Pediatr Nephrol (2005) 20:1376–1381
DOI 10.1007/s00467-005-1964-z

EDITORIAL COMMENTARY

Asha Moudgil · Arvind Bagga · Stanley C. Jordan

Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions

Received: 18 October 2004 / Revised: 5 April 2005 / Accepted: 21 April 2005 / Published online: 24 June 2005

Abstract Clinicians are often faced with therapeutic dilemmas and challenges while treating children with frequently relapsing steroid-dependent nephrotic syndrome (SDNS) and steroid-resistant nephrotic syndrome (SRNS). In the past, children with SDNS have been treated with long-term alternate day steroids cyclophosphamide, cyclosporine (CSA), chlorambucil, levamisole, and azathioprine. The essential aim of these therapies is to maintain remission while limiting exposure to steroids. These medications have variable efficacy and undesirable toxicity profiles. Recently, mycophenolate mofetil (MMF) has emerged as a new therapeutic option for the management of SDNS in a few uncontrolled clinical trials. Preliminary data are encouraging. MMF was found to be useful in maintaining remission and has a steroid-sparing effect. Clearly, more data are needed to further characterize the safety and efficacy of MMF, define adequate length of treatment, and optimize drug exposure and monitoring. The management of SRNS is primarily aimed at decreasing proteinuria and inducing remission, if possible. By doing so, one would aim to preserve renal function. CSA therapy is known to be useful in this regard but has undesirable side effects, the most concerning being nephrotoxicity. MMF in combination with steroids and angiotensin-converting enzyme-inhibitor drugs is known to have some efficacy in the management of SRNS. These preliminary data have prompted the National Institutes of Health to sponsor a multicentric controlled trial to compare the safety and efficacy of MMF with that of CSA in the treatment of steroid-resistant focal segmental glomerulosclerosis (FSGS). If MMF therapy is found to be efficacious, it would help obviate the need for CSA and its associated nephrotoxicity. Clearly, MMF has emerged as an important new therapeutic option for the treatment of childhood nephrotic syndrome and FSGS. Further data are required to assess those conditions most likely to respond.

Keywords Nephrotic syndrome · Focal segmental glomerulosclerosis · Mycophenolate mofetil · Steroid dependence · Steroid resistance · Chronic renal failure

A. Moudgil
Divisions of Pediatric Nephrology,
Children's National Medical Center,
Washington, DC, USA

A. Bagga
All India Institute of Medical Sciences,
New Delhi, India

S. C. Jordan (✉)
David Geffen School of Medicine at UCLA,
Cedars-Sinai Medical Center,
8635 W. 3rd St., Suite 590, Los Angeles, CA, 90048, USA
e-mail: sjordan@cshs.org
Tel.: +1-310-4238282
Fax: +1-310-4230234

Introduction

Approximately 80% of children presenting with an initial episode of nephrotic syndrome respond to steroids (steroid sensitive) whereas another 20% do not respond and are considered as steroid resistant [1]. Of children with steroid-sensitive nephrotic syndrome, 50–60% become frequently relapsing to steroid-dependent nephrotic syndrome (SDNS) on follow-up. Children with SDNS and steroid-resistant nephrotic syndrome (SRNS) pose therapeutic challenges, albeit of somewhat different nature. The standard therapy for these conditions has not changed in more than two decades with the exception of the introduction of cyclosporine A (CSA) [2, 3, 4]. Although useful, CSA therapy is associated with a significant side-effect profile, the most concerning of which are the potential for nephrotoxicity and development of CSA dependence. Clearly, better alternative therapies with improved efficacy and fewer side effects are desirable.

Steroid-dependent nephrotic syndrome

The majority of children with SDNS show minimal change in lesions on histologic examination, and a small

number may show focal segmental sclerosis (FSGS), mesangial proliferation (MesPGN), and other histologic lesions [5]. Therapies employed in the past to treat SDNS have included long-term alternate-day prednisone, oral cyclophosphamide, chlorambucil, levamisole, CSA, and tacrolimus [6, 7]. Recently, mycophenolate mofetil (MMF) was shown to be useful in the management of these children [8, 9, 10, 11].

