Efficacy of alternative treatment to steroid in Children with Steroid Dependent and Frequently Relapsing Nephrotic Syndrome

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Abstract

Background: Management of steroid dependent nephrotic syndrome and frequent relapsing nephrotic syndrome in children are more complicated than the management of simple steroid sensitive nephrotic syndrome.

Aim of study: Our purpose was to compare the efficacy of (levamisole, cyclophosphamide, cyclosporine A, mycophenolate mofetil and prednisolone) in patients with steroid dependent and frequent relapsing nephrotic syndrome.

Patients and methods: A retrospective study was conducted in the nephrology unit in central teaching hospital of pediatrics, Baghdad, Iraq. Records of patients from January 2011 to December 2015 were analyzed during the study period from the first of April 2016 to the first of February 2017, children (age from one to fifteen years) diagnosed with steroid dependent and frequent relapsing nephrotic syndrome, their data were collected based on the record of the patients (sex, age of patient at time of diagnosis, time at which the drug was started, treatment protocol, treatment duration, response to treatment, time of 1st relapse after administration of alternative drug with steroid, time of second relapse after treatment, and number of relapses during two years follow up) to evaluate the efficacy of (Levamisole, Cyclophosphamide, Cyclosporin A, Mycophenolate mofetil and Prednisolone) for long term remission up to two years in these patient.

Results: Seventy six children diagnosed with steroid dependent and frequent relapsing nephrotic syndrome were enrolled in this study, forty seven cases (61.84%) were diagnosed as steroid dependent nephrotic syndrome and twenty nine (38.15%) of them were frequent relapsing nephrotic syndrome. Relapse free survival for each medications as following; for Levamisole group 53.3%, 13.3%, 6.6% at six months, one and two years interval of treatment respectively, for Cyclophosphamide group 76%, 48%, 24% at six months, one and two years interval respectively, for Cyclosporine A group 63.6%, 36.3%, 13.6% at six months, one and two years interval respectively ,in Mycophenolate mofetile group 62.5%, 37.5%, 12.5% at six months, one and two years of treatment respectively and for Prednisolone group only two patients out of six (33.3%) remain relapse free for the first six months of treatment, the difference was significant in patients with remission during two years follow up between these five groups (P = 0.006, long-rank test).

Conclusions: Cyclophosphamide is more effective in short and long term treatment (more than two year of remission) of steroid dependent and frequent relapsing nephrotic syndrome, whereas Prednisolone the least effective in long term remission.

Cyclosporine A is more effective than Mycophenolate mofetile and Levamisole but most patients relapse after stop taking these drugs.
Key words: steroid dependent nephrotic syndrome, frequent relapsing nephrotic syndrome, levamisole, cyclophosphamide, cyclosporine A, mycophenolate mofetil, and prednisolone.

فاعليه العلاجات البديله للستيرويد في الاطفال المصابين بمرض التناذر الكلوي المعتمد على الستيرويد والمتكرر الانتكاسات

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الخلاصة

خلفية الدراسة: كان ولايزال علاج مرض التناذر الكلوي المعتمد على الستيرويد والمتكرر الانتكاسات يعتبر تحديا لاختصاص اطفال امراض الكلى. بالاضافه الى التاثير الجانبي الناتج عن استخدام الستيرويد مما يدعو الى البحث عن بدائل افضل واكثر امانا.

اهداف الدراسة: تهدف الدراسة الى مقارنة فعالية العديد من العلاجات كالليفاميسول ساسكلوفوسفامايد سايكلوسبورين أ المايكوفينوليت موفتل والبردنزلون في المرضى المصابين بالتناذر الكلوي المعتمد على الستيرويد والمتكرر الانتكاسات.

المنهجية: اجريت هذه الدراسة الاسترجاعية دراسه في وحده امراض الكلى في مستشفى الطفل المركزي في بغداد/ العراق بين شهر كانون الثاني الفان واحد عشر الى كانون الاول الفان وخمسه عشر.وخلال فتره الدراسه من الاول من نيسان الفان وسته عشر سنه مصابين بمرض التناذر الكلوي المعتمد 15-1الى الاول من شباط الفان وسبعه عشر. الاطفال من عمر على الستيرويد والمتكرر الانتكاسات.بياناتهم جمعت بالاعتماد على فايلات المرضى وقسمت حسب (الجنس والعمر المرض عند تشخيص الحاله وطريقه العلاج وفتره العلاج والاستجابه للعلاج ووقت اول انتكاسه بعد بدء العلاج ووقت ثاني انتكاسه بعد بدء العلاج وعدد الانتكاسات خلال فتره سنتين) لتقييم فعاليه العلاج (ليفاميزول والسايكلوفوسفامايد والسايكلوسبورين أ والمايكوفينوليت موفتيل والبردنزلون) على المدى القريب والبعيد.

