Mycophenolate mofetil (MMF) treatment efficacy in children with primary and secondary glomerulonephritis

Danuta Ostalska-Nowicka[1], Agnieszka Malinska[2], Magdalena Silska[1], Bartlomiej Perek[3], Jacek Zachwieja[1], Michal Nowicki[2]

[1]Department of Paediatric Cardiology and Nephrology, Poznan University of Medical Sciences, Poland
[2]Department of Histology and Embryology, Poznan University of Medical Sciences, Poland
[3]Department of Cardiac Surgery, Poznan University of Medical Sciences, Poland

Submitted: 23 February 2011
Accepted: 25 September 2011

Arch Med Sci 2011; 7, 6: 1042-1048
DOI: 10.5114/AOMS.2011.26618

Corresponding author:
Michal Nowicki MD, PhD
Department of Histology and Embryology
Poznan University of Medical Sciences
6 Swiecickiego
60-781 Poznan, Poland
Phone: +48 61 8546453
Fax: +48 61 8546440
E-mail: mnowicki@ump.edu.pl

Abstract

Introduction: The aim of our study was to analyse the efficacy and safety of mycophenolate mofetil (MMF) as part of the complex immunosuppressive therapy in children with different types of primary and secondary glomerulonephritis, who were not eligible for the standard treatment routine suggested by evidence-based guidelines.

Material and methods: The study group comprised 85 children with proteinuric glomerulopathies hospitalized between 2007 and 2010, who were non-responders to immunosuppressive therapy. The dose of MMF was established as 1 g/m^2/24 h. Remission was defined as negative proteinuria in three consecutive urinalyses.

Results: The patients were divided into 4 groups: idiopathic nephrotic syndrome (n = 35), primary glomerulonephritis (n = 15), auto-antibody associated glomerulonephritis (n = 20) and lupus nephropathy (LN, n = 15). Ten patients from the first group (29%) and 5 patients each from the second and third group (34% and 25% respectively) did not respond to MMF therapy. On the other hand, all the children diagnosed with LN have reached clinical and biochemical remission.

Conclusions: Alternative rescue MMF therapy should always be taken into consideration in proteinuric patients who are non-responders to steroids, cyclosporine A and cyclophosphamide in whom the initial glomerular filtration rate is higher than 60 ml/min/1.73m^2. It is recommended that MMF be administered as part of the standard treatment regimen in patients diagnosed with lupus nephropathy. In these groups of patients, the potent benefits of this therapy are higher than expected side-effects.

Key words: mycophenolate mofetil, nephrotic syndrome, outcome, paediatrics.

Introduction

Proteinuria is currently regarded as one of the most important factors impairing kidney function, inducing an inflammatory sequence within renal parenchyma and progressing to end-stage renal disease (failure) [1]. In children, idiopathic nephrotic syndrome (INS) is the most common cause of massive proteinuria, resulting *inter alia* in low concentration of serum albumin and hypercholesterolaemia [2]. Clinically these factors give rise to nephrotic syndrome, which is mainly characterized by generalized oede-

ma, thrombosis, and metabolic abnormalities such as hypocalcaemia and hypothyroidism, which are the consequence of albumin loss [3]. The most frequent histological form of INS is minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) [4]. Furthermore, in paediatric renal biopsies of INS children, mesangial hypercellularity (MH) can be diagnosed [5]. None of these histological forms are accompanied by immunological deposit formation evaluated by electron microscopy or in immunofluorescence studies. Among different types of secondary glomerulonephritis, systemic lupus erythematosus (SLE) is judged as the most hazardous cause of secondary glomerulopathy in teenagers [6]. Other causes of secondary glomerulonephritis, for example associated with anti-neutrophil cytoplasmic antibodies dependent vasculitis and bronchial asthma (Churg-Strauss syndrome), are less frequent in children but, similarly, are associated with unfavourable prognosis [7, 8].

The immunosuppressive therapy strategy in INS regularly starts with glucocorticosteroids (GC). Recent reports indicate that more than 90% of paediatric patients with INS respond to this therapy (steroid-sensitive INS) [3]. Unfortunately, steroid-dependent or steroid-resistant NS impels clinicians to introduce cyclophosphamide and/or calcineurin inhibitors [9-11]. This nature of INS remains a challenge for clinicians to achieve successful induction and maintenance of complete remission in nephrotic syndrome.

