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THE RESPONSE TO THE IMMUNOSUPPRESSIVE DRUGS IN CHILDHOOD NEPHROTIC SYNDROME IN AL KARAMA TEACHING HOSPITAL: RETROSPECTIVE COHORT STUDY

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ABSTRACT
Nephrotic syndrome is a common renal disease in children sometimes need treatment with immunosuppressive drugs apart from steroid. **Aim**: to evaluate the response to immunosuppressive drugs in childhood nephrotic syndrome, the rate of sustained remission and the adverse effect of these drugs. **Methods**: retrospective study of 120 recorded files from them 68 patients with steroid sensitive nephrotic syndrome SSNS and steroid resistance SRNS, aged 1-19 years old, these children were treated and followed in Alkarama teaching hospital for 4years, the study started in the first of of April to the end of November 2015, the information data recorded were age, gender, body mass index BMI, Blood pressure, hematuria, s. cholesterol, s. albumin, urine protein: creatinine ratio, s. creatinine at presentation. The number of patient use the immunosuppressive drug, dose, duration, response, and adverse effect of each drug. **Results**: Sixty eight patients file records were evaluated 40 patients were SSNS and 28 patients were SRNS, male: female ratio were 2.3:1 and 1.5:1 for SSNS and SRNS respectively, clinical and laboratory data at presentation were not statistically significant except for hypertension which is statistically significant among SRNS and urine protein: creatinine ratio among SSNS. The remission rate among patient used cyclosporine were 50%(20/40) for SSNS, and for SRNS 39%(11/28), Tacrolimus were 25%(10/40) for SSNS and 10.7%(3/28) for SRNS, mycophenolate mofetil MMF 12.5%(5/40) for SSNS and 10.7%(3/28) for SRNS, Cyclophosphamide CYP 10%(4/40) for SSNS and 3.57%(1/28) for SRNS, Rituximab 2.5%(1/40) for SSNS and 7.14%(2/28) for SRNS. The most reported adverse effects were observed with cyclosporine which are gum hypertrophy 23%, hypertension 23%, hirsutism 19.23% and hyperkalemia 15.3% were most reported, with Tacrolimus the patients developed hypertension 11% and hyperglycemia 11%, with MMF gastrointestinal problem 12.5%, with CYP infection 9% and leukopenia 9% and with rituximab leukopenia 20% and thrombocytopenia 20% of cases. **Conclusion**: the responder to steroid and infrequent relapsers are more frequent than frequent relapsers FRNS and the later more frequent than SRNS. Hypertension are more statistically significant among SRNS and urine protein to creatinine ratio among SSNS. The best IS drug among SSNS and SRNS was cyclosporine and the most reported adverse effect were gum hypertrophy, hypertension and hirsutism.

KEYWARDS: Nephrotic syndrome, steroid resistant, steroid sensitive, immunosuppressive drugs.

INTRODUCTION
Nephrotic syndrome is a common type of kidney disease seen in children. It is characterized by massive proteinuria, hypoalbuminemia, and edema, although additional clinical features such as hyperlipidemia are also usually present.[1,2] Nephrotic syndrome may be caused by a variety of glomerular and systemic diseases, but by far the most common type in childhood is idiopathic nephrotic syndrome.[1] The passage of albumin, with its net negative charge, through the glomerular filter is prevented by size-specific factors and charge-specific factors.[3]

There are experimental data to support the existence of soluble mediators that may alter capillary wall permeability in nephrotic syndrome.[1] Resolution of proteinuria and histological changes when transplanted kidneys with recurrent FSGS are reimplanted in patient with end-stage renal disease secondary to diseases other than FSGS.[4] There are numerous reports of abnormalities of both the humoral and cellular immune responses during relapse of nephrotic syndrome. However, the idea that nephrotic syndrome may be due to dysregualtion of T lymphocyte function was first proposed by Shalhoub and his colleagues.[1]

• The common histopathological variety seen in children with idiopathic nephrotic syndrome is "minimal change disease" (MCD). Less commonly seen are focal segmental glomerulosclerosis (FSGS), membranoproliferative (or mesangiocapillary) glomerulonephritis, or (rarely) membranous nephropathy (MN) as causes of nephrotic syndrome.[5]

Treatment of Nephrotic Syndrome
Prednisone (or prednisolone, used interchangeably)
Second-line agents are introduced to avoid long-term glucocorticoid related adverse effects or as alternative for glucocorticoid resistance. Treatment with second-line drugs depends on availability and affordability, adverse effect profile, physician comfort and family preference.[5]

Alkylating Agents: Cyclophosphamide and Chlorambucil: The alkylating agents bind to purine bases and impair normal DNA transcription.[6]

Calcineurin inhibitor: Ciclosporin The mechanism of action of this immunosuppressive agent is known to involve inhibition of T-lymphocyte activation via inhibition of calcineurin-induced IL-2 gene expression, a critical early event in T-lymphocyte activation.[1]

Tacrolimus has a similar mode of action to ciclosporin and there are an increasing number of reports of efficacy in patients who relapse on ciclosporin therapy.[6]

Mycophenolate Mofetil: Is an inhibitor of the de novo purine pathway with inhibitory effects on T lymphocyte and B lymphocyte proliferation.[1]

Rituximab: Chimeric (mouse-human) monoclonal antibody which binds specifically to the CD20 antigen located on pre-B and mature B lymphocytes, thus mediating B-cell lysis. CD20 is not expressed on plasma cells.[6]

The duration of remission lasted 9–28 months after the treatment.[7]

PATIENTS AND METHODS

Retrospective (electronicly recorded) chart review study of 68 children with SSNS and SRNS treated other than steroid. immunosuppressive drugs who were evaluated and followed up(for at least 6months) in the pediatric nephrology unit in Alkarama teaching hospital to evaluate patients file from the date January 2011 till June 2015.

The study started on 1st of April 2015 and ended on thirty of November 2015. The patients included aged between 1-19years old.

Exclusion Criteria
Patients for whom there were incomplete data from the initial presentation or who were followed up for <6 months, those with congenital NS, infantile NS, secondary causes NS or systemic diseases were excluded from this study.

The information data were taken from patient's record files include name, gender, current age (years), age at presentation(years), duration of illness(years), weight and height (body mass index was calculated), s. cholesterol at presentation (mg/dl),s.albumin, urine examination.

Hematuria is defined as presence of at least 5 red blood cells per microliter of urine.

