Selective Immunosupressors and Alkylating Agents for Steroid-Dependent Nephrotic Syndrome in Children in Kazakhstan

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Abstract: The study demonstrates the efficacy of cyclosporin A and mycophenolate mofetil in the therapy of steroid-dependent nephrotic syndrome. The study recorded no infectious complications on therapy with cyclosporin, while in terms of the gastrointestinal tract and haematological complications there were 7.1% of cases for each. The study recorded only infectious complications on therapy with mycophenolate mofetil – in 21.5% of patients. Therapy with chlorambucil caused bacterial-virus infections more frequently than that with cyclophosphamide (35.1% versus 24.1%, $p<0.05$). The frequency of fungal infections was also higher on therapy with chlorambucil than that with cyclophosphamide (7.8% and 4.5%, $p>0.05$). Infections of the urinary system on therapy with chlorambucil were recorded almost 7 times more frequently than on that with cyclophosphamide (19.9% and 2.8 %, $p<0,001$).

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1. Introduction

Immunosuppressive therapy (IST), being primary pathogenetic therapy for steroid-dependent nephrotic syndrome (SDNS), apart from its obvious therapeutic effect has numerous side effects [1-6]. That said, issues regarding the benefits and risk of IST remain the subject of study in the area of nephrology. As an alternative to steroidal therapy and alkylating agents, there are now publications on using cyclosporin A (CsA) and mycophenolate mofetil (MMF) [7,8]. These preparations, being selective immunosuppresants, do not carry those side effects which are typical of prednisolone and alkylating agents [9,10].

Aim of study:

Assessing the efficacy in patients with SDNS of such immunosuppressors as chlorambucil, cyclophosphan, cyclosporin A, and mycophenolate mofetil.

2. Patients and methods.

The study examined clinical and laboratory values in children with SDNS who received therapy with immunosuppressive preparations at the nephrological department of the Republican Children's Clinical Hospital *Aksay* (Almaty) over the period of 2003-2012. The study included a regular spectrum of research conducted at the pediatric nephrological department. 36 patients received nephrobiopsy, upon the conclusion of which corresponding immunosuppressive therapy was prescribed for them. The morphological investigation of the renal bioptate included three necessary studies: light, immunofluorescence (IF), and electronic (EM) microscopy, which were conducted by Russian nephropathologists A.V. Sukhanov (Moscow) and O.A. Vorobyova (Saint Petersburg). Efficacy was evaluated based on time for attaining remission and the duration of preservation of remission. 46 patients with SDNS on therapy with chlorambucil (CB) and cyclophosphan (CP) were selected retrospectively (renal biopsy was not conducted in Kazakhstan prior to 2004).

No substantial differences in the age of nephrotic syndrome (NS) in children on different types of immunosuppressive therapy were detected. All the patients were of about the same age and with the same age of the condition.

Chlorambucil was given to 20 patients with SDNS. Cyclophosphan was given to 26 patients with SDNS. The therapeutic dose of CP was 2 mg/kg/24 hr, CB – 0.2 mg/kg/24 hr, to be taken for 8 weeks with a switch to the supporting dose (half of the therapeutic dose) also to be taken for 8 weeks. Therapy with cycloposphan in all the patients with SDNS, just like therapy with chlorambucil, led to complete remission of the condition.

Cyclosporin A (CsA) was given to 19 patients (9 patients had NS with minimal changes based on the results of nephrobiopsy; 10 patients had focal segmental glomerulosclerosis), and MMF was given to 17 patients (based on the results of nephrobiopsy, all had membranoproliferative

glomerulonephritis, of which 6 had it associated with IgA-nephropathy).

The primary indication for prescribing CsA was the nephrobiopsy conclusion; in addition, the study checked whether the patients had steroidal complications in the form of cataract – in 35.7%, height growth retardation, and urinary system infection (USI) – in 21.4% each, complications on the part of the gastrointestinal tract (GIT) in the form of erosive gastritis, reactive hepatitis, and pancreatitis – in 7.1%, and other complications – in 14.3%. The indication for prescribing MMF for patients with SDNS was also the nephrobiopsy conclusion. Complications from repeat courses of prednisolone in this group were as follows: cataract – in 14.3% of patients, height growth retardation, and stubborn USI - in 28.5% of patients.

Results and discussion.

Most of the children received CsA therapy for an average of 22.8±3.8 months. All the patients completed the therapy – no indications of nephrotoxicity or intolerance of the preparation were recorded. The patients received a therapeutic dose of CsA (5 mg/kg every 24 hours) for 3.9±0.2 months concurrently with a supporting dose of prednisolone with gradual discontinuation; the supporting dose of CsA was administered for 18.6±2.7 months. For patients on therapy with MMF, the length of the intake of the therapeutic dose of MMF was based on the intake of 1000 mg/m^2 every 24 hours and was within 3.5±0.6 months, while the supporting dose was to be taken in for 18,2±2,0 months. All the children received a combination of MMF and moderate doses of prednisolone in an alternating manner with gradual reduction and, eventually, discontinuation. The duration of therapy in combination with prednisolone for all the patients on therapy with CsA and MMF was 4,4±0,5 weeks.