النتائج: سته وسبعون طفل مشخصين بتناذر كلوي معتمد الستيرويد ومتكرر الانتكاسات شملوا في هذه الدرسه ،كان منهم 35 ذكر (46,05% من الكلي) وبينما عدد الاناث 41 (53,94% من الكلي) وبينما عدد الاناث 41 (53,94% من الكلي) و 47 حالة (61,84%) معتمد على الستيرويد و 29 حالة (38,15%) متكرر الانتكاسات. تسعة عشر (25% من الكلي) عملوا خزعة من الكلى و التغييرات النسيجية في 12 منهم (63,1%) كانت لديهم تغييرات طفيفة و 5 (62,3%) منهم كان لديهم التصلب الكعبي القطعي البؤري و اثنان منهم (10,5%) تكاثر مسنجي. المرضى الذين لم يعانوا من انتكاسة لكل علاج كانت كالاتي, ليفاميسول 53,3%, 13,3%, 6,6% خلال ستة اشهر وسنة و سنتين بالترتيب وبالنسبة للسايكلوفوسفامايد 76%, 48%, 24% خلال ستة اشهر وسنة وسنتين بالترتيب وللسايكلوسبورين أ 63,6%, 36,3%, 13,6% خلال ستة اشهر وسنة وسنتين بالترتيب وللمايكوفينوليت موفيتيل 62,5%, 37,5%, 12,5%, خلال ستة اشهر وسنة وسنتين بالترتيب وللبريدنسولون فقط مريضين من ستة (33,3%) بقوا بدون انتكاسة خلال فترة الستة اشهر الاولى من العلاج وكانت النسبة التراكمية للذين بقوا بدون انتكاسة خلال سنتين ذات قيمة احصائية عالية بين الخمس مجموعات (قيمة ب = 0,006 باختبار لونك رانك).

الاستنتاج: السايكلوفوسفامايد هو الأكثر تاثير على المدى القريب والبعيد لمرضى التناذر الكلوي المعتمد على الستيرويد والمتكرر الانتكاسات وبيناما البردنزلون هو الأقل تاثير على المدى البعيد . السايكلوسبورين أ هو اكثر تاثير من المايكوفينوليت موفتيل والليفاميسول لكن اغلب المرضى ينتكسون بعد وقف هذه العلاجات.

Introduction

Nephrotic syndrome (NS) defined as the presence of edema, proteinuria more than 40 mg/m2/h or a urine protein-to-creatinine ratio more than 2.0 and hypoalbuminemia less than 2.5 g/dl [1]. (Nephrotic Syndrome is classified into primary or secondary, or according to age of onset (congenital, infantile, and late onset NS), also can be classified histopathologicaly into minimal change disease (MCD), mesangial hypercellularity, focal segmental glomerulosclerosis (FSGS), membranous

glomerulopathy, and membranoproliferative. The most practical classification is according to response to steroids (steroid sensitive or resistant, with steroid sensitive disease also classified into frequent relapses and steroid dependent NS) [2]. Steroid dependent nephrotic syndrome (SDNS) defined as the Patients who have steroid sensitive NS and develop a relapse during weaning of the dose of steroids, or within 2 weeks of discontinuing treatment with steroid while Frequent relapsing nephrotic syndrome (FRNS) defined as two or more relapses of nephrotic syndrome within a 6 months period after starting steroid or four or more relapses within any twelve month period [1, 3].