Nephrotic syndrome diagnosed in the presence of Edema, proteinuria >40 mg/m^2/hr or protein/creatinine ratio >0.2 g/mmol (>2 g/g) or 50 mg/kg/day or 3-4+ on urine dipstick, hypoalbuminemia <25 g/L (<2.5 mg/100 ml).[1]

Hypertension was defined as systolic and /or diastolic blood pressure above the 95th percentile for age, gender and height on three or more separate occasions.[1]

Renal biopsy results of 30 patients were available.

Ultrasound guided percutaneous renal biopsy was done after taking informed consent from the parents, thirty eight patients did not have renal biopsy. The biopsy was send for histopathology and examined under light microscopy and also used immunofluorescent staining.

Definition applied:
- SSNS: remission of proteinuria, urine protein:creatinine ratio (UP/Cr) <0.2, with corticosteroids;
- SDNS: subcategory of SSNS; relapse during corticosteroid therapy or within 2 weeks of discontinuing corticosteroids;
- FR-SSNS: >2 relapses in 6 months or ≥ 4 relapses in 12 months;
- SRNS: failure to induce remission within 8 weeks of corticosteroid treatment;
- Complete response: UP/Cr <0.2;
- Partial response: proteinuria reduction of >50% and non nephrotic-range proteinuria, UP/Cr >0.2 and <2
- No response: failure to achieve UP/Cr <2 or proteinuria reduction <50%.

Treatment Protocol for Childhood Nephrotic Syndrome
Subjects with new-onset nephrotic syndrome were empirically treated with an initial course of corticosteroids at standard dosing of 60 mg/m^2 daily for 4–6 weeks followed by a taper of 40 mg/m^2 every other day for 4–6 weeks. Second-line immunosuppressive therapies were utilized in subjects who were steroid resistant or suffered side effects from prolonged exposure to steroids (i.e. steroid dependant SDNS and FR-SSNS).

Subjects showing no response to the initial medication from the second-line group of therapies after 4–6 months or intolerance to a medication were switched to the next medication, the medication used:
(1) cyclosporine at 3-5mg/kg divided into 2doses
(2) tacrolimus at 0.1 mg/kg divided in 2 doses over 12-hour intervals,
(3) cyclophosphamide PO 2mg/kg/day for 12 weeks or 3mg/kg/day for 8wk.s
(4) mycofenolate mofetil or mycophenolate sodium at 600 mg/m^2 given twice a day
(5) rituximab at 375 mg/m^2 per dose until B-cell depletion (1–2 doses)

Adjunct treatment with angiotensin receptor blockers (ARBs) and/or angiotensin converting enzyme inhibitors (ACEi) specially for patients with SRNS.

The number of patient used each drug, the duration of use, the response, the number of relapses per year after use and the adverse effects recorded from each drug.

The definition of chronic kidney disease (CKD) is an estimated glomerular filtration rate (GFR)< 60 ml/min/1.73m^2. Estimated GFR was calculated using Schwartz formula and modified MDRD formula in patient. GFR stage 5 was defined as a GFR < 15ml/min/1.73m^2 or the need for renal replacement therapy.[3]

Statistical Analysis
Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences- version 21). Data were tested for normality and Shapiro test was confirmed its normality. Unpaired t test was used to assess significant difference among means, whereas, Chi-square test was used to assess the significant differences among proportions. $P \leq 0.05$ considered significant.

RESULTS
One hundred twenty recorded files of patient with nephrotic syndrome reviewed, 92 patients (76.66%) were SSNS and 28 patients (23.33%) were SRNS.

Fifty two patients (56.5%) of the 92 were normal responders to steroid infrequent relapsers did not need for second line immunosuppressive drugs (excluded from this study).

Thirty one patients (33.69%) were frequent relapser and 9 patients (9.78%) were steroid dependent (collectively 40 patients steroid sensitive nephrotic syndrome), both treated with immunosuppressive drugs.

Twenty eight patients (23.33%) of the 120 were steroid resistant and also treated with immunosuppressive drugs. Length of follow up 6months- 4.5years.

The subject cohort consisted predominately of male 70% (28/40) of SSNS and 60.7% (17/28) of SRNS, while female 30% (12/40) of SSNS and 39.28% (11/28) of SRNS but it is statistically not significant, male : female ratio were 2.3:1 and 1.5:1 for SSNS and SRNS respectively.

The mean age and age at the diagnosis not statistically significant between SSNS and SRNS, P-value 0.4 and 0.74 respectively.

At initial presentation, the number of patients who had hypertension were 11 out of 20 patients (55%) with SRNS which is statistically significant P- value 0.001, while in SSNS 4 patients (13.3%) out 30 had hypertension.

The mean for urine protein /creatinine ratio among SSNS is 9.83± 4.27 while SRNS the mean is 7.36± 6.05 so it is statistically significant, P – value 0.05.

The number of patients who had microhematuria among patients with SSNS are 6 out of 35 (17.14%) while 7 patients out of 23 (30.4%) of SRNS had microhematuria which is statistically not significant P – value 0.23.

Regarding the mean value of BMI, s. cholesterol, and estimated GFR are not statistically significant between SSNS and SRNS.

Renal biopsy done for 17patients out of 40 (42.5%) among SSNS and for 13 patients out of 28 (46.42%) among SRNS (the remainder of patients refused to do biopsy), the renal pathology among SSNS are minimal change disease in 12 patients out of 17 (70.58%) (the predominant pathology) then focal segmental glomeulosclerosis in 4patients out of 17 (23.5%) and IgM nephropathy in 1 patient (5.88%) while the renal pathology among SRNS are FSGS in 8 patients out of 13 (61.5%) (the predominant pathology) then MCD in 4 patients out of 13(30.76%) and 1patient with MPGN (7.69%). Shown in table 2.

The Response To Immunosuppressive Drugs. Table1, 2,3
The Response To Cyclosporine
Thirty three SSNS patients out of 40 (82.5%) and 19 SRNS patient out of 28 (67.8%) were given cyclosporine of those who were SSNS 19 patients out of 33(57.57%) achieved complete remission, 1patient (3%) achieve partial remission and 13 patients out of 33 (39.3%) had no remission. the combined rate of complete and partial remission to cyclosporine was 60.57% in SSNS patients. The mean duration of use was 19.41months. At last follow-up of 19 patients who achieved complete remission 8 continue on treatment with no relapse, 3 patients with 1relapse /year, 4 patients with 2 relapses /year, 1 patient with 3 relapses / year and 3 patients with 4 relapses / year. The patient who achieve partial remission developed 3 relapses /year.