In SLE dependent nephropathy the therapy procedure follows the clinical course and histological classification of renal biopsies, and is based on the well-experienced complexity of multi-drug immunosuppression [12, 13]. On the other hand, some of the primary as well as secondary glomerulopathies (e.g. Churg-Strauss syndrome) intricate by nephrotic-range proteinuria require parallel GC and optional immunosuppressive therapy (cyclophosphamide and/or azathioprine) determined by validated prognostic criteria (Five Factor Score) [8].

However, considerable toxicity of the above-mentioned procedure and inadequate clinical response to this therapy compelled us to search for more effective and safe treatment.

Mycophenolate mofetil (MMF) is an immunosuppressive agent, which is metabolized in the liver to the active moiety mycophenolic acid. It inhibits inosine monophosphate dehydrogenase, the enzyme that controls the rate of biosynthesis of guanine monophosphate in the *de novo* pathway of purine synthesis used in the proliferation of B and T lymphocytes, and mesangial cells [14]. According to some preliminary reports, MMF can be used not only in solid-organ transplantation but also as an alternative immunosuppressive therapy, in proteinuric nephropathies [15-17].

In line with the above, the aim of our study was to analyse the efficacy and safety of MMF as part of the complex immunosuppressive therapy in children with different types of primary and secondary glomerulonephritis, who were not eligible for the standard treatment routine suggested by evidence-based guidelines.

Material and methods

Patient population

Patients who were aged 2 to 18 years were eligible for entry into this study when they had evidence of either steroid-resistant NS (SRNS), steroid-dependent NS (SDNS) or frequently relapsing NS (FRNS). Relapse of NS before study entry was defined as proteinuria ≥ 2+ by dipstick for 3 or more consecutive days or recurrence of sufficient clinical features of NS to prompt therapy with daily steroids by the attending physician.

Steroid-resistant NS was defined in patients who failed to respond to a 4 + 4 week course of steroid (prednisolone 60 mg per m^2/day for 4 weeks, followed by 40 mg/m^2 three times a week for 4 weeks in the 6 months before entry). Steroid-dependent NS was defined in patients who had a relapse of NS after a decrease in the dosage of prednisone or within 28 days of stopping prednisone on two or more consecutive occasions in the 12 months before entry. One of these episodes must have been within 3 months before entry). Frequently relapsing NS was defined in patients who responded to prednisone treatment but who had four or more relapses within the 12 months before the screening visit or two or more relapses within the first 6 months after the initial response (if this was in the 6 months before entry).

Patients were allowed to receive a course of cyclophosphamide or chlorambucil *in the past* but again had to satisfy the entry criteria for steroid dependence and/or FRNS *after* the course of cytotoxic medication was completed. Female patients of childbearing potential were required to have a negative pregnancy test < 1 week before starting MMF. Such patients had to agree to use two reliable forms of contraception simultaneously before beginning study drug therapy, during therapy, and for 6 weeks after discontinuation of study drug therapy.

Exclusion criteria that were used in the study included the following: absolute neutrophil count < 4 G/l; haematocrit < 0.25; history of significant gastrointestinal disorder; active systemic infection or history of serious infection within 1 month of entry; known infection with HIV or the presence of hepatitis B surface antigen; other major organ system disease or malignancy; administration of live viral vaccine within 6 weeks before study entry; and

current or recent (within 30 days) exposure to any investigational drug.

The study group comprised 85 children with proteinuric glomerulopathies hospitalized between 2007 and 2010, who were non-responders to immunosuppressive therapy. They were admitted to the Department of Paediatric Cardiology and Nephrology, Poznan University of Medical Sciences in Poland. Forty-five boys (aged 12.2 ±6.3 years) and forty girls (aged 11.9 ±7.4 years) underwent a renal biopsy according to the International Study for Kidney Disease in Children recommendations [18, 19]. These indications included steroid-resistant NS (SRNS, n = 11), steroid-dependent NS (SDNS, n = 14), frequently relapsing NS (FRNS, n = 10), primary glomerulonephritis (n = 16), auto-antibody associated glomerulonephritis (AAGN, n = 19) and lupus nephropathy (LN; n = 15). According to WHO definitions, histological evaluation of the study group revealed the following: diffuse mesangial proliferation (DMP, n = 15), focal segmental glomerulosclerosis (FSGS, n = 20), glomerulosclerosis (GS, n = 25), primary mesangial glomerulonephritis (PMG, n = 10) and, finally, lupus nephropathy (n = 15) [20]. Diffuse mesangial proliferation diagnosis was based on the number of cells visible under the electron microscope per mesangial area. INS was classically characterized by the absence of significant deposits in immunofluorescence microscopy, except for FSGS and sclerotic lesions, which were found to bind IgM and C_3 antiserum without electron-dense deposits [5]. No IgA nephropathy was diagnosed in the studied population. Detailed information is shown in Table I.

