78	80	0.6	0.6
11/CHUWM	0.84	0.16	48	40	1.4	1.4

ND: not done.
CHLA: Childrens Hospital Los Angeles; CHSD: Children's Hospital San Diego; LRCH: La Rabida Children's Hospital; CHUWM: Children's Hospital University of Wisconsin-Madison.

these agents. In addition, a significant proportion of children have an inadequate renal response, underscoring the need for alternative therapeutic agents[13–14].

Clinical studies with mycophenolate mofetil, initially approved for the prevention of renal allograft rejection, have demonstrated that rejection rates in renal transplant patients with 2–3 g of daily MMF were lower than with azathioprine[19–21]. Adverse events included leukopenia and/or pancytopenia, gastrointestinal complaints such as nausea, diarrhea, gastritis, esophagitis, duodenal ulcer, pancreatitis, stomatitis, and alopecia. Central nervous system toxicity such as confusion, asthenia, and infections with cytomegalovirus or herpes simplex virus have also been reported[22,29,30].

The short term clinical superiority of MMF over cyclosporine A in glomerular disease complicated by nephrotic syndrome and/or renal insufficiency has been suggested[22]. Briggs, *et al* reported a substantial reduction in proteinuria, stabilization of serum creatinine and a potential steroid-sparing effect in 8 patients treated with MMF at a dose range of 0.75 to 1 g bid alone or in combination with low dose steroids. Dooley, *et al* described the efficacy of MMF/prednisone combination therapy in controlling major renal manifestations of SLE in 12 patients with resistant or relapsing DPGN following cyclophosphamide (CyP) therapy[23]. A significant reduction of serum creatinine, proteinuria, urine-creatinine ratio, and an improvement in

serum C3 and anti-dsDNA antibody levels was observed in most patients. Adverse events included leukopenia, in one case associated with a severe herpes simplex stomatitis, thinning of scalp hair, pneumonia without leukopenia, and one case of recurrent pancreatitis that led to discontinuation of MMF.

We report here the first clinical experience in 11 children treated with MMF for refractory lupus nephritis over a mean of 9.8 months (range 3 to 17). Although the children presented with different types of nephritis at onset, most were resistant to traditional immunosuppressive therapy (CyP and azathioprine) and required ongoing high dose steroids.

Our study demonstrates that MMF at a dose range of 1.25 to 2.25 g/day was fairly well tolerated and resulted in a marked reduction of disease activity, assessed through the SLEDAI score. MMF allowed a steroid taper in 6/11 children, without deterioration or, indeed, with improvement of renal function and disease activity, confirming that MMF has a considerable steroid sparing effect. Unfortunately, we also observed worsening of renal function or disease activity variables in 4 patients during steroid taper.

Of note a complete response to treatment was achieved in all 3 children with membranous glomerulonephritis with substantial reduction in proteinuria and serum creatinine, increase in creatinine clearance, marked reduction in autoantibody formation, and increased serum complement levels. MMF may therefore be a valuable alternative to steroids, azathioprine, and cyclosporine A in this subset of patients. This observation is even more important since disease course and outcome vary in children with membranous glomerulonephritis, and optimal treatment is controversial. In addition a complete response to therapy was observed in one child presenting with mixed membranous and proliferative lesions in the renal biopsy, a feature that seems to be associated with a higher risk of renal disease progression[31-32].

In contrast, efficacy of MMF in children with diffuse proliferative glomerulonephritis appeared less favorable than reported by studies in adults[22-23]. Despite an improvement in the SLEDAI scores, we observed deterioration in renal function in all 3 children presenting with DPGN. During the prednisone taper serum creatinine increased in all patients and proteinuria worsened or remained stable.

Eight children (73%) experienced one or more adverse events, that were possibly related to MMF. Infections were observed in 4 children (36%), in one case requiring a temporary discontinuation of MMF. Leukopenia was observed in 2 children (18%) and minor side effects in 5 children (45%). Opportunistic infections were presumably caused by increased immunosuppression, possibly related to MMF. Unfortunately, our cohort is too small to draw any further meaningful conclusions.

In summary, we conclude that MMF may represent a valuable alternative to traditional cytotoxic agents in the treatment of renal disease of pediatric SLE. In our small cohort of children, MMF had a notable effect on membranous glomerulonephritis, but not on DPGN. MMF acted as a steroid sparing agent, which is of particular importance for children. Infections were frequently observed and may limit the use of this agent in some patients. The small patient number and the non-controlled nature of the study limit the reliability of our results. Controlled, prospective, randomized pediatric trials are needed to investigate the efficacy and safety of MMF in selected subsets of children with lupus nephritis.