The 13 patients who had no remission switched to other immunosuppressive drugs.

Of the 19 patients who were SRNS, 8patients (42%) achieved complete remission, 3patients (15.78%) achieved partial remission and 8 patients (42%) had no remission. The combined rate of complete and partial remission to cyclosporine was 57.78% in SRNS patients. The mean duration of use 15.89 months. At last follow-up, of 8 patients who achieved CR 4 patients continue on treatment with no relapse/year, 3 patients with 1 relapse / year and 1 patient with 2 relapses / year. The 3 patients who achieved PR had 2 relapses/year.

The 8 patients who had NR, 7patients switched to other immunosuppressive drugs while one patient failed to response and progressed to ESRD and dead.

The response to Tacrolimus

Eleven patients out of 40 SSNS patients (27.5%) and 7 patients out of 28 SRNS patients(25%) were used tacrolimus. Of those who were SSNS 7 patients out of 11 (63.6%) achieved CR, 3 patients (27%) achieved PR and 1 patient (9%) had no remission. The combined rate of CR and PR was 90.6% in the SSNS. The mean duration of use was 22.72 months.

At last follow-up, of the 7 patients who achieved CR, 1 patient developed 1 relapse /year, 4 patients with 2 relapses/year, 1 patient with 3 relapses /year and 1 patient with 4 relapses / year.

The 3 patients who achieved PR, 1 patient developed 2 relapses/year and 2 patients with 3 relapses /year.

The 1 patient who had NR switched to other immunosuppressive drugs.

Of those who were SRNS, 1 patient out of 7 (14%) achieved CR, 2 patients (28.5%) achieved PR and 4 patients (57%) had NR. The combined rate of CR and PR was 42.5% in the SRNS. The mean duration of use was14.85 months.

At last follow-up, the patient who achieve CR continue on tacrolimus with no relapse, the patients with PR 1patient continue with no relapse and 1patient with 3 relapses/year.

The 4 patients with NR, 3 patients switched to other immunosuppressive drugs, while 1 patient progressed to ESRD and he is dead.

The Response To Mycophenolate Mofetil

Six SSNS patients out of 40 (15%) and 10 SRNS patient out of 28 (35.7%) were given MMF.

Of those who were SSNS 4 patients out of 6 (66.6%) achieved complete remission, 1patient (16.6%) achieve partial remission and 1patients out of 6 (16.6%) had no remission. the combined rate of complete and partial remission to MMF was 83.2% in SSNS patients. The mean duration of use was 29.33months. At last follow-up of 4 patients who achieved complete remission 2 patients continue on treatment with no relapse, 2 patients with 2relapses/year. The patient who achieve partial remission developed 3 relapses /year.

The 1 patient who had no remission switched to other immunosuppressive drugs.

Of the 10 patients who were SRNS, 3 patients (30%) achieved partial remission and 7 patients (70%) had no remission, no patient achieved CR. The mean duration of use 22.6 months. At last follow-up, of 3 patients who achieved PR, 1 patient continue on treatment with no relapse /year, 1 patients with 1 relapse / year and 1patient with 2 relapses / year. The 7 patients who had NR, 4patients switched to other immunosuppressive drugs, 2patients developed CKD and 1patient failed to response to MMF and progressed to ESRD.

Response to Cyclophsphamide

Five SSNS patients out of 40 (12.5%) and 6 SRNS patient out of 28 (21.4%) were given cyclophosphamide Of those who were SSNS 4 patients out of 5 (80%) achieved complete remission, no patient achieve partial remission and 1patients out of 5 (20%) had no remission. The mean duration of use was 2.80 months. At last follow-up, of 4 patients who achieved complete remission 2 patients continue on treatment with no relapse and 2 patients with 2relapses/year. The 1 patient who had no remission switched to other immunosuppressive drugs.

Of the 6 patients who were SRNS, 1 patient (16.6%) achieved complete remission, 1 patient (16.6%) had partial remission and 4patients (66.6%) had no remission. The mean duration of use 3 months. At last follow-up, the patients who achieved CR continue on treatment with no relapse /year The patient who achieved PR had 4 relapses/y. The 4 patients who had NR 3 switched to other immunosuppressive drugs and 1 failed to response to treatment and progressed to ESRD and then dead.

The response to Rituximab

One SSNS patient out of 40 (2.5%) and 4 SRNS patient out of 28 (14.2%) were given Rituximab.

The one patient SSNS achieved complete remission. At last follow-up the patient continue with no relapse.

Of the 4 patients who were SRNS, 2 patients (50%) achieved partial remission and 2 patients (50%) had no remission, no patient achieved CR. The length of follow-up since the first cycle was a median of 8.5 months (range 7-9). At last follow-up, the 2 patients who achieved PR had 3 relapses/year.

The 2 patients who had NR, 1patients developed CKD and 1patient failed to response to drug and progressed to ESRD.

The best IS drugs as first, second,third and fourth line drug among SSNS and SRNS Table 4

In this study there is astatistical difference in the response among first line IS drug for SSNS, P-value <0.0001, with the high percent for Cyclosporine 47.5% and low percent for cyclophosphsmide 2.5%.

There is also a statistical difference in the response among first line IS drug for SRNS, P-value <0.0001, with a high percent for Cyclosporine 39% and low percent for other drugs 3.57%.

Regarding the second line drugs there is also a statistical difference in the response among IS drug for SSNS, P-value <0.01, with a high percent for Tacrolimus 20% and low percent for cyclosporine and cyclophosphamide 2.5%. There is no statistical difference in the response among second line IS drug for SRNS, P-value 0.24.

There is no statistical difference in the response among third and the fourth line IS drug for SSNS and SRNS, P-value 0.55 and 0.24 respectively.

In comparison of the 5 drugs among SSNS the higher rate of remission achieved by cyclosporine 50%(20/40) and lower rate was with rituximab 2.5%(1/40) which is statistically significant p-value < 0.0001, among SRNS the higher rate of remission achieved by cyclosporine 39%(11/28) and lower rate was with cyclophosphamide was 3.57%(1/28) which is statistically significant p-value 0.003. table 3,4.