Since MMF is not yet approved for conventional therapy administered in different proteinuric glomerulopathies in Poland [15], we obtained the necessary approval from the Polish Health Department, which authorized MMF use in this group of children. Equally, the study protocol was ratified by the local Ethics Committee of Poznan University of Medical Sciences, and the parents of the study participants gave written, informed consent for the investigation. The study fulfilled the standards recommended by the Helsinki convention.

Treatment protocol

The dose of MMF was established as 1 g/m^2/24 h in two therapeutic doses given precisely at 7 am and 7 pm. This daily dose was then modified according to the clinical course of proteinuric glomerulopathies. Because there is still no possibility to evaluate plasma concentration of MMF and its metabolites in our department, we carefully studied all the possible clinical side effects, and checked complete blood morphology as well as plasma renal and liver markers to detect any changes necessitating prompt drug withdrawal. According to Bagga *et al*., all the patients treated with MMF were additionally given prednisolone 0.5 mg/kg/48 h [21]. Remission was defined as absence of proteinuria (urine albumin nil or trace for three consecutive days by dipstick or boiling test).

Follow-up and safety assessment

The more precise patient status was evaluated at the time: zero, 3, 6, 12, 18 and 24 (when applicable) months starting from the beginning of MMF therapy. At each follow-up visit, not only clinical status, but also blood pressure, complete blood morphology including white blood cell count (WBC), serum creatinine, glomerular filtration rate (GFR), electrolytes, lipid profile, bilirubin and liver enzymes (alanine aminotransferase, aspartate aminotransferase), glycaemia and 24-h urinary protein excretion were recorded. Study participants were also monitored for the presence of viral infections (HBV, HCV, EBV and BKV). In addition, in patients diagnosed with LN as well as patients recognized with GN associated with ANCA positive antibodies the serum concentrations of auto-antibodies (anti-ANA, anti-dsDNA, anti-cardiolipin and anti-ANCA) were checked every third month. Each infectious episode was systematically assessed and followed by microbiological tests of blood, sputum or broncho-alveolar lavage and urine analysis (culture). The treatment protocol was arrested in all the patients who developed leucopenia (WBC < 4 G/l). These children were transitionally given only GC and were included back in the treatment protocol when WBC was estimated > 4 G/l in three subsequent blood analyses.

Statistical analysis

Data are expressed as mean ± SD unless otherwise stated. A Wilcoxon ranks test was applied to determine whether there was a significant change in relapse rate before and after therapy with MMF. Two variables (proteinuria and GFR) in all the patients were analysed at time zero (at the beginning of the study) as well as at 3, 6, 12, 18 and 24 months of MMF therapy using Spearman's rank correlation coefficient (Spearman's rho). Significance was set as $p < 0.05$; statistical analysis was performed using Statistica 8.0 PL software.

Results

Patients were divided into four groups: idiopathic nephrotic syndrome (n = 35), primary glomerulonephritis (n = 15), auto-antibody associated glomerulonephritis (n = 20) and lupus nephropathy (n = 15). Ten patients from the first group (29%) and 5 patients from the second as well as the third group (33.3% and 25% respectively) did not respond to MMF therapy. On the other hand, all the children