Long-term alternate-day prednisone in tapering doses has been the mainstay of therapy for a few decades. Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN) was first to show that prolongation of steroid therapy for the initial episode to 12 weeks rather than 8 weeks, as proposed by the International Study of Kidney Disease in Children (ISKDC), is usually associated with more durable remissions [12]. Recently, Hiraoka et al. have also shown that prolonged therapy for the initial episode of nephrotic syndrome with 4 weeks of daily prednisone and then tapering doses of alternate-day prednisone for 6 months was associated with more cumulative remissions in children younger than 4 years of age [13]. While long-term alternate prednisone therapy has the best track record in the management of frequently relapsing steroid-sensitive nephrotic syndrome, it is usually not the most acceptable therapy to the patients. Long-term steroid therapy is complicated by side effects such as excessive weight gain, cushingoid features, altered body habitus, hypertension, growth retardation, glucose intolerance, cataracts, mood changes, decreased bone mineralization in growing children, acne, and hirsutism. Cosmetic features are particularly unacceptable to teenagers in an ever-growing body-image-conscious society. This becomes particularly difficult in steroid-dependent children. Thus, alternate therapies are desireable.

Oral cyclophosphamide therapy for 8–12 weeks can induce long-term remission in 25–60% of children with frequently relapsing and SDNS [14]. The results are less beneficial in children with steroid-dependent type [15]. Side effects include marrow suppression and increased risk of infections. Usually, there are no long-term side effects of limited cyclophosphamide therapy. Repeated courses are fraught with dangers of marrow suppression, gonadal toxicity, hemorrhagic cystitis, alopecia, and increased risk of malignancy. Gonadal toxicity is more marked in males. These side effects are dependent upon the cumulative dose of cyclophosphamide used [16]. Therefore, repeated courses of cyclophosphamide are not desirable and should be avoided. Chlorambucil has similar efficacy and side-effect profile [17].

Since early 1990, CSA has emerged as a useful therapy in children with frequently relapsing and SDNS. About 80% of these children respond to CSA, and steroids can be tapered off. A minority of children may need a small dose of steroids in addition to CSA to keep them in remission. However, CSA withdrawal is usually associated with disease relapses in 90% of children, necessitating reinstitution of cyclosporine [18]. Long-term CSA therapy is associated with a number of side effects that include nephrotoxicity, hypertension, cosmetic side effects (hirsutism, gum hyperplasia), tremors, glucose intolerance, dyslipidemia, hyperkalemia, increased risk of infections, and increased potential for malignancy. Nephrotoxicity is related to the dose and duration of CSA therapy and the extent of proteinuria [19]. In limited uncontrolled studies, tacrolimus (FK 506) was shown to be effective in the treatment of SDNS [20, 21]. Tacrolimus has a similar side effect profile to CSA except for reduced cosmetic side effects and slightly decreased incidence of nephrotoxicity, hypertension, and dyslipidemia. However, its use is associated with an increased incidence of diabetes compared to CSA [22].

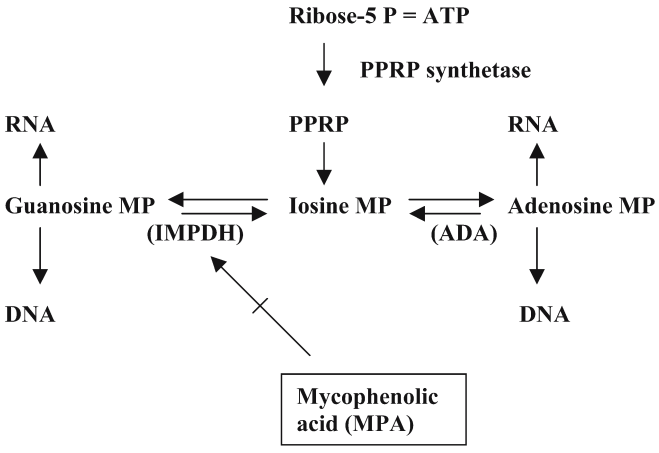

Fig. 1 Inhibition of de novo purine synthesis by mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MMF). *PPRP* phosphoribosyl triphosphate, *ADA* adenosine deaminase, *IMPDH* inosine monophosphate dehydrogenase