The recorded Adverse Effects of The Immunosuppressive Drugs

1) Infection reported in 2 patients using cyclosporine out of 52(3.8%), one of them developed recurrent UTI during course of treatment and the other chicken pox, 1 patient using MMF out of 16(6.25%) developed bacterial pneumonia and 1 patient using cyclophosphamide out of 11(9%) developed recurrent UTI.
2) Leukopenia (WBC count <5000) reported in 3 patients using MMF (6.25%), Cyclophsphamide (9%) and rituximab (20%)
3) Thrombocytopenia (platelet count $<150*10^9$ in 1 patient using Rituximab out of 5 (20%).
4) Hypertension (BP above 95^{th} percentile for age, gender and height) in 12 patients out of 52 (23%) using cyclosporine and 2 patients out of 18(11%) using tacrolimus
5) Tremor in 2 patients using cyclosporine (3.8%).
6) Gum hypertrophy in 12 patients using cyclosporine (23%).
7) Gastrointestinal problems in 2 patients using MMF out of 16 (12.5%).
8) Hirsutism in10 patients using cyclosporine (19.23 %).
9) Hyperkalemia in 8 patients using cyclosporine (15.3%).
8) Hyperglycemia in 2 patients using Tacrolimus (11%).
9) Elevated s. creatinine level in 3 patients using Cyclosporine (5.76%).

Table 1: Medication History.

Drugs	SSNS	SRNS	P-value
Cyclosporine			
Usage	82.5%(33/40)	67.8%(19/28)	
Duration of use, months	19.41 ± 11.82	15.89 ± 10.28	
Response			0.27
CR	57.57%(19/33)	42%(8/19)	
PR	3%(1/33)	15.78%(3/19)	
NR	39.3%(13/33)	42%(8/19)	
Tacrolimus			
Usage	27.5%(11/40)	25%(7/28)	
Duration of use,months	22.72 ± 7.86	14.85 ± 6.91	
Response			0.04
CR	63.6%(7/11)	14%(1/7)	
PR	27%(3/11)	28.5%(2/7)	
NR	9%(1/11)	57%(4/7)	
Mycophenolate mofetil			
Usage	15%(6/40)	35.7%(10/28)	
Duration of use,months	29.33 ± 15.52	22.6 ± 8.79	
Response			0.28
CR	66.6%(4/6)	0(0/10)	
PR	16.6%(1/6)	30%(3/10)	
NR	16.6%(1/6)	70%(7/10)	

Cyclophosphamide			
Usage	12.5%(5/40)	21.4%(6/28)	
Duration of use, months	2.80 ± 0.44	3 ± 0	
Response			0.29
CR	80%(4/5)	16.6%(1/6)	
PR	0(0/5)	16.6%(1/6)	
NR	20%(1/5)	66.6%(4/6)	
Rituximab			
Usage		14.2%(4/28)	
Response	2.5%(1/40)		
CR		0(0/4)	
PR	100%(1/1)	50%(2/4)	
NR		50%(2/4)	

Table 2: The Response To The Is Drugs According To The Renal Biopsy.

IS	No. of patient(%)	MCD		FSGS		IgM Nephropathy		MPGN
		R	NR	R	NR	R	NR	NR
CSA	SSNS 15(45%)	5 (33.3%)	5 (33.3%)	1 (6.66%)	3 (20%)		1 (6.66%)	
	SRNS 7(36.8%)	1 (14.28%)	2 (28.5%)		4 (57%)			
Tac.	SSNS 4(36.6%)	3 (75%)			1 (25%)			
	SRNS 3(42.85%)	1 (33.3%)		2 (66.6%)				
MMF	SSNS 5(83%)	2 (40%)	1 (20%)	2 (40%)				
	SRNS 7(70%)	1 (14.28%)	1 (14.28%)	1 (14.28%)	3 (42.8%)			1 (14.28%)
CYP	SSNS 4(80%)	3 (75%)	1 (25%)					
	SRNS 3(50%)		1 (33.3%)	1 (33.3%)	1 (33.3%)			
RTX	SSNS 1(100%)					1 (100%)		
	SRNS 3(75%)	1 (33.3%)			2 (66.6%)			

Table 3: The Remission Rate, Rate of Sustained Remission Among Immunosuppressive Drugs.

Drugs	Group	Remission Rate	Relapse Free Remission%(n)	Mean Duration Mon. (range)
Cyclosporine	SSNS	50% (20/40)	24%(8/33)	38.75(10-52)
	SRNS	39% (11/28)	21%(4/19)	27.5(6-48)
Tacrolimus	SSNS	25% (10/40)	0	0
	SRNS	10.7% (3/28)	28.57%(2/7)	28(20-36)
MMF	SSNS	12.5% (5/40)	33%(2/6)	48
	SRNS	10.7% (3/28)	33%(1/3)	24
Cyclophosphamide	SSNS	10% (4/40)	40%(2/5)	12
	SRNS	3.57% (1/28)	16.6%(1/6)	24
Rituximab	SSNS	2.5% (1/40)	100%(1/1)	7
	SRNS	7.14% (2/28)	0	

Table 4: The Remission Achieved By Immunosuppressive Drugs According To The Line Of Use Between Ssns And Srns.

		Cyclosporin	Tacrolimus	MMF	Cyclophosphamide	Rituximb	Chi Square Value	P-value
First line IS drug	**SSNS**	47.5% (19/40)	5% (2/40)	5% (2/40)	2.5% (1/40)	0% (0/40)	60.32	<0.0001
	SRNS	39% (11/28)	3.57% (1/28)	3.57% (1/28)	3.57% (1/28)	0% (0/28)	27.80	<0.0001
Second line IS drug	**SSNS**	2.5% (1/40)	20% (8/40)	7.5% (3/40)	5% (2/40)	0% (0/40)	16.94	<0.01
	SRNS	0% (0/28)	3.57% (1/28)	7.14% (2/28)	0% (0/28)	0% (0/28)	5.45	0.24
Third and fourth line IS drug	**SSNS**	0% (0/40)	0% (0/40)	0% (0/40)	2.5% (1/40)	2.5% (1/40)	3.03	0.55
	SRNS	0% (0/28)	3.57% (1/28)	0% (0/28)	0% (0/28)	7.14% (2/28)	5.45	0.24

DISCUSSION

The subject cohort consisted predominately of male in SSNS and SRNS but it is statistically not significant.

In a study by Amr El-Husseini et al the number of male were 54/74 (73.0%) for SDNS while they were 29/43(67.4%) in SRNS.[8]

The mean age and age at the diagnosis were 11.50±3.88 and 5.98±3.01 respectively were not statistically significant between SSNS and SRNS, P-value 0.4 and 0.74 respectively. A study by Amr El-Husseini et al reported that mean age and disease duration were 11.0±3.6 and 6.1±3 respectively for SDNS and 12.1±5.9 and 6.1±3.2 respectively for SRNS.[8]

The renal pathology among SSNS are minimal change disease in 12 patients (the predominant pathology) then focal segmental glomeulosclerosis in 4patients and IgM nephropathy in 1 patient while the renal pathology among SRNS are FSGS in 8 patients (the predominant pathology) then MCD in 4 patients and 1patient with MPGN.