Table I. Characteristics of the study group

Clinical indication for MMF treatment		Histology	Age [years]	GFR	Pre-MMF therapy	MMF therapy treatment/remission [months]	% of patients who did not respond to MMF therapy
Idiopathic nephrotic syndrome	FRNS	FSGS	16.3 ±1.3	93 ±11	PRED, MetPRED, CP, CsA, Tacrolimus, PP	24 ±2/18 ±3♠	29
			15.9 ±1.8	60 ±21		24 ±3/21 ±5♠	
	SDNS + CsA DNS	DMP	9.9 ±4.4	152 ±3	PRED, CP, CsA	12 ±3/11 ±4	
			8.5 ±2.9	164 ±7			
	SDNS	GS	11.1 ±3.9	121 ±4		24 ±4/21 ±5	
	SRNS + CsA toxicity		13.7 ±3.6	44 ±13	PRED, CP, CsA, PP	8 ±2/No remission♦	
	SRNS + CsA DNS	DMP	9.2 ±6.7	80 ±19	PRED, MetPRED, CP, CsA, PP	6 ±3/No remission♦	
Primary glomerulonephritis		MesGN	13.5 ±2.2	57 ±21	PRED, MetPRED, CsA	12 ±3/6 ±2♠	33.3
			15.7 ±5.1	81 ±15	PRED, CP, CsA	18 ±5/12 ±4	
		GS	6.5 ±2.0	28 ±6	PRED, MetPRED	6 ±2/No remission♦	
Auto-antibody associated glomerulo-nephritis	Churg-Strauss syndrome	FSGS	17.1 ±0.9	75 ±17	PRED, MetPRED	12 ±3/12 ±5♦	25
	Patent ANCA		14.6 ±2.7	97 ±22		12 ±1/12 ±4	
	CsA RNS	GS	15.4 ±1.3	100 ±18	PRED, MetPRED, CP, CsA	12 ±4/2 ±1♠	
	SRNS + CsA toxicity		14.7 ±2.9	11 ±3	PRED, MetPRED, PP, CsA	2 ±1/No remission♦	
Lupus nephropathy		III C/A LN	15.0 ±2.3	104 ±32	PRED, MetPRED, CP, PP, CsA	12 ±3/9 ±3	0*
		IV A LN	13.1 ±4.1	92 ±19		12 ±2/10 ±4	
			13.2 ±2.8	75 ±15	PRED, MetPRED, CP, PP	6 ±3/5 ±2	

MMF – mycophenolate mofetil, age/sex – age [years] at the moment of MMF beginning, GFR – glomerular filtration rate [ml/min/1.73 m^2], FRNS – frequently relapsing nephrotic syndrome, FSGS – focal segmental glomerulosclerosis, PRED – prednisolone, MetPRED – methylprednisolone, CP – cyclophosphamide, CsA – cyclosporine A, PP – plasmapheresis, FVI – frequent viral infection of upper respiratory tract, SDNS – steroid-dependent nephrotic syndrome, CsA DNS – cyclosporine A dependent nephrotic syndrome, DMP – diffuse mesangial proliferation, leucopenia – a single episode of white blood cell count < 4 G/l, GS – glomerulosclerosis, SRNS – steroid-resistant nephrotic syndrome, ESRD – end-stage renal disease, NS – nephrotic syndrome, MesGN – mesangial glomerulonephritis, patent ANCA – both perinuclear-staining and cytoplasmic-staining antineutrophil cytoplasmic antibodies still present during steroid administration, CsA RNS – cyclosporine A resistant nephrotic syndrome, LN – lupus nephropathy

*♠ – remission achieved after 25% MMF dose increase, ♦ – MMF interruption secondary to ESRD or chronic NS, ♣ – chronic WBC < 4 G/l, *p < 0.05*

diagnosed with LN reached clinical and biochemical remission ($p < 0.05$ as compared to the former three groups). Non-respondent subjects progressed to ESRD (15 children needed renal replacement therapy) and five patients expressed the next relapse of nephrotic syndrome which needed cyclosporine A therapy to achieve remission. These children were sex and age independent.

Interestingly, 15/25 (60%) children, who were recognized with glomerulosclerosis in renal biopsy evaluation, did not respond to MMF therapy. These children also had a significantly lower GFR as compared to the rest of patients, who achieved remission secondary to MMF administration.

Eighteen patients required a 25% MMF dose increase to obtain remission. They were enrolled from the idiopathic nephrotic syndrome group ($n = 9$), and primary glomerulonephritis ($n = 5$) and auto-antibody associated GN ($n = 4$). Again, LN children did not need MMF dose alteration. The necessity of MMF dose increase was independent of age, sex, initial histology or GFR. It was exclusively related to the clinical course, during which patients who did not respond to the initial MMF dose could be given a higher therapeutic dose.