Levamisole has a marginally beneficial effect on the course of children with frequently relapsing and SDNS. It has steroid sparing properties with a rather safe side effect profile. However, most children tend to relapse upon discontinuation of the drug [23, 24, 25]. Vasculitis is a known side effect of the drug that is usually reversible on drug discontinuation [26]. This drug is unfortunately not available in the US market. Azathioprine was not found to be useful in the treatment of frequently relapsing and SDNS in early trials in the 1970s [27]. There was renewed interest in the drug, but limited beneficial effects were seen [28].

MMF is a prodrug of mycophenolic acid that is rapidly absorbed following oral administration and is hydrolyzed to form mycophenolic acid (MPA). MPA, the active metabolite of MMF, is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an enzyme required for de novo purine synthesis (Fig. 1). MPA inhibits T- and B-lymphocyte proliferation, as these cells are critically dependent upon de novo purine synthesis for their proliferation whereas other cell types can utilize salvation pathways for purine synthesis. MPA also prevents glycosylation of lymphocyte and monocyte glycoproteins that are involved in the intercellular adhesion of leukocytes to endothelium [29]. MPA may induce lymphocyte apoptosis and alter

cell-surface adhesion molecules and cytokine gene expression [30].

Since its FDA approval in 1995 for use in renal transplantation, considerable interest has arisen regarding the potential benefits of MMF in the treatment of immune-mediated glomerular diseases, including childhood nephrotic syndrome [8, 9, 10, 11, 31, 32, 33, 34, 35, 36, 37]. We recently reported a study on the beneficial effects of MMF in 19 children (ten with minimal change, three with FSGS, and six not biopsied) with SDNS [10]. Patients with two consecutive relapses of nephrotic syndrome while receiving prednisolone at a dose of 1.5 mg/kg on alternate days or within 15 days of its discontinuation were defined as SDNS. The initial therapy of SDNS comprised long-term treatment with tapering doses of alternate-day prednisolone. Patients requiring prednisolone dosage of more than 0.5 mg/kg on alternate days or/and features of steroid toxicity were treated using levamisole or cyclophosphamide. Those who continued to show SDNS despite therapy with levamisole and/or cyclophosphamide were considered for treatment with MMF. These children were a group of very difficult nephrotics who were previously treated with a long course of alternate-day steroids (19/19), cyclophosphamide (15/19, four with more than one course), and levamisole (16/19) before treatment with MMF. On an average, these children had 6.6 relapses/year preceding MMF therapy. During 12 months of MMF therapy, the relapse rate decreased to two relapses per year, and cumulative doses of steroids decreased from 0.7 mg/kg per day to 0.3 mg/kg/day ($p<0.01$). Five patients had transient abdominal pain. None had diarrhea, vomiting, leukopenia, or thrombocytopenia. The frequency of serious systemic infections before, during, and after MMF therapy was similar. Therapy was well tolerated, and no patient had to stop therapy because of side effects. Unfortunately, the effect was not always sustained. The number of relapses increased to 4.2 per year following cessation of MMF, and the cumulative dose of steroids increased to 0.4 mg/kg per day.

This is an interesting preliminary study, and a number of important questions arise:

1. *Effect of MMF in different racial groups:* This study was carried out in India with a rather homogeneous Asian population. How the results will translate to the other racial groups remains to be seen. People of African descent need a higher dose of MMF to achieve protection from rejection in allograft recipients [38]. It is possible, therefore, that children of African descent may require a higher dose in treatment of frequently relapsing and SDNS.
2. *Optimal duration of MMF therapy:* How long one should treat with MMF is not known. In this study, treatment with MMF was carried out for 12 months. It is possible that prolonged therapy for a few years may have a more sustained effect (we know 12 months is not enough) and needs to be investigated. How long is too long for a sustained effect to be aquired needs to be determined since unnecessary prolongation of therapy may cause undue risks associated with immunosuppression. Monitoring for viral infections and other parameters associated with excess immunosuppression may minimize this risk.
3. *Timing of MMF therapy in relation to the onset of nephrotic syndrome:* In this study, patients were treated with alternate therapies for over a year prior to institution of MMF. Whether treatment with MMF earlier in the course of nephrotic syndrome will alter the course of steroid dependence is not known. The repeated episodes of massive proteinuria induce fibrotic changes in the tubulointerstitial compartment that may not be beneficial for long-term renal survival [39].

