Using Mycophenolate Mofetil in Steroid-Resistant Nephrotic Syndrome

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Recent work has increased our understanding of podocyte biology which may be the key structure involved in nephrotic syndrome. Interestingly, many treatment options which were thought to work via circulating plasma factors such as angiopoetin-like 4 in minimal change disease or soluble urokinase-type plasminogen activator receptor in focal glomerulosclerosis (FGS) due to immunologic factors are now known to have a direct nonimmunological impact on the glomerular filtration barrier, especially the podocyte.[1] Steroid-resistant nephrotic syndrome (SRNS), generally, and FGS, specifically, are associated with a 50% risk for end-stage renal disease within 5 years of diagnosis, if patients do not achieve a partial or complete remission.[2] Persistent nephrotic syndrome is associated with poor quality of life, hypertension, peritonitis, and other serious complications such as persistent coagulopathy-thromboembolism and dyslipidemia, and death.[3-6] Children reaching end-stage renal disease have a greatly reduced life expectancy, 19 years on average following initiation of dialysis, and an approximate life expectancy of 40 years following transplantation.

The potential benefit of therapy includes disease cure, control of nephrotic syndrome, and prevention of complications or slowing the progression to kidney failure. Management of children with SRNS requires confirmation of resistance to corticosteroids, for a minimum of 8 weeks. Additional remissions were reported after an extended exposure to steroids with low-dose prednisone in the control arms of randomized controlled trials and after high doses of intravenous or oral corticosteroids in observational studies. Thus, the definitions of resistance can be a minimum exposure of 8 weeks of prednisone 2 mg/kg/d or 60 mg/m^2/d for 4 weeks followed by 1.5 mg/kg or 40 mg/m^2 per dose alternate-day for 4 weeks. At this point, steroid resistance dictates the requirement for kidney biopsy to define the histopathology. Meanwhile, steroids may be continued for an additional 4 weeks, totaling 12 weeks, while awaiting pathology results.[7]

Almost 10% of children with primary nephrotic syndrome are considered to be steroid resistant.[8] After classifying the patient in the SRNS group, cyclosporine A with alternate prednisone or cyclophosphamide and pulse intravenous corticosteroid (prednisone) has been the first-line therapy.[9] However, these drugs are not without risk; cyclosporine has been associated with significant adverse effects including nephrotoxicity, hypertension, gum hypertrophy, and development of cyclosporine dependence.[10] Cyclophosphamide induces gonadal toxicity and poses a high carcinogenic risk.[11] Recently, the Kidney Disease: Improving Global Outcomes guideline excluded cyclophosphamide from the treatment of SRNS, including FGS.[12]

Mycophenolate mofetil (MMF) is a potent selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase that inhibits the de novo pathway of guanosine nucleotide synthesis. The de novo pathway is especially important for T- and B-lymphocyte proliferation; thus, the drugs display potent cytostatic effects on T lymphocytes and lower B-lymphocyte antibody production and expression of adhesion molecules.[13] It has the advantage of not being nephrotoxic or gonadotoxic. All of the qualities mentioned above allow the use of MMF in children with glomerulopathy secondary to immunological disorders (disorders of T-lymphocyte function) such as idiopathic SRNS.[14] Several uncontrolled

clinical trials have demonstrated the efficacy of MMF in steroid-dependent nephritic syndrome with or without prior use of cyclophosphamide and in children with nephrotoxicity due to prolonged treatment.