A study by Amr El-Husseini et al reported that renal pathology were MCD in 27/74 (36.49%) for SDNS and 11/43 (25.6%) for SRNS, FSGS in 47/74 (63.51%) for SDNS and 32/43 (74.4%) for SRNS.

This study show no statistical significance between SSNS and SRNS like our study.[8]

Cyclosporine

In this study the complete remission achieved by cyclosporine among SSNS who used this drug 57.57%, and represent 50% of all SSNS included in this study which is comparable to study done by j.kim in which CR 57% but no partial remission and NR 43%.[9]

In a study by Ihab Mahmoud et al the SDNS patients (61 children), CsA was maintained for 22.6±10 months. Fifty-six(91.8%) children attained complete remission in response to combined therapy with CsA and prednisone and five children were resistant (8.91%) this remission rate is much higher than this study may be due to higher sample number and no s.level in our study.[10] The response to CsA has been correlated more with steroid response than with underlying histopathology.[11]

Fifteen SSNS patients undergone renal biopsy among those used cyclosporine. Of those with MCD, 5 patients achieve remission and 5 patients had no remission, Of those with FSGS, 3patients had no remission with cyclosporine, only 1 patient achieved remission and 1patient with IgM nephropathy had no remission with cyclosporine. This similar to study by niaudet regarding remission in MCD which is about 48% and for FSGS (25%).[12]

Among SRNS patients who used cyclosporine, 57.7% achieved remission, and about 39% remission among all patients with SRNS included in this study which is comparable to the result by Ponticelli C et al.[13] and Lieberman KV.[14] and also to study done by Bassam saeed et al in which remission achieved in 50% of patients (although CR in 14.2% and PR 35.7%).[15]

In a study done by Christian Plank et al, two of the 15 enrolled patients achieved complete remission by 12 weeks and maintained this at 24 weeks, In addition. Partial remission was seen in seven children treated with CSA at 12 and 24 weeks.[16] In another study by Ihab Mahmoud et al In SRNS patients (45 children), CsA was maintained for 21±12 months. Twenty patients (44.4%) attained complete remission in response to combined therapy with CsA and prednisone. Eight children showed partial remission.[10]

In our study 1 patient with SRNS failed to achieved remission and progressed to ESRD and dead, In a study done by Arpana Iyengar et al Children who are CsA resistant are at high risk to develop significant infections and CRF.[17] Seven SRNS patients undergone renal biopsy among those used cyclosporine. Of those with MCD,1patient achieve remission and 2 patients had no remission, those with FSGS had no remission with

cyclosporine (100%). unlike study In a large case study by Niaudet et al.[18], 48% of MCD patients and 30% of FSGS patients achieved complete remission, may be due to less number of patients did renal biopsy in our study.

In a study done by A. A. Nikibakhsh et al The highest response rate to CyA and prednisolone was observed in patients with MCD, The number of responder are 10(62.5%) and non responder are 6 (37.5%) while FSGS the responder are 1 (10%) and the non responders are 9 (90%).[19]

A study by- Kenji Ishikura et al report that patients experiencing relapse of nephrotic syndrome during treatment with cyclosporine are at high risk of relapse after discontinuation of the drug.[20]

Most patients with steroid-sensitive nephrotic syndrome have a good prognosis.[21,22] Nephrotoxicity is the most important adverse effect of CyA.[23,24] In daily clinical care, even partial remission seems to improve long-term renal survival.[25] A study by- Hodson EM et al confirmed the positive effect of CSA, with complete remission in 36% of the patients.[26]

In our study the reported adverse effect were infection 3.8%, hypertension 23%, tremor 3.8%, gum hypertrophy 23%, hirsutism 19.23%, hyperkalemia 15.3%, elevated s. creatinine 5.76%.

In a study by durkan et al Adverse effects are significant with 4% of children developing hypertension, 9% reduced renal function, 28% gum hypertrophy and 34% hirsutism.[27] In a study by K Ishikura et al, Hypertension 2 (10%), Hypertrichosis 3 (15%), Gingival hypertrophy 4 (20%).[28]

In our study the sustained remission rate was 24% with a mean duration 38.75 months (10-52)which is comparable to a study of K Ishikura et al, at month 24, the estimated sustained remission rate was 25%.[28]

Tacrolimus

In this study the remission achieved by tacrolimus among SSNS who used this drug (90.6%), and represent 25% of all SSNS included in this study this is lower than a study done by j kim et al in which CR 78%, PR 18% and NR in 4% may be due to difference in racial, genetic, geographical area and sample numbers.[10]

Four SSNS patients undergone renal biopsy among those used tacrolimus. Those with MCD achieved remission (100%) and 1patient with FSGS had no remission with tacrolimus.

Among SRNS patients who used tacrolimus, 42.5% achieved remission and about 10.7% remission among all patients with SRNS included in this study. Which is much lower than in study by j Kim et al (CR 54%, PR 23% and NR 23%).[10] This could be explained by differences in genetic, racial factors and s. level unavailable.

In a study by Sanjeev et al 19 children who received adequate therapy and were able to achieve target levels, CR was seen in 16 (84%) children, 2 (10.5%) attained PR and 1 was nonresponsive These remission rates are much better than the average remission rate of 60–65% that have been reported with other immunosuppressive agents in SRNS.[29] Loeffler et al. Found tacrolimus to be effective and well –tolerated for children with SRNS, with complete remission rate of 81% and a partial remission rate of 13%.[30] TAC was found to be beneficial in SRNS children who were nonresponsive to other treatments, including CsA.[29,30]

Gulati et al. reported a CR rate of 84% in a cohort of North Indian children treated with Tac and steroids.[29]

In our study 3 SRNS patients undergone renal biopsy among those used tacrolimus 42.85%. The patient with MCD achieve remission (100%) and those with FSGS achieved remission with tacrolimus (100%).