In another study of seven children with frequently relapsing nephrotic syndrome [six with minimal-change nephrotic syndrome (MCNS) and one with FSGS] in Europe, MMF was found to be beneficial [11]. These children were steroid sensitive and had been previously treated with CSA for a mean of 67.4 months. All had evidence of CSA nephrotoxicity as determined by decrease in glomerular filtration rate (GFR), decreased effective renal plasma flow (ERPF), and changes on renal biopsy. In five of six children with MCNS, no relapses were seen whereas one patient with low MPA levels showed a relapse. CSA could be discontinued in all six children with MCNS with an improvement in GFR and ERPF. These children have been on MMF therapy for a mean of 25.4 (15.3–39) months with no significant side effects. As expected, the renal histologic changes were not reversible. In one patient with FSGS, CSA therapy could be reduced successfully with institution of MMF, and the child went into complete remission that persisted over a follow-up of 28 months. At least in this pilot study, MMF seems to be promising in sustaining remission in children with frequently relapsing MCNS and partially reversing decline in ERPF and GFR. This study raises an interesting question of adjusting MMF dose by monitoring MPA levels, at least in some children not showing a desired response.

Barletta et al. treated ten children with CSA-dependent nephrotic syndrome with MMF. Four of these children had evidence of CSA toxicity, and eight showed evidence of tubulointerstitial fibrosis. They were able to completely taper CSA in five children after 1–2 years and both CSA and MMF in one patient. In a group of four children with SDNS where CSA was not used, MMF did not decrease frequency of relapses [34]. In this small, single-center, uncontrolled experience, MMF therapy in patients with CSA-dependent nephrotic syndrome appeared to be effective in reducing CSA exposure and significantly decreasing the frequency of relapses whereas MMF was not useful in children with SDNS in whom CSA was not used.

Ulinski et al. from France recently reported their results in nine children with SDNS and SRNS who were treated with MMF [35]. These children were on treatment with CSA and had shown a decrease in their GFR as measured

by inulin clearance. MMF was introduced progressively until the full dose of 1 gm/1.73 m^2 twice daily was reached. CSA treatment was stopped after introduction of MMF. Steroid dose was reduced if possible. After a median follow-up of 261 days, no adverse effects of MMF, such as diarrhea or hematologic abnormalities, were noted. After switch from CSA to MMF, the children with SDNS remained in remission and children with SRNS had no significant change in their residual proteinuria. The GFR improved from 76.9+4.8 to 119.9+5.9 ($p<0.001$). Oral steroid dose could be reduced from a median of 0.85 mg/kg per day pre-MMF to 0.29 mg/kg per day. This single-center, small, preliminary study shows beneficial effects of MMF in this group of patients showing decreased GFR on treatment with CSA; MMF therapy resulted in improvement of GFR, had a steroid-sparing effect, and maintained remission without causing any adverse effects. Since the follow-up interval was rather short, long-term efficacy and side effects of MMF therapy in this group of patients cannot be commented upon.

Recommendations

As MMF holds therapeutic promise in a small number of uncontrolled trials, prospective, randomized, controlled trials are needed to compare the efficacy and safety of MMF with CSA in frequently relapsing and SDNS. In our opinion, until more data become available, clinicians may want to use MMF in frequently relapsing and SDNS before trying CSA. If useful, it will obviate CSA nephrotoxicity and other undesired side effects. If not found to be helpful after 4–6 months, it is unlikely to be beneficial and MMF should be discontinued. As appropriate duration of treatment with MMF is undetermined, it will need to be tailored in individual patients. Given the accumulating data regarding efficacy and safety of MMF therapy in other autoimmune diseases, it seems likely that long-term use of MMF may be safe in children with SDNS and offer a less-toxic alternative to current therapies [40].