REFERENCES

1. Gare BA. Epidemiology of rheumatic disease in children. Curr Opin Rheumatol 1996;8:449-54.
2. Tucker LB, Menon S, Schaller JG, et al. Adult and childhood onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol 1995;34:866-72.
3. Donadio JV, Hart GM, Bergstrahl EJ, et al. Prognostic determinations in lupus nephritis: a long-term clinicopathologic study. Lupus 1995;4:109-15.
4. Graham TB, Lovell DJ. Outcome in pediatric rheumatic disease. Curr Opin Rheumatol 1997;9:434-9.
5. Cameron JS. Lupus nephritis in childhood and adolescence. Pediatr Nephrol 1994;8:230-49.
6. Valeri A, Radhakrishnan J, Estes D, D'Agati V, Pirani C, Appel GB. Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: A prospective five-year study. Clin Nephrol 1994; 42:71-8.
7. Boumpas DT, Austin HA, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992; 340:741-5.
8. Lehman TJ, Sherry DD, Wagner-Weiner L, McCurdy DK, Emery HM, Magilavy DB. Intermittent intravenous cyclophosphamide therapy for lupus nephritis. J Pediatr 1989;114:1055-60.
9. Austin HA, Klippel JH, Balow JE, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-9.
10. Silverman E: What's new in the treatment of pediatric SLE? J Rheumatol 1996;23:1657-60.
11. Austin HA, Balow JE: Natural history and treatment of lupus nephritis. Semin Nephrol 1999;19:2-11.
12. Boumpas DT, Austin HA, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: Emerging concepts. Part I. Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. Ann Intern Med 1995;122:940-50.
13. Dooley MA, Hogan S, Jennett CJ, Falk RJ. Cyclophosphamide therapy for lupus nephritis: Poor renal survival in black Americans. Kidney Int 1997;51:1188-95.
14. Austin AH 3rd, Boumpas DT, Vaughan EM, Balow JE. High-risk features of lupus nephritis: Importance of race and clinical and histological factors in 166 patients. Neprhol Dial Transplant 1995;19:1670-8.
15. Yocum DE. Cyclosporine, FK-506, rapamycin and other immunomodulators. Rheum Dis Clin N Am 1996;22:133-53.
16. Burkhardt H, Kalden JR. Xenobiotic immunosuppressive agents: therapeutic effects in animal models of autoimmune diseases. Rheumatol Int 1997;17:85-90.
17. Eugui EM, Almquist S, Muller CD, Allison AC: Lymphocyte selective cytostatic and immunosuppressive effects of

mycophenolic acid in vitro: Role of deoxyguanosine nucleotide depletion. Scan J Immunol 1991;33:161-73.
18. Corna D, Morigi M, Facchinetti D, Bertani T, Zoja C, Remuzzi G. Mycophenolate mofetil limits renal damage and prolongs life in murine lupus autoimmune disease. Kidney Int 1997;51:1583-9.
19. Sollinger HW, for the US. Renal Transplant Mycophenolate Mofetil Study Group: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995;60:225-32.
20. European Mycophenolate Mofetil Cooperative Study Group: Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and glucocorticoids for prevention of acute rejection. Lancet 1995;345:1321-5.
21. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group: A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996;61:1029-37.
22. Briggs WA, Choi MJ, Scheel P. Successful mycophenolate mofetil treatment of glomerular disease. Am J Kidney Dis 1998;31: 213-7.
23. Dooley MA, Cosio FG, Nachman PH, et al. Mychophenolate mofetil therapy in lupus nephritis: Clinical observations. J Am Soc Nephrol 1999;10:833-9.
24. Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. Clin Exp Rheumatol 1993;11 Suppl:S117-S119.
25. Zimmer-Molsberger B, Knauf W, Eckhard T. Mycophenolate mofetil for severe autoimmune hemolytic anemia. Lancet 1997;350:1003-4.
26. Nowack R, Birck R, van der Woude FJ. Mycophenolate mofetil for systemic vasculitis and IgA nephropathy (letter). Lancet 1997;349:774.
27. Tan EM, Cohen AS, Fries J. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
28. Bombardieri C, Gladman DD, Urowitz Mb, Caron D, Chang CH, and the Committee on Prognosis Studies in SLE: Derivation of the SLEDAI: a disease activity index for lupus patients. Arthritis Rheum 1992;35:630-40.
29. Pirsh JD, Sollinger HW. Mycophenolate mofetil: Clinical and experimental experience. Ther Drug Monit 1996;18:357-61.
30. McDiarmid SV: Mycophenolate mofetil in liver transplantation. Clin Transpl 1996;10:140-5.
31. Sloan RP, Schwartz MM, Korbet SM, Borok RZ. Long-term outcome in systemic lupus erythematosus membranous glomerulonephritis. Lupus Nephritis Collaborative Study Group. J Am Soc Nephrol 1996;7:299-305.
32. Balow JE, Boumpas DT, Austin HA. Systemic lupus erythematosus and the kidney. Chapter 81. In: Lahita RG, editor. Systemic lupus erythematosus, 3rd ed. Churchill Livingstone: New York; 1998.