Bhimma et al. subsequently reported a CR rate of 40% and a PR rate of 45% in 20 South African children with SRNS from idiopathic FSGS who received a 12-month course of Tac.[31]

In our study the reported adverse effects were hypertension in 11% and impaired glucose tolerance in 11% which improve with decrease the dose,in astudy by xiayu Li et al the adverse events during the period of TAC therapy. One patient suffered reversible acute nephrotoxicity after 2 weeks of TAC therapy, and this patient recovered following treatment cessation. Two patients developed infections, one patient developed hepatotoxicity, as determined by an elevation of ALT (86 IU/L; normal: 3–50 IU/L), one patient experienced new-onset hypertension and was given antihypertensive therapy, and one patient developed gastrointestinal symptoms, characterized by nausea with vomiting.[32] The most common side effect was watery diarrhoea, which was seen in 7 of the 22 children. Acute renal dysfunction was observed in 3 children; it resolved with a decrease in dose in 2 children while one child developed TAC-induced HUS and required discontinuation of therapy. Hyperglycaemia was seen in 2 of the 22 children.[29]

The relapse free remission 28.57% in our study for SRNS but non for SSNS, the mean duration of follow up was 28 months (20-36). In a study Of the 16 children who attained CR, 2 patients are off steroids and TAC and in sustained remission, while the rest 14 are still on TAC therapy. The mean duration of follow-up is 290 ± 126 days.[29] In a study by ashima at 6 months, remission was sustained in more patients receiving tacrolimus (73.1%).[33]

MMF

In the study remission achieved by MMF among SSNS who used this drug 83%, and represent 12.5% of all SSNS included in this study (5/40), it is comparable to study done by j. kim et al CR 63%, PR 2% and NR 35%.[9]

Five SSNS patients undergone renal biopsy among those used MMF. Of those with MCD,2 patients achieve remission and 1 patient had no remission Those with FSGS achieved remission with MMF.

Mendiza´bal et al. reported on MMF treatment in 26 children with idiopathic nephrotic syndrome including 11 cases of steroid/cyclosporine-dependent MCN. Five patients received prednisone and MMF for 6–9 months: three maintained remission for over 6 months without immunosuppressive treatment (that is MMF, cyclosporine A or steroids) and two patients maintained remission without immunosuppressive treatment for 2–6 months. Six patients received prednisone and MMF for 6–19 months and relapsed after treatment.[34]

Among SRNS patients who used MMF, 30% achieved partial remission, and about 10.7% remission among all patients with SRNS included in this study (3/28).

Menzibal et al, treated 5 patients with SRNS and only one achieved complete remission.[34] Cattren et al reported 4 out of 18 patients showed partial remission. Nine out of 18 patients were resistant to MMF and renal function deteriorated in five patients.[35]

In a study of Catalina Velez Echeverri et al (n = 6), 4 patients (66.6%) had complete remission and 2 had (33.3%) partial remission.[36] Li et al., 24 children with SRNS, all patient received prednisone and mycophenolate for 6-12 months, complete remission was achieved in 62.5% of the patients.[37]

Of those with MCD, 1patient achieve remission (50%) and patient had no remission (50%), those with FSGS had no remission in 3 patients with MMF (75%) and 1patient achieved remission (25%), the patient with MPGN had NR with MMF.

Mendiza´bal et al. reported on MMF treatment in 26 children with idiopathic nephrotic syndrome including 13 patients with FSGS. A. MMF was given to FSGS patients for a mean period of 12 months as an alternative treatment to cyclosporine A. Nine out of 13 patients achieved a full remission, one patient remained in remission after complete drug withdrawal for more than 6 months.[34]

In our study 6.25%(1/16) had infection, leukopenia in 6.25%(1/16) and gastrointestinal problems in 12.5%(2/16).

Two patients out of 10 SRNS (20%) developed CKD and 1 patient (10%) progress to ESRD.

In a study done by catalina et al MMF was well tolerated, 11.5% of the patients (n = 3) developed diarrhea, and 15.4% severe infections (n = 4), in those patients MMF was temporarily suspended. In spite of that, none of these complications were severe enough to require a change of treatment.[36]

In our study Two patients out of 10 SRNS developed CKD and 1 patient progress to ESRD.

A study of catalina et al reported 11.5% (3/26) of the patients developed chronic renal failure; in these patients the MMF was definitively suspended. No patient died during this treatment.[36]

Cyclophosphamide

A complete remission achieved by Cyclophosphamide among SSNS who used this drug 80% and represent 10% of all SSNS included in this study comparable to a study by Sanjeev Gulati et al remission was (70%).[38]

Four SSNS patients undergone renal biopsy among those used Cyclophosphamide, all of them MCD,3 patients achieved remission and 1 patient had no remission with Cyclophosphamide. Which is like a study by Sanjeev Gulati et al that MCD has a much better long term response to cyp and study by Broyer M et al.[38,39]

Vester et al. have reported a relapse-free survival of 44%, 34% and 24% at 1, 2 and 10 years after CYP in a cohort of 94 children with biopsy-proven minimal change disease.[40]

In a cohort of 93 Dutch patients with biopsy-proven minimal change disease, 33 (35%) never experienced relapse after the first course of CYP.[41]

Among SRNS patients who used Cyclophosphamide, (33.2%) achieved remission, and about 3.57% remission among all patients with SRNS included in this study. In a study done by Ihab Mahmoud et al, Fifty-four children (25 SRNS and 29 SDNS), who showed evidence of steroid toxicity, received oral cyclophosphamide therapy (2 mg/kg/day) for 12 weeks. Three SRNS patients (6.7%) and 10 SDNS patients (16.4%) were responsive. Meanwhile, 22 SRNS children (48.9%) and 19 SDNS children (31.1%) were resistant.[10]

Three SRNS patients undergone renal biopsy among those used Cyclophosphamide. The patient with MCD no remission (100%), those with FSGS one had no remission with Cyclophosphamide (50%) and the other achieved remission (50%).

In our study the reported adverse effect;1 patient using cyclophosphamide out of 11 developed recurrent UTI and Leukopenia (WBC count <5000) reported (9%) in 1

patient. The adverse effects noted in study by Florentina CUCER were: leukopenia (1 patient), acute chemical cystitis (1 patient), allopecia (1 patient) and two cases with severe infections (tuberculous serositis – 1 patient, primary peritonitis – 1 patient).[42]

In our study sustained remission achieved in 40%(2/5) SSNS patients with a mean duration of 12months and in 16.6%(1/6)SRNS patients with a mean duration of 24 months. In a study by Benoît Cammas et al ongoing remission after CYP was obtained in 29 of 143 SSNS patients (20.5%) after a median follow-up of 1.9 years (range 3 months to 7 years).[43]

Rituximab

A complete remission achieved by Rituximab in one SSNS patient used this drug 100% and represent 2.5% of all SSNS included in this study.