Steroid-resistant nephrotic syndrome

Children with SRNS pose the most difficult therapeutic challenge. These children are at risk of complications of unremitting nephrotic syndrome as well as developing end-stage renal disease (ESRD). Most children with SRNS have FSGS as the underlying lesion. Some may have MCNS, mesangial proliferative glomerulonephritis, or other lesions [1]. The rate of progression to ESRD is faster in African American and Hispanic children compared with Caucasians [41, 42]. Treatment options include high doses of pulse steroids with a combination of cyclophosphamide or chlorambucil. This regimen has met with variable success rates of inducing remission ranging from 10% to 70% [43, 44, 45, 46, 47, 48]. Many patients exhibit features of severe steroid toxicity. This regimen has been found to be less effective in African American children [48]. Prolonged pulses of IV cyclophosphamide over a few months induced remission in 25–60% of children with SRNS [48, 49, 50]. CSA reduces proteinuria in 50–70% children with SRNS and is used most commonly [4, 5].

MMF has been used in a few children with SRNS with FSGS [32]. It was shown to decrease proteinuria, increase serum albumin, and decrease serum cholesterol although complete remission was not achieved. These patients were pretreated with three pulses of Solumedrol prior to initiation of MMF therapy. Angiotensin-converting enzyme (ACE) inhibitors decrease proteinuria by about 50% in children with SRNS [52, 53]. Based on these uncontrolled findings, the National Institutes of Health has initiated a prospective, randomized, multicentric, controlled trial to compare CSA with a combination of pulse oral dexamethasone and MMF in steroid-resistant children and young adults with FSGS. Both groups will receive low-dose alternate-day prednisone and an ACE inhibitor. This study should answer questions regarding the efficacy of MMF in combination with steroids and ACE inhibitors in SRNS when compared with CSA. Unfortunately, this study does not include patients with SRNS who do not have an established diagnosis of FSGS. It is possible that some patients with FSGS may need a combination of CSA and MMF. However, this study is not intended to answer that question.

Future concepts for the use of MMF

Pharmacokinetic monitoring

Although initial reports suggested inter-individual variability of MPA to be rather low, more recent data have shown extensive variability at fixed-dose treatment [54]. Clinical trials have shown a strong correlation between plasma MPA levels and the likelihood of developing an acute rejection after kidney transplantation [55]. Pharmacokinetic data on MMF are limited in children, and most data are centered on pediatric renal transplant recipients [56]. Area under the curve (AUC) 0–12 h of free MPA in children receiving a dose of 1,200 mg/m^2 per day in two divided doses corresponds to adults receiving 2 gm/day of MMF. Pharmacokinetics of MMF will need to be evaluated, especially in children with nephrotic syndrome. Hypoalbuminemia may alter the free MPA level and therefore affect toxicity and efficacy [57]. Glucocorticoids stimulate hepatic glucuronyl transferase, the key enzyme for the metabolism for MPA. Therefore, concomitant administration of glucocorticoids may affect MPA levels [58].

Pharmacodynamic monitoring

Large interindividual differences exist in baseline IMPDH enzyme activity. It is conceivable that the variability in the baseline IMPDH activity is caused by genetic differ-

ences in the IMPDH gene. The in vitro assessment of IMPDH activity and the analysis of cell-surface markers in activated T cells may be some of the newer pharmacodynamic approaches to further optimize MMF therapy [55].

Conclusions

In summary, early experience at single centers with MMF has shown benefit in children with frequently relapsing SDNS and SRNS, and its use may provide a steroid-sparing effect. However, of equal importance is a more benign side effect profile of MMF compared with currently available alternate choices of prednisone and CSA. Its use is not associated with abnormalities of lipid and carbohydrate metabolism, organ toxicity (nephrotoxicity, hepatotoxicity, and neurotoxicity), or body disfigurement. Future studies will have to address a number of questions and concerns: (1) Results will need to be validated in large controlled studies. (2) Optimal duration of MMF therapy and when and how to withdraw treatment in relapse-free patients will need to be determined. (3) Its efficacy in different racial groups and histologic subtypes will need to be studied. (4) The best way to monitor its efficacy and tailor its dose in individuals with varying circumstances, such as hypoalbuminemia, renal insufficiency, and use of concomitant drugs, needs to be determined. Clearly, the therapeutic potential of MMF needs more intensive investigation. It is not the only answer to treatment of childhood nephrotic syndrome but represents a new alternative with the potential to reduce side effects of existing agents that have been used for decades.