On therapy with CsA, the study recorded an increase in the values of arterial pressure in a third of patients (Table 1) who additionally received hypotensive therapy in the form of calcium channel blockers (normodipine, lacipil). No changes on the part of AP (systolic – SAP, diastolic – DAP) in patients on therapy with MMF were detected. The study recorded a verifiable decrease in proteinuria in patients in both groups, who received selective immunosuppressors ($p<0.05$), which was accompanied by an increase in the levels of albumen and total protein in blood serum. The erythrocyte sedimentation rate (ESR) also reduced to normal ($p<0.05$) both on CsA and MMF therapy.

Table 1. The dynamics of clinical-laboratory values on IST in steroid-dependent patients.* verifiable changes compared with baseline values

IST	AP, mmHG						ESR, mm/h		Proteinuria g/24 hr	
	SAP			DAP						
	before	during	after	before	during	after	before	after	before	after
CB	111± 1,4	110± 0,9	109± 2,4	69± 1,1	69± 1,8	62± 1,7	29± 5,1	*8,3± 2,1	2,2± 0,4	*0
CP	108± 2,7	107± 1,9	110± 1,8	64± 0,8	65± 1,1	62± 1,9	31,5± 2,2	*6,9± 1,5	2,0± 0,2	*0
CsA	109,5± 2,4	118,2 ±4,4	110,2± 2,3	65,4 ±2,8	70,3± 3,5	65,5± 2,2	29,5± 4,6	*7,3± 3,1	1,9± 0,5	*0
MMF	110,1± 1,9	109,5 ±2,2	109,7± 1,7	62,3 ±2,2	63,1± 1,3	60,9± 1,7	30,7± 3,1	*9,2± 1,8	2,1± 0,3	*0

Biochemical values normalized the same way in patients on CsA and MMF therapy right during the intake of the therapeutic dose (Table 2). Control values were determined on the 10-12th week of applying the therapeutic dose of selective immunosuppressors. The values of total protein and albumens were verifiably in conformity with the norm by the designated time. The study recorded a trend towards increase in the values of potassium and urea on CsA therapy ($p>0.05$). No such changes were recorded on MMF therapy.

Table 2. The dynamics of biochemical values on IST in steroid-dependent patients. * verifiable changes compared with baseline values

IST	Total protein, g/l		Albumen, %		Potassium, µmol/l		Creatinine, µmol/l		Urea, µmol/l	
	before	during	after	during	before	during	before	during	before	during
CB	47,9±0,3	*62,0± 2,1	31,2±0,5	*41,4± 0,9	4,2±0,1	4,4± 0,3	0,07± 0,002	0,06± 0,004	6,2±0,3	5,1± 0,3
CP	46,8±0,3	*64,2± 0,9	31,0±1,1	*42,1± 0,8	4,3±0,2	4,1± 0,3	0,07± 0,003	0,06± 0,002	6,3±0,5	4,5± 0,2
CsA	47,2±0,5	*62,0± 2,1	30,2±1,2	*40,5± 1,3	4,1±0,1	5,5± 0,2	0,08± 0,004	0,09± 0,005	5,2±0,3	6,1± 0,3
MMF	48,3±0,4	*64,2± 0,9	30,0±1,2	*42,1± 0,7	4,2±0,1	4,2± 0,3	0,06± 0,003	0,06± 0,004	4,3±0,5	3,9± 0,2

The short-term impairment of functional values and certain biochemical values (of potassium and urea) on CsA therapy is associated, in our view, with the preparation's effect on the afferent arteriole, which led to the impairment of intraglomerular hemodynamics.

The levels of proteinuria faster and more considerably reduced in patients with steroid-dependent NS on CsA therapy compared with MMF therapy (Figure 1). By the second month of therapy with CsA, proteinuria had disappeared in patients completely, while on MMF therapy the levels of proteinuria were 0.5±0.002 g/24 hr. Nevertheless, by the beginning of the 3rd month, with a switch to the supporting dose of MMF, proteinuria had disappeared completely as well.

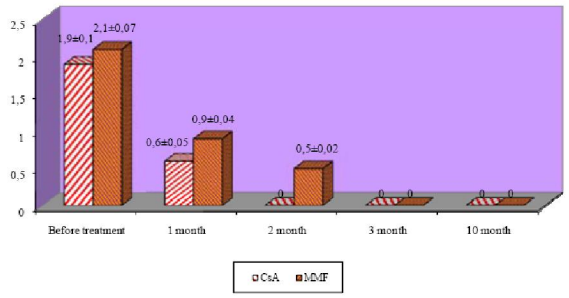

Figure 1 – The levels of proteinuria (g/24 hr) in patients with SDNS depending on the length of therapy with CsA and MMF

Functional values somewhat reduced on CsA therapy but reached the norm after the end of therapy (Table 3). MMF therapy did not affect the functional values of the kidneys: they remained unchanged and demonstrated a trend towards improvement (p>0.05).