Alternative treatments: Steroid sparing agents used in patients with the dose of steroid more than 0.7 mg/kg which is necessary for remission and when signs of steroid toxicity are developed [4]. Alternative treatments include: Levamisole used in a dose of 2.5 mg/kg every other day to decrease the risk of relapse in steroid dependent patients. A significant steroid-sparing effect at a dose of 2.5 mg/kg every other day [5]. Oral cyclophosphamide used in a dose of 2-3 mg/kg/daily with prednisolone 1 mg/kg every other day for 8-12 weeks induces sustained remission in 25-60 % of patients with FRNS or SDNS at 2-5 year follow up [6]. Cyclosporine A (CSA) also used in treatment of patients with FRNS and SDNS. The dose of CSA is 4-6 mg/kg (100-150 mg/m2) daily, achieves blood trough levels of 150-250 ng/ml [7]. Tacrolimus at a dose of 0.1 mg/kg daily divided every 12 hours and achieves trough level about 5-10 ng/ml [8]. Mycophenolate mofetil (MMF) is used in patients with SDNS and can be used for a longer duration than 12 months. Doses of 450–600mg/m2 /day in two divided doses [9]. Rituximab (anti-CD20 monoclonal antibody) has been successfully used to treat patients with refractory NS including SDNS in the last decade [10].

Patients and methods

The records of 76 children, who attended the pediatric nephrology unit at Central Teaching Hospital of pediatrics, in Baghdad between January 2011 and December 2015 were analyzed retrospectively during the study period from the 1st of April 2016 to the 1st of February 2017. Children age from 1 to15 years were diagnosed with SDNS/FRNS and met the inclusion criteria that will be explained later were involved our study. Data were collected based on the records of patients, their sex, age of patient at time of diagnosis, time at which the drug was started, treatment protocol, treatment duration, response to treatment, time of 1^{st} relapse after administration of alternative drug with steroid, time of second relapse after treatment, and number of relapses during 2 years follow up. Inclusion criteria include children age at time of diagnosis more than 1 year to less than 15 years, children were diagnosed with SDNS or FRNS, and patients continue follow up at least 6 months from the starting of treatment. Exclusion criteria include congenital NS, infantile NS, SRNS and NS secondary to systemic illnesses were excluded, Patient who lost follow up early in the treatment or who did not complete at least 6 months after starting treatment, Some drugs like (Rituximab, Chlorambucil, and Tacrolimus) were not included in our study because most patients used these drugs did not meet the inclusion criteria .Patients who developed serious side effects and discontinued treatment or changed line of treatment, and patient with abnormal renal function tests at time of presentation.

Definitions: cases were diagnosed and selected according to the definition of nephrotic syndrome triad of edema, proteinuria more than 40 mg/m2/h or a urine proteinto:creatinine ratio more than 2.0 and hypoalbuminemia less than 2.5 g/dL, SDNS

was defined as 2 consecutive relapses during treatment with corticosteroid, or within 14 days of discontinue treatment with steroid. Whereas FRNS was defined as 2 or more relapses during 6 months of initial response, with four or more relapses in any twelve months period. Patients regarded as complete remission when urine proteins <1+ on dipstick (manufactured by Melson Medical Corporation Limited/china) for 3 consecutive days and relapse when 3+ or more protein on urine dipstick for 3 consecutive days. Patients who did not have relapse from the time of administration of alternative medications to steroid were regarded as relapse free survivals.

Treatment protocols: all children were received prednisolone (60 mg/m2/day orally) daily, for 4-6 weeks, then (40 mg/m2 every other day) for 4 weeks before start decreasing prednisolone at 15 mg/m2 every 2 weeks for about 4 to 6 months period .when relapse occurred, prednisolone was given (60 mg/m2/day) daily until the child reaches remission, then prednisone (40 mg/m2) every other day for 4 weeks, followed by alternate-day prednisolone with tapering doses until a dose of (10-30 mg/m2)is reached while the patient still in remission. This dose then might continue for 12 to 24 months .

Levamisole was started at a dose of 2.5 mg/kg/day after inducing remission by steroid and the dose of prednisolone was given 40 mg/m2 every other day for 4 weeks and then decrease the dose gradually to 0.5 mg/kg every other day at 6 months and 0.25 mg/kg every other day for 1 year. Levamisole was given for at least 6 months before considering it ineffective, and it might continue for 12 months. Cyclophosphamide was given at a dose (2-3 mg/kg/daily) for 8-12 weeks and PDN (1 mg/kg) on alternate days then tapered and stopped. Cyclosporine A was given at a dose of 4-6 mg/kg/day (100-150 mg/m2/day) for 6 months with oral prednisolone given at the same time at a dose of 0.5 mg/kg/day in FRNS and at double the dose of dependency in SDNS [4]. Mycophenolate mofetil 20–30 mg/kg per day (maximum dose 1 g) (450600mg/m2/day) in two divided doses for about 12 months in combination with low dose steroids.