References

1. Churg J, Habib R, White RHR (1970) Pathology of nephrotic syndrome in children: a report for the International Study of Kidney Disease in Children. Lancet 760:1299–1302
2. Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, Zacchello G, Confalonieri R, Altieri P (1993) Cyclosporine versus cyclophosphamide for patients with steroid dependent and frequently relapsing idiopathic nephrotic syndrome: a multicenter randomized controlled trial. Nephrol Dial Transplant 8:1326–1332
3. Inoue Y, Iijima K, Nakamura H, Yoshikawa N (1999) Two-year cyclosporine treatment in children with steroid dependent nephrotic syndrome. Pediatr Nephrol 13:33–38
4. Cattran DC. Appel GB. Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, Maxwell DR, Kunis CL for the North America Nephrotic Syndrome Study Group (1999) A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis Kidney Int 56:2220–2226
5. Habib R, Klein knechtle (1971) The primary nephrotic syndrome of childhood-classification and clinicopathologic study of 406 cases. Path Annu 6:417–474
6. Durkan AM, Hodson EM, Willis NS, Craig JC (2001) Immunosuppressive agents in childhood nephrotic syndrome: A meta-analysis of randomized controlled trials. Kidney Int 59:1919–1927
7. Filler G (2003) Treatment of nephrotic syndrome in children and controlled trials. Nephrol Dial Transplant [Suppl 6]:75–7810
8. Choi MJ, Eustacew JA, Gimenez LF, Atta MG, Scheel PJ, Sothinathan R, Briggs WA (2002). Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int 61:1098–1114
9. Chandra M, Susin M, Abitbol C (2000) Remission of relapsing childhood nephrotic syndrome with mycophenolate mofetil. Pediatr Nephrol 14:224–226
10. Bagga A, Hari P, Moudgil A, Jordan SC (2003) Mycophenolate mofetil and prednisolone therapy in steroid dependent nephrotic syndrome. Am J Kidney Dis 42:1114–1120
11. Gellermann J, Querfeld U. Frequently relapsing nephrotic syndrome: treatment with mycophenolate mofetil (2004) Pediatr Nephrol 19:101–104
12. Ehrlich JH, Brodehl J (1993) Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. Eur J pediatr 152:357–61
13. Hiraoka M, Tsukahara H, Matsubara K, Tsurusawa M, Takeda N, Haruki S, Hayashi S, Ohta K, Momoi T, Ohshima Y, Sugunuma N, Mayumi M, for the West Japan Cooperative Study of Kidney Disease in Children (2003) A randomized study of two long- course prednisolone regimens for nephrotic syndrome in children. Am J Kidney Dis 41:1155–1162
14. Vester U, kranz B, Zimmerman S, Hoyer PF (2003) Cyclophosphamide in steroid-sensitive nephrotic syndrome: outcome and outlook. Pediatr Nephrol 7:661–664
15. Donia AF, Gazareen SH, Ahmed HA, Shoeib AA, Ismail AM, Khamis S, Sobh MA (2003) Pulse cyclophosphamide inadequately suppresses reoccurrence of minimal change nephrotic syndrome in corticoid dependent children. Nephrol Dial Transplant 10:2054–2058
16. Blumenfeld Z, Dann E, Avivi I, Epelbaum R, Rowe JM (2002) Fertility after treatment for Hodgkin's disease. Ann Oncol 13 [Suppl 1]:138–147
17. Niaudet P (1992). Comparison of cyclosporine and chlorambucil in the treatment of steroid-dependent nephrotic syndrome: a multicentric randomized controlled trial. The French Society of Paediatric Nephrology. Pediatr Nephrol 6:1–3
18. Habashi D, Hodson E, Craig J (2004) Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane database system review 2: CD 003594
19. Iijima K, Hamashira K, Tanaka R, Kobayashi A, Nozu K, Nakamura H, Yoshikawa N (2002) Risk factors for cyclosporine-induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. Kidney Int 61:1801–1805
20. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE (1993) Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome. Nephrol Dial Transplant 11:1286–1290
21. Schweda FLiebl R, Riegger GA, Kramer BK (1997) Tacrolimus treatment for steroid- and cyclosporine- resistant minimal change nephrotic syndrome. Nephrol Dial Transplant 12:2433–243
22. Moxey-Mims MM, Kay C, Light JA, Kher KK (1998) Increased incidence of insulin dependent diabetes mellitus in pediatric renal transplant patients receiving tacrolimus (FK 506). Transplantation 65:617–619
23. Niaudet P, Drachman R, Gagnadoux MF, Broyer M (1984) Treatment of idiopathic nephrotic syndrome with levamisole. Acta Pediatr Scand 73:637–641
24. British Association for Paediatric Nephrology (1991) Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. Lancet 337:1555–1557
25. Bagga A, Sharma A, Srivastava RN (1997) Levamisole therapy in corticosteroid dependent nephrotic syndrome. Pediatr Nephrol 11:415–417
26. Barbano G, Ginevri F, Ghiggeri GM, Gusmano R (1999) Disseminated autoimmune disease during levamisole treatment of nephrotic syndrome. Pediatr Nephrol 13:602–603
27. Barratt TM, Cameron JS, Chantler C, Counahan R, Ogg CS, Soothill JF (1977) Controlled trial of azathioprine in treatment of steroid responsive nephrotic syndrome of childhood. Arch Dis Child 52:462–463