As regards the previous therapeutic regimens given to our patients prior to MMF commencement, the majority of patients received prednisolone, methylprednisolone, cyclophosphamide and cyclosporine A treatment. Individuals were additionally given tacrolimus and underwent plasmapheresis.

The most common MMF side-effect was frequent viral infection of the upper respiratory tract. That inconvenience affected 53% of children and was independent of MMF dose. The second common side-effect was irregular (episodic) leucopenia. It was diagnosed in 24% of subjects, but first of all referred to LN patients. In a single patient diagnosed with Churg-Strauss syndrome, a constant and chronic leucopenia (over 3 months) was the main side-effect and, consequently, the reason for discontinuation of MMF therapy. That boy, regardless of the beneficial MMF effect on kidney function (GFR improved from 75 ml/min/1.73 m^2 to 94 ml/min/1.73 m^2), was the last subject, besides MMF non-responders, who stopped MMF treatment.

Initially, before commencement of MMF treatment, proteinuria was observed in 65/85 patients (76.5%) (proteinuria exceeded 50 mg/kg/24 h in 44/65 patients (67.7%). During the MMF treatment protocol this sign of kidney failure decreased gradually and finally was absent in the study participants with the exception of 19 children (including 15 patients in whom MMF therapy was arrested). Spearman's correlation of proteinuria and MMF treatment time was significant ($r = –0.575$; $p < 0.01$; Figure 1).

On the other hand, twenty children were estimated to have GFR less than 60 ml/min/1.73 m^2. During the MMF treatment strategy, fifteen of them progressed to ESRD (non-effective rescue therapy; all with glomerulosclerosis), whereas 5 of them showed improvement of kidney function as evidenced by normal GFR and achieved remission with no proteinuria. Again, Spearman's correlation of GFR and MMF treatment period was significant ($r = 0.293$; $p < 0.05$; Figure 2).

Discussion

Our challenge to summarize the results of MMF therapy in children with different primary and secondary glomerulonephritides was due to the general opinion that MMF could serve as an alternative drug in the non-responding proteinuric nephropathy treatment regimen [11, 13, 15, 21].

Mycophenolate mofetil is one of the immunosuppressant drugs which have been used to pre-

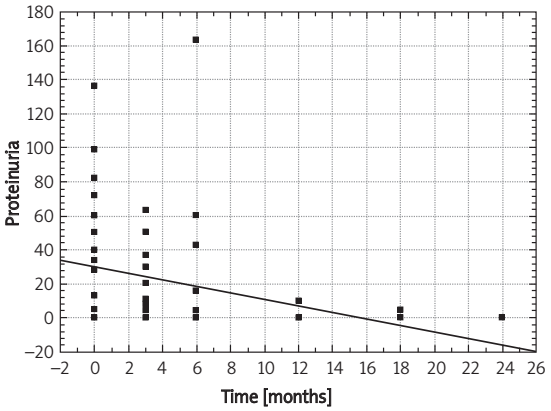

Figure 1. Proteinuria (mg/kg/24 h) in children with primary and secondary glomerulonephritis during MMF therapy

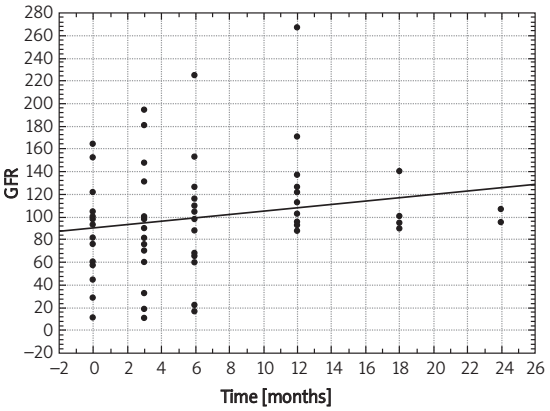

Figure 2. GFR (ml/min/1.73 m^2) of children with primary and secondary glomerulonephritis during MMF therapy

vent rejection in organ transplantation. Generally it is used as part of a three-compound regimen of immunosuppressants, including a calcineurin inhibitor (cyclosporine or tacrolimus) and prednisolone. As an immunosuppressant that has drastically decreased the incidence of acute rejection in solid transplant recipients, mycophenolate is increasingly utilized as a steroid-sparing treatment in immune-mediated disorders including immunoglobulin A nephropathy, small vessel vasculitis as well as psoriasis [23, 24].