In the study of Guigonis et al., patients received two to four infusions of 375 mg/m2 of rituximab including seven patients who were nephrotic at the time of treatment; three of these achieved a full remission.[40]

In a study by Markus et al After the initial rituximab treatment, 26/37 (70.3%) patients remained in remission for 12 months.[44]

One SSNS patient undergone renal biopsy who used Rituximab and had IgM nephropathy who achieved remission (100%) with Rituximab.

Another study by Gilbert RD et al reported the successful use of RIT in a paediatric patient with high-dose steroid-dependant MCD and multiple relapses. She remained in remission for 9 months until her CD19 cells reappeared and shortly after she had a relapse. At 16 months, she had two further dosages of RIT with further remission.[45] B-cell depletion was defined as a CD19+ cell count <10 cells/mm 3 at any time, and B-cell re-emergence was defined as a CD19+ cell count >10 cells/mm.[46] Smith et al.[47], Bagga et al.[47] and Hofstra et al.[48] recently reported five further cases in total of successful use of RIT in NS secondary to MCD.

Relapse free remission occur in 100%(1/1) after 7 months which is higher than in a study by markus et al Twenty-four of 37 (64.8%) patients developed relapses at a median of 9.6 (5.2–64.1) months after the initial course of rituximab but our study include one patient only.[44] Another recent study from Kamei et al. from Japan showed that a single dose of rituximab was able to initiate steroid-free remission in all 12 patients included. However, 75% of patients relapsed and only three had sustained remission for >1 year.[50]

Among SRNS patients who used Rituximab, 50% achieved PR and about 7.14% remission among all patients with SRNS included in this study (2/28).

Three SRNS patients undergone renal biopsy among those used Rituximab. The patient with MCD achieve remission and those with FSGS had no remission with Rituximab. Bagga et al. reported the successful use of RIT in steroid-resistant NS patients in two patients with FSGS and three with MCD.[48]

A recent international study reported a superior initial response of steroid-sensitive (82%) compared to steroid-resistant patients (44%) comparable to our study; again, median remission in this report was only 4.5 (range 1–10) months.[51]

In our study the reported adverse effects were leukopenia in 20%(1/5), and thrombocytopenia in 20%(1/5), in the study with Bagga and Hofstra.[43,35] no major adverse effect was reported in both studies.

Complications of rituximab treatment have been reported, including death due to pulmonary complications.[52,46]

In our study the relapse free remission was 100%(1/1) for a duration of 7 months.

In a study by Bitzan M et al, The disease in all patients remained in remission for a median of 2.2 years after their first RTX infusions. However, three relapses occurred in 3 patients (patients 2–4) following the start of RTX (the period from starting RTX to relapse was 2.2, 1.9, and 2.3 years, respectively); all of these relapses developed in parallel with the re-emergence of B cells.[46]

CONCLUSION

There is statistical significant difference regarding hypertension among SRNS and statistical significant difference regarding urine protein /creatinine ratio among SSNS. The renal pathology was predominantly MCD among SSNS and FSGS among SRNS. The best IS drug in achieving remission was the cyclosporine in both SSNS and SRNS then Tacrolimus. MMF represent a suitable alternative to calcineurin inhibitors especially those patients with renal impairment because it is be useful for treating patients with fewer side effects and in achieving sustained remission. Rituximab is an effective new option for patient with SSNS in achieving remission although the study include one patient only. The most reported adverse effects were with cyclosporine and the most reported were gum hypertrophy, hypertension, hirsutism and hyperkalemia.

ETHICAL APPROVAL

All data concerning patients and their records remained confidential. The protocol trial was approved by the local ethic.

REFERENCES

1. Gb. Rasheed and Smoyer. WE. Nephrotic Syndrome. Comprehensive pediatric nephrology. 1st ed. Philadelphia: Elsevier, 2008; 12: 205-218.