Patient follow up

All children during relapse were followed up one time weekly in the first month, then every two weeks in the second month and then every month, patients were sent for laboratory assessment, urine analysis (urine dipstick analysis for protein, and sometimes 24 hour urine collection for protein), blood analysis (serum protein, serum albumin), renal function (blood urea and serum creatinine), serum electrolyte (calcium, sodium, potassium) and complete blood picture.

Statistical analysis

The efficacy of each drug was analyzed in three areas. Patients with no relapse during the 1st 6 months, 12 months and more than 1 year follow up. For statistical analysis, the IBM SPSS Statistics 22 and Microsoft Excel programs were applied. Kaplan–Meier survival analysis to compare those groups of patients. Long rank test to compare the number of relapse and relapse free during 2 years follow up between these drugs, P-value less than 0.05 was defined as significant.

Results

A total number of 76 cases was enrolled within this study that were diagnosed with SDNS/FRNS. According to the gender there was 35 male (46.05% of total cases) Vs 41 female (53.94% of total cases), 47 cases (61.84%) were diagnosed as SDNS and 29(38.15%) of them were FRNS. About SDNS there were 22(28.94%) males and 25(32.89%) females, but for FRNS there were 13(17.1%) males and 16(21.05%)

females. The age of 76 patients ranged from 1 to 15 year, median age at time of diagnosis was 3 years, 53 patients (69.7%) their age range from 1 to 5 years at presentation , 32(42.1%) of them were SDNS and 21(27.6%) were FRNS,18 patients (23.6%) their age range (>5-10) years, of them 12(15.7%) and 6(7.8%) were diagnosed as SDNS and FRNS respectively, and 5 patients(6.5%) more than10 years of age 3 of them (3.9%) were SDNS and 2 (2.6%)were FRNS.

Medications used in treatment of nephrotic syndrome (cyclophosphamide, cyclosporine A, mycophenolate mofetil, levamisole, prednisolone) and the number of patients used these drugs were classified accordingly; for CYP 25(32.8%) patients involved in this study, LEV 15(19.7%) patients, MMF 8(10.5%) patients, PDN 6(7.8%) patients, and CSA 22(28.9%) who meet the inclusion and exclusion criteria and involved in this study as shown the following table (1).

Table 1: Numbers and percentage of patients and drugs involved in the study.

Drugs	No. of patients	Percentage%
Cyclophosphamide	25	32.8%
Cyclosporine A	22	28.9%
Levamisole	15	19.7%
Mycophenolate mofetil	8	10.5%
Prednisolone	6	7.8%
Total	76	100%

Relapse free survival for each group according to their treatment were analyzed during three period of time, for levamisole (LEV) group 53.3%, 13.3%, 6.6% at 6 months, 1 and 2 years respectively, for cyclophosphamide (CYP) group 76%, 48%, 24% at 6 months, 1 and 2 years respectively, for cyclosporine A (CSA) group 63.6%, 36.3%, 13.6% at 6 months, 1 and 2 years respectively ,in mycophenolate mofetil (MMF) group 62.5%, 37.5%, 12.5% at 6 months, 1 and 2 years respectively and for prednisolone (PDN) group only 2 patients of 6 (33.3%) remain relapse free for the 1st 6 months of treatment as shown in the following table (2).

Table 2: Relapse free survival for each group of drugs.

Time period	LEV	CYP	CSA	MMF	PDN
Relapse free 1st 6 months	8 (53.3%)	19 (76%)	14 (63.6%)	5 (62.5%)	2 (33.3%)
Relapse free during 1 yr	2 (13.3%)	12 (48%)	8 (36.3%)	3 (37.5%)	Nil
Relapse free during 2 yr	1 (6.6%)	6 (24%)	3 (13.6%)	1 (12.5%)	Nil
Total	15	25	22	8	6

We used Kaplan–Meier survival analysis to compare time without relapse (cumulative sustained remission) during treatment with levamisole, cyclosporine, cyclophosphamide, mycophenolate mofetil and prednisolone, there was a significant difference in the cumulative sustained remission during 2 years follow up between these 5 groups (P = 0.006, long-rank test) as shown in the following figure (1).