Its increasing application in LN treatment has demonstrated more frequent complete response and less frequent complications [25] as compared to cyclophosphamide bolus therapy, a regimen with risk of bone marrow suppression, infertility, and malignancy [26]. Further work addressing maintenance therapy showed mycophenolate to be superior to cyclophosphamide, again in terms of response and side-effects [27]. Walsh *et al.* even proposed that mycophenolate could be considered as a first-line induction therapy for treatment of LN in patients without renal dysfunction [28], suggesting that mycophenolate will be encountered more frequently in medical practice.

In our study, fifteen patients with LN were treated with MMF to induce remission (during the first 6 months of treatment). All of them expressed remission of proteinuria. It cannot be excluded that in some of the patients there was spontaneous remission, although this is not a very common occurrence. All of the children with LN also expressed a diminished number of leucocytes in peripheral blood morphology with negative autoantibodies during immunosuppressive treatment. This inconvenience was, however, episodic.

We have demonstrated that the MMF treatment regimen could also be beneficial in certain cases of steroid and cyclosporine A dependent nephrotic syndrome, primary glomerulonephritides, and autoantibody associated glomerulopathies. We postulate that such a treatment strategy should always be taken into consideration in all patients in whom a standard and recommended treatment protocol fails. Mycophenolate mofetil administration usually generates less frequent and more gentle side-effects. It should be re-considered even in patients with initially low GFR, although the final decision as regards its administration in that group of patients should be evaluated after 3 months to 6 months of treatment. Otherwise, expected benefits could be less than progressive side-effects.

Common adverse drug reactions associated with mycophenolate therapy include diarrhoea, nausea, vomiting, infections, leukopenia, and/or anaemia. Mycophenolate mofetil is also believed to be commonly associated with fatigue, headache, and/or cough [29]. Intravenous administration of MMF is sometimes associated with thrombophlebitis and thrombosis. Infrequent adverse effects (0.1-1% of patients) include oesophagitis, gastritis, gastrointestinal tract haemorrhage, and/or invasive cytomegalovirus (CMV) infection [30]. Our studied children have primarily developed frequent viral infections of the upper respiratory tract, which, however were independent from leucopenia. Single leucopenic episodes were observed in 20 patients (including all LN subjects). A single child, diagnosed with Churg-Strauss syndrome, had chronic leucopenia which was augmented independently from MMF dose. This only example of severe leuco- and granulopenia could be related to the basic problem of this patient, but naturally such an observation would need further expanded studies. We did not observe any other side-effects as listed above in the rest of patients, even when they received the 25% higher dose of MMF.

In conclusion, we postulate that alternative rescue MMF therapy should always be taken into consideration in proteinuric patients not responding to steroids, cyclosporine A and cyclophosphamide in whom the initial glomerular filtration rate is higher than 60 ml/min/1.73 m^2. We recommend that MMF be administered as part of the standard treatment regimen in patients diagnosed with lupus nephropathy. In this group of patients, the potent benefits of this therapy are higher than expected side-effects.

Acknowledgements

This work was supported by the State Committee for Scientific Research (NCBiR grant no. NR13-0033-10/2010). The authors also wish to thank Dr. Melissa Stahle from the Department of Genetics, University of Melbourne, Australia for her perfect lingual edition of the text.

The manuscript has been seen and approved by all authors and it is not under consideration for publication elsewhere in a similar form, in any language, except in abstract form.

The corresponding author (on behalf of all authors in the paper) declares no 1) financial interests or arrangements with a company whose product was used in the study or is referred to in the manuscript, 2) financial interests of arrangement with a competing company, 3) direct payment to an author(s) from any source for the purpose of writing the manuscript, or 4) other financial connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated – including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