2. Valentine RP. and Smoyer. WE. Nephrotic Syndrome. Cinical pediatric nephrology. 2nd ed. United kingdom: informa, 2006; 11: 155-185.
3. S. Simon, A. Neil,et al. diseases of the kidney. Oxford handbook of nephrology and hypertension. 2nd ed. United Kingdom, 2014; 7: 529-602.
4. Savin VJ, Sharma R M et al. ciculating factors associated with increase permeability to albumin in recurrent focal segmental glomerulosclerosis. New Engl J Med., 1996; 334: 878-883.
5. Bitzen M. Glomerular diseases. Manual of pediatric nephrology. 1st ed. Verlage Berlin Heidelberg: Springer, 2014; 3: 141-227.
6. Rees L, Brogan PA., et al. Oxford specialist handbook in pediatric nephrology. 2nd ed. United kingdom, 2012; 9: 192-222.
7. Patrick Niaudet and Olivia Boyer. Idiopathic nephrotic syndrome in children: clinical aspect. pediatric nephrology. 7th ed. Verlage Berlin Heidelberg: Springer, 2016; (28): 840-882.
8. El-Husseini A., El-Basuony F., Mahmoud I.et al. Long- term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. Nephrol Dial Transplant, 2005; 20: 2433–2438.
9. J. Kim N. Patnaik N. Chorny R. Frank L. Infante C. Sethna. Second-Line Immunosuppressive Treatment of Childhood Nephrotic Syndrome: A Single-Center Experience. Nephron Extra, 2014; 4: 8–17.
10. Mahmoud I., Basuni F., Sabry A., El-Husseini A. et al. Single-centre experience with cyclosporin in 106 children with idiopathic focal segmental glomerulosclerosis. Nephrol Dial Transplant, 2005; 20: 735–742.
11. Phadke K, Ballal S, Maiya V. Cyclosporine experience in nephrotic syndrome. Indian Pediatrics, 35: 111-116.
12. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French society of pediatric nephrology. J Pediatr, 1994; 125: 981–986.
13. Ponticelli C, Edefonti A, Ghio L et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. Nephrol Dial Transplant, 1993; 8: 1326–1332.
14. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. J Am Soc Nephrol, 1996; 7: 56–63. [PubMed: 8808110]
15. Saeed B. et al,. Cyclosporine utilization in idiopathic nephrotic syndrome in children. Saudi journal of kidney diseases and transplantation, Dec, 2006; 17(4): 497-502.
16. P.Christian, K. Veronica et al. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome—a randomized controlled multicentre trial by the Arbeitsgemeinschaft für Pädiatrische Nephrologie. Pediatr Nephrol, September, 2008; 23(9): 1483–1493.
17. Iyengar A., Karthik S.et al. Cyclosporine in Steroid Dependent and Resistant Childhood Nephrotic Syndrome. INDIAN PEDIATRICS, JANUARY, 2006; 17: 43.
18. Niaudet P, Fuchshuber A, Gagnadoux MF, Habib R, Broyer M. Cyclosporine in the therapy of steroid resistant idiopathic nephrotic syndrome. Kidney Int, 1997; 58: S85–S90. [PubMed: 9067953].
19. Nikibakhsh A.A., Mahmoodzadeh H.et al. Treatment of Steroid and Cyclosporine-Resistant Idiopathic Nephrotic Syndrome in Children. International Journal of Nephrology, Dec, 2011; 2011: 930965.
20. Ishikura K., Yoshikawa N.et el. Two-Year Follow-Up of a Prospective Clinical Trial of Cyclosporine for Frequently Relapsing Nephrotic Syndrome in Children Clin J Am Soc Nephrol, October, 2012; 7: 1576–1583.
21. Koskimies O, Vilska J, Rapola J et al. Long-term outcome of primary nephrotic syndrome. Arch Dis Child, 1982; 57: 544–548.
22. Trompeter RS, Lloyd BW, Hicks J et al. Long-term outcome for children with minimal-change nephrotic syndrome. Lancet, 1985; 1: 368–370.
23. Meyrier A. Treatment of idiopathic nephrotic syndrome with cyclosporine A. J Nephrol, 1997; 10: 14–24.
24. Radhakrishnan J, Halevy D. Cyclosporin treatment of glomerular diseases. Expert Opin Investig Drugs, 2000; 9: 1053–1063.
25. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet, 2003; 362: 629–639. [PubMed:12944064]
26. Hodson EM, Habashy D, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst, 2006 Rev: CD003594.
27. Durkan AM, Hodson EM, Willis NS, Craig JC Immunosuppressive agents in childhood nephrotic syndrome: a metaanalysis of randomised controlled trials. Kidney Int, 2001; 59: 1919–1927.
28. Ishikura K, Ikeda M. et al. Effective and safe treatment with cyclosporine in nephrotic children: A prospective, randomized multicenter trial. Kidney International, 2008; 73: 1167–1173.
29. Gulati S., Prasad N.et al. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant, 2008; 23: 910–913.
30. Loeffler K, Gowrishankar M, Yiu V. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol, 2004; 19(3): 281–287.
31. Bhimma R, Adhikari M, Asharam K, Connolly C. Management of steroid-resistant focal segmental glomerulosclerosis in children using tacrolimus. Am J Nephrol, 2006; 26(6): 544–551.

32. Xiayu Li, Nan Xu, Heng Li et al. Tacrolimus as rescue therapy for adult-onset refractory minimal change nephrotic syndrome with reversible acute renal failure. Nephrol Dial Transplant, 2013; 28: 2306–2312.
33. Gulati A., Sinha A.et al. Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. Kidney International, 2012; 82: 1130–1135.
34. Mendizabal S, Zamora I, Berbel O, Sanahuja MJ, Fuentes J, Simon J. Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome. Pediatr Nephrol, 2005; 20(7): 914–919.
35. Cattran DC, Wang MM, Appel G, Matalon A, Briggs W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis.Clin Nephrol, 2004; 62(6): 405–411.
36. Echeverri C V, Valencia G A Z, et al. Immunosupressive therapy in children with steroid-resistant nephrotic syndrome: single center experience J Bras Nefrol, 2013; 35(3): 200-205.
37. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, et al. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. Pediatr Nephrol, 2010; 25: 883-8.
38. G. Sanjeev, Pokhariyal S. et al. Pulse cyclophosphamide therapy in frequently relapseing nephrotic syndrome. Nephrol Dial Transplant, 2001; 16: 2013-2017.
39. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal change and focal glomerular sclerosis. In: Davidson AM, Cameron JS, Grunfeld JP, Kerr DNS, Ritz E, Winerals CG(eds). Oxford textbook of clinical nephrology. Oxford University Press, Oxford, 1998; 493-535.
40. Guigonis V, Dallocchio A, Baudouin V et al. Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol, 2008; 23: 1269–1279.
41. Kyrieleis HA, Levtchenko EN, Wetzels JF. Long-term outcome after cyclophosphamide treatment in children with steroid-dependent and frequently relapsing minimal change nephrotic syndrome. Am J Kidney Dis., 2007; 49: 592–597.
42. CUCER F., MIRON I. et al, Treatment with Cyclophosphamide for steroid-resistant nephrotic syndrome in children. Maedica A Journal of Clinical Medicine, 2010; 5: 3.
43. Cammas B., Harambat J.et al. Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. Nephrol Dial Transplant, 2011; 26: 178–184.
44. Markus J. Kemper, Jutta Gellermann, Sandra Habbig et al. Long-term follow-up after rituximab for steroid-dependent idiopathic nephrotic syndrome. Nephrol Dial Transplant, 2012; 27: 1910–1915.
45. Gilbert RD, Hulse E, Rigden S. Rituximab therapy for steroiddependent minimal change nephrotic syndrome. Pediatr Nephrol, 2006; 21: 1698–1700. [Epub 2006 Aug 24]
46. Bitzan M, Anselmo M, Carpineta L. Rituximab (B-cell depleting antibody) associated lung injury (RALI): a pediatric case and systematic review of the literature. Pediatr Pulmonol, 2009; 44: 922–934.
47. Smith GC. Is there a role for rituximab in the treatment of idiopathic childhood nephrotic syndrome? Pediatr Nephrol, 2007; 22: 893–898. [Epub 2007 Feb 20]
48. Bagga A, Sinha A, Moudgil A. Rituximab in patients with the steroid-resistant nephrotic syndrome. NEngl J Med., 2007; 356: 2751–2752.
49. Hofstra JM, Deegens JK, Wetzels JF. Rituximab: effective treatment for severe steroid-dependent minimal change nephrotic syndrome? Nephrol Dial Transplant, 2007; 22: 2100–2102.
50. Kamei K, Ito S, Nozu K et al. Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol, 2009; 24: 1321–1328.
51. Ravani P, Magnasco A, Edefonti A et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol, 2010; 6: 1308–1315.
52. Chaumais MC, Garnier A, Chalard F et al. Fatal pulmonary fibrosis after rituximab administration. Pediatr Nephrol, 2009; 24: 1753–1755.