28. Hiraoka M, Tsukahara H, Hori C, Oshima Y, Momoi T, Seo A, Mayumi M (2000) Efficacy of long-term azathioprine for relapsing nephrotic syndrome. Pediatr Nephrol 14:776–778
29. Laurent AF, Dumont S, Poindron P, Muller CD (1996) Mycophenolic acid suppresses protein N-linked glycosylation in human monocytes and their adhesion to endothelial cells and some substrates. Exp Hematol 24:59–67
30. Gummert JF, Barten MJ, Sherwood SW, Vangelder R, Billingham ME, Morris RE (1999) Pharmacodynamics of immunosuppression by mycophenolic acid: inhibition of both lymphocyte proliferation and activation correlates with pharmacokinetics. Pharmacol Exp Ther 291:1100–1112
31. Remuzzi G, Zoja C, Gagliardini E, Coma D, Abbate M, Benigni A (1999) Combining an antiproteinuric approach with mycophenolate mofetil fully suppresses progressive nephropathy of experimental animals. JASN 10:1542–1549
32. Day CJ, Cockwell P, Liokin GW, Savage CO, Howie AJ, Adu D (2002) Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. Nephrol Dial Transplant 17:2011–2013
33. Mogyorosi A, Lippman HR, Feldman GM (2002) Successful treatment of steroid resistant minimal change disease with mycophenolate mofetil. Am J Nephrol 22:569–572
34. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB (2003) Use of mycophenolate mofetil in steroid-dependent and steroid-resistant nephrotic syndrome Pediatr Nephrol 18:833–837
35. Ulinski T, Duborg L, Said MH, Parchoux B, Ranchin B, Cochat P (2005) Switch from cyclosporine A to mycophenolate mofetil in nephrotic children. Pediatr Nephrol 20:482–485
36. Montane B, Abitbol C, Chandar J, Strauss J, Jillerulo G (2003) Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. Pediatr Nephrol 18:772–777
37. Zhao M, Chen X, Chen Y, Lieu Y, Lu F, Zhang Y, Wang H. Clinical observations of mycophenolate mofetil therapy in refractory primary nephrotic syndrome (2003) Nephrology (Carlton) 8:105–109
38. Neylan JF (1997). Immunosuppressive therapy in high-risk transplant patients: dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. Transplantation 64:1277–82.
39. Tejara N, Gomez-Garre D, Lazaro A, Gallego-Delgdo J, Alamo C, Blanco J, Oritz A Egido J (2004) Persistent proteinuria upregulates angiotensin II type 2 receptor and induces apoptosis in proximal tubular cells. Am J Pathol 164:1817–1826
40. Contreras G, Parado V, Leclereg B, Lenz O, Tozman E, O'Nan P, Roth D (2004) Sequential therapies for proliferative lupus nephritis. N Engl J Med 350:971–980
41. Ingulli E, Tejani A (1991) Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. Pediatr Nephrol 5: 393–397
42. Sorof J, Hawkins EP, Brewer ED, Boydstun II, Kale AS, Powell DR (1998) Age ethnicity affect the risk and outcome of focal segmental glomerulosclerosis. Pediatr Nephrol 12:764–768