References

1. Hallan SI, Ritz E, Lydersen S, et al. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol 2009; 20: 1069-77.
2. Mathieson PW. Minimal change nephropathy and focal segmental glomerulosclerosis. Semin Immunopathol 2007; 29: 415-26.
3. Chesney RW. The idiopathic nephrotic syndrome. Curr Opin Pediatr 1999; 11: 158-61.
4. Swartz SJ, Eldin KW, Hicks MJ, Feig DI. Minimal change disease with IgM+ immunofluorescence: a subtype of nephrotic syndrome. Pediatr Nephrol 2009; 24: 1187-92.
5. Fogo AB. Minimal change disease and focal segmental glomerulosclerosis. Nephrol Dial Transplant 2001; 16: 74-6.
6. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet 2007; 369: 587-96.
7. Zwerina J, Eger G, Englbrecht M, et al. Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum 2009; 39: 108-15.
8. Zaffanello M, Cataldi L, Franchini M, Fanos V. Evidence-based treatment limitations prevent any therapeutic recommendation for acute poststreptococcal glomerulonephritis in children. Med Sci Monit 2010; 16: RA79-84.
9. Ehrich JH, Pape L, Schiffer M. Corticosteroid-resistant nephrotic syndrome with focal and segmental glomerulosclerosis: an update of treatment options for children. Paediatr Drugs 2008; 10: 9-22.
10. Sümegi V, Haszon I, Bereczki C, et al. Long-term follow-up after cyclophosphamide and cyclosporine-A therapy in steroid-dependent and -resistant nephrotic syndrome. Pediatr Nephrol 2008; 23: 1085-92.
11. Vécsei AK, Müller T, Schratzberger EC, et al. Plasmapheresis-induced remission in otherwise therapy-resistant FSGS. Pediatr Nephrol 2001; 16: 898-900.
12. Appel GB, Contreras G, Dooley MA, et al. Aspreva Lupus Management Study Group and Collaborators (91). Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009; 20: 1103-12.
13. Woodroffe R, Yao G, Meads C, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess 2005; 9: 1-194.
14. Chaigne-Delalande B, Guidicelli G, Couzi L, et al. The immunosuppressor mycophenolic acid kills activated lymphocytes by inducing a nonclassical actin-dependent necrotic signal. J Immunol 2008; 181: 7630-8.
15. Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. J Am Soc Nephrol 2010; 21: 2028-35.
16. Dal Canton A, Amore A, Barbano G, et al. One-year angiotensin-converting enzyme inhibition plus mycophenolate mofetil immunosuppression in the course of early IgA nephropathy: a multicenter, randomised, controlled study. J Nephrol 2005; 18: 136-40.
17. Navaneethan SD, Viswanathan G, Strippoli GF. Treatment options for proliferative lupus nephritis: an update of clinical trial evidence. Drugs 2008; 68: 2095-104.
18. Bohlin AB, Edström S, Almgren B, et al. Renal biopsy in children: indications, technique and efficacy in 119 consecutive cases. Pediatr Nephrol 1995; 9: 201-3.
19. Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). Pediatrics 2000; 105: 1242-9.
20. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15: 241-250. Erratum in: J Am Soc Nephrol 2004; 15: 835-6.
21. Bagga A, Hari P, Moudgil A, Jordan S. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. Am J Kidney Dis 2003; 42: 1114-20.
22. Kowalczyk T, Pleszczyńska E, Ruland F. Grade models and methods for data analysis with applications for the analysis of data populations. Studies in Fuzziness and Soft Computing vol. 151. ISBN 9783540211204. Berlin, Heidelberg, New York. Springer Verlag, 2004.
23. Hogg RJ, Wyatt RJ. Scientific Planning Committee of the North American IgA Nephropathy Study. A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy [ISRCTN62574616]. BMC Nephrol 2004; 25: 3.
24. Joy MS, Hogan SL, Jennette JC, et al. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. Nephrol Dial Transplant 2005; 20: 2725-32.
25. Appel AS, Appel GB. An update on the use of mycophenolate mofetil in lupus nephritis and other primary glomerular diseases. Nat Clin Pract Nephrol 2009; 5: 132-42.
26. Turnbull J, Harper L. Adverse effects of therapy for ANCA-associated vasculitis. Best Pract Res Clin Rheumatol 2009; 23: 391-401.
27. Mak A, Cheak AA, Tan JY, et al. Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. Rheumatology 2009; 48: 944-52.
28. Walsh M, James M, Jayne D, et al. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2007; 2: 968-75.
29. Brister K, Yau CL, Slakey D. Enteric coating of mycophenolate reduces dosage adjustments. Transplant Proc 2009; 41: 1657-9.
30. Brum S, Nolasco F, Sousa J, et al. Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. Transplant Proc 2008; 40: 752-4.