Noncompliance to steroid therapy can also be responsible for multiple relapses and may be misinterpreted as steroid dependency and may therefore lead to unjustified increase of immunosuppressive treatment and increase side effects. Whereas the treatment of the primary course of idiopathic nephritic syndrome is well established, steroid-dependent and steroid-resistant forms are still a challenge for pediatric nephrologists. Both undertreatment with multiple relapses with disease or steroid-associated morbidity on the one hand and overtreatment with specific side effects of immunosuppressive drugs may have severe consequences for the patients. The Kidney Disease: Improving Global Outcomes guideline 2012 recommended MMF in the treatment for SRNS in children who fail to achieve remission with calcineurin inhibitor therapy, MMF with high-dose corticosteroids (2D), or a combination of these agents (2D) be considered in children who fail to achieve complete or partial remission with calcineurin inhibitors and corticosteroids.[12] There is only one randomized controlled trial using MMF versus cyclosporine with FGS pathology. In this randomized controlled trial of 138 children and adults comparing cyclosporine (n = 72) to MMF combined with high-dose oral dexamethasone (n = 66). Cyclosporine A resulted in a 19.4% complete remission and 26.4% partial remission during 12 months of therapy. Patients in the MMF arm of this trial had a 33% combined complete and partial remission rate with 12 months of therapy. The study did not demonstrate a significant difference between the treatment arms.[15] Similarly, observational studies involving children with SRNS who were treated for a minimum of 6 months with MMF demonstrated a complete remission rate from 23% to 62%, a partial remission rate of 25% to 37%, and no remission in 8% to 40%.[16,17]

Baudouin and colleagues[18] conducted a trial of MMF in children with steroid-dependent nephritic syndrome. All patients were required to have received prior alkylating agent treatment. Sixty-seven percent of them had also received levamisole. Patients received MMF (1200 mg/m^2/d) and prednisone according to a defined schedule. Twenty-four children (median age, 6.0 years; range, 2.8 to 14.4) entered into the study and 23 completed it. Analysis of the data showed 4 patients relapsed during the first 6 months and 2 at months 8 and 11.5. In the 19 patients free of relapse during the first 6 months, the median prednisone maintenance dose decreased from 25 mg/m^2 to 9 mg/m^2. Mycophenolate mofetil reduces relapse rate and steroid dose in children with steroid-dependent nephritic syndrome and should be proposed before cyclosporine and cyclophosphamide.

In this issue of the *Iranian Journal of Kidney Diseases*, Nikavar and colleagues[19] reported the efficacy of MMF in 36 steroid-resistant and steroid-responsive children with frequent relapses. Twelve of 36 children (33.3%) were set in the group of steroid responsive with frequent relapses and 24 (66.7%) were categorized into the group of steroid resistant. The result of kidney biopsy reports as follows: 11 of 36 (30.6%) had minimal change disease, 13 of 36 (36.1%) had diffuse mesangial proliferative disease, and 12 of 36 (33.3%) had FGS. Eleven of 12 patients (91.6%) in the steroid responsive with frequent relapses group and 2 of 24 (8.3%) of patients in the SRNS group responded to MMF. Therapy with MMF was more effective in diffuse mesangial proliferative disease, followed by minimal change disease and FGS. This finding clearly confirmed most recent observational studies in this field. The interesting point is that most of the FGS cases not responded to steroid will not respond to MMF either, so the pediatrician in charge will not include MMF in this group. The reason can not exactly be settled down, but it most probably can be due to different immunological mechanism and circulating factors responsible for pathogenesis of FGS and minimal change disease.

In conclusion, MMF may be a useful and attractive therapy of childhood SRNS with few adverse effects. In these patients, it represents a suitable alternative to calcineurin inhibitors as a treatment for many patients, especially those with kidney impairment. Mycophenolate mofetil can be used as first-line therapy when there is a contraindication to the use of cyclosporine A. Many children who are treated with cyclosporine can be safely converted to MMF with no major adverse events while maintaining a complete remission.[20]

Therefore, the use of MMF during SRNS should be taken into account. However, randomized controlled studies with larger representative samples are needed to reach significant conclusions.

CONFLICT OF INTEREST

None declared.

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How Neutrophil Gelatinase-associated Lipocalin Can Be Presented in Plasma and Urine

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Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25-kD protein massively released from renal tubular cells after various injuring stimuli is emerging as a promising new