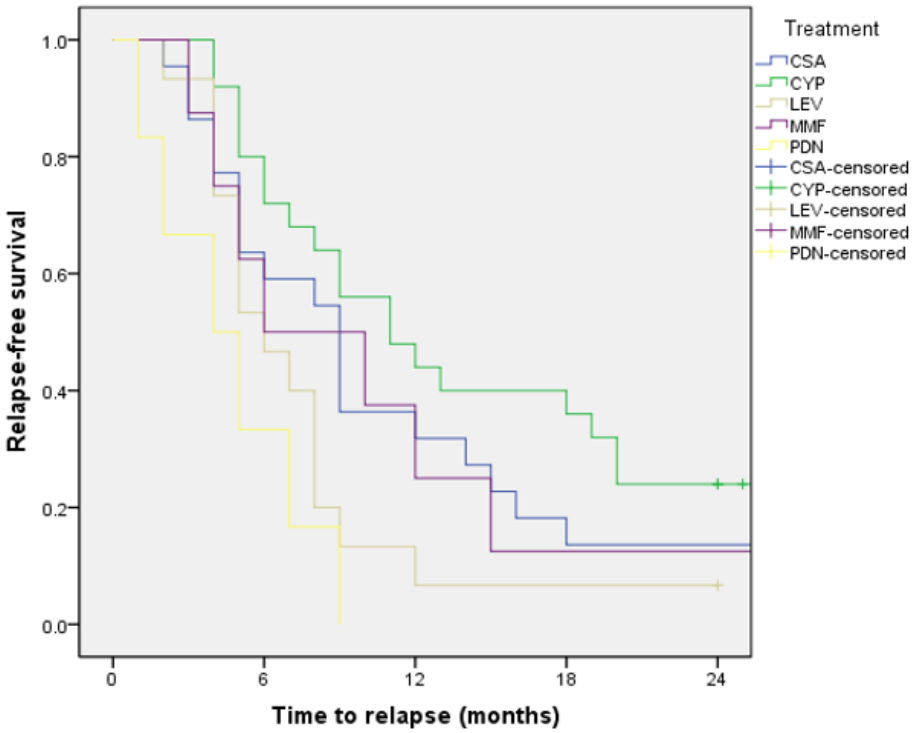

Figure 1: Relapse free survival curve for each drug

The mean time for first and second relapse with standard error for each drug was demonstrated in the following table (4) which shows for prednisolone 4.66 ±1.22, 6.16 ±0.9 for 1st and 2nd relapse respectively, for mycophenolate mofetil was 10.12 ±2.7, 11.66±2.9 for 1st and 2nd relapse respectively, for cyclosporine A 10.63±1.63, 12.69±0.94 for 1st and 2nd relapse respectively, for cyclophosphamide 13.72±1.62, 16.5±1.64 for 1st and 2nd relapse respectively, and for levamisole 7.4±1.35, 9.3±1.4 for 1st and 2nd relapse respectively. P value was significant between these five groups of drugs during the time of first relapse (0.026) and the time second relapse (0.001).

Table 3: Mean time for first and second relapse for each drug groups

Type of medication	Time of first relapse (months)		Time of second relapse (months)	
	No	Mean ± SE	No	Mean ± SE
Prednisolone	6	4.66±1.22	5	6.16±0.9
Mycophenolate Mofetil	8	10.12±2.7	7	11.66±2.9
Cyclosporine A	22	10.63±1.63	13	12.69±0.94
Cyclophosphamide	25	13.72±1.62	3	16.5±1.64
Levamisole	15	7.4±1.35	6	9. 3±1.4
Statistical analysis	P value	0.026		0.001

The following chart demonstrate mean of first and second relapse after administration of each drug figure (2).