Table 3 – The dynamics of functional values in patients with SNDS on IST

IST	GFR, ml/min			Concentration function		
	before	during	after	before	during	after
CB	78,1±1,7	85,2±1,9	88,8±0,9	1015±2,9	1019±1,0	1020±1,6
CP	75,4±1,5	87,5±1,1	92,2±1,2	1018±1,2	1023±1,9	1022±1,4
CsA	73,9±0,7	85,2±1,9	93,8±0,8	1019±0,9	1019±1,6	1021±0,6
MMF	72,2±0,5	93,8±0,7	100,2±0,7	1016±1,2	1023±0,9	1023±1,1

The efficacy of CsA is governed by its concentration in blood serum, its initial concentration (C_0) being 100-150 ng/ml. In patients with NS, its peak concentration after 2 hours (C_2) is within 700±200 ng/ml [7]. CsA concentrations were investigated in 77.1% of patients on the therapeutic dose of the preparation and did not exceed the recommended initial one – 110,2±1,1 ng/ml.

The comparison of the frequency of immunosuppressive therapy side effects in steroid-dependent patients revealed that therapy with selective immunosuppressors produces fewer complications than that with alkylating agents (Figure 2). On therapy with CsA, patients with NS did not demonstrate any infectious complications; on the part of the GIT and in terms of haemotological complications there were 7.1% cases for each (an increase in bilirubin; anemia). Only infectious complications were recorded on MMF therapy – in 21.5% of patients.

The largest number of infectious complications was recorded on therapy with alkylating agents (frequent URTI, herpetic infection, anginas, pustular skin and pituitary disorders, pneumonias, candidiases). There also prevailed haemotological complications (leukopenia and anemia) and complications on the part of the gastrointestinal tract (nausea, vomiting, an increase in transaminases and the thymol test, severe dysbacteriosis). Therapy with chlorambucil more frequently caused bacterial-virus infections than therapy with cyclophosphamide (35.1% versus 24.1%, p<0.05). The frequency of fungal infections also was higher on therapy with chlorambucil (7.8% and 4.5%, p>0.05). Urinary system infections were recorded almost 7 times more frequently on CB therapy than on CP therapy (19.9% and 2.8%, p<0.001).

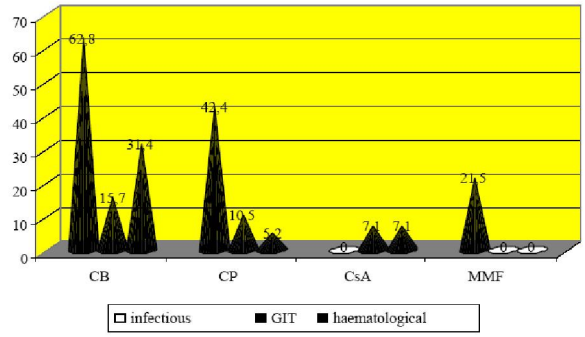

Figure 2 – The frequency of side complications from conducted immunosuppressive therapy in steroid-sensitive patients

It was revealed that in patients with SDNS, the frequency of preserved remission depends directly on the duration of the intake of the preparation. The longer the intake of the selective immunosuppressor, the lower the risk of a repeat recurrence occurring. Thus, with the length of CsA therapy being 6-10 months, after discontinuation of the intake of the preparation, recurrences are inevitable. When CsA therapy lasted for 12 months, recurrences occurred in a third of patients within 2-7 months after discontinuation of CsA intake. With therapy lasting for 18 months or longer, no recurrences of NS after discontinuation of intake were recorded throughout the observation period (1-5 years). Similar results were obtained for patients on MMF therapy as well. With MMF therapy lasting for 6-8 months, recurrences of NS after discontinuation of the intake of the preparation were detected in half of the patients. With therapy lasting for 12 months or longer, there were no recurrences of NS throughout the observation period (1-5 years).

Conclusion.

The study demonstrates the efficacy of CsA and MMF in the therapy of steroid-dependent nephrotic syndrome. Complete remission on therapy with selective immunosuppressors was attained in 100% of cases. Recurrences on therapy with CsA were recorded in 21.4% of patients, and with MMF in

14.3% of patients. Recurrences after the end of therapy with CsA were recorded in 15.7% of patients, and after discontinuing MMF intake – in 18.5%. We find it especially important to underscore the absence of nephrotoxicity in patients on therapy with CsA. Children who received CsA and MMF had an important advantage over other steroid-dependent patients – they were able to avoid numerous symptoms of steroidal toxicity and escape the prescription of alkylating agents with their short- and long-term complications. When it comes to the therapy of steroid-sensitive NS, we opt for cyclosporine A and mycophenolate mofetil over alkylating agents on account of the sufficient efficacy of selective immunosuppressors and the lower number of complications.

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