43. Grisweld WR, Tune BM, Reznik VM, Varquez M, Prime DJ, Brock P, Mendoza SA (1987) Treatment of childhood prednisone resistant nephrotic syndrome and focal segmental glomerulosclerosis with intravenous pulse methylprednisolone and oral alkylating agents. Nephron 46:73–77
44. Adhikari M, Bhimma R, Coovadia HM (1997) Intensive pulse therapies for focal glomerulosclerosis in South African children. Pediatr Nephrol 11:423–428
45. Mendoza SA, Reznik VM, Grisweld WR, Krensky AM, Yorgin PD, Tune BM (1990) Treatment of steroid-resistant focal segmental glomerulosclerosis with intravenous pulse methylprednisolone and alkylating agents. Pediatr Nephrol 4:303–307
46. Hari P, Bagga A, Jindal N, Srivastava RN (2001) Treatment of focal glomeulosclerosis with pulse steroids and cyclophosphamide. Pediatr Nephrol 16:901–905
47. Tune BM, Kirpekar R, Sibley RK, Reznik VM, Grisweld WR, Mendoza SA (1995) Intravenous pulse methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: A long-term follow-up. Clin Nephrol 43:84–88
48. Waldo FB, Benefield MR, Kohaut EC (1992) Methylprednisolone treatment of patients with steroid-resistant nephrotic syndrome. Pediatr Nephrol 6:503–505
49. Elhence R, Gulati S, Kher V, Gupta A, Sharma RK (1994) Intravenous pulse cyclophosphamide—a new regime for steroid-resistant minimal change nephrotic syndrome. Pediatr Nephrol 8:1–3
50. Rennert WP, Kala UK, Jacobs D, Goetsch S, Verhaart S (1999) Pulse cyclophosphamide for steroid-resistant focal segmental glomerulosclerosis. Pediatr Nephrol 13:113–11651
51. Bajpai A, Bagga A, Hari P, Dinda A, Srivastava RN (2003) Intravenous cyclophosphamide in steroid-resistant nephrotic syndrome. Pediatr Nephrol 18:351–356
52. Delucchi A, Cano F, Rodriguez E, Wolff E, Gonzalez X, Cumsille MA (2000) Enalapril and prednisone in children with nephrotic-range proteinuria. Pediatr Nephrol 14:1088–1091
53. Korbet SM (2003) Angiotensin antagonists and steroids in the treatment of focal segmental glomerulosclerosis. Semin Nephrol 23:219–228
54. Bullingham R, Monroe S, Nichols A. Hale M (1996) Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single dose oral and intravenous administration. J Clin Pharmacol 36:315–324
55. Shaw LM, Korecka M, Venkatatamanan R, Goldberg L, Bloom R, Brayman KL (2003) Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. Am J Transplant 3:534–542
56. Weber LT, Shipakova M, Armstrong VW (2002) The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: a report of German study group on mycophenolate mofetil therapy. J Am Soc Nephrol 13:759–768
57. Nowak I, Shaw LM (1995) Mycophenolic acid binding to human serum albumin: characterization and relation to pharmacodynamics. Clin Chem 41:1011–1017
58. Gataneo D, Perico N, Gaspari F, Gotti E, Remuzzi G (2002) Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. Kidney Int 62:1060–1067