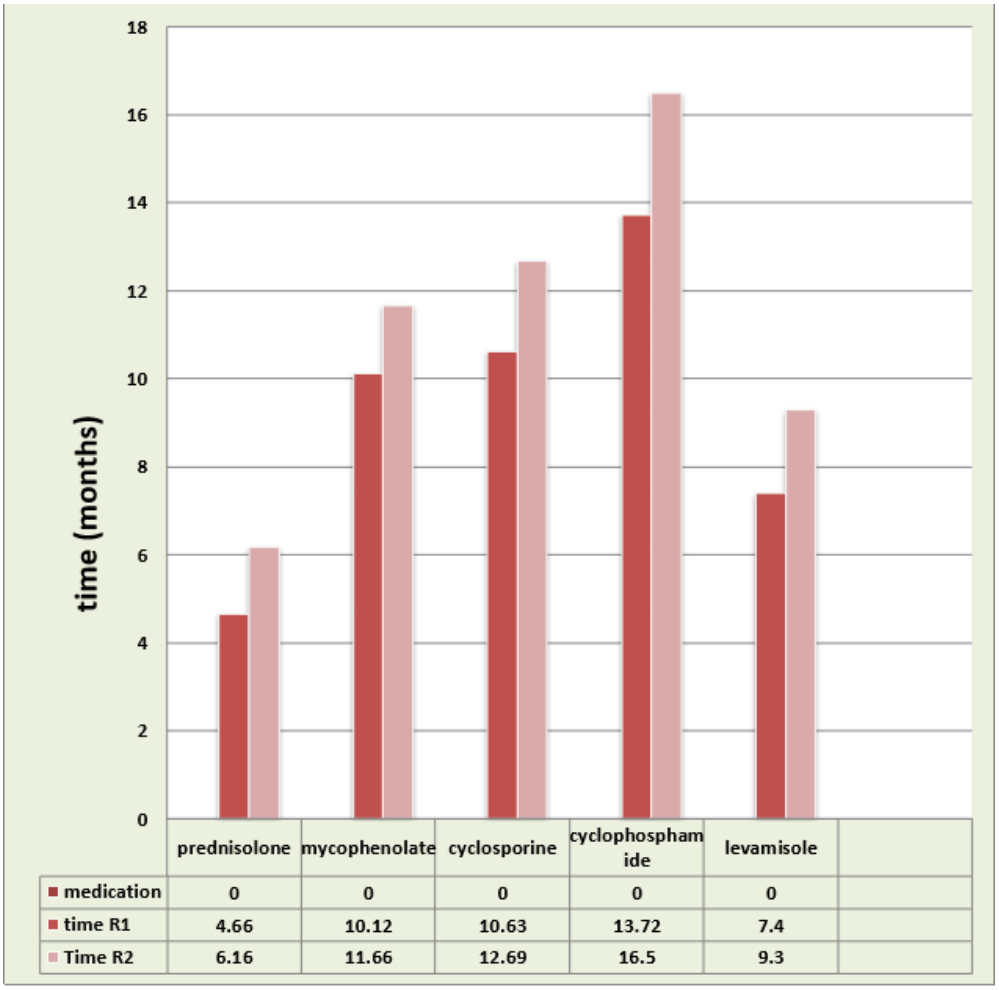

Figure 2: Mean time of first and second relapses for each drug

During two year follow up median time of study was (18±6) months during that period relapse number for each drug was as shown in table(8) for prednisolone (3.5±0.42), mycophenolate mofetil (2.5±0.56), cyclosporine A (1.86±0.25), cyclophosphamide (1.24±0.21) and levamisole (2.53±0.29).There was statistically significant p-value (<0.0001).

Table 4: Median relapse number (No) for medication used during follow up

Type of medication	No.	Relapse through two year
Prednisolone	6	3.5±0.42
Mycophenolate Mofetil	8	2.5±0.56
Cyclosporine A	22	1.86±0.25
Cyclophosphamide	25	1.24±0.21
Levamisole	15	2.53±0.29
P value		< 0.0001

DISCUSSION

In this study of 76 children diagnosed with SDNS or FRNS and treated in nephrology unit of Central Teaching Hospital of pediatrics over a period of 5 years. The efficacy of five drugs (Prednisolone, Levamisole, Cyclophosphamide, Cyclosporine A, and Mycophenolate mofetil) were reviewed and compared with each other during 2 years

follow up, we found cyclophosphamide more effective in long term remission (more than 2 year) compared to other drugs and prednisolone was the least effective in long term remission and higher relapse frequency.

In this study, mean age in initial diagnosis was 3 years and most of them below 5 years (69.7%), SDNS constitute about 61.84% and 38.15% were FRNS which was almost similar to the Al Saran *et al.* [11] in which the mean age of diagnosis was 3.3 years. Regarding levamisole group, relapse free survival were 53.3% during the first 6 months of treatment which was approximately similar to Novak *et al.* [12] which was 50 %(9 out of 18 patients) of levamisole group had no relapse after 6 months of treatment. In this study,13.3% of levamisole group have no relapse at 1 year of treatment approximately similar to Basu *et al.* [13] which was 16% and lower than Novak *et al*. [12] that was 41% and al Saran *et al.* [11] 20/32 (62.5%) of them using levamisole were free from relapse in one year follow up. And only 6.6% of them had long term remission after 2 years. These differences might be due to different population sampling.

For cyclophosphamide group 76% of patients were still in remission 6 months after treatment which was higher than Cammas et al that shows relapse-free survival was 65% in the 1st 6 months of therapy [14]. Several studies including patients with FRNS or SDNS showed that cyclophosphamide resulted in remission in 57–93 % of patients at 1 year, 31–66 % at 5 years [15]. While in our study, about half 48% of children have no relapse during the first 12 months following the cyclophosphamide course which was almost similar to Cammas *et al.* [14] and Vester et al that have reported a free from relapse survival of 44% at 1 year [16]. Twenty four percent of cyclophosphamide group have sustained remission at 2 years of follow up that was almost similar to Cammas *et al.* [14] 27% and lower than Vester *et al.* that have reported a free from relapse survival of 34% at 2 years after cyclophosphamide in a cohort study of 94 children with FRNS [16]. In a cohort of 93 Dutch patients with FRNS, 33 (35%) never suffering from relapse after the first course of cyclophosphamide [17], and in Kemper et al reported that only 6 from 20 children had a remission following a 12-week course of cyclophosphamide [18].These variations are may be due to differences in patient populations as patients with steroid dependent NS have a lower response rate than patients with FRNS. The degree of dependence on steroid also affects rates of remission and cyclophosphamide is less effective in patients with SDNS compared to patients with FRNS.

For cyclosporine A group 63.6% of patients received CSA have no relapse at the first 6 months of treatment which was less than Novak *et al*. [12] 86.7% had no relapse after 6 months interval that difference might be due to long period of administratio of CSA that make patients skip some doses during therapy and also effect of other risk factors on relapse during treatment. After 12 months of CSA therapy only 36.3% of children had sustained remission which was lower than Hulton *et al.* 60% at 1 year [7], Gellermann *et al.* [19] and Novak *et al.* [17] since most of cyclosporine using children had relapse after stopping therapy probably due to different in ages between these studies and also many other risk factors like infections (UTI and URTI) could induce relapse in some patients. In our study, relapse free survival further decrease to13.6% after 2 years that was approximately the same to Ishikura et al which shows 15.3% relapse-free survival at 24 months [20] and lower than Hulton *et al.* [7] which was 40% at 2 years follow up because all the 40 children in Hulton *et al.* study received CSA for 1 year.

For mycophenolate mofetil group 62.5% at 6 months had no relapse which was a little lower than Hogg *et al.* [21] in which 24/32 (75%) of patients stayed in remission throughout the 6 months of MMF therapy. At 1 year of mycophenolate mofetil therapy 37.5% of patients were still in remission which was the same to Hogg *et al.* [21] at 1 year and Basu *et al.* [18] and lower than Novak et al 63.6% of them relapse free survival at 1 year [17] and Gellermann *et al.* [24]. During the first year, there was just one patient with nine relapses; so a total of 38 patients (64%) showed no relapses on treatment with MMF, whereas 50 patients (85%) showed no relapses with CSA therapy. In a multicenter, prospective, open-label study of 33 patients with frequently relapsing NS Afzal *et al.* [22] Of the 32 patients who received MMF, eight remained in remission for 18 to 30 months that was higher than in our study 12.5% after 24 months of therapy. MMF has been compared with CSA in FRNS in two studies Ulinski *et al.* [23] and Banerjee *et al.* [24]. In a few number of patients the comparative study by Dorresteijn *et al.* [25] there was no significant difference in the number of relapses at 12 months, although CSA had a better outcome.

Most patients in our study relapsed while they were on prednisolone alone and 66.7% of them had early relapse within 6 months of treatment and no one had sustained remission for 1 year indicating that prednisolone was the least effective drug in long term remission.

Conclusion

Cyclophosphamide is more effective in short and long term treatment of steroid dependent nephrotic syndrome and frequent relapsing nephrotic syndrome. Prednisolone alone is the least effective in maintaining remission if compared with other drugs in treatment of SDNS and FRNS. Cyclosporine A is more effective than mycophenolate mofetil and levamisole but most patients relapse after stop taking these drugs. Further prospective controlled trials are needed to determine the efficacy and safety of alternative treatment of SDNS/FRNS under the controlled time and circumstances.

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